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## 2017 National Veterinary Scholars Symposium Program Booklet

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All Abstract Titles and Posters are listed on the event website:

August 4, 2017

Welcome to the 2017, and now 18th Annual, National Veterinary Scholars Research Symposium. It is my pleasure and privilege to welcome you to the National Institutes of Health for this symposium as your host and co-organizer, along with Andrew Zoeller and Dr. Ted Mashima of the Association of American Veterinary Medical Colleges (AAVMC). As The National Cancer Institute, Center for Cancer Research’s formal co-sponsor for the symposium, AAVMC is a vital partner in organizing and producing this event.

True to the history of this annual conference many others have played significant roles in creating the opportunity this year for genuine scientific exchange on focused topics of immense societal importance in which veterinary medicine is a peer discipline, promoting health care and conducting life-saving biomedical research. We call your attention to the agenda following, announcing our invited speakers who will address plenary topics in Global Health and Neuroscience and Genetics; individuals who would naturally be invited to speak at the NIH on any given week. Concurrent scientific sessions on Conservation Medicine and Comparative Oncology continue the theme of important contributions in biomedical research being made integrally with veterinary medicine that impact humans and animals for a healthier planet.

Launching the opening Friday morning, we are pleased to be joined by the NIH Deputy Director for Intramural Research Dr. Michael Gottesman, who will formally welcome you to the NIH and our campus-wide intramural laboratory research program. As steward of medical and behavioral research for the nation, NIH has a mission to pursue fundamental knowledge about living systems and to apply scientific knowledge to extend healthy life and reduce illness and disability throughout the world.

This symposium continues the commitment to veterinary student research communication during our poster sessions, as well as features an interactive career development session led by Dr. Mashima to foster information exchange on pursuing career directions, including pathways to research. In the appendices of these proceedings we have included additional information and links to web resources about the NIH that highlight training opportunities, the majority of which are open to veterinarians and/or veterinary students.

There are many who deserve recognition for their contributions and regretfully I am not able to do justice to all. In addition to the AAVMC, we would like to recognize the generosity of sponsors who are supporting the AAVMC in the production of the symposium, those available at the time of production are included in the following materials, and we thank them. With the advantage of advice and support from Dr. Vilma Yuzbasiyan-Gurkan, Michigan State University, and Dr. Ed Murphey, AVMA, as well as NCI staff including John Hickerson and Shelley Hoover, I am pleased to invite you to enjoy this symposium and your visit to NIH, Bethesda and Washington, D.C.

Sincerely,

R. Mark Simpson, D.V.M., Ph.D.
Senior Scientist and Head, Molecular Pathology Unit
Director, NIH Comparative Biomedical Scientist Training Program
NIH Bethesda Campus Visitor Access and Parking Information

All visitors must enter campus through the NIH Gateway Center. You will be asked to submit to a vehicle or personal inspection and must provide a form of government-issued photo ID such as a driver's license or passport. Visitors are encouraged to use public transportation such as the Metrorail system which has a convenient stop on the Red Line (Medical Center) for the NIH campus. The Hyatt Hotel is located at the Bethesda Metro Stop. The NIH Gateway Center is located adjacent to the Medical Center Metro Station at the South Drive entrance to campus from Rockville Pike (Rte. 355). It combines visitor parking, non-commercial vehicle inspection and visitor ID processing, all in one location. The Gateway complex includes MLP-11, a multi-level underground parking garage. This visitor-only lot is the primary visitor parking for the NIH campus. Vehicles parking in MLP-11 are outside of the perimeter security and will not go through vehicle inspection, reducing the amount of time it takes to get on campus. The cost to park in MLP-11 on Friday is $2.00 per hour for the first three hours, $12.00 maximum for the entire day. Saturday parking is free. Visitors parking in MLP-11 should proceed to the Gateway Center to get a visitor badge and take a short walk (or take a shuttle bus) to their destination. Vehicles left in the MLP-11 parking garage after 11pm on weekdays or during weekends are subject to ticketing and towing. MLP-11 is closed on Saturdays. When MLP-11 is closed, visitors can park in visitor lots on the main campus. (See Full Campus Map on Following Page)
NIH Gateway Center for Visitors is located adjacent to the Medical Center Metro Station at the South Drive entrance to campus from Rockville Pike (Route 355).
A Brief History of the National Institutes of Health (NIH)

The National Institutes of Health is the primary agency of the United States government responsible for biomedical and public health research, founded in the late 1870s. It is part of the U.S. Department of Health and Human Services. The NIH comprises 27 separate institutes and centers with approximately 20,262 employees.

In the late 1870s, Congress allocated funds to investigate the causes of epidemics like cholera and yellow fever, and it created the National Board of Health, making medical research an official government initiative. In 1930, Congress introduced the "Ransdell Act" to establish and operate a National Institute of Health, to create a system of fellowships in said institute, and to authorize the Government to accept donations for use in ascertaining the cause, prevention, and cure of disease affecting human beings, and for other purposes. Over the next few decades, Congress would increase its funding tremendously to the NIH, and various institutes and centers within the NIH were created for specific research programs. In 1944, the Public Health Service Act was approved, and the National Cancer Institute became a division of NIH. In 1948, the name changed from National Institute of Health to National Institutes of Health. By 1971, cancer research was in full force and President Nixon signed the National Cancer Act, initiating a National Cancer Program, National Cancer Advisory Board, and 15 new research, training, and demonstration centers. During the 1990s, the NIH committee focus shifted to DNA research and the Human Genome Project was launched. More current research initiatives include the 21st Century Cures Act, the BRAIN initiative, Cancer Moonshot, and many others.

For over a century, NIH scientists have paved the way for important discoveries that improve health and save lives. In fact, 148 Nobel Prize winners have received support from NIH. The NIH conducts its own scientific research through its Intramural Research Program (IRP) and provides major biomedical research funding to non-NIH research facilities through its Extramural Research Program. NIH devotes 10% of its funding to research within its own facilities (intramural research). The institution gives 80% of its funding in research grants to extramural (outside) researchers. The extramural funding consists of about 50,000 grants to more than 325,000 researchers at more than 3,000 institutions.
## Symposium Schedule

**Friday, August 4, 2017**  
**Scientific Sessions, NIH Bethesda Campus, Natcher Conference Center, Building 45**

<table>
<thead>
<tr>
<th>TIME</th>
<th>ROOM/ LOCATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>7:00AM – 8:00AM</td>
<td>Registration</td>
</tr>
<tr>
<td>7:00AM – 8:00AM</td>
<td>Breakfast and Posters set up by 7:55AM (Posters displayed side by side even and odd numbers)</td>
</tr>
</tbody>
</table>
| 8:05AM – 8:20AM       | Welcome! To NIH  
**Michael M. Gottesman, M.D.**  
Deputy Director for Intramural Research, Office of the Director, National Institutes of Health, and  
Senior Investigator, Multidrug Resistance Section Head, and  
Chief, Laboratory of Cell Biology  
Center for Cancer Research, National Cancer Institute  
**Session Introductions and meeting host:**  
**R. Mark Simpson, D.V.M., Ph.D.**  
Senior Scientist and Head, Molecular Pathology Unit  
Director, Comparative Biomedical Scientist Training Program  
Laboratory of Cancer Biology and Genetics  
Center for Cancer Research, National Cancer Institute |
| 8:20AM – 8:30AM       | Fabian M. Kausche, MS, Dr med vet  
Head of Global Research and Development, Animal Health Business Unit  
Boehringer Ingelheim, Duluth, GA  
*A History of the National Veterinary Scholars Symposium* |
| 8:30AM – 9:20AM       | Plenary Session – Global Health  
**Julie Pavlin, M.D., Ph.D., MPH**  
Director, Board on Global Health  
National Academies of Sciences, Engineering and Medicine, Washington, D.C.  
*Global Health, Emerging Infections and One Health* |
| 9:20AM – 10:10AM      | Corrie Brown, D.V.M., Ph.D.  
Josiah Meigs and University Distinguished Professor |
## Symposium Schedule

**Friday, August 4, 2017 continued**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>(50 min)</td>
<td>College of Veterinary Medicine, University of Georgia, Athens, GA</td>
</tr>
<tr>
<td>10:10AM – 10:20AM (10 min)</td>
<td>&quot;Lessons and Lesions from Around the World&quot;</td>
</tr>
<tr>
<td>10:20AM – 10:30AM (10 min)</td>
<td>Panel Discussion</td>
</tr>
<tr>
<td>10:30AM – 12:00PM (90 min)</td>
<td>Student Poster Session A (Even Numbers)</td>
</tr>
<tr>
<td>12:00PM – 1:00PM (60 min)</td>
<td>Lunch</td>
</tr>
<tr>
<td>1:00PM – 2:30PM (90 min)</td>
<td>Student Poster Session B (Odd Numbers)</td>
</tr>
<tr>
<td>2:30PM – 3:20PM (50 min)</td>
<td>Plenary Session – Neuroscience and Genetics</td>
</tr>
<tr>
<td>3:20PM – 4:10PM (50 min)</td>
<td>Hugo Bellen, D.V.M., Ph.D. Howard Hughes Medical Institute Investigator</td>
</tr>
<tr>
<td>4:10PM – 4:20PM (10 min)</td>
<td>Panel Discussion</td>
</tr>
</tbody>
</table>

**Plenary Session – Neuroscience and Genetics**

- Hugo Bellen, D.V.M., Ph.D.
  - Howard Hughes Medical Institute Investigator
  - Professor, Department of Molecular and Human Genetics
  - Baylor College of Medicine, Houston, TX
  - "Drosophila to Identify and Unravel Pathogenic Mechanisms of Human Diseases"

- R. Douglas Fields, Ph.D.
  - Senior Investigator and Chief
  - Nervous System Development and Plasticity Section
  - National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD
  - "Beyond the Neuron Doctrine: White Matter Plasticity in Response to Functional Activity"
2017 National Veterinary Scholars Symposium

Center for Cancer Research, National Cancer Institute
National Institutes of Health
Bethesda, Maryland

With
The Association of American Veterinary Medical Colleges
Washington, D.C.

August 4 – 5, 2017

Symposium Schedule

Friday, August 4, continued

<table>
<thead>
<tr>
<th>TIME</th>
<th>EVENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>4:30PM – 5:00PM (30 min)</td>
<td>Return to Hotel</td>
</tr>
<tr>
<td>5:30PM</td>
<td>Transportation to The National Zoo, Washington, D.C.</td>
</tr>
</tbody>
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Reception, Special Speaker (On Location)
(Content programmed by AAVMC)

<table>
<thead>
<tr>
<th>TIME</th>
<th>EVENT</th>
</tr>
</thead>
</table>
| 6:30PM – 8:30PM | Donald Neiffer, V.M.D.  
Chief Veterinarian, Smithsonian’s National Zoo and Conservation Biology Institute  
Buses Return to Hotels at 8:30PM |

Saturday, August 5, 2017
Scientific Sessions, NIH Bethesda Campus, Natcher Center, Building 45

<table>
<thead>
<tr>
<th>TIME</th>
<th>ROOM/ LOCATION</th>
</tr>
</thead>
</table>
| 7:30AM – 8:30AM (60 min) | Breakfast and Posters set up by 8:25AM  
(Posters displayed side by side even and odd numbers) |
| 8:30AM – 9:15AM (45 min) | Scientific Presentations  
AVMA/AVMF Young Investigator Award Finalists  
Moderated by: Mark Suckow, D.V.M., Chair of AVMA Council on Research  
Meghan Vermillion, D.V.M.  
Johns Hopkins University  
“Modeling Congenital Zika Virus (ZIKV) Infection in Immunocompetent Mice”  
Zachary Freeman, D.V.M., Ph.D.  
Johns Hopkins University School of Medicine, currently at University of Michigan  
“Immune Checkpoints Are Discordantly Regulated by Chromatin Remodeling” |

The National Zoo,  
3001 Connecticut Ave. NW, Washington, D.C.  
20008
2017 National Veterinary Scholars Symposium

Center for Cancer Research, National Cancer Institute
National Institutes of Health
Bethesda, Maryland
With
The Association of American Veterinary Medical Colleges
Washington, D.C.
August 4 – 5, 2017

Symposium Schedule
Saturday, August 5, continued

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Location</th>
</tr>
</thead>
</table>
| 9:15AM – 9:40AM (25 min) | Scientific Presentations and Boehringer Ingelheim Awards (2 presenters and awards)  
2017 Boehringer Ingelheim Veterinary Graduate Award  
Ann Massie, D.V.M., University of California-Davis  
Award presented by Diane Larsen, D.V.M., Ph.D., Head of Pharmaceutical Development, Boehringer Ingelheim Animal Health  
2017 Boehringer Ingelheim Veterinary Research Scholar Award  
Ann DiPastina, Michigan State University  
Award presented by Monica Figueiredo, D.V.M., Ph.D., Director, External Innovation R&D, Boehringer Ingelheim | Natcher Auditorium |
| 9:40AM – 10:30AM (50 min) | Professional Student Development Session  
"Professional Development for Tomorrow’s Veterinarians"  
Moderated by Dr. Ted Mashima, Association of American Veterinary Medical Colleges (AAVMC)  
Tiffany Lyle, D.V.M., Ph.D., Assistant Professor, Purdue University, West Lafayette, IN  
Sue VandeWoude, D.V.M., Professor and Associate Dean for Research and Graduate Education, Colorado State University, Fort Collins, CO  
Ted Mashima, D.V.M., Senior Director for Academic and Research Affairs, AAVMC, Washington, D.C. | Natcher Auditorium |
| 10:30AM – 10:40AM (10 min) | Break                                                                                       |                   |
| 10:40AM – 11:15AM (35 min) | Professional Development Panel Discussion (Programmed by Ted Mashima, D.V.M., AAVMC)        | Natcher Auditorium |
### Symposium Schedule

**Saturday, August 5, continued**

<table>
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<tr>
<th>Time</th>
<th>Session 1</th>
<th>Session 2</th>
<th>Location</th>
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<tbody>
<tr>
<td>11:15AM – 12:45PM (90 min)</td>
<td>Student Poster Session C (Even Numbers)</td>
<td>Lunch Training Directors and the Boehringer Ingelheim Veterinary Scholars Program (B-IVSP)</td>
<td>Natcher Center Atrium and Rooms E1/E2, F1/F2, and G1/G2</td>
</tr>
<tr>
<td>12:45PM – 1:45PM (60 min)</td>
<td>Student Poster Session C (Even Numbers)</td>
<td>Lunch Training Directors and the Boehringer Ingelheim Veterinary Scholars Program (B-IVSP)</td>
<td>Natcher Center Room C1/C2</td>
</tr>
<tr>
<td><strong>Concurrent Sessions</strong></td>
<td><strong>Session 1 Conservation Medicine</strong></td>
<td><strong>Session 2 Comparative Oncology</strong></td>
<td><strong>Session 2 Comparative Oncology</strong></td>
</tr>
<tr>
<td>1:50PM – 2:15PM (25 min)</td>
<td>A. Alonso Aguirre D.V.M., M.S., Ph.D., Chair and Professor, Department of Environmental Science and Policy, George Mason University, Fairfax, VA  &quot;Do You Want to be a Conservation Medic?: Dealing with the Gaps and Challenges of One Health for a Greener Planet&quot;</td>
<td>Amy LeBlanc, D.V.M., Head of Comparative Oncology, Molecular Imaging Program, Center for Cancer Research, National Cancer Institute, Bethesda, MD  &quot;The NCI Comparative Oncology Program: Past, Present and Future&quot;</td>
<td>Session 1 Balcony A, B, C Natcher Center  Session 2 Main Auditorium, Natcher Center</td>
</tr>
<tr>
<td>2:15PM – 2:40PM (25 min)</td>
<td>Dawn Zimmerman, D.V.M., M.S., Associate Program Director, Global Health Program, Conservation Biology Institute, National Zoological Park, Smithsonian Institution, Washington, D.C.  &quot;Conservation Medicine – Saving a Species Through One Health&quot;</td>
<td>Nicola Mason, Ph.D., BVetMed, Associate Professor of Medicine and Pathobiology, University of Pennsylvania, Philadelphia, PA  &quot;An Integrative and Comparative Approach to Preventing Metastatic Disease in Canine and Pediatric Osteosarcoma&quot;</td>
<td>Session 1 Balcony A, B, C Natcher Center  Session 2 Main Auditorium, Natcher Center</td>
</tr>
<tr>
<td>2:40PM – 3:00PM (20 min)</td>
<td>Break</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3:00PM – 4:00PM (60 min)</td>
<td>AVMA Excellence in Research Awards  Moderator Mark Suckow, D.V.M., Chair of AVMA Council on Research, and Professor, Veterinary Population Medicine, University of Minnesota</td>
<td></td>
<td>Natcher Auditorium</td>
</tr>
</tbody>
</table>
# 2017 National Veterinary Scholars Symposium

Center for Cancer Research, National Cancer Institute  
National Institutes of Health  
Bethesda, Maryland  
With  
The Association of American Veterinary Medical Colleges  
Washington, D.C.  
August 4 – 5, 2017

## Symposium Schedule

### Saturday, August 5, continued

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Location</th>
</tr>
</thead>
</table>
| 4:00PM – 4:10PM (10 min) | AVMA Clinical Research Award  
Michael Lappin, D.V.M., Ph.D., Colorado State University (10 min)  
AVMA Career Achievement Award in Canine Research  
Darryl Millis, D.V.M., MS, University of Tennessee (10 min)  
AVMF/Winn Feline Foundation Research Award  
Duncan Lascelles, BSc, BVSc, Ph.D., North Carolina State University (10 min)  
AVMA Lifetime Excellence in Research Award  
Patricia Ann Conrad, D.V.M., Ph.D., University of California-Davis (20 min) | Natcher Auditorium                |
| 4:10PM – 5:40PM (90 min) | Presentation of Young Investigator Awards  
Award presented by Mark Suckow, D.V.M., Chair of AVMA Council on Research | Natcher Center Atrium and Rooms E1/E2, F1/F2, and G1/G2 |
| 5:45PM          | Meeting concludes; take down all posters, return to hotel  
(sorry, we cannot be responsible for posters left at Natcher) |                                  |
| 6:30PM          | Free Evening in Washington, D.C. and Metro area                                             |                                  |

### Sunday, August 6

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>7:30AM</td>
<td>Hotel Checkout</td>
<td>Bethesda Area Hotels</td>
</tr>
</tbody>
</table>
A. Alonso Aguirre, D.V.M., MS, Ph.D.
Professor and Chair, Department of Environmental Science and Policy
Chair, University Interinstitutional Animal Care & Use Committee
George Mason University, Fairfax, Virginia

Symposium Speaker, Concurrent Session, Saturday, August 5

“Do You Want to be a Conservation Medic?: Dealing with the Gaps and Challenges of One Health for a Greener Planet”

Dr. Aguirre is Chair and Professor at the Department of Environmental Science and Policy at George Mason University, Fairfax, Virginia, where he heads a program of collaborative research that focuses on the ecology of wildlife disease and the links to human health and conservation of biodiversity. He also chairs the university IACUC. He has worked for the past three decades in over 23 countries focusing on integrative research, transdisciplinarity and leadership professional courses and capacity building. He served as the Executive Director of the Smithsonian-Mason School of Conservation. Previously he was Senior Vice President at EcoHealth Alliance (formerly known as Wildlife Trust) in New York also holding different appointments at the Consortium for Conservation Medicine, the Center for Environmental Research and Conservation at Columbia University and the Center for Conservation Medicine at Tufts University Cummings School of Veterinary Medicine. Dr. Aguirre cofounded the emerging discipline of conservation medicine and is senior editor of both seminal books. He co-edited “Tropical Conservation: Perspectives on Local and Global Priorities” and has published over 160 peer-reviewed articles. He also cofounded the Journal EcoHealth and the International Association of Ecology and Health. He has advised governments of several countries in the Americas, Southeast Asia and Western Europe. He also has briefed the U.S. and Mexican Congresses. Dr. Aguirre has received numerous awards including the Colorado State University Warner College of Natural Resources Distinguished Alumnus Award, the Harry Jalanka Memorial Medal from Finland for outstanding contributions to wildlife medicine and the Conservation Award of the Year from the Mexico State Commission of Natural Parks and Wildlife for his role in conserving protected areas for monarch butterflies. His work has been the focus of extensive media coverage including Bioscience, Conservation in Practice, E-Magazine, Environmental Health Perspectives, National Geographic, The New York Times, Science News, Trends in Ecology and Evolution, Newsweek, National Public Radio, Al Jazeera Stream TV, CBS, LTV and other international magazines, TV and radio shows.
Hugo Bellen, D.V.M., Ph.D.
Howard Hughes Medical Institute Investigator
Professor, Department of Molecular and Human Genetics
Baylor College of Medicine, Houston, Texas

Symposium Speaker, Neuroscience and Genetics, Friday, August 4

“Drosophila to Identify and Unravel Pathogenic Mechanisms of Human Diseases”

Dr. Bellen is a Howard Hughes Investigator and Distinguished Service Professor at the Baylor College of Medicine, USA. His group has made major contributions to our understanding of nervous system development, synaptic transmission, and neurodegeneration. Professor Bellen uses flies to examine the function of human genes associated with neurodevelopmental and neurodegenerative phenotypes. He is the principal investigator of the Model Organism Screening Center for the Undiagnosed Disease Network of the National Institute of Health in the USA. The goal of this center is to determine which mutations underlie human disease by using fruit flies and zebrafish. His group has discovered several new human diseases in the past two years. In addition, his lab members are trying to elucidate the precise pathogenic mechanisms related to Friedreich Ataxia, Alzheimer Disease, Parkinson Disease, and several other neurodevelopmental and/or neurodegenerative diseases, using genetic, molecular, cell biological, biochemical, electrophysiological and genomic approaches. Professor Bellen’s research demonstrates the benefits that can emerge from studies in model organisms to improve diagnosis and human health.
Corrie Brown, D.V.M., Ph.D.
Josiah Meigs and University Distinguished Professor
College of Veterinary Medicine,
University of Georgia, Athens, Georgia

Symposium Speaker, Global Health, Friday, August 4

“Lessons and Lesions from Around the World”

Dr. Brown is a Josiah Meigs Distinguished Professor at the University of Georgia, where she teaches in the College of Veterinary Medicine. She holds a DVM from the University of Guelph and a PhD in Comparative Pathology from the University of California at Davis. She is a Diplomate of the American College of Veterinary Pathologists.

Brown has worked internationally in building animal health infrastructure and diagnostics for much of her career, conducting workshops on basic field necropsy and diagnostic techniques in multiple countries. She spent ten years as Head of Pathology at the USDA Foreign Animal Disease Diagnostic Laboratory at Plum Island. She has authored four books on transboundary animal diseases and field diagnostics in resource-poor settings. Dr. Brown has served on many national and international expert panels about animal health and has received numerous awards for her efforts, including the AVMA International Award and a Fulbright Award, and has twice received the Student AVMA National Teaching Award. She is happiest when working with students as they explore the realms of pathology and pathogenesis.
Dr. Fields is the Chief of the Nervous System Development and Plasticity Section, at the Eunice Kennedy Shriver National Institute of Child Health and Human Development, at the National Institutes of Health. Dr. Fields’ long-standing interest is in how environmental experience and functional activity in the nervous system affect nervous system development and plasticity. His current research emphasis is on neuron-glia interactions and in particular on regulation of myelination by impulse activity. His research has identified several mechanisms for activity-dependent myelination in support of the concept that modifying conduction velocity by myelination may contribute to information processing and plasticity by achieving optimal synchrony of spike time arrival and supporting oscillations of appropriate frequencies. In addition, his research explores the cellular mechanisms of learning (LTP, LTD, and homeostatic synaptic plasticity) and regulation of gene expression in neurons and glia by specific patterns of action potentials. He was founding editor of the journal *Neuron Glia Biology* from 2004-2011, and he serves on the editorial board of *Glia*, *Scientific Reports*, *The Neuroscientist*, *Neuroscience Letters*, and other journals. He received the PhD degree from UC San Diego and conducted postdoctoral research at Stanford University, Yale University, and the National Institutes of Health (NIH) in Bethesda, Maryland. He is currently head of Nervous System Development and Plasticity Section at the NIH. In addition to his official duties Dr. Fields enjoys writing about science for the public for *Scientific American*, *BrainFacts.org*, *Huffington Post*, *Psychology Today*, and others. He serves on the board of *Scientific American Mind* and he is author of two neuroscience books for the general reader, *The Other Brain* (Simon and Schuster), about glia, and *Why We Snap* (Dutton/Penguin), about the neuroscience of sudden aggression.
Michael Gottesman, M.D.
Deputy Director for Intramural Research, Office of the Director
National Institutes of Health, and
Senior Investigator, Multidrug Resistance Section Head, and
Chief, Laboratory of Cell Biology
Center for Cancer Research
National Cancer Institute
Bethesda, Maryland

Symposium Speaker, Friday, August 4

“Welcome! To NIH”

Dr. Gottesman has been Deputy Director for Intramural Research at NIH since 1993. A graduate of Harvard College and Harvard Medical School, Dr. Gottesman completed an internship and residency at the Peter Bent Brigham Hospital in Boston. He was a research associate at NIH from 1971 to 1974. He returned to Harvard Medical School as an assistant professor before returning to NIH in 1976. Dr. Gottesman became Chief of the Laboratory of Cell Biology in the National Cancer Institute in 1990. From 1992 to 1993, he was Acting Director of the National Center for Human Genome Research, and he was Acting Scientific Director of the NCHGR in 1993. During his 26 years of service in the U.S. Public Health Service as a Commissioned Officer, he achieved the rank of two-star rear admiral as assistant surgeon general. His research interests have ranged from how DNA is replicated in bacteria to how cancer cells elude chemotherapy. He has published extensively on these subjects, with over 500 scientific publications to his credit. During the past thirty years, he has helped to identify and characterize the human gene that causes cancer cells to resist many anticancer drugs. He has shown that this gene encodes a protein that pumps anticancer drugs out of drug-resistant human cancers and has used this information to create gene transfer vectors, to study the pharmacology of many drugs, and to circumvent drug resistance in cancer. He is an elected fellow of the AAAS and the American Association of Physicians, and has been an elected member of the National Academy of Medicine since 2003 and the American Academy of Arts and Sciences since 2008. His scientific work has been recognized by highly competitive awards such as the AACR Rosenthal Foundation Award, the Milken Family Medical Foundation Cancer Research Award, the ASPET award, the ASBMB Bert and Natalie Vallee Award, and the DHHS Secretary’s Award for Distinguished Service, among others. Dr. Gottesman has been actively involved in initiating several training and mentoring programs for high school students and teachers, as well as college, medical and graduate students. As Deputy Director for Intramural Research at NIH, he has initiated an NIH-wide lecture series, and reformulated tenure and review processes in the intramural program. He has also instituted training programs for underrepresented minority and disadvantaged students, programs to advance the careers of women scientists, loan repayment programs for clinical researchers at NIH, and a clinical research training program for medical students and early career clinical investigators.
As Global Head of Research & Development for the Animal Health Business Unit of Boehringer Ingelheim (and previously of Merial Inc.), Fabian has led the company’s global research since 2014, bringing many years of experience in the animal and human health industries in both biological and pharmaceutical R&D as well as companion animal sales. His expertise covers a unique combination of both science and business. Fabian heads a team of more than 1,200 scientists, clinicians, regulatory specialists and other technical experts at sites around the world in advancing the scientific and technical aspects of BI Animal Health research and development programs. Fabian received a veterinary degree and a Dr. med. vet. (PhD equivalent) from the Hanover Veterinary School in Germany, as well as a Masters of Science degree from Iowa State University. He has held a variety of positions at Novartis and Pharmacia & Upjohn (later acquired by Pfizer) and authored numerous scientific publications, abstracts and invited presentations. Having completed the Advanced Management Program in 2005, he is also an alumnus of Harvard Business School.
Amy K. LeBlanc, D.V.M.
Head of Comparative Oncology, Molecular Imaging Program
Center for Cancer Research
National Cancer Institute
Bethesda, Maryland

Symposium Speaker, Concurrent Session, Saturday, August 5

“The NCI Comparative Oncology Program: Past, Present and Future”

Dr. LeBlanc is the Director of the intramural National Cancer Institute’s Comparative Oncology Program. In this position, she conducts preclinical mouse and translational canine studies that are designed to inform the drug and imaging agent development path for human cancer patients. She also advises leading pharmaceutical companies as well as NCI’s Division of Cancer Treatment and Diagnosis on the inclusion of pet dogs with cancer into the development path of novel approaches for a variety of malignancies, including immunotherapeutics, targeted small molecules, oncolytic viruses, and cancer imaging agents. She also directly oversees the NCI Comparative Oncology Trials Consortium (COTC), which provides infrastructure necessary to connect participating veterinary academic institutions with stakeholders in drug development to execute fit-for-purpose comparative clinical trials in novel therapeutics and imaging agents. Prior to her appointment at NIH, Dr. LeBlanc was an Associate Professor with tenure and Director of Translational Research at the University of Tennessee College of Veterinary Medicine (CVM) and UT Graduate School of Medicine (GSM). Dr. LeBlanc’s group at the University of Tennessee published the first comprehensive studies describing molecular imaging of dogs and cats using PET/CT, focusing on the forward and back-translation of $^{18}$F-labelled radiopharmaceuticals.
L. Tiffany Lyle, D.V.M., Ph.D.
Assistant Professor, Department of Comparative Pathobiology
Purdue University, West Lafayette, Indiana

Symposium Speaker, Professional Student Development Session
Saturday, August 5

Dr. Lyle is an Assistant Professor of Veterinary Anatomic Pathology in the Department of Comparative Pathobiology at Purdue University College of Veterinary Medicine in West Lafayette, IN. She received her DVM from the University of Georgia in 2008, completed a residency in Anatomic Pathology at Purdue University in 2011, and became a Diplomate of the American College of Veterinary Pathologists in 2012. Dr. Lyle received her PhD from Purdue University in 2016 through the Comparative Biomedical Scientists Training Program, a graduate partnership program between Purdue University and the National Cancer Institute (NCI). During her graduate research at the NCI, Dr. Lyle identified pathologic and functional alterations of the blood-brain barrier in experimental models of brain metastases of breast cancer. Most recently, Dr. Lyle has established the Comparative Blood-Brain Barrier Laboratory at Purdue University. Her research group is working to identify therapeutic molecular targets of the blood-brain barrier in metastatic and primary brain tumors that impact humans and companion animals. In addition to conducting her primary research, Dr. Lyle is also the director of the Histology Research Laboratory, a core laboratory which provides pathology support to Purdue University investigators. In this capacity, Dr Lyle has active research collaborations in microbiology, neuroscience, nutrition, biomedical engineering, biology, chemistry, and pharmacology. The ultimate goal of Dr. Lyle’s research is to apply veterinary anatomic pathology as a tool to understand molecular mechanisms of naturally occurring disease affecting animals and humans.
Dr. Mashima is the Senior Director for Academic and Research Affairs for the Association of American Veterinary Medical Colleges, a nonprofit association that coordinates the affairs of the veterinary colleges in the US and internationally. He previously served as the president and executive director of the Asian & Pacific Islander American Scholarship Fund, associate director for the Center for Public and Corporate Veterinary Medicine (Virginia-Maryland College of Veterinary Medicine), and projects director for the National Association of Physicians for the Environment. He has a BA (zoology) from the University of Hawaii at Manoa and a DVM from Colorado State University. He completed an internship at Kansas State University and a residency at North Carolina State University, and is board certified in zoological medicine and veterinary preventative medicine. He is the co-editor of *The Rhino with Glue-On Shoes, and Other Surprising True Stories of Zoo Vets and Their Patients.*
Dr. Mason is an Associate Professor of Medicine and Pathobiology at the University of Pennsylvania in Philadelphia, PA. Dr. Mason is a board-certified veterinary internist and immunologist with extensive experience in the performance of clinical trials using immunotherapy and evaluation of immunological responses in dogs with spontaneous cancer. She performed her postdoctoral research in the laboratory of Dr. Carl June, where she worked on developing the canine model for evaluating chimeric antigen receptor T cell therapies. Since this time she has successfully translated several promising strategies to generate anti-tumor immunity from the lab and preclinical murine models into client-owned dogs suffering from lymphoma, osteosarcoma and hemangiosarcoma. Her work with Dr. Yvonne Paterson, Professor of Microbiology at the UPENN School of Medicine, pioneering the translation of a live, recombinant HER2 targeting *Listeria* (ADXS31-164) into dogs with spontaneous osteosarcoma earned her the inaugural One Health Award, together with Dr. Paterson in 2013. This is an Award for Excellence in promoting One Health Initiatives and Interprofessional Education at the University of Pennsylvania. Dr. Mason has been actively involved in evaluating the immunological consequences of immune-based therapies in client-owned dogs for over 10 years, and she has extensive experience in flow cytometric phenotyping of canine T cells and functional assays including ELISpot and cytotoxicity assays to investigate canine T cell responses. Her in vitro and in vivo work with RNA-transfected CD40-activated B cells and recombinant *Listeria* technology has shown that tumor-specific immune responses can be generated in dogs with spontaneous cancers (lymphoma and osteosarcoma) and effectively measured ex vivo. The Mason lab also is currently developing CAR T cell therapies for dogs with B cell lymphoma, and Dr. Mason serves as the PI and lead investigator on the first clinical trial evaluating CAR T cell therapies in dogs. Both systems, first brought into the canine clinic by Dr. Mason, represent robust platforms to induce and evaluate neo-antigen–specific immune responses in dogs and determine safety and therapeutic efficacy of neo-epitope vaccines and immune therapies.
Donald Neiffer, V.M.D., C.V.A., M.H.S.
Chief Veterinarian, Smithsonian’s National Zoo
Washington, D.C.

Dr. Neiffer is currently Chief Veterinarian of the Smithsonian’s National Zoo in Washington, D.C. He coordinates and directs all medical operations to ensure sound veterinary practices. He also conducts clinical and conservation research and training programs. For more than fifteen years, Dr. Neiffer worked as the Veterinary Operations Manager for Walt Disney World’s Animal Programs in Lake Buena Vista, FL and its associated facilities in Hawaii and the Bahamas. In this role, he implemented preventative health-care programs, oversaw research, managed medical cases, and trained and consulted staff on diet and husbandry needs. He also served as a committee member for the Disney Wildlife Conservation Fund. He previously held positions at the Pittsburgh Zoo, the National Aviary, and The Wilds, an affiliate of the Columbus Zoo and Aquarium. Dr. Neiffer earned his B.S. in Biology from Millersville University in 1987 and his Doctorate in Veterinary Medicine from the University of Pennsylvania in 1992. In addition to the standard veterinary school curriculum, Dr. Neiffer completed externships and training programs at the National Aquarium in Baltimore, Bronx Zoo, University of Florida, and Marine Biological Laboratory. Dr. Neiffer earned board certification in zoological medicine from the American College of Zoological Medicine in 2005, and certification in veterinary acupuncture through the Chi Institute of Traditional Chinese Veterinary Medicine in 2013. Tomorrow (yes, tomorrow) he will be receiving a Master of Health Science—One Health Concentration degree from the College of Public Health and Health Professions, University of Florida. Dr. Neiffer has authored or co-authored a number of peer-reviewed articles and texts, and has spoken at professional meetings and workshops both nationally and internationally. His professional interests include in situ related species and environmental health assessments/conservation programs both locally and globally, disease transmission at the wildlife-human-livestock interface, developing anesthetic protocols, hoofstock medicine and management, fish medicine, soft tissue surgery, and teaching. Most recently Dr. Neiffer returned from a trip to Kruger National Park in South Africa where he served as principal investigator on two studies, one that evaluated an anesthetic protocol for use in free-ranging warthogs, and one that investigated selected disease prevalence and relationships in warthogs that may have implications for disease transmission in northeastern South Africa.
Julie Pavlin, M.D., Ph.D., MPH
Director, Board on Global Health
National Academies of Sciences, Engineering and Medicine
Washington, D.C.

Symposium Speaker, Global Health, Friday, August 4

“Global Health, Emerging Infections and One Health”

Dr. Pavlin is the Director, Board on Global Health at the National Academies of Sciences, Engineering, and Medicine where she coordinates analyses of health developments beyond US borders and areas of international health investment that are most likely to benefit the health of the US population and promote global well-being, security, and economic development. Prior to joining the National Academies, she was the Research Area Director for Emerging Infectious Diseases and Antimicrobial Resistance and Deputy Research Area Director for HIV at the Infectious Disease Clinical Research Program, part of the Uniformed Services University, and before that the Deputy Director of the Armed Forces Health Surveillance Center. She is a retired Colonel in the US Army and previous assignments included the Chief of the Global Emerging Infections Department at the Armed Forces Research Institute of Medical Sciences in Bangkok, Thailand, where she developed surveillance programs for infectious diseases in Asia; the Chief of the Field Studies Department at the Walter Reed Army Institute of Research, where she played a pivotal role in developing the Electronic Surveillance System for the Early Notification of Community-based Epidemics (ESSENCE), the Department of Defense real-time surveillance system; and Assistant Chief of the Operational Medicine Division at the US Army Medical Research Institute for Infectious Diseases. Dr. Pavlin received her AB from Cornell University, her MD from Loyola University, her MPH from Harvard University, and her PhD in Emerging Infectious Diseases at the Uniformed Services University.
Dr. Simpson is a Senior Scientist in the National Cancer Institute (NCI) Center for Cancer Research intramural Laboratory of Cancer Biology and Genetics. He is a veterinary graduate of the University of Georgia and obtained by clinical practice experience in mixed species and emergency medicine. He completed combined postgraduate clinical training in pathology and a PhD in comparative and experimental medicine at the Louisiana State University. After completing his training, he served as a faculty member at the North Carolina State University College of Veterinary Medicine. His NIH career began with a return to the laboratory where he completed a summer research internship while a veterinary student. As a staff scientist in the Laboratory of Immunogenetics, National Institute of Allergy and Infectious Disease, he conducted research modeling the pathogenesis of Human Immunodeficiency Virus and Human T-Cell Leukemia Virus-I. His work included mechanistic elucidation of transplacental antenatal HIV transmission from mother to fetus. Dr. Simpson subsequently became the founding director for the NIH Comparative Biomedical Scientist Training Program (CBSTP) and initiated the Molecular Pathology Unit in the NCI. The unique CBSTP training opportunity for veterinarians includes interdisciplinary training in comparative pathology and human disease biomedical research. The program also supports pre-doctoral summer fellowships for veterinary students to obtain research experience, similar to the opportunity that helped mold Dr. Simpson’s career in public health and biomedical research as a veterinarian. His current laboratory in the NCI is focused on developing combined molecular-targeted approaches to rare forms of melanoma in humans, including studies of naturally occurring melanoma in dogs from a comparative oncology perspective. In addition, his group has a focus in developing automated computer-assisted cancer diagnostic platforms in digital pathology informatics. He is adjunct graduate professor or clinical professor at four colleges of veterinary medicine. He is a diplomate and past president of the American College of Veterinary Pathologists as well as recipient of several NIH Director’s awards for mentoring and leading diversity in the Center for Cancer Research.
Sue VandeWoude, D.V.M.
Professor and Associate Dean for Research and Graduate Education
Colorado State University, Fort Collins, Colorado

Symposium Speaker, Professional Student Development Session
Saturday, August 5

Dr. VandeWoude received undergraduate training at the California Institute of Technology and veterinary training at the Virginia-Maryland Regional College of Veterinary Medicine and completed a postdoctoral fellowship in comparative medicine at The Johns Hopkins Medical Institute. She is currently Associate Dean for Research and Professor of Comparative Medicine in the Department of Microbiology, Immunology, and Pathology in the College of Veterinary Medicine and Biomedical Sciences at Colorado State University. In her current role she oversees intramural research programs for CVMBS and pre- and post-doctoral veterinary research fellowship training, and provides oversight/support for DVM-PhD training. She has mentored over 40 veterinary students, DVM-PhD students, and post-graduate veterinarians and has served as Program Director on several veterinary research training grants funded by NIH. She also serves as lead contact for the University of Colorado, Denver CTSA award supporting the Colorado Clinical and Translational Science Institute. Dr. VandeWoude is a strong advocate for the role veterinarians can play in biomedical research, and has participated on national committees and workshops to promote this issue, the NIH Physician Scientist Workforce (PSW) group, charged by NIH director, Dr. Francis Collins. Dr. VandeWoude’s laboratory’s primary area of investigation includes host and viral responses to species-adapted and cross-species lentiviral transmissions, and impacts of ecology and management on transmission of diseases in domestic and nondomestic felids. Dr. VandeWoude is recipient of the 2014 Colorado State University and AAVMC Excellence in Research Award, sponsored by Zoetis, the 2015 Virginia-Maryland College of Veterinary Medicine’s Lifetime Achievement Alumni Award, and the 2016 ACLAM Comparative Medicine Scientist award.
Dawn Zimmerman, D.V.M., M.S.
Associate Program Director, Global Health Program,
Conservation Biology Institute
National Zoological Park
Smithsonian Institution, Washington, D.C.

Symposium Speaker, Concurrent Session, Saturday, August 5

“Conservation Medicine – Saving a Species Through One Health”

Dr. Zimmerman is associate program director of the Smithsonian Conservation Biology Institute’s Global Health Program, which uses a One Health approach to the conservation of critically endangered wildlife species and the mitigation of emerging infectious diseases at the wildlife-human interface. As a zoo and wildlife veterinarian, Dawn has spent much of her career working towards the conservation of endangered species through in situ clinical care, research, and capacity building worldwide, to include critical work with the USAID Emerging Pandemic Threats PREDICT program, and with international projects such as UC Davis’ Gorilla Doctors in Africa. Dawn will focus on conservation medicine, exploring the link between One Health and saving species.
Presenting the 2017 Boehringer Ingelheim Veterinary Graduate Award

Diane Larsen D.V.M., Ph.D.
Head of Pharmaceutical Development, Boehringer Ingelheim Animal Health

Dr. Larsen earned her veterinary degree at the University of Wisconsin-Madison. Following graduation, she spent 5 years as an associate veterinarian in small animal practice. She then returned to the University of Wisconsin to complete a PhD in veterinary virology/immunology, followed by a year-long postdoctoral program with USDA in Athens, Georgia. Diane joined Merial in April 2001 as a pharmaceutical Project Leader where she directed the development of a variety of veterinary pharmaceutical products. For the past 2 years, she has been the Head of Pharmaceutical Development, leading a group of talented Project Leaders and Project Planners. Merial is now part of Boehringer Ingelheim Animal Health. Diane is based in Duluth, GA.

Recipient of the 2017 Boehringer Ingelheim Veterinary Graduate Award

Anna Massie, D.V.M.
University of California, Davis

Dr. Massie received her bachelor’s and veterinary degrees from the University of Illinois. Following graduation, she completed a rotating internship in small animal surgery and medicine at Purdue University and a surgical specialty internship at North Houston Veterinarian Specialists. She is currently starting her 3rd year of residency in Small Animal Surgery at the University of California-Davis.
Presenting the 2017 Boehringer Ingelheim Veterinary Research Scholar Award

Monica Figueiredo, D.V.M., Ph.D.
Director, External Innovation R&D, Boehringer Ingelheim

Dr. Figueiredo earned her veterinary degree at the Universidade Federal Fluminense, Rio de Janeiro, Brazil. Following graduation, she completed a two-year equine internship at the Marion DuPont Scott Equine Medical Center, Virginia, followed by a three-year residency program in Large Animal Medicine at Cornell University, New York. She then moved to the College of Veterinary Medicine at the University of Georgia, where she earned her PhD in the Department of Physiology and Pharmacology. Monica joined Merial in 2008 as a Veterinary Scientist in R&D, where she primarily worked in the area of canine vaccine development. In the last four years, she has served as Director of External Innovation and has been thrilled to work with the latest technology in a variety of fields related to improving animal health. Merial is now part of Boehringer Ingelheim. Monica is based in Athens, GA.

Recipient of the 2017 Boehringer Ingelheim Veterinary Research Scholar Award

Ann DiPastina
Michigan State University

Ann DiPastina is a third-year veterinary student at the Michigan State University College of Veterinary Medicine. She earned a Bachelor of Science in the Animal Science major from Cornell University in 2015. As the recipient of the Boehringer Ingelheim Veterinary Research Scholar Award, she will be presenting the work that she completed in the summer of 2016 under the guidance of Yrjö Gröhn as part of the Cornell University Veterinary Investigators Program. While this project marks her debut in system dynamics modeling, Ann’s first exposure to research came in 2014, when she began an undergraduate honors thesis for which she studied the implementation of plate waste as a feed source for growing lambs and compared the growth rates of naturally and artificially reared lambs. This summer, Ann has returned to Cornell as a participant in the Cornell Leadership Program for Veterinary Students, repriming her role in Dr. Gröhn’s lab to expand on their current model and clarify the relationship between the use of antimicrobials in the US dairy industry and the development of resistant microbes. Ann is originally from New Hampshire and is the youngest of four siblings. In her spare time, she enjoys running, swimming, and playing hockey.
Presenter of the 2017 AVMA Excellence in Research Awards
Moderator and Session Chair Young Investigator Awards

Mark Suckow, D.V.M.
Chair, American Veterinary Medical Association
Council on Research, Schaumburg, Illinois

Dr. Suckow received his DVM from the University of Wisconsin in 1987 and subsequently completed a post-doctoral residency in laboratory animal medicine at the University of Michigan in 1990. He spent 8 years as a clinical laboratory animal veterinarian at Purdue University and then 17 years at the University of Notre Dame where he served as director of the research animal facility and as Associate Vice President for Research Compliance. With an interest in cancer models, biomaterials models, and vaccines, Dr. Suckow has functioned as an independent and collaborative investigator, with over 90 publications in refereed journals and six issued patents. He has written or edited over 20 books on topics related to research and laboratory animal medicine. Further, he served as the 2006 President of the American Association for Laboratory Animal Science and the 2011 President of the American Society of Laboratory Animal Practitioners, and currently he serves as Chair of the AVMA Council on Research and is a member of the Council on Accreditation of AAALAC, International. Dr. Suckow has been at the University of Minnesota as Director of the Research Animal Resources and as Professor of Veterinary Population Medicine since August 2015.
Recipient of the AVMA Lifetime Excellence in Research Award

Patricia Conrad D.V.M., Ph.D.
Associate Dean for Global Programs
School of Veterinary Medicine
University of California, Davis

Dr. Conrad is Associate Dean for Global Programs at the School of Veterinary Medicine, University of California, Davis and Co-Director of the UC Global Health Institute. Dr. Conrad is a Distinguished Professor of Parasitology whose research is focused on the transmission of protozoal parasites between wildlife, humans and domestic animals. She received her DVM from Colorado State University and PhD from the University of Edinburgh, Scotland.

After doing post-doctoral research at the International Laboratory for Research on Animal Diseases in Nairobi, Kenya, she joined the faculty of the University of California, Davis’s School of Veterinary Medicine. Dr. Conrad has published over 225 scientific papers and book chapters in the fields of emerging infectious diseases, parasitology, ecology of fecally-transmitted waterborne pathogens and One Health, demonstrating the value of collaborative research and education that considers the interconnectedness of humans, animals and environmental change worldwide. As a scientist and advocate for the One Health approach, she promotes engagement and experiential learning by students working with underserved communities in California and globally. She is actively engaged in collaborative research and education that includes the development of novel computerized educational programs to encourage active problem-based learning in global health. She is the recipient of the Carl J. Norden Distinguished Teaching Award, Pfizer Award for Research Excellence, Oscar Schalm and Norman Levine Lectureships and an Aldo Leopold Leadership Fellowship. Dr. Conrad is an American Academy of Microbiology Fellow and member of the National Academy of Medicine.
Recipient of the AVMA Clinical Research Award

Michael R. Lappin, D.V.M., Ph.D.
Kenneth W. Smith Professor in Small Animal Clinical Veterinary Medicine, Colorado State University, Fort Collins, Colorado

Dr. Lappin graduated from Oklahoma State University and then completed an internship, internal medicine residency, and PhD in parasitology at the University of Georgia. Dr. Lappin is the Kenneth W. Smith Professor in Small Animal Clinical Veterinary Medicine at Colorado State University and director of the Center for Companion Animal Studies, and he helps direct the shelter medicine program. His principal areas of interest are prevention of infectious diseases, the upper respiratory disease complex, infectious causes of fever, infectious causes of diarrhea, and zoonoses. His research group has published over 300 primary papers or book chapters concerning small animal infectious diseases. Awards include the Norden Distinguished Teaching Award, the European Society of Feline Medicine International Award for Outstanding Contribution to Feline Medicine, the Winn Feline Research Award, the ACVIM Robert W. Kirk Award for Professional Excellence, and the WSAVA Scientific Achievement Award.
Recipient of the AVMF/Winn Feline Foundation Research Award

B. Duncan X. Lascelles, BSc, BVSc, Ph.D.
Director, Comparative Pain Research and Education Centre,
North Carolina State University
College of Veterinary Medicine, Raleigh, North Carolina

Dr. Lascelles is Professor of Small Animal Surgery and Pain Management and Director, Comparative Pain Research and Education Centre, North Carolina State University College of Veterinary Medicine, Raleigh, NC. After graduating from the veterinary program at the University of Bristol, U.K., with honors, Dr. Lascelles completed a PhD in aspects of pre-emptive/perioperative analgesia at the University of Bristol. After an internship there, he completed his surgical residency at the University of Cambridge, U.K. He moved to Colorado for the Fellowship in Oncological Surgery at Colorado State University, then a period of post-doctoral research in feline pain and analgesia at the University of Florida, and is currently Professor of Small Animal Surgery and Pain Management at North Carolina State University. He runs the Comparative Pain Research and Education Centre, which is dedicated to answering critical questions through high-quality, innovative research. He is board-certified in small animal surgery by the Royal College of Veterinary Surgeons, the European College of Veterinary Surgeons, and the American College of Veterinary Surgeons. His career has been focused on developing algometry methods (methods to measure pain) in spontaneous disease animal models (pets with naturally occurring disease), and probing tissues from well-phenotyped animals with spontaneous disease to understand the neurobiology, with a strong translational focus. The aim of his research is to improve pain control in companion cats and dogs and facilitate better pain control in humans. He has authored over 150 peer-reviewed research papers and reviews and 160 research abstracts, as well as over 30 book chapters. In cats, his work defining how chronic pain is measured has shaped the approach to acute and chronic pain management.
Darryl Millis, MS, D.V.M.
Professor of Orthopedic Surgery
University of Tennessee
College of Veterinary Medicine, Knoxville, Tennessee

Dr. Millis is a Diplomate of the American College of Veterinary Surgeons, a Diplomate of the American College of Veterinary Sports Medicine and Rehabilitation, and Professor of Orthopedic Surgery at the University of Tennessee College of Veterinary Medicine. He is the Director of the CARES Center for Veterinary Sports Medicine, a co-editor of several textbooks, and a primary faculty member of the University of Tennessee Certificate Program in Canine Rehabilitation. Dr. Millis has received the World Small Animal Veterinary Association Iams Paatsama Award in recognition of clinical and scientific achievements in orthopedic surgery and physical rehabilitation. Dr. Millis’s research has focused on osteoarthritis, physical rehabilitation, and fracture healing. He has evaluated gait analysis techniques and treatments for osteoarthritis. Specifically, Dr. Millis has investigated perioperative analgesic protocols for dogs undergoing tibial plateau leveling osteotomy, as well as control for chronic orthopedic pain. A Morris Animal Foundation Award allowed him to examine alternative and complementary treatments for dogs with osteoarthritis. He has also described 3-D motion of the pelvic limb in dogs with cranial cruciate ligament (CCL)–deficient stifle joints. He has analyzed bone and lean tissue changes following CCL transection and stifle stabilization, which showed a significant loss of bone mineral content and lean tissue. Dr. Millis helped determine that use of canine somatotropin enhances bone healing in dogs. Most recently, he was part of a team that developed a scale to more objectively evaluate mobility in dogs and will be inexpensive to apply in clinical practice.
Training Programs at the National Institutes of Health

Website: https://www.training.nih.gov/programs/sip

PROGRAMS FOR ALL DEGREE LEVELS

The Summer Internship Program (SIP) welcomes eligible high school, college, graduate, and professional students to spend eight to ten weeks conducting biomedical research with NIH investigators. SIP includes subprograms run by the NIH Office of Intramural Training & Education: CCSEP, the Community College Summer Enrichment Program; HiSTEP, the High School Scientific Training and Enrichment Program; HiSTEP 2.0; the AMGEN Scholars at NIH Program; and GSOAR, the Graduate Summer Opportunities to Advance Research Program.

Other Summer Programs at the NIH: Note that two of these programs, the Biomedical Engineering Summer Internship Program (BESIP) and the NINR-Summer Genetics Institute (NINR-SGI), also use the SIP application.

Internships at Other Times of the Year: Individuals who are (1) at least 16 years of age and (2) enrolled in high school, college, or graduate/professional school can come to the NIH as Student IRTAs. Responsibility for arranging the internship rests with the potential trainee. The guidelines provided to SIP applicants in the SIP FAQs, particularly those under “After Applying” may be of help in managing this process. IMPORTANT NOTE: you must remain enrolled at your institution during your time at the NIH.

PROGRAMS FOR COLLEGE STUDENTS

The Undergraduate Scholarship Program (UGSP) provides up to $20,000 in scholarship support per year to eligible undergraduates who are pursuing degrees in fields related to biomedical research.

POSTBAC PROGRAMS (for recent college graduates)
The Postbaccalaureate Intramural Research Training Award (IRTA) Program is a biomedical research program that enables eligible recent college graduates who are planning to apply to graduate or professional school to spend one or two years working with investigators at the NIH.

The NIH Academy offers trainees the opportunity to learn about health disparities, enhance their knowledge of gaps in health outcomes, and investigate what is being done to address health disparity issues. Any Postbac or Technical IRTA is welcome to apply to participate in the Academy.
GRADUATE PROGRAMS

The Graduate Partnerships Program (GPP) provides graduate students with the opportunity to conduct all or part of their dissertation research in the resource-rich NIH environment. Students come to the NIH either as part of formal institutional partnerships or via individual agreements negotiated between their university mentor and an investigator at the NIH. In all cases, degrees are granted by the university partner.

PROGRAMS FOR MEDICAL AND DENTAL STUDENTS

Medical and dental students can come to the NIH in several ways. They can spend a year on the NIH Bethesda campus conducting research under the direct mentorship of an NIH investigator as part of the National Institutes of Health Medical Research Scholars Program (MRSP), a comprehensive, year-long research enrichment program designed to attract the most creative, research-oriented medical, dental, and veterinary students to the main campus of the NIH in Bethesda, MD. Students can also complete 4- or 8-week clinical rotations in the NIH Clinical Electives Program at the NIH Clinical Center.

POSTDOCTORAL PROGRAMS

Postdoctoral Training in the NIH Intramural Research Program: Eligible U.S. citizens and permanent residents who have recently received a doctoral degree can come to the NIH as Postdoctoral IRTAs to complete up to five years of postdoctoral research. Eligible international scholars who are recent doctoral degree recipients can conduct up to five years of postdoctoral research at the NIH as Visiting Fellows; they generally come to the NIH on J1 visas. Both groups are considered NIH trainees, rather than employees.

Other Postdoctoral Programs at the NIH

Research Fellows
Postdoctoral fellows can be promoted to Research Fellow, an appointment that makes them NIH employees, albeit temporary. An individual can spend an additional three years as a Research Fellow after reaching the five-year limit of the Postdoctoral Fellow appointment. Research Fellows are eligible for Intramural Loan Repayment.

Residents and Clinical Fellows
Physicians and dentists seeking specialty or subspecialty clinical-research training will find a vast array of both ACGME-accredited and other clinical and translational programs at the NIH. Training requirements and program durations vary. Like Research Fellows, Residents and Clinical Fellows are considered temporary NIH employees and are eligible for Intramural Loan Repayment.
The NIH Intramural Research Program (IRP)

The National Institutes of Health is the steward of medical and behavioral research for the nation. Its mission is science in pursuit of fundamental knowledge about living systems and the application of that knowledge to extend healthy life and reduce illness and disability throughout the world. The Intramural Research Program is conducted on several dedicated NIH campuses across the country. Although we constitute a small fraction of the total NIH budget, our facilities and funding structure provide us with a distinctive research environment. We are able to leverage the extensive resources and expertise across the IRP to perform truly interdisciplinary research from the bench to the bedside. We are also well-positioned to capitalize quickly on new scientific opportunities.

Within the framework of the overall NIH mandate, the IRP mission is to:
• Conduct distinctive laboratory, clinical, behavioral, translational and population-based research that breaks new ground and defines scientific excellence
• Facilitate new approaches to improve health through prevention, early detection, diagnosis, and treatment by developing and/or using innovative technologies, approaches or devices
• Respond rapidly to critical public health needs
• Train the next generation of biomedical and behavioral researchers
• Foster sharing of information and dissemination of the IRP’s major discoveries to the public through partnerships with academic institutions and industry

The Intramural Research Program (IRP) is the internal research program of the National Institutes of Health (NIH), known for its synergistic approach to biomedical science. With 1,200 Principal Investigators and more than 4,000 Postdoctoral Fellows conducting basic, translational, and clinical research, the IRP is the largest biomedical research institution on earth. Its unique funding environment means the IRP can facilitate opportunities to conduct both long-term and high-impact science that would otherwise be difficult to undertake. More than 50 buildings on NIH campuses are devoted to the research enterprise, from state-of-the-art animal care facilities to homes for 7-Tesla MRIs and confocal microscopes to a neurosciences cluster designed to foster collaborations across disciplines. Our 240-bed research hospital is devoted to clinical research protocols. With rigorous external reviews ensuring that only the most outstanding research secures funding, the IRP is responsible for many scientific accomplishments, including the discovery of fluoride to prevent tooth decay, the use of lithium to manage bipolar disorder, and the creation of vaccines against hepatitis, *Haemophilus influenzae* (HIB), and human papillomavirus (HPV).
Summer Internship Program in Biomedical Research for Veterinary Students

- Be innovative
- Develop your investigative skills
- Conduct research
- Work in multidisciplinary teams
- Use scientific literature
- Present research
- Learn about careers for veterinarians and investigators
- Meet scientists with diverse interests pursuing cutting edge ideas
- Discover
- Find out you have much to contribute in biomedical research

This unique opportunity for veterinary medical students, made available through the National Cancer Institute, Center for Cancer Research, is designed to provide 8-9 weeks of hands-on laboratory research experience while working at the world’s largest biomedical research agency, combining both clinical and basic research. Students develop skills while working side by side with leading biomedical scientists using cutting edge technologies.

In addition, enrichment opportunities are provided to allow interaction with veterinarians at NIH including those training in translational and interdisciplinary research in the NIH Comparative Biomedical Scientist Training Program. Summer Interns learn about comparative molecular pathology and comparative oncology initiatives and discover the many roles performed by veterinarians working in a research environment. As the culmination of the summer internship, students prepare and present their research findings in a poster session at the National Veterinary Scholars Symposium, held each year in August.

Summer Internships run from early June through early to mid-August. To be eligible for this program you must currently be in good academic standing in an accredited veterinary medical college professional degree program, and may not be currently enrolled in a combined D.V.M./Ph.D. program or hold a Ph.D. degree in an applicable science. You must be a U.S citizen or permanent resident. Interns are expected to participate for the entire fellowship appointment period. Summer stipends are available.

Interested Students can visit our website to learn more: http://nih-cbstp.nci.nih.gov
If you plan to apply, please send us an e-mail at: ncmolpathol@mail.nih.gov
Application site: https://www.training.nih.gov/programs/sip
The NIH Comparative Biomedical Scientist Training Program (CBSTP) for graduate veterinarians

This program, tailored for those with doctoral degrees in veterinary medicine, is an NIH Graduate Partnership Program (GPP), administered by NCI’s Molecular Pathology Unit in collaboration with 4 NIH institutes and 5 colleges of veterinary medicine. It combines the unique training strengths from both leading graduate programs at partner universities with training in biomedical research and Ph.D. dissertation research at the National Institutes of Health (NIH).

Program Goals and Opportunities:

• Research training in comparative molecular pathology and biomedical research leading to a Ph.D. and eligibility for certification as a medical specialist in veterinary pathology

• Prepare comparative pathologists for careers as experimentalists and comprehensively trained scientific research investigators

• NIH partners for dissertation research in our intramural laboratories: National Cancer Institute, National Heart, Lung, and Blood Institute, National Institute of Neurological Disease and Stroke, and National Institute of Allergy and Infectious Diseases

• This program allows for integration across many disciplines including: Autoimmunity, Bioterrorism, Carcinogenesis, Cell/Stem Cell and Developmental Biology, Immunology, Infectious diseases, Oncology/Cancer Biology, Molecular Pathology, Neurological Disorders, Stroke, Virology, Vaccine Development, and many others.

For more information see our website: http://nih-cbstp.nci.nih.gov

To apply go to the NIH OITE website: https://www2.training.nih.gov/
**Housing**

The MRSP is a residential program and participants are required to live in the housing provided.

All rents include utilities (gas/electric, and water), and apartments are furnished with the basics for living. Students are expected to provide their own linens. No pets are allowed.

“The NIH MRSP was a once-in-a-lifetime opportunity to learn about how biomedical research can impact the health care we provide to our patients.”

Joseph Rimando, MD
Medical College of Georgia at Georgia Regents University

**Curriculum**

- Lectures on seminal basic, translational and clinical research topics that highlight the continuum of discovery, as well as include issues in bioethics, science policy and emerging technologies
- Training in clinical protocol development and the conduct of human subjects research
- Participation in clinical rounds focusing on the research patient population in the NIH Clinical Center
- Assigned and dedicated yearlong advisor
- Assigned and dedicated research mentor
- Access to NIH Clinical Center courses including Introduction to the Principles and Practice of Clinical Research and the Ethical and Regulatory Aspects of Clinical Research

**NIH**

Medical Research Scholars Program

“Medical discoveries of tomorrow depend on the students we train today.”

-Dr. Francis Collins, NIH Director

Website:
http://www.cc.nih.gov/training/mrsp
The National Institutes of Health (NIH) Medical Research Scholars Program (MRSP) is a comprehensive, yearlong research enrichment program designed to attract the most creative, research-oriented medical, dental, and veterinary students to the intramural campus of the NIH in Bethesda, MD.

**BACKGROUND**

"NIH is the motherland of collaborative, diverse, and impactful biomedical research—the perfect place to learn. The MRSP offers the perfect venue to learn...allowing us to choose from a huge number of PIs and projects across the entirety of NIH."

Scott Galey, MD
Cleveland Clinic Lerner College of Medicine of Case Western University

**Eligibility**

- **Target Audience:** Medical, dental, and veterinary students are eligible for this program.
- **Year in Program:** This program is designed for students who have completed their initial clinical rotations (i.e., typically third year). However, students with strong research interests are welcome to apply prior to having completed these rotations. Dental and veterinary students are encouraged to participate after either their second or fourth year. Accepted fourth-year students must defer graduation before participation.
- **MD/PhD:** Candidates in double degree programs (e.g., MD/PhD) are eligible to apply.
- **Eligibility:** Candidates must be U.S. citizens or permanent residents currently enrolled in one of the following:
  - a medical school accredited by the Liaison Committee on Medical Education
  - a dental school accredited by the Commission on Dental Accreditation
  - an osteopathic school accredited by the American Osteopathic Association
  - a veterinary medical college located in the United States, U.S. Commonwealth territories, or Canada accredited by the American Veterinary Medical Association

**Application**

2018-2019 Application Cycle:
October 1, 2017 – January 12, 2018

Application consists of the following:
1. Personal statement
2. Curriculum vitae
3. Research areas of interests
4. Contact information for three references
5. Undergraduate and graduate/professional school transcripts

All applications must be submitted electronically by January 12, 2018. All letters of recommendation must be received by January 12, 2018.

“As a veterinarian in the program, MRSP was a unique and excellent opportunity to share ideas on how animal and human health can complement one another. It’s a great year to apply classroom knowledge to find solutions to some of science’s most vexing challenges.”

Lisa Gretebeck, VMD
University of Pennsylvania School of Veterinary Medicine
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How does Xist deletion affect X-linked gene expression in splenic T cells?

Erin Achilles, Montserrat Anguera

Department of Biomedical Sciences, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

The X-chromosome contains a high density of immune genes, and females (XX) respond faster to immune challenges than males (XY). Despite this apparent increase in competence, females are at a higher risk for developing autoimmune diseases such as systemic lupus erythematosus (SLE). Because females carry two copies of the X chromosome, their cells undergo X chromosome inactivation as a form of dosage compensation. This process, initiated by expression of the noncoding RNA Xist, recruits heterochromatin complexes for transcriptional silencing. These epigenetic changes result in the formation of a cytologically visible RNA cloud that remains closely associated with the inactive X chromosome (Xi). The Anguera lab has recently demonstrated that female lymphocytes lack both a canonical Xist RNA cloud and heterochromatic modifications to the Xi. As a result, these immune cells may be predisposed to partial reactivation of the Xi and overexpression of certain X-linked genes. The goal of this research is to determine if Xist deletion in splenic T cells increases expression of two immunity-related genes, Cd40lg and Cxcr3. Using RNA fluorescence in-situ hybridization, we compared Xist localization in wild type, homozygous Xist knockout, and heterozygous Xist knockout mice. We then analyzed mRNA expression of Cd40lg and Cxcr3 in these three groups. We hypothesize that KO/KO mice will have the highest biallelic X-linked gene expression as they lack Xist RNA clouds. Results from this novel study will help to further characterize gene expression from the Xi, and will contribute to our understanding of the role these genes play in the development of autoimmune disease.

Research Grant: National Institutes of Health, Grant Number R21AI124084
Student Support: National Institutes of Health T35 Training Grant, Grant Number T35OD010919

Serocomplement sensitivity of strains of Borrelia burgdorferi to identify possible host-strain associations

Tess Adams, Seungeun Han, Jean Tsao

College of Veterinary Medicine (Adams), Comparative Medicine and Integrative Biology (Han), Department of Fisheries and Wildlife (Tsao), Large Animal Clinical Sciences (Tsao), Michigan State University, East Lansing, MI

Borrelia burgdorferi sensu stricto, the spirochete that causes Lyme disease, is transmitted by the tick Ixodes scapularis and is maintained in nature by several competent hosts. In the Northeastern and Midwestern United States, where the majority of US Lyme disease cases occur, B. burgdorferi prevalence among vector ticks is similar between the regions, but the relative abundance of strains differs. Strains can be differentiated by the rDNA intergenic spacer (IGS) region, which can be grouped into three RFLP types (RST). Higher proportions of RST 1 strains are found at sites in the Northeast compared to the Midwest. Recent literature suggests that host-association of strains may exist and contribute to the differences in regional distributions. Some strains have been found to be supported by one or a few host species while others are supported by many hosts. Serocomplement sensitivity tests can be used to determine the degree of competence of a host for a strain by examining the bactericidal effect of the sera. Six strains (two per RST) were cultured, and a serum complement sensitivity test and growth inhibition assay will be performed for each strain by using sera from a variety of hosts for I. scapularis. We hypothesize that serocomplement sensitivity will vary among strains based on patterns of association observed among wildlife. Also, we predict that the RST 2 and RST 3 strains will have similar serocomplement sensitivities and will differ from that of RST 1 strains due to phylogenetic relatedness. The results of this study will help elucidate how the host communities may have played a role in the current spatial distribution of strains, with possible clinical and epidemiological consequences for human Lyme disease.

Research Grant: NSF EF-0914476, Michigan Lyme Disease Association
Student Support: NIH Grant T35OD016477
Evaluation of tumor histotype classification based on digital pathology image features

Maylin Akella, Elijah F. Edmondson

Virginia Maryland College of Veterinary Medicine, Virginia Tech, Blacksburg, VA (Akella), Frederick National Laboratory for Cancer Research, National Cancer Institute, Fort Detrick, Frederick, MD (Edmondson)

Histopathological image interpretation is a critical component in determining diagnosis and prognosis for neoplastic lesions in both clinical and research settings. Digital image analysis can aid in reproducibility, accuracy, and speed of image interpretation and has the potential to capture subtle differences in histology images which are not easily detected by pathologists. In our study, whole slide and tissue microarray (TMA) digital images are examined that represent multiple histologic subtypes obtained from The Cancer Genome Atlas (TCGA) and Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trials. Data from tumor samples are extracted following cell detection algorithms and segmentation of tumor and stromal components. The process of quantitative morphological feature extraction is automated and implemented on whole-slide images. Exported data are compared between tumor histotypes using clustering methods. Clustering by tumor histotype using quantitative morphologic features will be presented at the meeting. The goal is to discover and validate computational morphologic features that can discriminate between various tumor histotypes.

Research Grant: None
Student Support: NIH Summer Internship in Biomedical Research

Optimization of liquid chromatography-tandem mass spectrometry to detect hepatic diacylglycerol in horses

Kennedy Aldrich, Elizabeth Tadros

Department of Pathobiology and Diagnostic Investigation, Veterinary Diagnostic Laboratory, College of Veterinary Medicine, Michigan State University, Lansing, MI

Laminitis, a devastating form of lameness associated with Equine Metabolic Syndrome (EMS), results from irreversible weakening of soft tissues (laminae) anchoring the hoof capsule to the underlying bone; severe pain often compromises athleticism and can lead to euthanasia. Hyperinsulinemia, a component of the insulin dysregulation (ID) that underlies EMS, induces laminitis by directly damaging laminar tissues. Dyslipidemia, another component of ID, can cause hepatic accumulation of toxic lipid intermediates like diacylglycerol (DAG); impaired liver function may contribute to chronic hyperinsulinemia. We hypothesized that high pressure liquid chromatography (HPLC) and electrospray-ionization tandem mass spectrometry (ESI-MS/MS) could be successfully adapted for use on equine liver tissue to detect and quantify DAG. Total hepatic lipids were extracted from equine liver samples using an ASE 200 Accelerated Solvent Extractor. A reverse-phase Agilent Zorbax SB C8 column was used for chromatographic separation by solvents 1.5mM ammonium formate/0.1% formic acid in water and 2mM ammonium formate/0.15% formic acid in methanol. Mass spectrometry was conducted in positive ion multiple reaction monitoring (MRM) mode to detect DAG as an ammonium adduct. Total hepatic lipids ranged from 0.6-2.8% wet liver weight. Detection of DAG was verified by direct injection into the ESI-MS/MS system without chromatography; the correct MRM fragmentation ratios were observed among parent ion 586m/z and product ions 313m/z and 551m/z. Detection of DAG is possible with these protocols and can be used to characterize hepatic lipid metabolism in EMS-affected horses; determining the liver’s role in ID may lead to novel therapeutic targets.

Research Grant: Michigan State University College of Veterinary Medicine
Student Support: Boehringer-Ingelheim and MSU College of Veterinary Medicine and Graduate School
Hormonal/dietary effects on endocannabinoid inhibition of transmission in the hypothalamic feeding circuitry

Natalia A. Alicea, Edward J. Wagner

College of Veterinary Medicine (Alicea), Department of Basic Medical Sciences, College of Osteopathic Medicine of the Pacific (Wagner), Western University of Health Sciences, Pomona, CA 91766

Obesity is correlated with major medical consequences including hypertension and diabetes mellitus. The mechanism by which obesity creates a homeostatic imbalance has not been fully elucidated, creating limitations in the development of prevention & treatment. This is especially so considering the regulation of energy homeostasis is sexually disparate. The objective of this application is to assess the ability of estrogen to attenuate orexigenic pathways & protect against diet-induced obesity (DIO). Pro-opiomelanocortin (POMC) neurons elicit anorexigenesis under a positive energy balance. Orexigenic mediators like endocannabinoids inhibit this anorexigenic stimulus via CB-1 receptor binding and a subsequent decrease in glutamate release onto POMC neurons; causing hyperphagia. Cannabinoid-induced hyperphagia & inhibition of glutamate release onto POMC neurons is abrogated by estrogen, whereas androgens enhance hyperphagia & inhibition of excitatory neurotransmission. In addition, DIO magnifies cannabinoid-induced hyperphagia and inhibition of excitatory neurotransmission in males. Given that estrogen & insulin work in concert to increase POMC excitability, our working hypothesis is that estrogen will protect females from DIO by abrogating cannabinoid-induced inhibition of transmission, which will be assessed by estrogen’s ability to negate the endocannabinoid-induced decrease in the amplitude of optogenetically-evoked excitatory transmission at steroidogenic factor-1/POMC synapses during recordings from ovariectomized female Nr5a1-cre mice fed either the standard chow or a high-fat diet. These results will benefit individuals suffering from obesity, by providing a basis for future development of sex-specific treatments.

Research Grant: PHS Grant DA024314
Student Support: Merial Veterinary Research Scholars Program

Measuring immune system perturbations associated with the use of buprenorphine in laboratory mice

Alexis A. Allen, Lon V. Kendall

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Laboratory animals are often administered analgesics to alleviate pain caused by experimental treatments. One of the most commonly used analgesics in mice is buprenorphine (Bup), both in the standard and sustained-release (SR) formulations. There is concern by investigators that buprenorphine use in experimental animals will alter the host immune response and, thus, potential data. The objective of this project was to measure immune function in mice pre- and post-treatment with Bup and SR-Bup. Mice were immunized with ovalbumin (n=20) and treated with SR-Bup, Bup, SR-vehicle, or saline for three weeks. Three days prior to euthanasia, mice were immunized a second time with ovalbumin. At the time of euthanasia, blood and spleens were collected; splenocytes were cultured and stimulated with ovalbumin. TNF-α, IFN-γ, and IL-10 production was measured by ELISA, as well as serum antibody responses to ovalbumin. There was a significant decrease in cytokine responses of the Bup treated group compared to the other three groups, but there was no significant difference in cytokine concentration of the SR-Bup or SR-vehicle groups compared to the saline control. There was also no significant difference in antibody responses in any of the treatment groups compared to the saline control. The results from this study suggest there are minimal effects of buprenorphine on the host immune response that would justify withholding analgesics following an experimental procedure.

Research Grant: Office of Vice President for Research, Colorado State University
Student Support: Kenneth F. Burns Summer Fellowship
Determination of novel BMP-Smad1/5 signaling interactions in fibrodysplasia ossificans progressiva

Robyn S. Allen, Eileen M. Shore, and Mary C. Mullins

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Fibrodysplasia ossificans progressiva (FOP) is a rare, debilitating human genetic disorder that perturbs skeletal development and induces heterotopic ossification. Classical FOP is caused by a single nucleotide substitution in the BMP/TGFβ cell surface receptor, ACVR1 (617G>A, R206H). This mutation results in over-activation of receptor signaling through the Phospho-Smad1/5 (pSmad1/5) pathway. The mechanism through which the mutant receptor confers enhanced signaling activity remains uncertain. To assay for mutant ACVR1 activity, we used zebrafish embryonic dorsoventral (DV) pattern- ing, which is established by a gradient of BMP signaling activity. We confirmed that ACVR1-R206H misexpression causes over-activation of pSmad1/5 activity and ventralization of zebrafish embryos. We found several other rare ACVR1 mutations of FOP similarly result in increased activity. Recent studies suggest that ACVR1-R206H and other FOP variant mutant receptors may have altered ligand affinity compared to WT ACVR1. We confirmed that BMP ligand enhances pSmad1/5 signaling through ACVR1-R206H. Surprisingly, Activin A, a ligand that normally signals through pSmad2/3, also enhances pSmad1/5 signaling by ACVR1-R206H. We examined if other receptors are required with ACVR1 to induce signaling. We found that BMPR1, a receptor normally required for pSmad1/5 signaling and DV patterning in the zebrafish, is not required for pSmad1/5 over-activation by ACVR1-R206H or the variant mutant ACVR1-G328R. These and further studies of the signaling interactions of ACVR1-R206H will allow for identification of novel therapeutic targets to treat FOP and give us unique insight into how this fundamental cell signaling pathway functions in development.

Research Grant: NIH R01 GM56326, The Cali Family
Student Support: None

Equine herpesvirus-1 latency in experimentally infected horses

Allison Allum, Lutz S. Goehring, Kim Giessler, Susanna Samoilowa, Carine Holz, Lila M. Zarski, Gisela Soboll Hussey

Dept. of Pathobiology & Diagnostic Investigation, College of Veterinary Medicine, Michigan State University, East Lansing, MI (Allum, Holz, Zarski, Hussey), and Dept. of Equine Internal Medicine & Reproduction, Center for Clinical Veterinary Medicine, Ludwig-Maximilians University, Munich, Germany (Goehring, Giessler, Samoilowa)

Equine Herpesvirus-1 (EHV-1) is an infectious equine disease that causes neurologic signs, respiratory disease, and abortions. Different EHV-1 strains show different levels of viremia and neuropathogenicity; the Ab4 strain is a known viremic and neuropathogenic strain. A polymerase mutation, N vs. D at position 752, typically results in less viremia and lower incidence of EHM. EHV-4, another alphaherpesvirus, does not cause viremia or EHM. EHV-1 establishes latency after primary infection and reactivates throughout life. In latency only the immediate early (IE) gene, located on open reading frame 64 (ORF64), is expressed. Known sites of latency can include neural tissues and respiratory associated lymphatic tissue and lymphocytes. We hypothesize latent EHV-1 will be found in various tissues of experimentally infected horses, and mutants of differing neuropathogenicity will establish latency in different locations. Horses were infected with EHV-1 mutants: Ab4 wild type, N752, Ab4 gD4. Pre- and post-infection PBMC and post-infection lymphoid tissues and trigeminal ganglia were collected. RNA and DNA were isolated and qPCR was performed to detect latency indicated by absence of late gene expression (gB) and presence of IE gene expression (ORF64). Viral gB DNA and gB RNA were negative for most samples. Ab4 WT and N752 infected horses expressed ORF64 in lymphatic tissue, while Ab4 gD4 infected horses expressed ORF64 in trigeminal ganglia. No samples expressed ORF64 in PBMC samples. The Ab4 WT and N752 mutant appear to establish latency in the lymphatic tissues, and the Ab4 gD4 mutant appears to establish latency in the neural tissue indicating differing tissue tropism. The PBMC do not appear to be significant in latency.

Research Grant: Grayson-Jockey Club Research Foundation
Student Support: NIH T35 Grant No T35OD016477
Effects of innate immune stimulation on naturally occurring respiratory disease in beef calves

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Stress and virus-induced immunosuppression is considered a major risk factor for the development of bovine respiratory disease (BRD). We hypothesized that stimulation of innate immune responses on arrival to a feedlot could overcome this immunosuppression and decrease the prevalence and severity of BRD. Sixty calves at high risk of disease were temporally divided into 4 cohorts and randomly assigned to receive aerosolized immunostimulant or phosphate-buffered saline control solution delivered via nebulization. Body weight, rectal temperature, serum haptoglobin, fibrinogen, and results of targeted lung ultrasounds were recorded at baseline and regular intervals up to 1 month after arrival. Animals exhibiting clinical signs were treated according to farm protocols. Animals dying during the study period received a full postmortem examination. Pilot studies established that aerosolization of immunostimulant was well tolerated and resulted in transient increases in temperature, respiratory rate and neutrophils in bronchoalveolar fluid. Unexpectedly, the mortality rate attributed to \textit{M. bovis} was 20% (6/30) in calves receiving the bacterial lysate compared to 3% (1/30) in control calves. Significant respiratory disease was seen in 70% of immunostimulated calves versus 53% of control calves. Calves receiving the immunostimulant had lower weight gains at one month after arrival versus control calves. Inflammatory markers and lung ultrasound scores were similar between the two groups. Although stimulation of innate immune responses was unsuccessful in preventing BRD, the results of this study suggest a potential relationship between pulmonary inflammation and \textit{M. bovis} pneumonia.

\textbf{Research Grant:} Natural Science and Research Engineering Research Council
Zoetis
Beef Farmers of Canada
Ontario Ministry of Agriculture, Food and Rural Affairs
Ontario Veterinary College

\textbf{Student Support:} Undergraduate Research Assistant

A clinical trial to investigate the efficacy of tramadol as an antitussive in anesthetized dogs

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This study utilized a non-invasive technique to evaluate the antitussive properties of tramadol in anesthetized dogs. Fifty one healthy dogs were enrolled into the study and were randomly assigned using a random number table to one of three intervention groups: placebo (empty capsule), positive control (butorphanol 0.055 mg/kg sq), or experimental (tramadol 8 mg/kg po). Each dog was anesthetized with intravenous propofol (8 mg/kg to effect) 1-2 hours after the intervention was administered. After intubation, each dog was maintained at an anesthetic depth that allowed for a palpebral reflex, rhythmic breathing and inhibited jaw and tongue movement. Propofol was administered at 0.3-0.5 mg/kg/min to maintain optimal anesthetic depth. To induce coughing, a mist of sterile water (0.0625 mls per kg of body weight) was sprayed through a 2 mm diameter catheter into the proximal carina. Two blinded researchers counted the number of coughs over a 60 second period. Each 60 second cough measurement period was recorded in video format. A cough was defined as a rapid and deep inhalation of air immediately followed by a forceful exhalation. The placebo group of dogs coughed an average of 4.97 times; the positive control butorphanol group coughed an average of 3.13 times; the experimental tramadol group coughed an average of 3.15 times. This preliminary descriptive data demonstrates possible efficacy of tramadol as an antitussive in dogs. Further full scale studies should evaluate more parameters including dosage and duration of effect. Tramadol is inexpensive, has a wide margin of safety, and is widely available to veterinary practitioners.

\textbf{Research Grant:} Merial Scholar Grant
\textbf{Student Support:} None
Evaluating acute post-procedural pain response in alternative and industry standard disbudding methods

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While heat cautery disbudding of neonatal goat kids is the standard industry practice for the long-term welfare of the animals, it is a painful experience for young dairy goats and alternate disbudding methods should be evaluated. This study compared acute (<72 hour) pain associated with four alternate methods of disbudding to both heat cautery and sham controls to determine if there is a superior method for pain mitigation in dairy goat disbudding. Sixty-five dairy buck kids (< 1 week of age) were assigned to pen groups and randomly allocated to a disbudding treatment (CLOVE, CRYOGEN, FREEZE, HEAT, PASTE, and SHAM). All procedures were performed without adjunct anesthesia or analgesia. Vocalization frequencies were recorded for the duration of each disbudding procedure. Pain-related behavior frequencies were observed via video recordings by a trained observer blinded to treatment using a standardized ethogram. Mechanical nociceptive threshold (MNT) at the horn bud was measured via pressure algometry on days -1, 0, 1, and 2, with day 0 being disbudding day. Mean vocalization frequencies were significantly greater for the FREEZE group than for SHAM (p < 0.001); no difference was observed between other treatment groups and either SHAM or HEAT controls. Preliminary algometry results show decreased MNT values (kgF) between day -1 and the following trial days. A significant difference between treatments on some trial days was also observed. Pain related behavior frequency observations are currently in progress. This study demonstrates the best practices in kid disbudding in terms of mitigating pain in dairy goats.

Research Grant: American Dairy Goat Association
Student Support: Boehringer Ingelheim Veterinary Research Scholars Program

Serum microRNAs as novel biomarkers for respiratory syncytial virus vaccine efficacy

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Respiratory syncytial virus (RSV) is the most common cause of severe lower respiratory tract illness in young infants and cattle. Bovine RSV (BRSV) and human RSV (HRSV) strains share common epidemiological, pathological, and clinical disease profiles. In addition, BRSV is a major contributor to bovine respiratory disease (BRD) complex, which is the most devastating disease of the US cattle population. BRD complex is caused by a variety of pathogens including viruses and bacteria; however, like HRSV there is no efficacious BRSV vaccine. Furthermore, crossspecies RSV vaccine development has been hampered by the dramatic HRSV vaccine failure in the 1960s. Currently, only supportive measures can be used to control RSV disease in humans, bovines and ovises in part due to a lack of understanding of immune and disease correlates. MicroRNAs (miRs) are emerging as promising biomarkers for a variety of diseases. These small noncoding RNA molecules function via RNA silencing and posttranscriptional regulation of gene expression. In this study, we utilized a miR PCR array to characterize the serum miR expression profiles in BALB/c mice in response to HRSV vaccine platforms in order to correlate dysregulated miR expression with the host immune response and RSV disease outcome. We identified unique miR biomarkers pre- and post-challenge with RSV A2 between vaccinated and control mice, as well as between RSV experienced and naive mice. To our knowledge, this is the first report to identify miR expression profiles as potential biomarkers for RSV vaccine efficacy and disease outcomes. These findings provide valuable insights for vaccine development and novel targets for therapeutic interventions for inflammatory diseases of the lung.

Research Grant: Georgia Research Alliance and ARCS Foundation Atlanta Chapter
Student Support: DVM-PhD Veterinary Medical Scientist Training Program Fellowship
The effects of various anti-inflammatories on prostaglandin production within fetal membranes

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It is widely known that prostaglandins PGE2 and PGF2α play a major role in maintaining pregnancy and inducing preterm parturition in many mammalian species, including horses. Furthermore, mares with experimentally induced placentitis have shown elevated prostaglandin levels in fetal fluid and tissue prior to abortion. However, no study has documented a reduction in prostaglandin production by fetal tissues in response to anti-inflammatory therapy. To address this, LPS induced prostaglandin production was quantified in chorioallantoic (CA) tissue following treatment with traditional and non-traditional anti-inflammatory agents. Fetal membrane tissue was flushed from nine pregnant mares at approximately thirty days of gestation. Tissues were dissected into equal pieces and placed in culture media containing DMEM/F12 50/50, insulin, L-glutamine, ascorbic acid, and penstrep. Following dissection, the CA tissue was incubated for an hour in culture media pretreated with 1mM ibuprofen to eliminate underlying inflammation. Subsequently, tissues were treated in duplicate with media alone, LPS (POS), LPS + *Moringa olifeira* extract (MO at .2 μg/mL), LPS + Flunixin meglumine (FM at 7.5 μg/mL) or LPS + Altrenogest (ALT at 7.7 μg/mL) for 24 hours. Altrenogest and Flunixin meglumine were applied in concentrations similar to those found in tissue after systemic administration. At eight hours post incubation supernatant was removed and frozen at -80 degrees. Prostaglandin quantification was performed through a commercial ELISA assay (Cayman). At this time final results are still pending.

**Research Grant:** None  
**Student Support:** Merial Veterinary Scholars Research Program  
Grayson Jockey Club Research Foundation

Dissecting the enzymatic pathway of fenretinide induced apoptosis in two feline squamous cell carcinoma lines

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The most common oral neoplasia in cats is squamous cell carcinoma. Current therapies, including surgery, radiation, and chemotherapy rarely control this aggressive tumor, and patients’ overall survival and quality of life are poor. Vitamin A derived retinoids are currently being investigated as an oncologic treatment or prevention agent given their ability to induce cellular differentiation and apoptosis in a variety of cancers. A synthetic retinoid, fenretinide, has shown effectiveness as a therapy with few long term side effects in a wide variety of cancers. Thus far, four key enzymes are associated with fenretinide’s ability to induce apoptosis: ceramide synthase, neutral sphingomyelinase, acidic sphingomyelinase, and 12-Lipoxygenase. This study aimed to determine the specific enzymatic mechanism of action of fenretinide in two lines of feline squamous cell carcinoma (SCCF-1, SCCF-2). Inhibition of the enzymes ceramide synthase and sphingomyelinase did not inhibit cell death. However, inhibition of 12-Lipoxygenase did significantly reduce cell death. It is therefore suspected that 12-Lipoxygenase is the primary enzyme utilized by fenretinide to achieve death of feline squamous cell carcinoma cells.

**Research Grant:** None  
**Student Support:** Boehringer Ingelheim Veterinary Scholars Program
Seroepidemiology of leptospirosis in pigs in Grenada

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Leptospirosis is a neglected tropical disease that is infectious and zoonotic in nature. While brown rats of the *Rattus norvegicus* species have been primarily implicated in the spread of leptospirosis, pigs have also been responsible and yet overlooked for their role in the transmission of disease to other animals, humans as well as environmental contamination. In this cross-sectional study, we sought to determine the seroepidemiology of leptospirosis among pigs on livestock farms on the island of Grenada in the Caribbean. Farms were randomly selected amongst Grenada’s six parishes and blood was collected through venipuncture from a total of 368 pigs. Enzyme-linked immunosorbent assay tests (ELISA) were performed to screen for antibodies to *Leptospira* spp. Overall, seroprevalence to *Leptospira* spp was 23.36% (95% CI: 0.1933 to 0.2796). The percentage of positive cases based on parish is as follows: St. Mark, 42.2%; St. Andrew, 36.2%; St. George, 25.3%; St. Patrick, 13%; St. David, 6% and St. John, 6%. Age was determined to be a risk factor for testing positive for leptospirosis (*p* < 0.05; *X*²). Though the calculated seroprevalence of 23.36% falls short of a hypothesized seroprevalence of 35%, leptospirosis in pigs in Grenada should still be further assessed. Attention should be directed to the parishes of St. Andrew and St. Mark due to greater numbers of positive cases. It is recommended that Grenada’s Ministries of Agriculture and Health target farmers to bolster their awareness of leptospirosis to curb zoonotic transmission as well as to minimize the negative economic impact associated with the disease.

**Research Grant**: Merial Veterinary Scholars Program

**Student Support**: St. George’s University Island Veterinary Scholars Program, Merial Veterinary Scholars Program

Computed tomographic findings in rabbits (*Oryctolagus cuniculus*) with dental disease: 100 cases (2009-2017)

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Rabbits frequently present to veterinarians with dental disease, which requires accurate diagnosis in order to provide appropriate treatment. Computed tomography (CT) is a sensitive and preferred diagnostic tool for dental problems since it provides good bone detail and eliminates superimposition of anatomical structures. CT can be useful for diagnosing problems earlier and therefore improving the prognosis of dental disease. The aim of this study was to first characterize the computed tomographic features in domestic rabbits with dental disease and then evaluate the distribution of those findings across the population of rabbits with dental disease. For this purpose, medical records from the UC Davis Veterinary Medical Teaching Hospital were searched for client-owned rabbits that had received skull CTs. One hundred CT studies from 2009-2017 of rabbits with abnormal dental findings were re-evaluated; both clinical (group 1) and subclinical (group 2) cases were included. Signalment, pertinent history and clinical signs, oral examination findings and computed tomographic findings were recorded. Sixty-two males and 38 females were included in the study. Ages ranged from 1 to 10-years-old. The most common breeds reported included lopped eared rabbit, Holland lops and Dutch dwarf. The most common abnormal findings in CT, in order of frequency, were premolar/molar teeth curvature (transverse plane)[KP1], cheek teeth apical elongation, premolar/molar curvature (sagittal plane), periodontal ligament space widening, dental points, mandibular canal deformation, incisor reserve crown elongation, mandibular lymphadenopathy, pulp cavity changes, periapical lucencies, abscess associated cortical lysis and tooth resorption.

**Research Grant**: None

**Student Support**: Merial Veterinary Scholars Program
**An efflux pump that contributes to the disinfectant resistance of *Staphylococcus pseudintermedius***

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Efflux pump mediated resistance to disinfectants is an important concern in Staphylococci. In companion animal medicine, antimicrobial resistance is an ever-increasing concern. This study plays a critical role in determining the mechanism of resistance to disinfectants. With this information, the medical community will better advise on judicious and ethical use of antimicrobial substances. Plasmid mediated transfer of the Qac gene is associated with resistance in *Staphylococcus aureus*, but little work has been done on this in *Staphylococcus pseudintermedius*, the major cause of pyoderma in dogs. Acquisition of resistance to disinfectants is important because of survival of the bacteria after routine surface cleaning procedures and the risk of nosocomial infections, as well as the use of disinfectants to treat infections caused by multi-drug resistant organisms. This study included testing for the presence of, and characterization of putative efflux pumps in strains of *Staphylococcus pseudintermedius*. Isolates were screened by PCR for the Qac gene and select PCR products were sequenced. In addition, phenotypic testing involved detection of fluorescent dye excretion from bacteria by flow cytometry and quantitative measurement of minimum inhibitory concentrations (MICs) to a disinfectant compound. A significant aspect of this study is that it utilized a collection of well characterized Staphylococcus isolates that were previously obtained from diagnostic laboratories throughout the United States. Of the 31 isolates screened, 29 were positive with both primers used in PCR, 2 were negative, each to a respective primer. The MIC value range was 0.208-0.67ug/mL.

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**Student Support:** Morris Animal Foundation

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**Characterization of MHC class I genes in the horse using linked-read genome sequencing**

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The Major Histocompatibility Complex (MHC) is an important and intensely studied region of the genome. This study concerns the class I MHC proteins expressed on most cells in the body. Class I proteins present “self” peptides, derived from intracellular proteins and foreign peptides derived from intracellular pathogens. Class II proteins are expressed only on antigen presenting cells and present exogenous proteins. The class I genes are especially important in anti-viral immunity and have been shown to be involved with many other clinically relevant processes in the horse; for example, equine herpes virus, equine sarcoids, insect bite hypersensitivity, maternal tolerance of the fetus, and immune recognition of allogenic stem cells. It’s clear that the MHC class I region is very salient, but there remain large gaps in our knowledge about it. Only one equine MHC region has been entirely sequenced, and that is the ELA-A3 MHC haplotype, of the NCBI reference genome. Very little is known about other MHC haplotypes. Looking further at other haplotypes could lead to clinical applications, or shed insight into the unusual evolution of this gene region. Sequencing of the MHC is challenging because of significant duplication and repetition. There are MHC genes that have been identified that have not been mapped to the genome, and most likely, MHC genes that have not been recognized at all. This project proposes to fill those knowledge gaps by identifying and annotating MHC genes in the long contiguous sequences generated by 10x Genomics Chromium linked-read sequencing technology. We will also study those sequences to evaluate 10x Genomics technology as a valid and cost effective method to sequence other MHC haplotypes.

**Research Grant:** NIH

**Student Support:** NIH, Dorothy Russell Havemeyer Foundation
Characterization of extended spectrum cephalosporin resistant enterobacteria isolated from companion animals

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Extended spectrum cephalosporin resistant Enterobacteriaceae (ESCRE) is a growing problem in public health, but little is known about ESCRE in companion animals. 50 K. pneumoniae, 8 Klebsiella oxytoca, and 35 Escherichia coli were collected from the veterinary diagnostic laboratory at Mississippi State University from 2015 to 2017. Phenotypes of ESCRE and genotypes of extended spectrum β-lactamase (ESBL) were analyzed using antibiotic sensitivity test and multiplex PCR, respectively. 19 K. pneumoniae isolates (38%) showed ESCRE resistance to multiple cephalosporin classes including cefazolin (n=19, 38%), cefoxitin (n=7, 14%), cefpodoxime (n=17, 34%) and cephalothin (n=18, 36%) and isolates carried multiple ESBL genes (TEM n=21, 42%, OXA-1 n=15, 30%, CTX-M group 1 n=11, 22%, and CIT n=4, 8%). 2 K. oxytoca isolates were resistant only to cefazolin with no ESBL genes detected. 8 E. coli isolates (22.6%) were ESCRE showing resistance to cefazolin (n=6, 17.1%), cefoxitin (n=3, 8.5%), cefpodoxime (n=6, 17.1%) and cephalothin (n=8, 22.6%) and also carried multiple ESBL genes (TEM n=5, 14.3%, OXA-1 n=2, 5.7%, CTX-M group 1 n=3, 8.6%, and CIT n=7, 20%). The resistance to 1st and 3rd generations of cephalosporin by ESCRE was correlated with the heavy use of cefazolin/cephalexin in veterinary hospitals. The ESBL genes found are encoded in transferrable plasmids, which also poses a potential public health risk to the increased emergence of ESCRE. Considering the close interaction between humans and companion animals, this study suggests a need for nationwide investigation of ESCRE in veterinary medicine and establishing an antibiotic stewardship program with One Health concept to prevent ESCRE threats in public health.

Research Grant: Unknown
Student Support: NIH 2T35OD010432-16, College of Veterinary Medicine, Mississippi State University

NeuroAIDS in rhesus macaques: neuropathology of SIV infection in encephalitic and non-encephalitic animals

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Human immunodeficiency virus (HIV) infects the CNS early in the course of infection, which can progress to HIV-induced encephalitis (HIVE/neuroAIDS). Due to persistent HIV replication and/or inflammation, patients can develop motor and cognitive impairments collectively called HIV-associated neurocognitive disorder (HAND). Simian immunodeficiency virus (SIV) infection of rhesus macaques is a relevant model for neuroAIDS pathogenesis in humans. The neuropathology of SIV-induced encephalitis (SIVE) is similar to HIVE, which is characterized by multinucleated giant cells (MNGCs). Our lab’s previous work has shown increased numbers of mononuclear cells, specifically CD4+ memory T-cells (mCD4) and macrophages (MΦ), in the brains of encephalitic animals compared to non-encephalitic animals, suggesting pleocytosis in SIVE animal brains. Using cell sorting and SIV qPCR, it was shown that both mCD4s and MΦ harbor SIV DNA. The objective of this study was to compare brain tissue by examining the mesencephalon of encephalitic and non-encephalitic rhesus macaques via immunofluorescence assay (IFA) to visually characterize SIV infection of mCD4 and MΦ. Microscopic images were obtained from formalin-fixed paraffin-embedded tissue (FFPE) using DNAscope and IFA combined. Antibodies against CD163 and CD68 receptors identified MΦ, and anti-CD4 antibodies identified mCD4. Our data shows encephalitic macaques to have classic neuropathologic lesions. Infected mCD4 were found in both encephalitic and non-encephalitic animals, and we observed increased overall number of infected cells in the brains of SIVE animals. This study visually verified qPCR data of sorted mCD4 and MΦ from SIV-infected macaques.

Research Grant: None
Student Support: NIH Summer Internship Program in Biomedical Research for Veterinary Students, NCI
Impact of weaning age on gene expression of chemo-cytokines as markers of gut immune development in the pig

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In wild pigs, weaning is a gradual process occurring at ~ 3 months of age. However, in commercial swine production systems, piglets are commonly weaned between 18-21 d of age to maximize efficiency of production. However, current early weaning practices put a tremendous amount of stress on young pigs which includes maternal and littermate separation, disruption of social hierarchy, vaccination and abrupt transitions in diet from milk to solid feed. Previous research from our laboratory demonstrated that early weaning stress (EWS) can have long-lasting deleterious impacts on development of gut immune and epithelial barriers resulting in sub-optimal performance and increased disease susceptibility, compared with later weaned control (LWC) pigs weaned at >26 d of age. The objective of this study was to investigate the influence of EWS on immune system development. We analyzed the chemokines and homing receptors such as CCL19, CCL21, and Mad-Cam1, alpha 4 beta 7 integrin as well as cytokine expression (TNFα, IL-2, IL-9, IL-10, FOXP3, and IDO) in secondary lymphoid organs such as mesenteric lymph nodes (MLN), spleen and ileum. Our preliminary results indicated that EWS pigs exhibit increased gene expression of CCL19, CCL21, FoxP3, and IL-9 in the MLN and spleen, compared with LWC pigs; however, statistical analysis is pending. Future analyses will include the measurement of immune markers in the intestinal mucosa and post-vaccination serum titer levels for Porcine Circovirus 2 (PCV-2) vaccine antigen as a measure of immune function. These preliminary results may indicate that EWS induces long-term changes in the chemokines and immune cell homing receptor expression while inducing T-regulatory cells.

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Student Support: None

IL-4 receptor knockout partially rescues IgE-mediated passive systemic anaphylaxis in Itk deficient mice

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The tyrosine kinase Interleukin-2 inducible T-cell kinase (Itk) plays a pivotal role in the immune system as a regulator, signal amplifier, and efficiency facilitator. Itk−/− mice exhibit reduced allergic responses, evidenced by reduced passive systemic anaphylactic (PSA) response. Previous studies have suggested that the high serum IgE found in Itk−/− mice occupies FcεRI receptors on mast cell surfaces, making it difficult for allergen-sensitized IgE to compete for binding and thus activation of mast cells. In this study, we explored the possibility that a reduction in serum IgE, accomplished through removal of the IL-4 receptor alpha chain (IL-4Ra), thus blocking IL-4 signal induced class-switch in B cells to IgE, would rescue PSA. PSA was induced in Itk−/−, IL-4Ra−/− and Itk/IL-4Ra double-knockout mouse strains by sensitizing with α-DNP-IgE intraperitoneally 12 hours prior to intravenous injection of DNP. Analysis of temperature changes was performed over 60 minutes to document physiological response. IgE levels in serum, peritoneal mast cell (PMC) numbers and surface FcεRI and IgE in untreated mice were also determined. The results confirm that Itk deficient mice are protected from IgE-mediated PSA. Furthermore, removal of IL-4Ra partially recovers development of IgE-mediated PSA. Confirming a role for elevated IgE in this process, PMCs of Itk deficient mice exhibited elevated surface IgE, which was reduced to WT levels by removal of the IL-4Ra. Our results suggest that this partial rescue of IgE-mediated PSA in Itk/IL-4Ra double-knockout mice is due to the effects of the absence of IL-4 signaling, but that there may be residual IgE, suggesting an IL-4 independent pathway for IgE class switch in these mice.

Research Grant: Boehringer Ingelheim Veterinary Research Scholars Program

Student Support: Cornell Veterinary Investigators Program
Measurement of IL-1 beta in chelonian plasma by ELISA using anti-human IL-1 beta antibodies

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Interleukin-1 beta (IL-1 beta) is a cytokine produced by monocytes and macrophages that contributes to the acute phase response of inflammation. In mammals, IL-1 beta concentrations in the blood are elevated during inflammatory disease states. In comparison, cytokine activity is poorly understood in reptiles and reagents specific for detection of reptile cytokines have not been developed. The enzyme-linked immunosorbent assay (ELISA) uses antibodies to detect and quantify proteins and is used frequently for cytokine measurements. The purpose of this study was to determine if a commercial ELISA kit containing anti-human IL-1 beta antibodies could be used to measure IL-1 beta in chelonian plasma. Plasma from red-eared sliders (Trachemys scripta elegans) that were experimentally infected with ranavirus (frog virus 3) was used as a positive control for cross-reactivity with human antibodies. Plasma from both infected turtles and uninfected turtles had measurable concentrations of IL-1 beta. The presence of IL-1 beta in uninfected turtles may be due to stress associated with shipment of the turtles or the presence of other inflammatory processes. Plasma from wild Eastern box turtles (Terrapene carolina carolina) was also tested for IL-1 beta by ELISA. A better understanding of the activity of cytokines in reptiles can provide insight into the manifestation and course of inflammation in these species. The ability to measure cytokines by ELISA could serve as a valuable tool for wildlife epidemiology by providing a practical and quantitative means of disease surveillance.

Research Grant: Wildlife Epidemiology Laboratory
Student Support: University of Illinois College of Veterinary Medicine

IL-6/gp130-related signaling in a novel model of supporting limb laminitis

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In equine laminitis, structural failure of the lamellae occurs due to lamellar epidermal stretching and dysadhesion from the underlying dermal lamellae. Supporting limb laminitis (SLL) is a type of laminitis that occurs as a sequela to another primary condition affecting one limb that results in excessive unilateral weight-bearing of the contralateral limb. Previous studies on the other types of laminitis (sepsis-related and endocrinopathic laminitis) indicate that IL-6/gp130-related signaling may play a role in lamellar failure. We hypothesized that IL-6/gp130-mediated activation of mTORC1/p70S6K/RPS6 and JAK2/STAT3 signaling occur in the lamellar epidermis in SLL. In the current study, laminitis was induced in Standardbred horses by use of a V-shaped shoe (unloaded limb) to cause unilateral/preferential weight-bearing to the opposite forelimb (supporting limb). Mounted ground sensors were used to confirm preferential weight-bearing of the supporting limb. At the end of a 72 hour period, lamellae were harvested and snap frozen for protein analysis via Western blot and immunofluorescence. The supporting limb lamellae had increased concentrations (vs. control animals) of phospho (P)-RPS6 (Ser 240/244 [p=0.0140] and Ser 235/236 [p=0.0023] moieties) and P-STAT3 (Ser 727 [p=0.0012] and Tyr 705 [p=0.0082] moieties). The majority of signaling was localized to lamellar epidermal cells on immunofluorescence. There was a strong correlation between lamellar IL-6 and P-RPS6 concentrations (r=0.964, p < 0.003). These findings provide a basis for further evaluation of IL-6/gp130, mTORC1/p70S6K/RPS6 and JAK2/STAT3 signaling in an effort to discover potential therapeutic targets to prevent lamellar failure in horses with SLL.

Research Grant: Grayson Jockey Club Research Foundation
Student Support: NIH T35 Training Grant
Effects of water decontamination methods and bedding material on the gut microbiota

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Rodent models are invaluable to understanding health and disease in many areas of biomedical research. Unfortunately, many models suffer from lack of phenotype reproducibility. Our laboratory has shown that differences in gut microbiota (GM) can modulate phenotypes of models of colon cancer and inflammatory bowel disease. We and others have also shown that a number of factors associated with rodent research, including vendor, cage system, and bedding can alter GM. The objective of this study was to expand these studies to examine the effect of additional bedding materials and methods of water decontamination on GM diversity and composition. To this end, Crl:CD1 (ICR) mice were housed on corn cob or compressed paper bedding and provided water that was decontaminated by four commonly used methods: reverse osmosis, autoclaving, sulfuric acid, or hydrochloric acid treatment. Feces was collected at day 0, and at day 28 (endpoint), fecal and cecal samples were collected. DNA was extracted from samples, amplified by PCR using conserved bacterial primers and subjected to next generation sequencing. Resulting metagenomics data was analyzed using principal coordinates analysis (PCoA) and permutational multivariate analysis of variance (PERMANOVA). Two factor PERMANOVA of cecal GM data revealed significant changes when comparing bedding and water decontamination methods, while no significant effects were noted in the fecal GM data. Subsequent PERMANOVA and PCoA of cecal data revealed that several combinations of bedding and water decontamination methods resulted in differing GM, with corn cob bedding most often associated in changes. These findings highlight the complexity by which environmental factors interact to modulate GM.

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Student Support: Endowment established by IDEXX-BioResearch

Development of a fecal microbiota transplant preparation protocol for dogs

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Fecal microbiota transplants (FMT) are highly effective in humans for treating recurrent Clostridium difficile, but have mixed efficacy for other gut dysbiosis conditions. Oxygenation during donor sample processing, and its negative impact on anaerobic bacteria, is a likely cause for this observation. Many processing methods for donor stool samples have been reported, but little is known about their effect on bacterial viability. As there are no established protocols for FMT in veterinary medicine, our goal was to analyze the impact of sample processing on fecal bacteria and create a clinically useful FMT processing protocol. We hypothesize that oxygen-exposed FMT samples will have decreased viability of anaerobic bacteria, and that the addition of L-cysteine, a reducing agent, to fecal homogenate solutions will mitigate the deleterious effect of oxygen exposure. Fecal samples from six healthy dogs were collected and homogenized in normal saline with 10% glycerol or 0.1% L-cysteine in normal saline with 10% glycerol. An aliquot of the donor homogenate solution was sparged with air to mimic sample oxygenation during homogenization. An aliquot was also treated with propidium monoazide (PMA) to assess bacterial viability. PMA, a membrane-impermeable DNA binding agent, modifies DNA from dead bacterial cells allowing for sequencing of living cell DNA only. Additional aliquots of each buffer were subjected to several freeze-thaw cycles before the addition of PMA. Sample processing is underway and, when completed, genomic DNA will undergo purification and Illumina sequencing of 16S rDNA. Overall, a novel FMT protocol for veterinarians would enhance the treatment options available for animals with intestinal dysbiosis.

Research Grant: None
Student Support: Boehringer Ingelheim Veterinary Scholars Program
Blood and fecal microbiota in healthy dogs

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Microbial identification utilizing metagenomics has allowed characterization of communities of bacteria present in the gut of healthy individuals. Recent data from our laboratory and others using sequencing of the microbial 16S rRNA gene challenges the dogma that blood is free of bacteria in healthy individuals. The origin of these microbes is thought to be the gut; however, especially in illness, microbes may translocate from other regions of the body. The study objective was to document the presence of and characterize the healthy canine blood microbiota and compare to fecal samples. We hypothesized that using 16S rRNA amplicon sequencing of microbial DNA from healthy dog blood there would exist a rich and diverse blood microbiota similar to the gut microbiota. Paired blood and fecal samples were collected from 13 healthy dogs including 2 controls obtained by inserting the needle in the vessel without withdrawing blood. Samples underwent DNA extraction and purification, followed by sequencing using Illumina MiSeq platform. Mean ± SD richness was significantly lower in blood than feces (69 ± 20 versus 188 ± 37 unique sequences, respectively; p < 0.001). Blood had a significantly lower γ-diversity than feces (Shannon index 2.5 ± 0.6 vs 3.1 ± 0.5, respectively; p=0.016). Three microbial profiles were noted in blood. One resembled the controls, one was similar to feces with Megamonas and Fusobacterium species predominating, and the last contained primarily Acinetobacter sp. and unclassified Bradyrhizobiaceae family. PCA plots showed microbial communities between blood and feces were significantly different (p=0.0001). This knowledge can allow for future comparisons of the microbiota in the blood during inflammatory disease states.

Research Grant: None
Student Support: Mizzou Advantage initiative in One Health/One Medicine

Effects of Culex tarsalis saliva on Rift Valley fever virus MP-12 replication in bovine primary macrophages

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Rift Valley fever virus (RVFV) is a zoonotic, arthropod-borne phlebovirus in the family Bunyaviridae, which infects domestic and wild ruminants such as cattle, sheep, and goats. RVFV is endemic in sub-Saharan Africa and outbreaks of RVF can be devastating to farmers due to abortion storms and high neonatal mortality. The virus is transmitted by two genera of mosquitoes, Aedes and Culex. Due to their different ecological needs, these mosquitoes potentially contribute to different aspects of the RVFV transmission cycle. This study evaluates the effect of C. tarsalis saliva on RVFV MP-12 replication in bovine peripheral blood mononuclear cell (PBMC)-derived macrophages. Female C. tarsalis mosquitoes were intrathoracically inoculated with RVFV MP-12, and their saliva was collected after fourteen days. Whole blood was collected from six cows at the Kansas State University Dairy. PBMCs were isolated by gradient centrifugation and then cultured in flasks for infection and in chamber slides followed by for IFA. After seven days, macrophages were infected with MP-12 at an MOI of 0.1 as well as with the infected or uninfected saliva of six C. tarsalis mosquitoes. Supernatant was collected 8 hours post-infection (hpi). Infectious virus was quantified by plaque assay and viral copy number was determined by RT-qPCR of RVFV M and L segments. A dual immunofluorescence assay (IFA) targeting the macrophage specific marker, anti-IBA-1, and anti-RVFV nucleoprotein verified that PBMCs had differentiated into macrophages and their susceptibility to MP-12 infection. We hypothesize that saliva from Culex tarsalis will increase viral replication of RVFV resulting in a higher titer, lower CT values, and more intense anti-RVFV labeling at 8 hpi.

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Student Support: Boehringer Ingelheim Veterinary Scholars Program.
Using blood nutritional markers to evaluate the effect of diet on health in green sea turtles (Chelonia mydas)

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Green sea turtles (Chelonia mydas) are unique because hatchlings and pelagic juveniles are carnivorous, while later life stages are primarily herbivorous. Dietary requirements at each life stage are poorly understood, making diet selection during rehabilitation challenging. Although turtles are typically transitioned to an herbivorous diet before release, food items high in animal protein are often offered early in rehabilitation to combat poor appetite and emaciation. This may result in gastrointestinal pathologies and obesity. As part of a larger project to understand the impact of diet on health and recovery, blood nutritional parameters in green sea turtles undergoing rehabilitation at the Georgia Sea Turtle Center (n = 34) were compared to those of healthy, free-ranging turtles captured in St. Lucie County, Florida (n = 34). Free-ranging turtles were evaluated at a single timepoint. Rehabilitated turtles were monitored at admission, mid-rehabilitation, and recovery, following a shift from a primarily carnivorous, seafood-based diet at admission to a primarily herbivorous diet at recovery. Several bloodwork parameters improved over time in rehabilitation, including total protein, uric acid, potassium, and vitamins A and E. Other parameters remained significantly different in recovery compared to free-ranging animals, including elevated cholesterol, triglycerides, and phosphorus, and low calcium, vitamin D, and magnesium. This information highlights the importance of diet in rehabilitation, and will facilitate the development of nutritionally complete gel diets. This is expected to enhance recovery of green sea turtles in rehabilitation and help maintain the nutritional health of animals held long term in captivity.

Research Grant: American Association of Zoo Veterinarians Wild Animal Health Fund, The Coca-Cola Company, and Georgia Aquarium
Student Support: UGA Veterinary Medical Scientist Training Program, PhD Scholars of Excellence Assistantship

The effects of quaternary ammonium compounds (QACs) on development of immunoglobulin A (IgA) responses

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Quaternary Ammonium Compounds (QACs) are a large class of chemicals; two of which, alkyl dimethyl benzyl ammonium chloride (ADBAC) and didecyl dimethyl ammonium chloride (DDAC) are common in household cleaning agents. ADBAC and DDAC are known to cause allergies and asthma in humans. This, plus preliminary studies from our lab showing that ADBAC+DDAC increase cytokine production in mouse macrophages, suggests that QACs may alter immune function. Environmental exposures before adulthood can result in suppression, hyperactivation, or misregulation of the immune system in adults. Immunoglobulin A (IgA) is found in mucosal secretions and protects against inhaled or ingested pathogens. We hypothesize that mice exposed to ADBAC+DDAC will have increase IgA production levels. Three groups of mice were tested: control, ambient exposure (from use of disinfectant in the mouse room), and dosed at 60 mg/kg/day. Parents were exposed throughout breeding, gestation, and lactation. Offspring received exposure until 3 weeks of age, allowing for both prenatal and postnatal exposure. Primary IgA response was evaluated before full immunocompetency (day 26) and after competency (day 35). Secondary response was measured on day 40. For primary response, mice were immunized with KLH on day 21 and bleed on day 26 and 35. For secondary response, mice were immunized on days 21 and 35 and bleed day 40. An ELISA was developed to assess IgA production. The primary response between day 26 and 35 was significantly increased in dosed mice, but not for other groups. A treatment effect was also seen with increased IgA production in dosed mice on day 35 compared to controls. These results could signify hyperactivation of the immune system.

Research Grant: VCOM-VMCVM Center for One Health Research Grant and Virginia-Maryland College of Veterinary Medicine
Student Support: Virginia-Maryland College of Veterinary Medicine
Presence and risk factors associated with *Staphylococcus aureus* carriage among veterinary health care workers

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*Staphylococcus aureus* is a bacterium that is not only a human commensal, but also an opportunistic pathogen capable of causing disease in both humans and animals. Due to its ability to gain antimicrobial resistance, it has become a concern for health officials worldwide. *S. aureus* can be transmitted via fomites, skin-to-skin contact, and zoonotic transfer, putting veterinary health care workers at increased risk of colonization and subsequent infection. However, risk factors associated with *S. aureus* carriage among veterinary health care workers are vastly uncharacterized. The purpose of this study was to determine prevalence of *S. aureus* among veterinary health care workers at the OSU-VMC and the associated risk factors. In this cross-sectional analysis, a risk assessment questionnaire was distributed and nasal and hand swabs were taken from 202 participants. Univariate analysis of associated risk factors determined from the questionnaire and positive sample swabs was completed and significant associations were reported. Of those risk factors examined, being a 4th year veterinary student and considered hospital personnel were significantly associated with carriage. Contaminated hands were also significantly associated with nasal carriage. It was also observed, that the lack of proper hand hygiene practices were significant risk factors associated with *S. aureus* carriage. The high prevalence of *S. aureus* carriage among veterinary health care workers represents a significant occupational hazard and public health risk. This study helps to identify practices that can be targeted for intervention strategies that can decrease *S. aureus* transmission among veterinary health care workers in veterinary hospital settings.

Research Grant: Unknown

Student Support: NIH T35 Training Grant T335OD012199

Characterization of the shelter feline gut microbiota and optimization of sample collection techniques

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The microbiome refers to the collection of organisms, their genomes, and the surrounding environmental conditions. Past research has explored the relationship between the gut microbiota (GM) and host health in humans, yet study of the feline microbiome is still in its infancy and more research is needed to investigate how environmental factors and disease influence the GM. The purposes of the present study are to 1) characterize the GM of shelter/feral cats to determine what environmental or host health factors influence composition and 2) assess whether litter contains components that interfere with the ability to obtain quality metagenomics data. We hypothesize that 1) felines exposed to related environments and disease states will have similar GM composition and 2) cat litter contains PCR inhibitors that are detrimental to obtaining quality metagenomics data. Fecal samples are being collected and DNA is being extracted with a commercial Power Fecal kit, amplified by PCR using conserved bacterial primers and subjected to next generation sequencing. Cats are being assessed for parameters including age, sex, and disease state. To evaluate the impact of litter contamination, house cat fecal samples obtained from paper towel-lined litter pans are being spiked with litter and metagenomics data compared to that of unspiked samples. We expect cats with similar age and disease states to share GM composition. Moreover, we anticipate that feces spiked with litter will yield inferior data when compared to unspiked samples. This research will provide critical information about factors that can modulate GM in shelter/feral cats, and lead to novel strategies to prevent and treat intestinal diseases in these populations.

Research Grant: Franklin discretionary funds

Student Support: University of Missouri College of Veterinary Medicine Office of Research
Evaluation of canine and feline platelet parameters during storage in MgSO$_4$ and EDTA anticoagulants

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Background: Magnesium sulfate (MgSO$_4$) is an alternative anticoagulant for human blood samples with platelet clumping induced by EDTA. Veterinarians often use regional laboratories for CBCs, which can delay sample evaluation for 24 to 48 hours and induce artifactual changes in platelets. This study evaluates the usefulness of MgSO$_4$ as an anticoagulant in veterinary medicine and its effect on platelet parameters over 48 hours. Methods: Whole blood from 9 dogs and 10 cats was collected directly into ThromboExact (Mg$^{2+}$ at 0.82mg/mL; S-Monovette, Sarstedt) and K$_3$EDTA tubes (S-Monovette, Sarstedt) in alternating order. The MgSO$_4$- and EDTA-anticoagulated blood samples were analyzed with Advia 120 hematology analyzer at 0, 12, 24, 36, and 48 hours. Parameters analyzed were platelet concentration, mean platelet volume (MPV), mean platelet component (MPC), plateletcrit (PCT), platelet distribution width (PDW), and mean platelet mass (MPM). Blood smears were stained and examined at each time interval and graded for platelet clumping. Results: In dogs, MgSO$_4$ induced significant platelet clumping and caused decreased platelet concentration, MPC, PCT, and MPM, as well as increased MPV and PDW. Feline MgSO$_4$-anticoagulated blood had similar results, except MPV was decreased. EDTA maintained stable platelet values for 48 hours in dogs; however, in cats, EDTA-induced changes were observed in platelet concentration, PCT, MPV, and MPC. Conclusions: MgSO$_4$ is not a suitable EDTA substitute for anticoagulation of canine and feline blood, as platelet parameters were significantly altered during storage. The results of this research contrast those of human literature, suggesting species-specific differences in platelet inhibition with MgSO$_4$.

Research Grant: None
Student Support: Kenneth F. Burns Trust

Investigating MARCKS protein as a novel therapeutic target for treatment of equine asthma

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Equine asthma is an allergic lower airway disease characterized by frequent coughing, labored breathing, and exercise intolerance. This disease is a significant burden on the equine industry, causing respiratory distress for affected horses and substantially limiting their athletic performance and longevity. Neutrophil accumulation within the airways of asthmatic horses contributes to the ongoing cycle of inflammation and disease symptoms; therefore, inhibition of neutrophil inflammatory functions within the airway could potentially benefit horses with asthma. One prospective target for inhibiting neutrophil inflammatory functions is Myristoylated Alanine-Rich C Kinase Substrate (MARCKS). MARCKS is a ubiquitously expressed actin binding protein that is upregulated and phosphorylated in activated neutrophils and plays a major role in neutrophil migration. We hypothesize that MARCKS is upregulated in pulmonary leukocytes of asthmatic horses compared to healthy horses. We will use immunoblot and ELISA to compare levels of total and phospho-MARCKS proteins present in bronchoalveolar lavage (BAL) cell lysates from healthy horses vs. horses with mild/moderate or severe asthma. Preliminary immunoblot data shows that one horse with severe asthma appears to have more total MARCKS present in pulmonary cells compared to one healthy and one mildly asthmatic horse. Additionally, qRT-PCR will be used to compare MARCKS mRNA expression level among the three groups. Together this data will provide new information regarding the role of MARCKS in equine asthma. Future studies will determine if a MARCKS inhibiting peptide can reduce pulmonary inflammation and serve as a new therapy for horses with this disease.

Research Grant: Morris Animal Foundation Grant D17EQ-029
Student Support: NIH T35 Training Grant T35OD011070
Silver nanoparticles affect glutamate/aspartate transporter expression in astrocytes derived from human ESCs

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Silver nanoparticles (AgNPs) are used as an anti-microbial in many products; cosmetics, paint, water filters, and clothing. Previous studies showed that AgNPs gain access to the central nervous system by crossing the blood-brain barrier resulting in their accumulation in various brain regions to cause neurodegeneration (Ahamed et al. 2010). A nanoparticle is between 1 and 200 nanometers. Silver nanoparticles produce many free radicals, which are thought to contribute to their neurotoxic effects. In this study, we used glutamatergic neurons derived from human embryonic stem cells as a cellular model to study 20 nm citrate-coated AgNPs (AgSCs). Previous studies we have done have shown that AgSCs damage neurite outgrowths, increase production of reactive oxygen species, and reduced the expression of MAP2, Glut1, and NMDA receptor proteins. In this study, our hypothesis was that AgSCs would increase the expression of membrane bound GLAST. Alternatively, high concentration of AgSC exposure will promote the ubiquitination of GLAST, and thus impair the excitatory transmission process and induce neuron excitotoxicity. Currently we are examining different contributions of AgSC on GLAST expression by immunostaining and qPCR. This study will give us valuable insight into the underlying mechanisms of astrocyte mediated neuroprotection, and indicate that stem cells are an excellent platform for neurotoxicity study.

Research Grant: National Institute of Health
Student Support: Merial Veterinary Research Scholars Program

Early lymphoid cell targets of chronic wasting disease prions in white-tailed deer

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Chronic wasting disease (CWD) is a naturally occurring prion disease affecting captive and wild cervid populations in almost half of the United States, two Canadian provinces, the Republic of Korea, and most recently, Norway. Symptomatic CWD may present as progressive weight loss and lethargy, accompanied by various neurodegenerative behavioral changes such as ataxia, head tremors, and hyperexcitability. Definitive diagnosis cannot be based on clinical signs alone, and the abnormal prion protein must be found in the animal’s tissue to confirm CWD infection. At terminal disease, aggregates of the disease-associated abnormal prion protein PrP<sup>CWD</sup> can be found in the central nervous system and lymphoid tissues associated with B cells and follicular dendritic cells. Previous studies have identified PrP<sup>CWD</sup> in the lymphoid system early in disease progression, serving as an intermediary between mucosal uptake and neuroinvasion. In this study, we aim to establish the PrP<sup>CWD</sup> lymphoid cell associations during the early phase of disease prior to neuroinvasion. We will analyze lymphoid tissues collected 1-4 months post-inoculation from white-tailed deer inoculated with CWD-positive brain homogenate by mouth. The co-localization of PrP<sup>CWD</sup> and lymphoid cells will be assessed using confocal microscopy immunofluorescence and the phenotype markers vimentin (mesenchymal cells), CD44 (pan-lymphocyte), CD21 and CD19 (B cells, macrophages, and FDCs), CD4 (T cells), CD45 (pan-leukocyte), and CD18 (macrophages). By identifying early PrP<sup>CWD</sup> lymphoid targets, we will uncover an unknown step in early CWD infection that is required for prion amplification, dissemination, and neuroinvasion.

Research Grant: NIH RO1 – NS061902
Student Support: Georgia Norris Foundation
Genome analysis of probiotic lactobacilli

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Light Turkey Syndrome is a condition where turkeys do not reach their genetic potential weight. A single causative agent has not been identified, but bacterial communities in the turkey ileum have been associated with turkey performance. Previous studies in our laboratory used 16S rRNA sequencing to compare the bacterial communities within the ileum of heavy and light turkey flocks. It was shown that there were significantly lower abundances of certain lactobacillus species in heavy flocks compared to light flocks. However, the interactions between these lactobacilli have been understudied. We hypothesized that these strains differ in their metabolic properties and these differences enable a symbiotic relationship between the strains themselves and their host. We used PathoLogic to create databases for 8 L. johnsonii strains, 3 L. aviarius strains, L. gallinarum, L. helveticus, L. crispatus, and L. ingluviei. We found that there were extensive variations in the mucus-binding proteins between species and strains, suggesting host-specific adaptations. We also found that L. aviarius strains lacked an NADPH-dependent FMN reductase and a methionine sulfoxide reductase that we found in all other species and strains, validating that L. aviarius is a strict anaerobe since these enzymes are involved in oxidative tolerance. Finally, all the lactobacilli had enzymes in the autoinducer-2 (AI-2) biosynthesis pathway. AI-2 has been shown to play a role in biofilm formation, interspecies bacterial communication, and pathogenicity. The in silica analysis of these lactobacilli genomes provides various routes to study the symbiotic relationships between lactobacilli in poultry.

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Student Support: The Merial Veterinary Scholars Program

The effect of long-term exposure to concrete flooring on behavioral indicators of pain in cattle

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Concrete and rubber are the most common flooring surfaces used in U.S. dairy freestall facilities. The long-term impact of flooring type on cow comfort and indicators of chronic pain is yet still unclear. Lying time is commonly used to measure cow comfort, but may not be a sensitive indicator of pain. A novel indicator of chronic pain is the time it takes a cow to transition from standing to lying, as cows experiencing pain may take longer to make these transitions. The aim of this study was to determine the effect of concrete or rubber flooring on the lying behavior of dairy cows over two lactations. Forty pregnant Holstein heifers were randomly assigned to a pen with rubber or concrete flooring at the Dairy Research Center at Purdue University (n = 20/treatment) and were housed in those pens during their first two lactations. Animals were fitted with 3D accelerometers (Afimilk Pedometer Plus) that automatically recorded daily lying time, number of lying bouts, and average lying bout duration. Eight cows per treatment were video-recorded on days 45 and 90 of both lactations to measure the duration of time it took them to transition from standing to lying (and vice versa) averaged across at least 3 bouts/d. We hypothesize that cows on concrete will take longer to stand up and lie down compared to those on rubber, and this variable will be highest in the 2nd lactation after long-term exposure to concrete. We also expect cows on concrete to have fewer lying bouts, longer lying bout durations, and lower daily lying time compared to those on rubber. The results of this study could reveal a novel indicator of chronic pain in dairy cattle, encouraging producers to change housing variables to ensure good welfare for their cows.

Research Grant: This project was funded internally by the USDA
Student Support: Epperson Research Fellow
Effects of particulate matter in male mice hippocampi and human derived neural progenitor cells

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There are multiple genetic and environmental factors believed to trigger the development of Alzheimer’s disease, however their roles have not been clearly defined. The only known genetic factor linked to Alzheimer’s disease is the apolipoprotein E4 gene (apoE4). Understanding the factors that contribute to the development of Alzheimer’s is important to develop preventative measures, if not a cure. One factor that is believed to contribute to the pathogenesis of Alzheimer’s disease is air pollutants. 44% of the US population lives in counties that have harmful air, so studying this effect is important for the health of all populations living in poor quality air. We hypothesize that environmental air pollutants contribute to the development of neurodegeneration and Alzheimer’s-like pathology, especially in carriers of the apoE4 gene. In this control study, we acutely exposed male wild-type mice and human neural progenitor cells derived from a male non-apoE4 carrier to traffic-associated particulate matter (PM) or vehicle control. A PCR array was performed examining the expression of 84 key genes regulated during exposure to toxicants. We anticipate the identification of specific stress response pathways activated by PM that will be informative in determining mechanisms of neurodegeneration. Future studies will repeat the experiments using apoE4 carrier mice and human derived cells as well as examine for development of amyloid-beta and tau fibrils, indicators of Alzheimer’s like pathology. These studies will provide more information on the understanding of Alzheimer’s disease as well as better measures toward public health to reduce the risk of Alzheimer’s and other neurodegenerative diseases.

Research Grant: Michigan State University Institutional Funds
Student Support: Michigan State University College of Veterinary Medicine Summer Research Program

The Diroscope: calibration of a smartphone microscope for quantitative diagnosis of canine heartworm infection

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Canine heartworm disease is caused by the mosquito-borne nematode *Dirofilaria immitis*, the most important canine parasite in the United States. The American Heartworm Society recommends annual testing for microfilariae (mf) in tandem with antigen testing. Mf may be detected qualitatively via direct microscopy, or quantitatively via thick smears or Knott’s test; however, these quantitative tests are time-consuming and subject to technical variability. A software-controlled smartphone microscope was recently developed to quantify *Loa loa*, a human filarial parasite, in fresh blood. This device counts mf in less than two minutes by analyzing short videos of blood within a glass capillary. We hypothesize that this device, after software modification, will rapidly count *D. immitis* mf and prove more accurate than traditional measurement methods. Our project aims to (1) complete the software recalibration and (2) test the accuracy of the Diroscope for quantitative diagnosis of heartworm infection. The algorithm was calibrated for *D. immitis* by an iterative process where we manually tagged mf in videos of dog blood with low and high mf concentrations (n=10/concentration) and scanned mf-free blood, then adjusted the software to optimize mf motility recognition. Next, we will spike blood with known numbers of mf (0, 50, 100, 250, 500, 1000, 10000 mf/mL) to measure the Diroscope’s accuracy using the formula: (mf observed / mf expected). Across all mf counting methods, accuracy and mf means will be compared using ANOVA and Tukey’s test, respectively. We expect that the Diroscope will provide a quantitative, point-of-care diagnostic test for clinicians, and also facilitate mf reduction tests in suspect anthelmintic resistant cases.

Research Grant: University of Georgia College of Veterinary Medicine
Student Support: Boehringer Ingelheim, Veterinary Medical Experiment Station, UGA College of Vet Medicine
Allometric scaling for intra-articular medication in the equine fetlock

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Intra-articular (I.A.) injections are used for the treatment of inflammation in joints. Using I.A. injections, sustained release formulas (SRFs) are used to create a high local concentration of active pharmaceutical ingredients (APIs) while avoiding significant systemic or organ exposure. For example, SRFs may contain analgesics, anti-inflammatories, growth factors, antimicrobials and therapeutic proteins. In I.A. applications traditional dose calculations based on body weight are not logical since many of these become resident in the synovial tissues, creating a depot from which API is released. Hence, dose scaling to the target tissues within the joint is more appropriate. Our preliminary work has shown that 0.66 mL of a SRF containing celecoxib controlled inflammation for 90 days in a sheep arthroplasty model. Using contrast enhancement and microCT imaging we have measured the surface area and volume of the metabolically active portion of the synovial membrane in the sheep, Yucatan minipig, human, dog and rat stifle/knee joint. Since horses are one of the most active sporting animals and often develop fetlock joint inflammation and joint disease, the purpose of this study is to determine the average area and volume of the synovial membrane in the equine fetlock joint. This is achieved by withdrawing synovial fluid from the joint space and injecting Lugol’s iodine contrast solution. The joint is then disarticulated and imaged in a Ringer’s Solution bath at 45μm resolution. Sesamoid bones are blanked from the image using the advanced region of interest tool and the threshold of the tissue is determined. The Isosurface tool is used to measure the area and volume of the synovial membrane. Data is being collected.

Research Grant: Ontario Centers of Excellence/Arthritis Innovation Corporation (Toronto).
Student Support: Andrea Leger Dunbar Summer Research Studentship, Ontario Veterinary College

Effects of a Listeria monocytogenes phosphodiesterase, PdeE, on phenotypes controlled by cyclic dinucleotides

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Listeria monocytogenes is an important foodborne pathogen that causes infection most commonly in pregnant women, newborns, elderly, and immunocompromised people. It is capable of replication inside host macrophages and enterocytes. Previously we discovered a listerial phosphodiesterase (PdeE) that is important for intracellular replication and virulence, and we determined that the enzyme hydrolyzes cyclic-di-AMP and cyclic-di-GMP. These cyclic dinucleotides are important signaling molecules that regulate listerial adaptation to different environments, including growth in the host and in biofilms. Listerial strains that have high levels of cyclic-di-GMP have distinct phenotypes, including binding Congo red and decreased motility. Similarly, listerial strains with high cyclic-di-AMP have slower growth. We hypothesize that overexpression of PdeE in L. monocytogenes strains that have high levels of cyclic-di-AMP or cyclic-di-GMP will reverse these phenotypes due to hydrolysis of these cyclic dinucleotides. To test this hypothesis, we overexpressed the pdeE gene from a plasmid and inserted it into L. monocytogenes mutants with high cyclic-di-AMP or cyclic-di-GMP. To confirm overexpression of PdeE from the plasmid, RNA was extracted from each strain and used for quantitative PCR (qPCR). Colony size, motility, and ability to bind Congo red was analyzed to determine whether overexpression of PdeE would reverse the phenotypes caused by high cyclic di-AMP and/or cyclic di-GMP. If our hypothesis is correct, this will be the first time an enzyme is found in L. monocytogenes that has confirmed hydrolytic activity against both cyclic-di-AMP and cyclic-di-GMP and can control phenotypes affected by both cyclic dinucleotides.

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Student Support: National Institutes of Health 2T35OD010432-16, Mississippi State College of Veterinary Medicine
Environmental heat exposure among pet dogs in rural and urban counties of the South

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The United Nations Intergovernmental Panel on Climate Change reports that the earth is warming like never before. Extreme temperatures have become more common and are expected to worsen in the future. Among dogs, exposure to elevated temperatures can cause life-threatening conditions, such as heat stroke. Heat stress indices are used to represent the overall effect environmental conditions have on an individual’s health and productivity. While heat stress indices have been formulated for humans and a few species of animals, there is little to no research that explores a specific index for dogs. The purpose of this project was to determine what factors should be considered in a heat stress index for dogs and what additional behavioral and lifestyle factors predispose dogs to increased heat exposure. It was expected that certain factors such as urban vs. rural setting, body condition, activity level, and owner characteristics predispose dogs to increased heat exposure. Thirty dog owners were recruited from urban Birmingham, Alabama and rural Wilcox County, Alabama. Participants were asked to complete questionnaires dealing with their personal demographics and additional questionnaires dealing with the signalment, behavior, and lifestyle of their dogs. The dog owners and their participating dogs wore iButton temperature monitors continuously for 6 days. The iButton monitors recorded the air temperature surrounding the participants every 5 minutes. The average daily and nightly temperatures experienced by the participants were compared using the factors contained in the questionnaires. Various heat stress indices were compared to determine the effectiveness of each index in portraying the heat experienced by the dogs.

Research Grant: Virginia-Maryland College of Veterinary Medicine
Student Support: 2017 Merial Veterinary Scholars Program (PO 1075449)

Evaluation of commercial ELISA kits for quantification of selected cytokines in feline urine

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Feline idiopathic cystitis (FIC) is a common bladder disorder of cats and diagnosis remains one of exclusion. Urine cytokines may be potential biomarkers for FIC. Enzyme-linked immunosorbent assays (ELISAs) are ideal for quantifying cytokines. However, variations in urine matrix characteristics can interfere with ELISA performance. Since few ELISAs have been validated for feline urine, our objective was to evaluate feline-specific ELISA kits for quantification of IL-2, IL-6, and IL-12 in feline urine. Urine was collected from healthy cats evaluated at the Michigan State University Veterinary Medical Center. Normal urine samples were pooled, modified to mimic disease conditions by adding water or hemolyzed blood, and then spiked with high, medium, and low concentrations of recombinant cytokines. Concentrations of IL-2, IL-6, and IL-12 were determined using commercially available feline-specific ELISA kits. The influence of urine matrix variables on test performance was evaluated by spike/recovery tests, linearity testing, and assessment of inter- and intra-assay variation. All assays underestimated high and medium spiked cytokine concentrations in urine as compared to standard assay diluents. Low spiked cytokine concentrations in urine were inconsistently detected. Urine spiked with IL-2, IL-6 and IL-12 achieved maximal quantitative recoveries of 80%, 90%, and 58% respectively. High USG contributed significantly to poor IL-2 and IL-12 recovery (p < 0.05). Hematuria had variable effect. Feline urine matrix characteristics appear to impact cytokine quantification by ELISA. Further studies are needed to optimize detection of cytokines in feline urine by ELISA and establish their use as diagnostic biomarkers for FIC.

Research Grant: Center for Feline Health and Well-Being at Michigan State University
Student Support: Owlbear Feline Health Fund at Michigan State University
Characterization and comparison of cell mediated immune responses in stressed and unstressed beef calves

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The goal of this study was to compare the cell mediated immune responses of multiple source, highly commingled, sale-barn origin calves (STR, n=10) to those of single source calves that had been weaned for 60 days (UNS, n=10). Peripheral blood mononuclear cells (PBMCs) and neutrophils (PMNs) were isolated from jugular venous blood of each calf. PBMCs were stimulated with Concanavalin A, BVDV-1, BVDV-2, BHV-1, M. haemolytica, and P. multocida and evaluated for clonal proliferation and secretion of IFN-γ and IL-17 into cell culture supernatants. The native functional capacities of PMNs were evaluated in response to stimulation with Zymosan, S. aureus antigen (SA), lipopolysaccharide (LPS), and peptidoglycan (PGN). Complete blood counts and serum biochemical profiles were performed for each animal at time of sample collection. Compared to STR calves, UNS calves had significantly greater lymphocyte proliferative responses following stimulation with viral and bacterial antigens (P < 0.05). In addition, PMNs isolated from UNS calves had a greater ability to phagocytose E. coli and S. aureus when compared to STR calves. Serum non-esterified fatty acids were significantly higher in STR calves (P < 0.01). Serum β-hydroxybutyrate was significantly lower in STR calves (P < 0.01). These data suggest that immunologic and physiologic differences exist between STR and UNS calves. While the underlying mechanisms for these differences are not clear, it is possible that combinations of energy imbalances, stress-induced immunosuppression, and general immune naivete, may predispose STR calves to an increased risk of morbidity and mortality due to bovine respiratory disease.

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Student Support: Boehringer Ingelheim, Veterinary Medical Experiment Station, UGA College of Vet Medicine

Mitochondrial oxygen consumption as an indicator of spermatozoal health for chilled storage of stallion sperm

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Stallion sperm predominantly rely on oxidative phosphorylation (OxPhos) to produce ATP to fuel sperm motility. Mitochondrial oxygen consumption, which is indicative of OxPhos efficiency, has been demonstrated to be a sensitive indicator of spermatozoal health in relation to cryopreservation in stallions. This study aims to determine the roll of mitochondrial oxygen consumption of stallion sperm as an indicator of spermatozoal quality and integrity during chilled storage of semen at 5°C. Employing an array of electron transport chain (ETC) inhibitors and uncouplers, we investigated sperm mitochondrial function and motility in ejaculates of commercial Quarter Horse stallions, in both fresh and 24-hour chilled samples. We hypothesize that mitochondrial oxygen consumption will be strongly associated with motility, and a sensitive predictor of motility preservation after 24-hour chilled storage. Our preliminary data demonstrates that mitochondrial oxygen consumption decreases after 24-hour chilled storage, and fresh ejaculates with higher initial mitochondrial oxygen consumption better maintain progressive motility after chilled storage than those with lower initial mitochondrial oxygen consumption.

Research Grant: American Quarter Horse Association (AQHA) Grant

Student Support: Students Training in Advanced Research (STAR) Award with NIH funding source
SOX9 deficiency in gut epithelium regulates antibody responses and allergic sensitization

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SOX9 is a transcription factor regulating the differentiation and maturation of Paneth cells within the intestinal crypts. The loss of function of the SOX9 gene in the gut epithelium of SOX9ΔIEC mice results in a lack of Paneth cells. Consistent with the fact that Paneth cells contribute to innate immunity primarily through production of antimicrobial peptides and other antimicrobial products, SOX9ΔIEC mice exhibit a profound dysbiosis of the gut microbiota. Furthermore, SOX9ΔIEC mice develop stronger allergic symptoms after oral sensitization. We addressed the relative contribution of the dysbiosis of SOX9ΔIEC mice on the production of mucosal and systemic antibodies. Fecal IgA levels were increased in SOX9ΔIEC mice compared to control wild-type mice. Bacteria-free fecal material extracts (FME) from SOX9ΔIEC mice significantly increased expression of costimulatory molecules (CD40 and CD86) by spleen cells after 24 hour incubation in vitro. Furthermore, addition of bacteria-free FME from SOX9ΔIEC mice to mesenteric lymph node cells cultured in the presence of anti-CD40 and IL-4 increased the frequency of B cells expressing IgE (IgE + B220+ cells). Ongoing studies will determine if transplantation of fecal material from SOX9ΔIEC mice to naive wild-type mice can enhance allergic sensitization of recipient mice and their allergic symptoms following subsequent allergen challenge. In summation, the findings of this study provide further insight into the relationship between the antimicrobial function of Paneth cells and a host’s susceptibility to allergic responses.

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Student Support: NIH T35 Grant

Prevalence and strain diversity of Anaplasma marginale in Kansas cattle herds

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Anaplasma marginale, the causative agent of bovine anaplasmosis, is an obligate-intracellular tick-borne rickettsial pathogen that can be found worldwide and is endemic throughout the United States. Bovine anaplasmosis is conservatively estimated to cost the U.S. cattle industry >$300 million per year. Towards understanding the impact of this disease in Kansas, the goal of this study is to determine the prevalence of active A. marginale infections in cattle herds across the state of Kansas. The specific aims of this study are to: i) examine the anaplasmosis infection prevalence in Kansas cattle herds; ii) evaluate within-herd anaplasmosis infection prevalence; and, iii) identify actively circulating A. marginale strains. Analysis of cattle blood by PCR detection of the A. marginale major surface protein 5 (MSP5) gene revealed that anaplasmosis occurs throughout Kansas, with the majority of infected herds residing in the eastern third of the state. Examination of actively circulating A. marginale strains by amplification of a portion of the major surface protein 1a (MSP1a) gene, demonstrated that many A. marginale strains are circulating throughout Kansas, with some herd infected with multiple strains. Our results support the need for continued research efforts on bovine anaplasmosis to identify drivers of disease transmission and to evaluate impact of disease to the Kansas cattle industry. The data generated from this study will be the basis for future studies examining bovine anaplasmosis disease ecology including evaluation of vector transmission variables and efficacy of current treatment and control practices.

Research Grant: Reif Laboratory Startup Funds Kansas State University CVM/DMP
Student Support: Center of Excellence for Emerging and Zoonotic Animal Diseases
Impact of acclimation and low stress handling on weight gain and hydration status in feedlot cattle

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Stress can have many negative health implications in cattle, such as decreasing immunity, weight gain, and production. It has been suggested that using acclimation and low stress handling (ALSCH) of feedlot cattle may decrease stress and thus promote better overall health and quality of production. The goal of this study was to determine if ALSCH of feedlot cattle affected weight gain and hydration status. Newly weaned calves were imported to a feedlot and separated into pens. Half of the calves were treated using ALSCH practices and the other half served as the control group, using standard feedlot protocols. Calves were processed on the third and tenth day post arrival, receiving vaccines, growth hormones, and anti-parasitic drugs. On processing days each calf was weighed. Similarly, nine randomly selected calves from both the treatment and control groups were bled and packed cell volume (PCV) values were recorded. Weights and PCV values were used to determine differences in weight gain and hydration status between the treatment and control groups. The average daily gain and total weight gain during the ten day period was higher in acclimated calves compared to control calves. Similarly, trends in PCV showed lower values for the acclimated calves than control calves although no data was statistically different. These results indicate that ALSCH may improve weight gain and hydration status, analysis of final data may increase the statistical significance of these differences. More research regarding behavior and cortisol differences between acclimated and control calves have yet to be analyzed and may show more insight into whether ALSCH contributes to better health in feedlot calves.

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Determining the best semen extender for chameleons

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Chameleons, when compared to other reptiles, represent a group of animals that not only have a high percentage of threatened or endangered species but are at an increased risk of extinction. Many factors are contributing to their demise, including their high rate of endemism to Madagascar, deforestation by anthropogenic factors, and the pet trade. Additionally, climate change is affecting the duration of the breeding season of these lizards. Despite these threats to chameleons, no research has been done to develop assisted reproductive programs to protect the genetics of these animals and ensure their long-term success. There have been only a paucity of studies done to characterize semen collection in reptiles, and even fewer studies on semen preservation in reptiles. No studies exist evaluating semen extenders in reptiles. The aim of this study is to evaluate the efficacy of different commercial semen extender types and the effect of cooling and refrigeration on the viability of stored semen of panther chameleons (Furcifer pardalis) and veiled chameleons (Chamaeleo calyptratus). A pilot study was conducted to determine the amount of extender needed in microcentrifuge tubes to prevent evaporation of the samples. There was a significant difference in sample volume (20 μl) by extender (F= 8.008, p=0.0001), with LRS and PBS extenders having significantly higher volumes than yolk and INRA extenders. There were no significant differences in sample volume by time (F=1.575, p=0.141) or temperature (F=1.912, p=0.167). PBS was found to lyse chameleon sperm.

Research Grant: None
Student Support: Morris Animal Foundation
**Validation of phosphorylated histone H3 as a marker for mitotic index**

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The mitotic index (MI) is often an important part of grading schemes used in tumor prognostication. Current methods used to assess MI have several drawbacks. Microscopic enumeration is subjective, lacks sensitivity, and is time consuming. DNA staining is influenced by several factors separate from mitosis, and lacks sensitivity. Immunolabeling of proteins involved in the cell cycle lacks specificity due to expression of these proteins in non-dividing cells. Histone H3 (HH3) is a core histone protein that has shown promise as a highly specific marker of mitosis. The properties of HH3 that convey this specificity include: phosphorylation of the Serine 10 residue only occurs during mitosis, rapid desphosphorylation upon completion of mitosis, and phosphorylation does not occur during apoptosis. We are currently working to validate HH3 as a marker for cell proliferation using flow cytometry and a canine B-cell lymphoma cell line. We are comparing phosphorylated HH3 levels to two means of monitoring cell divisions: carboxyfluorescein succinimidyl ester labeling of DNA and a fluorochrome that specifically binds to proteins containing primary amines. Cell divisions are recognized by halving of the two dyes, and hence a two-fold reduction in fluorescent intensity of the cells. Mitogens are included to drive cell proliferation as a positive control and heat-killed cells are used as a negative control. In the long term, we plan to test the prognostic value of phosphorylated HH3 levels in various canine neoplasms. If HH3 can be demonstrated to be a more sensitive and specific marker of cell proliferation, cytological diagnosis, speed and reproducibility of tumor grading, and prognostication could all be improved.

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**Regulated stochasticity in a bacterial signaling network permits tolerance to a rapid environmental change**

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Microbial populations can maximize fitness in dynamic environments through bet hedging, a process wherein a subpopulation assumes a phenotype not optimally adapted to the present environment but well adapted to an environment likely to be encountered. Here we show that oxygen induces fluctuating expression of the trimethylamine oxide (TMAO) respiratory system of *Escherichia coli*, diversifying the cell population and enabling a bet-hedging strategy that permits growth following oxygen loss. This regulation by oxygen affects the variance in gene expression but leaves the mean unchanged. We show that the oxygen-sensitive transcription factor IscR is the key regulator of variability. Oxygen causes IscR to repress expression of a TMAO-responsive signaling system, allowing stochastic effects to have a strong effect on the output of the system and resulting in heterogeneous expression of the TMAO reduction machinery. This work reveals a mechanism through which cells regulate molecular noise to enhance fitness.

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**Student Support**: NIH R01-GM080279, NIH T32-AI060516, NIH T32-GM007170, Penn Genome Frontiers Institute
Effect of soluble epoxide hydrolase inhibitor $t$-TUCB on recovery of ischemic-injured porcine jejunum

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Ischemic intestinal injury is most commonly associated with strangulating obstruction in veterinary patients and disrupts mucosal barrier function. Prostaglandins (PGs) play an important role in mucosal recovery. Soluble epoxide hydrolase (sEH) inhibitors may modulate the production of PGs. This study aimed to determine whether the sEH inhibitor, trans-4-[4-{3-[4-Trifluoromethoxy-phenyl]-ureido}-cyclohexyloxy]-benzoic acid ($t$-TUCB), aids in recovery of mucosal barrier function following ischemic injury to porcine jejunum. Six juvenile pigs were anesthetized and complete ischemic injury was induced in the jejunum for 45 minutes. Mucosal tissues were mounted on Ussing chambers and bathed in oxygenated Ringer’s solution. Indomethacin (5-$\mu$M), a cyclooxygenase (COX) inhibitor, was added to select tissues at time zero. $t$-TUCB (1-$\mu$M) was added after 30-minutes. Short circuit current (Isc) and potential difference (PD) were measured every 15 minutes over a 240-minute recovery period and used to calculate transepithelial electrical resistance (TER) as a sensitive index of barrier function. Serosal fluid samples collected at the 60 and 240-minute time points were assessed for PGE$_2$ concentration. Mucosa was collected for histologic assessment of recovery. The TER of $t$-TUCB-treated ischemic tissue increased over the 240-minute recovery period. This recovery was inhibited by indomethacin. Higher PGE$_2$ concentrations were detected in the $t$-TUCB-treated tissues, which was also inhibited by indomethacin. We concluded that $t$-TUCB aided in recovery of barrier function in ischemic-injured porcine intestine likely in a COX-dependent manner. This novel compound, $t$-TUCB, may be beneficial in conditions associated with ischemic injury.

Research Grant: None

Student Support: None

Characterization of alpaca immunoglobulins following immunization with Haemonchus contortus vaccine Barbervax

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Haemonchus contortus, commonly known as Barber’s Pole worm, is one of the most significant current challenges facing the viability of the camelid industry due to widespread drug resistance, limited host genetic pool, and other factors. A new $H$. contortus sheep vaccine is commercially available in Australia and South Africa. This vaccine, known as Barbervax, contains native enzymes from the parasite intestinal cells. Circulating antibodies, stimulated by vaccination, are ingested by the parasites with their blood meal and neutralize these enzymes, leading to maldigestion, reduced egg laying, and eventual parasite death. Camelids generate conventional mammalian antibodies and a unique version named heavy-chain antibodies (HCAb) that have a smaller molecular size and altered structure. The modified structure of HCAbs are thought to inhibit enzyme complexes more efficiently than conventional antibodies and therefore may be more effective against $H$. contortus intestinal cell enzymes. Our alpaca study compared sera from animals vaccinated with Barbervax to non-vaccinated controls and similarly treated sheep. Immunoglobulin production was assessed using indirect ELISA and Western blot. Serum and molecular sized fractions for heavy-chain antibodies were evaluated for their ability to bind to $H$. contortus cross-sections and to Barbervax antigens. Antibodies were significantly elevated (P-value 0.0025) in vaccinated compared to control alpacas at time points throughout the study and titers were greater than in similarly vaccinated sheep, suggesting the involvement of alpaca HCAbs. These results indicate a potential role for Barbervax in controlling $H$. contortus in alpacas, thus reducing reliance on therapeutic anthelmintics.

Research Grant: Alpaca Research Foundation

Student Support: NIH T35 Training Grant T335OD012199
Evaluation of various cyclosporine treatment regimens in cockatiels inoculated with avian bornavirus

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The immune-mediated pathogenesis of avian bornavirus (ABV)-induced proventricular dilatation disease (PDD) in psittacines has directed recent research efforts toward determining whether the administration of the immunosuppressive drug cyclosporine can successfully prevent or treat the disease. Studies performed in rats infected with Borna Disease Virus imply that cyclosporine may protect from disease only when administered prior to infection. However, it is unknown whether the same principle applies to ABV. This study followed 20 cockatiels (Nymphicus hollandicus) experimentally infected with avian bornavirus to determine whether a shorter duration or later onset of cyclosporine treatment could confer protection from PDD as successfully as a full, uninterrupted regimen of cyclosporine. Four treatment groups were established, each composed of five birds. Group 1, the negative controls, received a placebo for the full duration of the study while Group 2, the positive controls, received cyclosporine. Group 3 received placebo until day 21, then began cyclosporine treatments. Group 4 received cyclosporine until day 21, and then received placebo for the remainder of the study. All treatments were initiated 24 hours prior to viral inoculation. Birds were monitored throughout the study for clinical signs of PDD such as neurological deficits and severe weight loss. Preliminary results have shown that stopping cyclosporine treatment 21 days after inoculation may lead to more rapid disease development than if no treatment was administered. However, further elucidation of the effects of cyclosporine treatment is required as we await RT-PCR and histopathology findings for the remaining birds in the study.

Research Grant: None
Student Support: College of Veterinary Medicine & Biomedical Sciences, Texas A&M University

Personality and immune system function in wild cotton rats

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Personality, defined as consistent behavioral differences between individuals, has been linked to immune responsiveness in humans. For example, more extraverted subjects exhibit increased expression of pro-inflammatory genes, suggesting a correlation between boldness and a stronger immune response. A suite of recent wildlife studies has also found support for this link, however, much is still unknown about the association between personality and the immune system, including the extent to which this is a general phenomenon across mammals. In this study, we examined the relationship between personality and immune system function in wild cotton rats (Sigmodon hispidus). The cotton rat is an ideal system for studying this association as it is an established model of human infectious disease that is easily manipulated in its natural environment. Using subjects collected from field sites in Athens, GA, we hypothesized that boldness in wild cotton rats is correlated with stronger immune function, because bolder animals might compensate for increased pathogen exposure with stronger immunological defenses. To test this hypothesis, we assessed individual personality by quantifying the frequency with which individuals are trapped, exploration in a novel environment, and duration and distance of movement in a novel environment; three measures that support boldness. We also assessed two components of innate immune function, white blood cell counts (cellular immunity) and serum bacteria killing ability (humoral immunity). By shedding light on the influence of personality on immune defenses our work will contribute to a better understanding of how behavioral traits shape variation in individual susceptibility to infectious diseases.

Research Grant: Odum School of Ecology
Student Support: NIH Office of Research Infrastructure Programs, Grant Number 2T35OD010433-11
Effects of apyrase on partial-thickness burn wound healing and extracellular dATP/ATP levels in porcine model

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It has been reported that inflammation is a key factor in severe complications associated with acute burn injuries. These complications include delayed healing, onset of sepsis, scarring, and even death. A key factor in the promotion of inflammation and bacterial growth is extracellular ATP. We hypothesize that local application of apyrase, an ATP hydrolyzing agent, will increase rate of healing and significantly decrease the presence of extracellular ATP on partial-thickness burns. Using (3) 25-30 kg juvenile, female, commercial bred Yorkshire pigs, thermal contact burn wounds were applied dorsally using 180g aluminum blocks heated to 80°C for 20 seconds. The effects of two dosages of apyrase locally applied to thermal contact burn wounds were compared with the effects of saline as a control treatment, and sulfamylon and silver sulfadiazine as standards. Samples were collected and treatments were applied throughout a 21-day period at 1, 3, 7, 14, and 21 days post burn. Biopsies of the burn wounds were taken on these days and were assessed using immunohistochemistry, nucleic acid analysis, flow cytometry, histology and wound perimeter measurements. Apyrase significantly reduced the levels of extracellular ATP/dATP, but no significant difference was seen between dosages. Wounds treated with apyrase presented significant difference in wound closure compared to the control and standard groups, as shown by repeated measures ANOVA with post hoc Tukeys test between groups. Our findings supported the hypothesis that apyrase would increase wound closure and reduce extracellular ATP levels in partial thickness burns. Apyrase may improve therapies for burn wound treatment.

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Student Support: NIH Grant No T35OD016477

Environmental transmission of Mycobacterium avium ssp. paratuberculosis: an individual based model

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Understanding how animals become infected with Mycobacterium avium subsp. paratuberculosis (MAP), the causative agent of Johne’s disease is essential in evaluating control strategies to reduce its prevalence on dairy farms. It is well documented that animals become infected with MAP from ingesting contaminated material in their environment, but there are very few models that describe the role of the environment in transmission. Our model is the first individual based model (IBM) that describes the contribution of environmental transmission of MAP in a dairy herd. We developed an individual based model of a closed dairy herd with typical dairy herd dynamics. We then converted an existing MAP transmission model to the IBM to include a new infection structure where animals could become infected from an environment contaminated with MAP in addition to becoming infected in utero and from colostrum and milk. Using this model, we explored four management strategies to simulate the effect of different hygiene strategies on MAP prevalence. Our model more accurately described transmission pathways than previous models because it considered the environment explicitly as a major source of infection and includes herd and infection dynamics at the individual level. We also showed that better hygiene leads to decreased MAP prevalence. Our model can be a useful tool for farmers to control MAP prevalence, and can be used as a framework for future research.

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Student Support: NIH: National Institute Of Allergy And Infectious Diseases Award Number T35AI007227
Population pharmacokinetics of ceftazidime in wild turtles

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Antibacterial dosage regimens are poorly established for many reptile species. Many of the dosage regimens for turtles are extrapolated from other reptile species, or mammals. During rehabilitation from injury, many wild turtles in captivity are prone to bacterial infection. Because the bacteria causing infection can often be resistant to routine antibacterial agents, antibiotics approved for human use must often be administered. Ceftazidime is one of those agents. Ceftazidime is a third-generation cephalosporin widely used in reptiles because of its excellent activity for many bacteria, including fermenting bacteria such as *Pseudomonas aeruginosa* that are ordinarily resistant to other agents. Ceftazidime has been routinely used by the Turtle Rescue Team but dosage regimens were extrapolated from a 1999 study in Loggerhead sea turtles. Because more precise data for dosing is needed, a population-based pharmacokinetic study was performed using non-linear mixed-effects modeling (NLME). This approach allows for sparse sampling, which is necessary because the small size of the animals. We collected samples using a sampling grid from 0 to 120 hours and analyzed plasma samples using HPLC. A two-compartment pharmacokinetic model and NLME was applied to the data. Using this approach, we identified a long half-life of approximately 35 hours and a volume of distribution (VD) of 0.26 L/kg (VD was similar to mammals). Our results show that a dose of 20 mg/kg will maintain concentrations above the MIC of most bacteria for 5 days. We have successfully established a clinical dosing regimen that is predicted to maintain adequate concentrations for bacteria resistant to other agents with minimal stress and discomfort to the patient.

Research Grant: None
Student Support: Merial Veterinary Scholars Program

Prediction of canine cruciate ligament rupture with classification based data mining methods

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Canine cruciate ligament rupture (CR) accounts for ~20% of lameness. Over 99% of cases have a non-traumatic cause. Stifle synovitis and degenerative changes within the cruciate ligaments cause weakening and eventual ligament rupture, particularly affecting the cranial cruciate ligament. CR is a complex trait affected by genetic and environmental variables with heritability of 0.27-0.48. We used genome-wide single nucleotide polymorphism (SNP) markers from two commonly affected breeds, the Labrador Retriever and the Rottweiler. We determined whether classification based data mining methods can predict CR risk. Gradient-boosted trees (GBT), random forest, naive bayes and K-nearest neighbor models were used to analyze SNPs, with models using 5 to 100,000 SNPs. To assess algorithm prediction, we used holdout and 10-fold cross-validation. We found that random forest and GBT outperform other models. In holdout validation, averaged area under the receiver operating characteristic curve (AUC) plateaued at 0.62 for GBT models fitted on 3500 SNPs and a maximum of 0.67 for one GBT model fitted on 4000 SNPs. In 10-fold cross-validation, average AUC was lower across models (0.55), but certain splits performed well with AUC reaching 0.81. With across breed holdout validation, AUC for predicting Rottweiler CR from a Labrador training set was reduced, except for a GBT model using 25 SNPs with an average AUC of 0.66. These results show feasibility of CR prediction in dogs and suggest that common SNPs influence risk of CR across breeds. While accuracy is insufficient for clinical application, it can be improved with greater sample size. Accurate prediction models would enable selective breeding and informed management of at-risk dogs.

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Student Support: NIH T35 Training Grant T35OD011078
Use of vaginal impedance to stage the estrous cycle in rats given luteinizing hormone releasing hormone

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Vaginal cytology is the current gold standard for staging the estrous cycle in female rats; however, it requires extra training, is subject to interpretation, and the preparation and reading of the slides is time consuming. Because of this, estrous cycle monitoring is rarely utilized for female rats given exogenous hormone to synchronize estrous cycle for timed pregnancy or the induction of pseudopregnancy. Vaginal impedance offers a quicker and less technical alternative to cytology. The vaginal impedance meter measures the fluctuations in the inherent electrical resistance of the vaginal wall’s inner lining which changes during different stages of the estrous cycle. Vaginal impedance has been used successfully in normally cycling and breeding female rats. We hypothesize that vaginal impedance measurements can be used in female rats primed with luteinizing hormone releasing hormone (LHRH) for estrous synchronization. Three groups of 12 female Sprague Dawley (SD) rats were injected with LHRH intraperitoneally. Vaginal impedance was measured and vaginal cytology was performed 3 days later. The next day, females were placed with proven SD males for breeding. The following morning, females were separated from males and checked for vaginal plugs and the presence of sperm via vaginal cytology. Females were euthanized 10 days post-mating to assess breeding outcome. The concordance between impedance measurements, vaginal cytology, evidence of successful mating and pregnancy will be evaluated. Success using vaginal impedance has the potential to reduce animal numbers by increasing breeding efficiency and reducing costs due to downstream failures related to the use of animals that are not in the correct estrous stage when mated.

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Evaluation of induction of mucosal antibody responses dependent on route of immunization

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Researchers have been working on overcoming the use of parenteral vaccines and transition to more easily administrable mucosal vaccines that can provide additional mucosal protection. Parenteral vaccines induce systemic immunity, but not adequate mucosal immunity. Parenteral vaccines also are more invasive, require trained personnel, and have a higher reactogenicity than mucosal routes. Using live recombinant attenuated Salmonella vaccines (RASVs), we can induce a mucosal and systemic immune response to one or more heterologous antigens carried in a plasmid within the strain. Streptococcus pneumoniae is a leading cause of mortality and morbidity across the world, and new antibiotic-resistant strains have proven potential to threaten our abilities to treat pneumococcal disease, and the need for a preventative vaccine grows more urgent. Plasmid pYA4088 contains the gene sequence pspA, signaling for the synthesis of Streptococcus pneumoniae surface protein A (PspA) antigen, an established antigen that confers immunity to pneumococci. During this study, we verified S. Typhimurium strains χ11281 (pYA4088) and χ9241 (pYA3493) to be stable Δasd mutants utilizing a regulated delayed in vivo antigen synthesis. Furthermore, the strains growth was confirmed to be unaffected by PspA synthesis, and the LPS profile is smooth. We examined the difference in antibody titer levels produced in 7 week old female BALB/c mice after subcutaneous and oral immunization with RASV strain χ11281 (pYA4088). Immunization trials are currently underway and antibody response analysis is pending. The purpose of this study is to examine the antibody titers for secretory-IgA and IgG and compare efficacy of the parenteral vs mucosal immunization.

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Student Support: Boehringer Ingelheim Veterinary Research Scholars Program
Effect of intracoelomic dexmedetomidine-alfaxalone on righting reflex in garter snakes (Thamnophis sirtalis)

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Reptiles often require anesthesia for clinical procedures, but little is known about their response to common anesthetic agents. While alfaxalone has been evaluated in snakes, the effects of alfaxalone combined with sedatives such as dexmedetomidine are currently unknown. A randomized, controlled study was used to evaluate the effects of intracoelomic dexmedetomidine-alfaxalone in 8 common garter snakes (Thamnophis sirtalis). Loss and return of righting reflex (LRR and RRR) were examined following the administration of alfaxalone (30 mg/kg) combined with either 0.05 or 0.1 mg/kg of dexmedetomidine (DEX0.05 and DEX0.1) administered through a single intracoelomic injection. If LRR occurred, heart and respiratory rates were monitored until RRR. Loss of righting reflex occurred in 63% (5/8) and 38% (3/8) of snakes following administration of DEX0.05 and DEX0.1, respectively. For DEX0.05, the onset of LRR was variable with a range of 1 to 20 minutes, and duration of 62-124 minutes. Following DEX0.1, the onset of LRR ranged from 3 to 15 minutes, and duration ranged from 15-174 minutes. Following LRR, heart rate ranged between 20-40 beats per minute and respiratory rate ranged between 0-11 breaths per minute for both treatments at recorded time points. The co-administration of dexmedetomidine and alfaxalone in snakes resulted in marked variability in the presence and duration of LRR; however, fewer snakes demonstrated LRR at DEX0.1 compared to DEX0.05. A second phase of the study will evaluate dexmedetomidine and alfaxalone administered at separate injection sites to determine if the variability is due to pharmacokinetic or pharmacodynamic interactions.

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Yersinia pestis-infected-Oropsylla montana block at higher, sustained rates and maintain low mortality at 10°C

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Yersinia pestis is the flea-borne etiologic agent of the plague. Plague is maintained in wild rodents and their fleas in endemic foci worldwide. Y. pestis forms an obstructive biofilm in the flea foregut which prevents imbibing of a host blood meal. Unable to ingest a blood meal starving fleas make continuous ‘frustrated’ feeding attempts which leads to regurgitation of dislodged bacteria and blood back into the flea-bite site. Xenopsylla cheopis, the oriental rat flea which has been implicated in human plague pandemics, is the prototypical flea for which transmission of Y. pestis by the foregut blockage-regurgitation mechanism has been described. X. cheopis has a worldwide distribution in humid, warm environments and the blockage frequency of infected fleas tends to be highest at around 21°C. In comparison, the North American plague vector Oropsylla montana parasitizes ground squirrels, occurs in dry, colder to more temperate climates, blocks at a slightly lower frequency than X. cheopis at 21°C, yet transmits at higher rates at 10°C. Here to determine if climate influences the blockage rate and therefore transmission of Y. pestis we determined blockage and infection dynamics in O. montana and X. cheopis infected fleas at 10°C and 21°C. Our data demonstrates that O. montana fleas efficiently develop blockage at later time points post-infection, maintain longer periods of blockage development at 10°C and lower infection mortality as compared to X. cheopis. This study emphasizes that different climatic and ecological settings must be accounted for in the transmission dynamics of plague vectors at geographically distinct plague foci as these are significant factors when predicting plague outbreaks.

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Cold atmospheric plasma disrupts methicillin-resistant *Staphylococcus aureus* biofilms

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Methicillin-resistant *Staphylococcus aureus* (MRSA) infections pose a clinical challenge due to their antibiotic resistance and biofilm-forming capacity. Consequently, novel approaches for treatment of MRSA infections are needed. Cold atmospheric plasma (CAP) shows promise as an alternative to traditional antibiotics in the treatment of chronic wound infections. CAP is an ionized gas, such as argon, that generates reactive oxygen and nitrogen species with bactericidal effects. Our study examined two CAP treatment methods: (1) direct CAP application on saline-covered MRSA biofilms and (2) indirect treatment via transfer of CAP-treated saline onto MRSA biofilms. Bactericidal effects of direct and indirect CAP treatment were then compared to those of conventional wound therapies: antibiotics (ciprofloxacin and tetracycline), hydrogen peroxide \((\text{H}_2\text{O}_2)\), and sodium hypochlorite (NaOCl). All treatments were carried out on biofilms of USA300, a community-acquired MRSA strain, grown in 6-well plates. Following treatment, wells were washed and colony forming units (CFU) were quantified. Both indirect and direct CAP treatment of MRSA biofilms resulted in reduced CFUs compared to untreated biofilms or biofilms treated with clinically-relevant concentrations of antibiotics, 1.5% and 3% \(\text{H}_2\text{O}_2\), and 0.1% and 0.00625% NaOCl. Only a solution of 1% NaOCl, a concentration well above levels safe for human use, showed comparable levels of bacterial killing. These results indicate that indirect and direct CAP treatments effectively kill MRSA and disrupt biofilm integrity. Future research will use MRSA-infected wound models to explore CAP’s potential as an alternative to antibiotics *in vivo*.

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Inhibition of Scap/SREBP pathway as a potential therapy of fatty liver disease

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Nonalcoholic fatty liver disease is a complex metabolic syndrome that affects about 30% of the U.S. population. Fatty liver disease is closely associated with obesity and diabetes, conditions accompanied by elevated levels of hepatic fatty acid synthesis. The transcription for all of the fatty acid biosynthetic enzymes is under the control of Sterol Regulatory Element Binding Proteins (SREBPs). SREBPs are produced as inactive ER membrane-bound precursors that need to be transported to the Golgi where they are activated by two sequential proteolytic cleavages. We have previous shown that liver-specific ablation of Scap, an escort protein required for the proteolytic activation of all SREBPs, led to a complete blockade of SREBP processing, reducing lipid synthesis and preventing fatty liver development. Here, we explore whether inhibition of the Scap/SREBP pathway can reverse the fully developed fatty livers in the diet-induced mouse models of fatty liver. For this purpose, mice harboring the conditionally flox alleles of Scap were fed with high-fat, high-sucrose diet for 20 weeks to induce the whole spectrum of obesity, insulin resistance, and fatty liver. Thereafter, the mice were injected with a liver-specific Adeno-associated virus (AAV) that expresses the Cre recombinase (AAV-Cre). Six weeks post the AAV-Cre injection, the hepatic level of Scap and SREBPs are all reduced dramatically, leading to decreases of SREBP targeting mRNAs encoding fatty acid biosynthetic enzymes. The elevated levels of plasma and liver lipids in were also ameliorated by the AAV-Cre-mediated ablation of Scap. These data suggests that inhibition of the Scap/SREBP activity has the therapeutic potential to treat fatty liver diseases.

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Effects of intrauterine growth restriction on peripheral inflammatory mediators in a neonatal piglet model

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Infants born small for gestational age (SGA) due to intrauterine growth restriction (IUGR) are more likely to exhibit abnormalities in brain development and greater susceptibility to infection than their average for gestational age (AGA) counterparts. The purpose of this study was to determine if there was a difference in the level of expression of various inflammation mediating proteins between SGA and AGA infants using a piglet model. We hypothesized that the peripheral tissues of SGA piglets would contain lower inflammation-associated gene expression levels, and lower circulating plasma IL-6 levels, than their AGA counterparts. SGA and AGA piglets were weaned at postnatal day (PD) 2, and at PD 14 injected intraperitoneally with \textit{E. coli} lipopolysaccharide (LPS) or sterile saline. Blood was drawn pre- and 4 hours post injection, and ELISAs were performed to quantify plasma IL-6 levels. Four hours after injection, piglets were sacrificed and thymus, liver, and spleen was collected. RNA was isolated for cDNA synthesis and qPCR was performed for gene expression. We found no association between SGA status and plasma IL-6 levels. The thymus samples of SGA piglets showed decreased expression of the genes TMPO and RUNX1. Spleen and liver samples had a main effect of LPS injection with varying expression of several inflammation mediating genes. Only SGA piglet liver had increased levels of pro-inflammatory CCL2 gene after LPS injection. Possible implications of this work include further research targeting the thymus of SGA infants to better determine how hematopoietic proteins like TMPO and RUNX1 contribute to immunodeficiency, in order that effective therapeutics or preventatives can be developed in the future.

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The cutaneous and rectal microbiome of perianal fistulas and the effect of cyclosporine therapy

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Canine perianal fistulas (PAF) are painful sinus tracts that develop suddenly, and disproportionately afflict the German Shepherd dog (GSD). PAF are thought to be an immune-mediated disease, but there is a lack of data linking microbial populations to disease occurrence or severity. The purpose of this study is to examine the relationship between immunosuppressive therapy and PAF disease response or remission, and to simultaneously characterize the cutaneous and rectal microbiome of both affected and healthy GSD over time. This study also aims to identify potential community shifts associated with disease remission that may serve as therapeutic targets. 8 GSD with PAF (median 6 years old) were swabbed at 3 visits, 1 month apart, while undergoing treatment with ketoconazole and cyclosporine. Dogs were swabbed at the axillary region, fistula site, and rectum, and measurements and photographs were used to score improvement and severity of disease over time. 15 control dogs (median 5 years old) free of enteric and dermatologic disease were enrolled and received axillary, perianal, and rectal swabs over 2 study visits (1 month apart). These dogs abstained from any antimicrobial or immunosuppressive therapies during the study. DNA was extracted from all swabs using Invitrogen kits, and populations were sequenced and quantified using NextSeq Analysis and QIIME software. Results of this study could allow researchers to characterize the cutaneous and rectal microbiome of GSD with PAF for the first time, compare it to that of GSD without PAF, and perhaps relate population changes during cyclosporine and ketoconazole therapy to outcomes of disease.

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Circadian disruption impacts impulsivity and attention: examining neurochemical mechanisms in Long-Evans rats

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Circadian rhythms are 24-hour cycles that control physiological processes, and their disruption can have negative effects on health. Two forms of circadian disruption in people are working overnight shifts and exposure to artificial light at night. The purpose of this study is to examine the effects of circadian disruption on attention and impulsivity in adult Long-Evans rats using the five-choice serial reaction time task (5-CSRTT). The three circadian conditions were testing in dark phase (control), testing in dark phase with pulse of light (modeling artificial light-at-night), and testing in light phase (modeling shift work). Our results showed that both models of circadian disruption caused decreased attention and greater impulsivity than the control, with the light-at-night group exhibiting greatest impulsivity. This indicates that artificial light-at-night may be more harmful to cognitive functions than overnight shift work. Considering the neurochemical basis for the effects, dopamine modulates impulsive behavior while acetylcholine (ACh) modulates both attention and circadian rhythms. Therefore, we hypothesized that impulsivity resulting from circadian disruption results from an interaction between ACh and dopamine. To explore this, we tested the effects of a nicotinic acetylcholine receptor agonist (nicotine) and a dopamine-1 (D1) receptor antagonist (SCH 23390) on attention and impulsivity. Nicotine increased impulsivity while SCH decreased impulsivity. When administered together, SCH attenuated the effect of nicotine on impulsivity. These results suggest that D1 receptors are involved in impulsivity and that cholinergic signaling interacts with the dopamine system to influence impulsive behavior.

Research Grant: University of Illinois College of Veterinary Medicine
Student Support: Office of the Director, NIH, T35 OD011145

Evaluating the effect of Helicobacter pylori VacA toxin on parietal cell function

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Helicobacter pylori (Hp) is a human-specific gastric pathogen, infecting 50% of the world’s population and increasing the risk of gastric cancer. Hp infection results in peripheral immune cell infiltration, inflammation, and parietal cell proliferation. The vacuolating cytotoxin (VacA), named for its ability to induce vacuole production in human cells, has an unclear role in these processes. Parietal cells are dynamic, gastric-acid-secreting cells that exist in a resting or active state. The resting state sequesters apical membrane proton pumps into the cytosol as tubulovesicles. We hypothesize that VacA targets tubulovesicles to create a microenvironment for Hp colonization by maintaining inactive parietal cells. Parietal cells were isolated and cultured from mouse gastric mucosa, then challenged with VacA in a resting or histamine-stimulated active state. The apical and basolateral pH and ion concentrations were measured by metabolomics, and cell morphology and vacuolation visualized by TEM and light microscopy. We predict that VacA-challenged apical media will have an increased pH and concentration of anions, and minimal morphologic changes with co-histamine stimulation compared to controls. The parietal cell tubulovesicles are anticipated to be the observed VacA-mediated vacuoles. Because Hp infection induces a prolonged ineffective parietal cell state coupled with proliferation, we propose that VacA targets parietal cells to gather nutrients and create a microenvironment for Hp colonization. Understanding the role of VacA in Hp infection addresses a fundamental knowledge gap in the study of Hp infection, and provides new insight into host-microbe interactions and the importance of secreted microbial effectors.

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Student Support: Office of the Director, NIH, T35 OD011145
Leishmania-specific skin resident CD4 T cells are formed from recently activated effector T cells

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Tissue-resident memory T cells (Trm) are critical components of protective immunity against a variety of pathogens. The majority of studies have focused on Trm cells at the site of infection or immunization, where inflammation promotes T cell recruitment. In contrast, few studies have focused on how Trm cells gain access to non-inflamed sites, an important issue for designing vaccines to target these cells. In mice that have resolved a primary infection with Leishmania, skin-resident CD4 Trm cells have been shown to provide protection against challenge at sites distant from the initial infection site. We found that while Leishmania-specific CD4 T cells enter the site of infection within a few hours, T cells were not found in skin distant from the primary infection until 2 weeks post infection. However, using parabiosis of naive mice and immune mice which have resolved infection, we found that Leishmania-specific CD4 T cells present in the immune mouse could not enter the non-inflamed skin of the naive mouse. In contrast, upon re-challenge of the parabionts, these CD4 T cells regained the ability to enter the non-inflamed skin of the naive parabiont. To understand what allows entry of CD4 T cells into non-inflamed skin sites, we examined their proliferation and found that the cells entering non-inflamed skin sites have recently proliferated, suggesting that only activated effector T cells gain entry to non-inflamed skin. Combined, these data demonstrate that recently activated effector CD4 T cells, but not memory CD4 T cells, are capable of entering non-inflamed skin sites. Future studies will examine other factors are involved in this recruitment, and determine what promotes the retention of Trm cells in the skin.

Research Grant: NIH R01 AI125265
Student Support: HHMI Burroughs Wellcome Fund Medical Fellowship

Microclimate and larval density impact mosquito population dynamics and arbovirus transmission potential

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Mosquitoes are small, ectothermic organisms, so their development and population dynamics are highly dependent on abiotic factors such as temperature and relative humidity. Variation in land use across an urban landscape causes fine-scale variation in the microclimate that mosquito larvae experience. Additionally, biotic factors such as population density drive ecological change primarily on a fine-scale level. This experiment aimed to determine how both these abiotic and biotic factors affect mosquito traits in the larval and adult stages important to pathogen transmission potential. Nine field sites were selected and classified as urban (3), suburban (3), or rural (3), based on impervious surface cover. Three clusters of 4 bell jars were evenly interspersed across each site and filled with leaf infusion mixture. In each cluster, one jar contained a data logger to record the temperature of the larval environment, while the remaining three jars were seeded with either a low (n=30), medium (n=60), or high density (n=120) of first instar Aedes albopictus larvae. Sites were visited daily to collect emerging adults. Number of adults emerging, larval development rates, and mosquito body size were used to infer how land use and density impact mosquito population dynamics and arbovirus transmission potential. Preliminary data indicate that higher larval density was associated with lower larval survival and body size at all sites. Urban sites produced the fastest larval development, but the lowest overall larval survival and body size. This demonstrates that even small-scale biotic or abiotic alterations in the larval environment can have significant implications for adult mosquito populations and the pathogens they transmit.

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Student Support: NIH Office of Research Infrastructure Programs, Grant Number 2T35OD010433-11
Animal sentinels for human injury and environmental conditions a new look at hardware disease in Grenada

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Animal sentinels have been used to protect humans from environmental conditions for many years, in this study we will look at how using animal sentinels will be beneficial to small island states. Grenada in 2013 shows a relationship between animal injuries and human injuries due to metal sheets, metal wiring, and construction nails. The aim of this research is to raise awareness of the preventability of injuries caused by terrestrial waste products. This study will assist determining the economic burden of these injuries; such as, healthcare costs to government, loss of production in animal and human species, loss of animal, healthcare costs for animal, tourism impact, and more. The notion that hardware disease only affects livestock is inaccurate. This study aims to explain how humans and animals, alike, are broadly affected by hardware disease, as a result of terrestrial waste and illegal dumping. This is not new to livestock, but this is a challenge to the way we think about hardware disease. The use of animal sentinels for injuries due to terrestrial waste, is a cost-effective method of surveillance for small island states, like Grenada. According to Thompson in 2009, there is a greater need for data on debris in natural terrestrial and freshwater habitats. As in Jamaica, as observed by S.F. Brownie’s study, animals make an ideal sentinel for studying environmental injury as they share living space. This would give them access to the same areas of humans, making animals a good sentinel in this culture. The use of animal sentinels is beneficial to small island states for environmental conditions this in turn would allow for trends to be determined in future studies.

Research Grant: None
Student Support: Island and Merial Veterinary Scholars Programs
School of Graduate Studies –SGU

The effectiveness of the transcuneal extracorporeal shockwave therapy on equine navicular syndrome

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Equine veterinarians speculate that approximately 90% of lameness in horses stems from the foot and that navicular syndrome is one the most common causes of forelimb lameness in horses. Equine Navicular Syndrome (ENS) is a chronic debilitating disorder involving the navicular bone and its surrounding soft tissue structures. The lameness resulting from ENS can be career-ending and is a significant source of loss of use and income in the equine industry. Extracorporeal shockwave therapy (ESWT) is an emerging treatment modality for ENS. The resultant energy transmitted to underlying tissues results in microdisruption of cells and cell death, creating a controlled inflammatory process that promotes neovascularization and healing. Currently, there is no evidence that shock waves can reach the navicular bone, nor is there an established protocol for applying shockwave to the navicular bone. In this study, we evaluated the magnitude of shock waves that reach the navicular bone, and compare the magnitude that reach the navicular bone when the foot was soaked and unsoaked. Piezoelectric sensors were placed over the flexor surface of the navicular bone in order to measure the energy that reaches the bone when shockwave therapy is performed. Then, we measured strain over navicular bone in bisected equine cadaver feet when shock waves were applied to soaked and unsoaked feet. Based on the preliminary data, the shockwave treatment is effective at reaching the navicular bone and soaking the foot allowed a greater amount of shockwave transmission to the navicular bone. Future studies are warranted, but the preliminary results of this study may directly influence clinical protocols for navicular shockwave therapy in veterinary hospitals.

Research Grant: National Institutes of Health 2T35OD010432-16 and Mississippi State University College of Veterinary Medicine
Student Support: Mississippi State University College of Veterinary Medicine Summer Research Experience
Assessment of fertility in male cats through cytologic evaluation of testicular aspirates

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The assessment of testicular fertility in male felines is an issue of importance for the breeding animals ranging from domestic breeding felines to exotic endangered species. Minimal literature exists regarding how testicular cytology reflects the state of spermatogenesis in the tomat. In this study, we hypothesized that cytologic evaluation of testicular aspirates is an accurate assessment of spermatogenesis in the tomat. The testes of at least 50 intact male cats were collected following orchiectomy and classified into groups. The pre-pubescent group comprised of 10 testes and post-pubescent group consisted of 80 testes from tomcats ranging from 1 to 4.5 years of age. Aspirates and impressions of each testicle were made post-orchiectomy and stained by standard methods. Two hundred cells were counted per slide and identified appropriately. The quantified cell populations were used to establish a Sertoli cell index and sperm cell index for each testicle. In addition, each testicle was evaluated histologically to ensure normal spermatogenesis was taking place. The testicular cytology counts were subsequently grouped according to age ranges and analyzed statistically. Our results showed that the pre-pubertal testes contained only Sertoli cells, as expected. The youngest group of post-pubertal testes exhibited the greatest variation in the Sertoli cell index and sperm cell index. The groups consisting of testes from older felines displayed a more consistent range of indices. Our results show that evaluation of testicular aspirates can be a valuable supplemental test regarding fertility assessment in felines greater than one year of age.

Research Grant: None
Student Support: NIH T35 Short-term Training Grant

Prevalence of selected bloodborne pathogens in client owned cats from the Netherlands

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Multiple pathogens of cats are directly associated with clinical abnormalities or have primary importance as zoonotic agents impacting human health. However, limited or no prevalence data is available for many of these pathogens in cats from the Netherlands. The aims of this study were therefore to estimate the prevalence of selected bloodborne and zoonotic pathogens in cats from the Netherlands and to assess for associated risk factors and co-infections. Anti-coagulated blood, sera, and or plasma were obtained from 167 client-owned cats in the Netherlands and transported to Colorado for assay. Previously validated plate based ELISA assays were used to detect antibodies against Anaplasma species, Bartonella species, Borrelia burgdorferi and Toxoplasma gondii in plasma or serum. A commercially available kit was used to detect antibodies against feline immunodeficiency virus (FIV) and antigens of feline leukemia virus (FeLV) and Dirofilaria immitis (SNAP feline Triple; IDEXX) in sera or plasma. Total DNA and RNA will be extracted from the blood and previously validated molecular assays that amplify the nucleic acids of Anaplasma species, Bartonella species, Ehrlichia species, gammaherpesvirus, feline foamy virus and the hemoplasmas will be performed. Genetic sequencing will be performed to determine the species of some agents ant to validate the final results. The estimated seroprevalence rates for Bartonella spp. IgG (21 of 167 cats; 12.6%), T.gondii IgG (27 of 167 cats; 16.2%), FIV antibodies (6 of 123 cats; 4.9%) and FeLV (5 of 123 cats; 4.1%) have been calculated. Dirofilaria immitis antigen was not detected in any of the 123 samples tested.

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Student Support: Boehringer Ingelheim International Summer Scholar
Evaluation of cell function and viability of Molday ION labeled equine cord blood mesenchymal stromal cells

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Exercise-Induced Pulmonary Hemorrhage (EIPH) is a disease described in horses characterised by hemorrhaging from the lungs during or shortly after exercise. The etiology of EIPH is poorly understood and therefore therapy is not well developed nor is success prevalent with current treatments. Mesenchymal stromal cells (MSCs) show potential in their use as immune-modulatory and regenerative therapies for various conditions across animal models. Molday ION Rhodamine B (MIRB) is an ultrasmall superparamagnetic iron oxide contrast agent which is efficient in labelling MSCs and is suitable for use in vivo. The purpose of this study was to evaluate the effect of MIRB labelling on MSC viability and function in an in vitro model in order to evaluate the potential uses for in vivo models. Equine umbilical cord blood derived MSCs were expanded in cell culture and labelled with MIRB. MIRB labelling efficiency, cell proliferation doubling time, cell viability, and cell migration were assessed through imaging, cell counts, Trypan blue staining, and scratch assays respectively. A population of each MSC sample was also cryopreserved, thawed, then assessed for the same characteristics. Preliminary results suggest that MIRB stained MSCs may not differ significantly in these characteristics compared to negative controls. This indicates that MIRB labelling may not be significantly detrimental to cell function nor cryostability. Therefore, MIRB labelled MSCs may be acceptable for use in future studies. This study is preliminary to a study which will track intravenous (IV) injected MIRB labelled MSCs in an equine model to assess the potential for IV MSC therapy in pulmonary diseases such as EIPH.

Research Grant: Natural Sciences and Engineering Research Council of Canada, Equine Guelph
Student Support: OVC Summer Research Studentship

Validation of PRMT5 as a candidate therapeutic target in the canine model of non-Hodgkin lymphoma

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Lymphoma is a common cancer in dogs. Although it is generally responsive to chemotherapy, remission times are short and cures are rare. Protein arginine methyltransferase 5 (PRMT5), a type II protein arginine methyltransferase enzyme, has been shown to be involved in the regulation of multiple regulatory and tumor suppressor genes and major signaling pathways affecting cell death and malignant transformation. In this study, we characterized patterns of PRMT5 expression and correlated these with histologic subtypes using canine lymphoma tissue microarrays (TMAs). We characterized expression of PRMT5 in canine lymphoma tissues and its methylation targets in canine B-cell lymphoma cell lines and treated them with different PRMT5 inhibitors to determine their effects on PRMT5, target proteins, and antitumor activity. Canine lymphomas showed cytoplasmic staining for PRMT5 (42.2% strong, 57.8% weak, n = 360) compared to negative or weak staining in normal and hyperplastic lymph nodes (n = 20). Lymphoblastic T cell lymphoma samples showed strong nuclear staining (50%, n = 8). Similarly, canine B-cell lines showed high expression of PRMT5. The PRMT5 small molecule inhibitor HLCL65 inhibited growth of CLBL-1 and 17-71 cell lines with IC50s of 3.79 μM and 7.2 μM, respectively. Target PRMT5 expression was suppressed at the IC50s for each cell line. We have demonstrated that PRMT5 is expressed in canine lymphoma and that PRMT5 inhibition can suppress the growth of canine lymphoma cell lines. This supports the continued use of the spontaneous canine lymphoma model for the preclinical development of PRMT5 inhibitors. Currently, new second generation PRMT5 inhibitors are being investigated.

Research Grant: The Ohio State University College of Veterinary Medicine Canine Grants, Morris Animal Foundation
Student Support: The Ohio State University College of Veterinary Medicine Canine Grants
Functional analysis of the *Escherichia coli* and *Vibrio cholerae* multidrug resistance transporter MdtK

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According to the CDC, < 23,000 people die annually from antibiotic resistant bacterial infections, necessitating a better understanding of how bacteria evolve to evade antibiotics. Our laboratory has recently determined how *E. coli* can withstand the aminoglycoside Kasugamycin (Ksg); a single phenylalanine to valine mutation in the multidrug resistance transporter, MdtK, extending the phenotype to include Ksg. This mechanism is novel in that it does not rely on increased MdtK synthesis, but rather a gain of function mutation that is predicted to increase the pump’s affinity for Ksg, thus empowering greater drug export. With only the wild type and a single mutant available for analysis, we sought to gain a more comprehensive understanding of the contributions of the 18 other possible amino acids at this position and their effect on *E. coli* Ksg resistance. We hypothesize that depending on the substitution, these MdtK variants may represent anything from a non-viable product to a pump with even higher Ksg export activity or altered specificity profile. To gain a more detailed analysis of structure/function relationships, analogous mutants of *Vibrio cholerae* MdtK will also be characterized, as a crystal structure is available for this protein. In addition, bioinformatic analysis has been initiated to determine conservation and distribution of MdtK within the *Enterobacteriaceae*, as well as other more distantly related Gram-negative taxa. The information garnered through these bioinformatic and genetic analyses will increase our understanding of the evolution of antibiotic resistance in clinically important pathogens.

**Research Grant:** None  
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Evaluation of an ELISA and establishment of a reference interval for androstenedione in *Gopherus berlandieri*

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Plasma concentrations of reproductive hormones are useful to assess reproductive status, behaviors, and diseases of the reproductive system; they can also be used to assess breeding eligibility or readiness as well as seasonal influences or natural cycles of reproduction. Reference interval creation for androstenedione would allow comparison of an individual’s values to others of the species in an effort to evaluate excess or deficiency, and provide a basis for resolution of any discrepancy. This study aimed to validate an enzyme-linked immunosorbent assay (ELISA) and create a reference interval for androstenedione from captive Texas Tortoises (*Gopherus berlandieri*). The 25 animals sampled in this study are part of the teaching and research herd maintained at Texas A&M University’s Winnie Carter Wildlife & Exotic Animal Center, and includes individuals of known mycoplasma and fusarium exposure status. Twenty five adult male tortoises were sampled via venipuncture of the right jugular vein. Blood was transferred into a “clot” tube, and centrifuged for serum separation within 6 hours. Samples were stored in cryotubes at -80°F until androstenedione ELISA was performed as detailed in the manufacturer’s protocol. Androstenedione concentrations, in ng/ml, were [range, mean±SD, ng/ml] 0.52 - 19.61, 5.40 ± 5.16. It is the authors’ desire that this information will benefit the care and management of captive tortoises and that extrapolation be made to other species until their own intervals are established.

**Research Grant:** Internal funding.  
**Student Support:** Boehringer Ingelheim Veterinary Scholars Program & College of Veterinary Medicine, Texas A&M U.
Development of an ELISA to detect BHV-1 specific IgA in bovine nasal secretions

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Bovine Respiratory Disease (BRD), also known as shipping fever, causes substantial economic losses in stocker and feedlot operations. BRD is a multifactorial disease complex caused by a combination of environmental stress, primary viral infection, and secondary bacterial infection of the lower respiratory tract. Bovine herpesvirus-1 (BHV-1) causes immunosuppression and damage to the upper respiratory tract epithelium, allowing commensal nasopharyngeal bacteria to move into the lower respiratory tract, causing severe bronchopneumonia. Intranasal BHV-1 vaccines are commonly administered to prevent BRD, but it is not clear how stressors such as transport, which sometimes occur before vaccination, affect the mucosal immune response to intranasal vaccines. We developed an enzyme-linked immunosorbent assay (ELISA) to measure IgA specific to BHV-1 in nasal secretions to allow evaluation of the mucosal immune response in future research to determine the impact of management-related stressors on mucosal immunity following vaccination. Development of this indirect ELISA required optimization of concentration of viral antigen, concentration of nasal secretion samples, concentration of secondary anti-IgA antibody, incubation time and temperature, and blocking and wash buffers used. The ELISA successfully identified an increase in specific absorbance signal in nasal secretions collected from calves after intranasal BHV-1 vaccination, as compared to calves sampled before vaccination. However, nasal secretions caused relatively high nonspecific (background) staining; thus work is ongoing to determine the best blocking strategy to decrease nonspecific staining.

Research Grant: None
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Investigating canine IncRNA HOTAIR expression in canine diffuse large B cell lymphoma

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Diffuse large B-cell Lymphoma (DLBCL) is a common, aggressive cancer with an average survival time of one year. Diagnosis is usually made late in the disease which contributes to a poor long-term survival. Furthermore, there are few options for treatment after patients come out of remission following chemotherapy. Therefore, there is a critical need to identify new novel targets for anti-DLBCL therapy and develop prognostic biomarkers. In human oncology, long non-coding RNAs (lncRNAs) are a new class of genes being explored as novel therapeutic cancer targets and prognostic biomarkers. These are transcribed, non-protein-coding RNAs that can function as oncogenes which are essential for tumor development, proliferation, invasion and metastasis. The human IncRNA HOX transcript antisense intergenic RNA (HOTAIR) is an oncogenic lncRNA that is highly expressed in human DLBCLs compared to normal lymph nodes. High HOTAIR expression is associated with a poor prognosis. In this pilot study, we aim to determine if canine IncRNA HOTAIR is overexpressed in DLBCL compared to normal lymph nodes. We found using RT-qPCR that expression of HOTAIR was significantly upregulated in DLBCL compared with normal tissues. Preliminary results using RNA in situ hybridization and a semi-quantitative scoring method suggest a similar trend for overexpression of HOTAIR in DLBCL compared with normal tissues. Since we have only completed one third of our samples, we anticipate this will be significant after completion of our full sample size. Our next steps will be to determine if overexpression of HOTAIR correlates with clinicopathological features of DLBCL and prognosis.

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Student Support: NIH-T-35 Interdisciplinary Biomedical Research Training Program
Repeated proopiomelanocortin neuron stimulation leads to decreased food intake and weight loss in rodents

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Disorders of energy balance such as obesity are chronic illnesses with profoundly negative impacts on human and animal health, yet currently approved drugs are either not approved for long-term use, or if approved, produce multiple unwanted side effects. Thus, a need exists to develop improved pharmacotherapies for the treatment of obesity. Proopiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus are essential for energy balance regulation, as POMC deficits in both humans and animals have been shown to cause hyperphagia and excessive weight gain. In the current study, we tested the hypothesis that repeated POMC stimulation will lead to decreased food intake and weight loss in rodents. Designer Receptors Exclusively Activated by Designer Drugs (DREADD) technology was used to selectively and repeatedly stimulate POMC neurons in the arcuate nucleus of mice over 3 days. DREADDs are modified human muscarinic G-protein coupled receptors that no longer bind to acetylcholine and are instead activated by clozapine-n-oxide (CNO), an otherwise inert ligand. In the current experiments, stimulatory Gq-DREADD-flox mice were bred to POMC-cre mice, leading to DREADD expression only in POMC neurons. Data gathered thus far indicate that repeated activation of POMC neurons via CNO administration leads to decreases in food intake and subsequent decreases in bodyweight. The weight loss was maintained for 7 days following cessation of CNO administration despite ad libitum food access. The data indicate that repeated manipulation of POMC neurons could inform future anti-obesity therapeutics.

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Student Support: R01DK078749 to STH

Factors associated with snake fungal disease prevalence in a southeast Ohio free-ranging snake population

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Snake fungal disease is an emerging mycotic dermatitis caused by Ophidiomyces ophiodiicola, and has been demonstrated to negatively impact snake populations of conservation concern in the United States. Individuals present with lesions such as ulceration, nodules, hyperkeratosis, and erythema. The purpose of this study was to evaluate the prevalence of and factors associated with snake fungal disease in free-ranging snakes on the 9,000+ acre property of the Wilds, a safari park and conservation facility located in southeast Ohio. We swabbed and performed skin biopsies on wild-caught snakes to test for snake fungal disease via qPCR, culture and histopathology. Snout-vent length, gender, body weight, and presence of gross lesions were recorded. Six individuals were also surgically implanted with radio transmitters to track habitat use and over-wintering hibernaculum sites, which are theorized to be a venue for snake fungal disease transmission. Several individuals across 3 species tested positive via swab and/or tissue qPCR for snake fungal disease. These individuals were distributed across multiple sites on property. Females and males were affected in similar proportions, there was no clear association between snout-vent length or weight and test result, a higher proportion of individuals with gross lesions tested positive than those without gross lesions, and the majority of individuals that tested positive were caught in April or May. Histopathologic results are pending, but these preliminary findings suggest that this pathogen may affect individuals indiscriminately regardless of species, sex, or size of the individual, and highlight the relevance of this disease for snake conservation efforts.

Research Grant: The Wilds Department of Conservation Medicine.
Student Support: Cliff M. Monahan Student Research Fellow.
Epidemiology of feline foamy virus in Colorado mountain lions

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Feline foamy virus (FFV; genus: *Spumavirus*) is a retrovirus commonly found in domestic cats worldwide. Although FFV has been well-documented historically, its epidemiology is not well-understood, especially in wild feline species. Our study surveyed FFV in mountain lions (*Puma concolor*) in Colorado from the Uncompahgre Plateau on the western slope and the Front Range near the city of Boulder. Blood samples were collected between 2001 and 2012. Animal sex, location, and an age estimate were recorded at the time of capture. Samples were screened for FFV via quantitative PCR to determine exposure as well as proviral load, and positive samples were sequenced to determine phylogeny. The effect of sex and age on FFV exposure and viral load were evaluated using Bayesian mixed effect regression models with location as the random effect. Overall, 62.2% of mountain lions surveyed (n=166) were positive for FFV; furthermore, 59.2% (n=68) of male lions and 64.2% (n=84) of female lions tested were positive for FFV. Average viral load was 4.0 log10 copies/million cells (range= 1.7-5.8). Our models showed that sex and age had little to no effect on FFV exposure. FFV viral loads did not vary by age in males; however, load was lower in young females, relative to adult females. Two different FFV strains were identified by sequence analysis, but viral load was similar for both strains. Our study documented a high incidence of FFV in mountain lions in Colorado and our analyses support previous work in domestic cats that FFV prevalence does not vary by sex. Observations of increasing viral load in females may have implications for transmission dynamics.

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Characterization of genes involved in infection by *Brucella abortus* by the oral route

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*Brucella* spp. are zoonotic pathogens, most commonly causing abortions in animals and undulating fever in humans. Persistent disease results from infection with these facultative intracellular bacteria, and the bacteria remain insidious due to their inhabiting the host’s macrophages, easily evading the immune system by hiding within it. Brucellosis can be combatted by extended treatment with antimicrobials and animal disease eradication programs, but this does not always prove curative and no human vaccine exists. Infection with *Brucella* occurs most frequently via oral ingestion of unpasteurized dairy products. Therefore, characterization of genes involved in infection by *Brucella abortus* by the oral route merits further scrutiny. The purpose of this study was to investigate *B. abortus* genetic survival mechanisms in the harsh environment of deoxycholate bile acid. Previous transcriptomic data demonstrated increased expression of genes *bab1_2138, bab1_1534, bab1_0418* and *bab1_0420* in deoxycholate. Measuring the increased expression levels of these genes using quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) outlined *B. abortus* protective protein mechanisms to deoxycholate stress. In addition, creating over-expression and double-deletion plasmid constructs of specific genes *bab1_0418* and *bab1_0420* allowed investigation of phenotypic changes in *B. abortus* exposed to deoxycholate, which may prove to be additional survival methods of these bacteria. Characterization of these protective gene expressions and phenotypic changes may allow development of prophylactic measures against oral route of infection by negating the survival methodology of *Brucella* spp. in the digestive tract.

Research Grant: Virginia-Maryland College of Veterinary Medicine
Student Support: 2017 Merial Veterinary Scholars Program (PO 1075449)
Evaluation of the effect of two dosing frequencies on the development of famotidine tolerance in cats

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Famotidine is a competitive histamine-2 receptor antagonist (H2RA) commonly used to reduce gastric acid and alleviate gastrointestinal (GI) signs in cats. Famotidine can be given with food, is immediately effective, and is associated with less adverse effects than proton pump inhibitors. However, chronic, daily famotidine use results in decreased efficacy over time in dogs and humans. We have concerns that prolonged famotidine administration results in tolerance in cats. Studies in humans suggest that every other day administration of H2RAs prevents tolerance. As famotidine is widely used by feline practitioners, our objectives were to determine if (1) daily famotidine administration induces tolerance, and, if (2) every other day administration prevents the induction of tolerance in cats. In a randomized, crossover study, eight healthy colony cats received 0.5-0.9 mg/kg PO famotidine q12h daily or every other day for 14 days. Continuous gastric pH, obtained via radiographic placement of a non-invasive, pH capsule placed in the gastric fundus on days 0 and 11, were compared on days 1 and 13 within and between treatments using two factor repeated measures mixed effects ANOVA. Healing of proximal GI tissue injury is based on sustaining gastric pH $\geq 3$, thus this parameter was used as a benchmark for our study. The mean percentage time gastric pH was $\geq 3$ was 42% and 43% on day 1 and 17% and 40% on day 13 for daily and every other day famotidine, respectively. These preliminary results suggest that continuous famotidine does induce tolerance in cats and that intermittent dosing may prevent the development of tolerance. These findings will be immediately and broadly applicable to veterinarians caring for our feline companions.

Research Grant: Winn Feline Foundation (Tolbert Oduyano W17-017)

Student Support: The Boehringer Ingelheim Veterinary Scholars Program

Antimicrobial resistance trends in northern California dairy cattle Salmonella isolates, 2002-2016

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Nontyphoidal Salmonella infections contribute to 1.2 million annual illnesses in the United States. Historical and recent outbreaks have been associated with dairy products, ground beef, and contact with cattle. Salmonella antimicrobial resistance (AMR) is a serious concern that can reduce successful treatment of infections, increasing recovery time, medical costs, and mortality rates in humans and animals. This highlights the need to track AMR in Salmonella isolated from cattle to improve treatment plans, manage current AMR, and prevent future AMR development. A total of 242 Salmonella isolates were retrieved from fecal samples from cattle submitted to the University of California, Davis Veterinary Medical Teaching Hospital from 2002 to 2016 and were tested for antimicrobial susceptibility using a standardized broth dilution panel. Multidrug resistance (MDR) was observed in 50.8% of isolates, and the most common MDR pattern was amoxicillin-ampicillin-cefotixin-ceftiofur-ceftiraxone-chloramphenicol-sulfisoxazole-tetracycline (23.2%). There were significantly higher odds for resistance to aminoglycosides (OR: 2.03), beta-lactam/beta-lactamase inhibitor combinations (OR: 1.79), folate pathway inhibitors (OR: 2.04), penicillins (OR: 1.87), and tetracyclines (OR: 1.87) for the 2002-2009 year period when compared to the 2010-2016 year period. Despite reduced odds of AMR to these drug classes in the recent year period, lack of a significant reduction in AMR for important drug classes such as cephalosporins, quinolones, and macrolides highlight the relevance of continual AMR surveillance in cattle with Salmonella infections to target future interventions.

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Student Support: Merial (Boehringer-Ingelheim) Veterinary Research Scholars Program
Water and dust baths for improved environmental enrichment for zebra finches (Taeniopygia guttata)

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Zebra finches are becoming an increasingly important biomedical research model, most frequently in the field of neurobiology. Historically, laboratory animal literature has given less attention to zebra finches than to more traditional laboratory animal species, particularly with regards to their husbandry and welfare; however, with the increasing interest in these birds as research models there is a greater need for focused studies concerning their care and keeping in the laboratory. Water and dust baths have been identified as options for methods of enrichment for zebra finches, but there is a dearth of evidence assessing the value of these baths in fulfilling species specific behavioral needs. 70 cull zebra finches were grouped randomly into mixed sex cages of 10 birds each. Each cage was provided with either a water or dust bath for at least 3 hours per day for 5 days, followed by 2 days with no bath access. The procedure was repeated using the alternate bath - those that received water baths were given dust baths and vice versa - for the same period of time. Each cage was then provided both a water bath and a dust bath for 3.5 hours per day for 6 days. All interactions with the baths were video recorded and retrospective analysis of behavioral parameters was completed to determine how and when the baths were used, and whether birds demonstrated a preference for one type of bath over the other.

Research Grant: Cornell Center for Animal Resources and Education Departmental Funding
Student Support: The American Society of Laboratory Animal Practitioners

Increased cholinergic drive contributes to apneas during active sleep in CNS serotonin deficient rat pups

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Sudden Infant Death Syndrome (SIDS), the most common cause of death in infants between 1 month and 1 year of age, occurs during sleep. Evidence shows that SIDS cases have sleep apnea and prolonged periods of active sleep (AS; similar to REM sleep in adults) prior to death. Apnea and resulting hypoxia are likely key factors in the sudden death of these infants during sleep. Studies have shown SIDS cases have abnormalities in the serotonin (5-hydroxytryptamine; 5-HT) neurons in the brainstem, including reduced CNS 5-HT. Infant rats lacking 5-HT experience apnea during prolonged AS. Given that 1) acetylcholine is a major driver of AS; 2) AS-driving cholinergic neurons project to respiratory patterning neurons; and 3) 5-HT can inhibit AS-driving cholinergic neurons, we hypothesize that increased cholinergic drive within the CNS contributes to the unstable breathing pattern of 5-HT-deficient rat pups. To test this hypothesis, we are using 14-16-day-old rat pups lacking tryptophan hydroxylase 2 (TPH2-/-), as well as wild-type controls. We have three groups for each genotype: 1) pups treated with atropine sulfate as the experimental group; 2) pups treated with a saline control; 3) pups treated with atropine methyl nitrate to control for the effects on the heart. Electromyography (EMG), behavioral observation, and whole-body plethysmography were used to monitor breathing pattern and sleep states as the pups cycled between states before and after drug injection. Compared to before drug injection, TPH2-/- pups had fewer apneas during AS after atropine sulfate injection (p=0.04). These results help support our hypothesis that increased cholinergic drive during AS contributes to the apneas experienced by future SIDS cases.

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Student Support: Department of Biomedical Sciences, University of Missouri College of Veterinary Medicine
Optimizing mice liver slices to assess nuclear and membrane estrogen receptor 1 role in mitochondrial function

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Females have longer life expectancies than males and this difference has been attributed to protective actions of estrogens. Mitochondria generate reactive oxygen species which damage proteins, lipids and mitochondrial DNA, contributing to aging. Mitochondria from females exhibit lower oxidative damage than age-matched males, suggesting that estrogens may regulate mitochondrial function. Estrogen receptor 1 (ESR1) is the main mediator of 17β-estradiol (E2) effects in the cell and E2 signaling through ESR1 regulates mitochondrial structure and promotes mitochondrial electron transport chain efficiency in various tissues. Although ESR1 is mostly nuclear/cytoplasmic, about 5%-10% is localized to the plasma membrane and transgenic mice expressing nuclear ESR1 (nESR1) but lacking membrane ESR1 (mESR1) have extensive reproductive and endocrine abnormalities. The Seahorse Extracellular Flux Analyzer (XF24) allows for real-time oxygen consumption rate (OCR) measurement and mitochondrial function can thus be assessed by partitioning mitochondrial bioenergetics parameters using pharmacological agents. The objective of this study was to investigate the relative roles of mESR1 and nESR1 in mediating E2 effects on mitochondrial function in mouse liver tissue. Using precision-cut tissue slicing protocols, we optimized liver tissue slice viability and developed a method that adapts the XF24 for the microplate-based measurement of mouse liver tissue OCR. We found that 2 mm diameter slices yielded OCR measurements within the dynamic range of the XF24. After optimizing these methods with wild-type mice, the goal is to measure liver slices from ESR1 knockout and nuclear-only knockout mice to determine the roles of mESR1 and nESR1.

Research Grant: NIH Supplemental Grant R03HD087528-01A1
Student Support: NIH; Boehringer Ingelheim Veterinary Research Scholars Program

Stem cell augmentation of viral myocarditis

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The heart is uniquely vulnerable to viral infection (myocarditis) and Reovirus provides a model for such infection in the mouse. The low turn-over of cardiac myocytes in the adult heart infers poor regenerative capacity of this organ after traumatic damage. Recently, a cardiac stem cell (CSC) population of the heart has demonstrated therapeutic benefits after cardiac infarct and is in Phase II clinical trials. We hypothesized that CSCs might be similarly therapeutic in the context of a virally infected heart. Surprisingly, however, results demonstrated that cardiac damage was increased upon stem cell administration in these experiments. This presents the possibility of adverse reaction to stem cell therapy because all patients are immunosuppressed and have latent viral infections which can emerge and lead to myocarditis. We hypothesized that CSCs delayed cardiac myocyte death, due to their rejuvenating properties, which permitted multiple rounds of viral infection in the heart, thus increasing tissue damage. Our objectives were to determine the mechanism by which CSCs or their secreted factors might enhance viral infection and expand our observations to another virus (Coxsackie) of a different family, using in vitro primary cultures of cardiac myocytes and fibroblasts. Viral replication was measured by RT-qPCR and plaque assay; preliminary data demonstrate that viral replication in these cultures is dependent on the source of CSC secreted factors and virus type. These studies will provide a better understanding of how CSCs and their secreted factors affect viral replication and offer insights for future engineering of CSCs to avoid adverse effects.

Research Grant: None
Student Support: CVM Veterinary Scholars Program, NIH T35 Training Grant (IBRTP) - T35OD011070
In hive LD50 of thiamethoxam toxicity on developing honey bees (Apis mellifera)

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In the last two decades, neonicotinoids have become by far the most commonly used insecticides in agriculture. Unfortunately, this widespread use has preceded the substantial increase in mortality of honey bees. Neonicotinoids kill insects by powerful neurotoxic effects executed by binding to their acetylcholine receptors. Thiamethoxam (THI) is a neonicotinoid commonly used on canola crops in Saskatchewan, and has been shown to have negative effects on non-target species like honey bees. The LD50 for larvae and adult honey bees has been previously determined under laboratory conditions. However, honey bees are social insects, thus preservation of their eusocial order may be important in toxicological studies. Accordingly, the objective of this study was to determine the LD50 of THI on developing honey bees within the entire honey bee colony (hive). Worker larvae in their natural comb cells (n=50 per dose group) were individually exposed to 6 different doses of THI: 0, 5, 50, 500, 2500, and 5000ng during the late larval stage (just prior to capping). A cumulative mortality from the day of exposure (Day 8) to emergence (Day 21) was expressed as a percentage for each treated group and the LD50 was calculated by probit analysis. Based on these preliminary results, the average LD50 ($SD$) was determined to be $54\pm43$ ng/larvae. This LD50 for larvae exposed to THI in the natural environment is dissimilar and lower than the LD50 determined in laboratory conditions at 118 - 229 ng/larvae. Consequently, preservation of eusocial order may influence the results of larval toxicity studies, potentially conferring a higher sensitivity to insecticides such as THI than compared to in vitro studies.

Research Grant: Western Grains Research Foundation, SaskCanola, Sask Agricultural Development Fund, North American Pollinator Protection Campaign, Canadian bee research fund, SBDC, and WCVM WHRF
Student Support: WCVM IUSS Research Scholarship and Merial Veterinary Scholars Award

Validation of a Luminex xMAP MultiFLEX Vector-borne Panel for canine blood-derived pathogens in Grenada

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Ehrlichia canis and Anaplasma platys are prominent tick-borne pathogens responsible for canine monocytic ehrlichiosis and anaplasmosis in canine populations worldwide, including the Caribbean island nation of Grenada. With their zoonotic potential, it is imperative to detect these pathogens in dogs and humans, alike, in an efficient and time-sensitive manner. The Multi-Analyte Profiling (xMAP) MultiFLEX bead-based assay provided by Luminex allows for the detection of E. canis and Anaplasma species simultaneously while requiring minute sample volumes. Unlike the conventional polymerase chain reaction (PCR) the xMAP MultiFLEX bead-based assay is both a qualitative and quantitative assay, which can additionally be useful for diagnostic purposes. This study used 124 canine blood samples to validate the xMAP MultiFLEX bead-based assay for its ability to detect E. canis and Anaplasma species in Grenada. DNA was extracted from all 124 blood samples and conventional PCR was conducted, using highly specific primers to detect E. canis and A. platys. The DNA from each sample was then separately analyzed using the xMAP MultiFLEX bead-based assay. Results showed 45.65% and 60.87% positive agreement between the xMAP MultiFLEX bead-based assay and the conventional PCR for E. canis and Anaplasma species, respectively. Moreover, the percent negative agreement between the two assays for E. canis and Anaplasma species were 75.64% and 86.14%, respectively. These findings demonstrate that the Luminex xMAP MultiFLEX Vector-borne Panel can detect and quantify the pathogens of interest simultaneously. However, there is a need to further optimize its ability to detect E. canis and A. platys variants in Grenada.

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Island Veterinary Scholars Program
Evaluation of the co-stimulatory domain ICOS in canine CAR T cell therapy

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Diffuse Large B-Cell Lymphoma affects 26,880 dogs in the US per year. Upon treatment and remission with chemotherapy, 90% relapse with drug-resistant disease within 6 to 9 months and die, so new treatments are required for durable remissions or cure. Chimeric antigen receptor (CAR) T cell therapy has seen success inducing durable remissions in humans with B cell malignancies. Here, T cells are modified to express an antigen-specific receptor linked to intracellular signaling domains, allowing these cells to recognize antigen without MHC and become activated without exogenous costimulatory ligands. In the clinic, human and canine patients treated with CAR T cells containing CD28 or 4-1BB costimulatory domains have experienced CAR T cell failure to persist in vivo. Initial data reveals that an ICOS costimulatory domain may lead to a pro-inflammatory Th17 cell phenotype and promote persistence in vivo. In this study, cCD20-ICOS-z and hCD19-ICOS-z CAR constructs were generated. Canine T cells were transfected ex vivo with ICOS, CD28, or 41BB CD20 CAR constructs and co-cultured with CD20 targets to determine the effects of ICOS on cytokine production, cytotoxicity, and proliferation. We hypothesize that the CD20-ICOS-z CAR will result in a Th17 cell phenotype with higher IFN-γ and IL-17 production than the other CAR constructs, as well as enhanced cytotoxicity and proliferation. We aim to evaluate the persistence of CD20-ICOS-z CAR T cells in vivo compared with other CARs using qRT-PCR. While CAR T cell therapy is a promising cell-based therapy, improvements are needed. This work evaluates the first-time use of canine ICOS in CAR T cell constructs to select the optimal CAR construct for dogs with relapsed B cell lymphoma.

Research Grant: Animal Cancer Foundation
Student Support: Merial Veterinary Scholars Program

Cross-reactive antibodies to Borrelia burgdorferi in dogs

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Lyme borreliosis (LB) is the most commonly diagnosed tick-borne disease within the United States, with the highest prevalence in the Northeast and Upper Midwest where the primary vector, Ixodes scapularis, is most common. Currently a specific, C6 peptide-based in-clinic Enzyme-Linked Immunosorbent Assay (ELISA) detecting antibodies to a surface protein expressed by Borrelia burgdorferi during active infection is the most common diagnostic tool utilized by small animal veterinarians, but many veterinary diagnostic laboratories still offer a whole cell Immunofluorescent Assay (IFA) as their primary serologic testing option. In our study IFA was performed on serum samples from 200 apparently healthy canine patients who presented to the Boren Veterinary Medical Teaching Hospital in Stillwater, OK, which is in a non-LB endemic region. All enrolled patients were negative for specific antibodies to B. burgdorferi via in-clinic C6 peptide-based testing, but 27% tested positive by IFA, suggesting the presence of potentially cross-reactive antibodies on the whole cell IFA assay. The region from which patient samples were obtained is within the range of Amblyomma americanum, which are known to harbor the non-LB associated Borrelia lonestari that may elicit cross-reactive antibodies that are detected on the less-specific IFA. Alternately, exposure to other non-LB associated Borrelia spp., exposure to other spirochetes, or prior vaccination against B. burgdorferi may be responsible for cross-reactive antibodies. This data is useful as a first step towards identifying the organisms that may elicit cross-reactive antibodies on IFA for B. burgdorferi, and to assess the overall utility of the IFA in diagnosing Lyme borreliosis in dogs.

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Student Support: Krull-Ewing Endowment at Oklahoma State University’s Center for Veterinary Health Sciences”
Role of sEH in chondrocyte endoplasmic reticulum stress and apoptosis

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An enzyme called soluble epoxide hydrolase (sEH) that degrades natural analgesic lipid metabolites known as epoxy fatty acids (EpFAs), plays a significant role in endoplasmic reticulum (ER) stress in peripheral neurons. Studies in rodents have shown that sEH inhibition controls neuropathic and inflammatory pain, and similar results were observed in preliminary trials in horses with osteoarthritis. The aim of this study is to determine whether or not blocking sEH will prevent apoptosis due to ER stress in chondrocytes. Cultured immortalized human chondrocytes were treated with the ER stress and apoptosis inducer tunicamycin in the presence or absence of the sEH inhibitor t-TUCB, and apoptosis was determined via enzyme-linked immunoassay (ELISA) technique. Preliminary results indicate that sEH inhibition decreases chondrocyte apoptosis. Additional studies are underway to confirm/rebut these preliminary findings.

Research Grant: None
Student Support: The University of Minnesota College of Veterinary Medicine

Evidence of hypertension and cardiac remodeling found in male TPH2 knockout rats compared to females

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Hypertension (HT) is associated with significant comorbidities including heart failure (HF), the leading cause of death in the US. HT and HF occur more frequently in young men compared to age-matched females. 5-hydroxytryptamine (5-HT) has been implicated in the control of blood pressure. Male rats deficient in tryptophan hydroxylase 2 (TPH2), the rate limiting enzyme in central 5-HT synthesis, are hypertensive at rest; a phenotype absent in females. We sought to determine if 5-HT plays a role in cardiac remodeling. We hypothesize there will be evidence of cardiac remodeling only in male rats lacking TPH2 and that females will be protected. Heart enlargement and increased fibrosis are signs of tissue remodeling indicating the presence of HF. Heart size and left ventricle wall thickness will be measured using echocardiogram analysis. Post mortem, tibia lengths (TL) were measured with a digital caliper and hearts were weighed. Evidence of an enlarged heart was determined by comparing heart weight (HW) to TL. Cardiac tissue was collected from the left ventricle. Signs of cardiac tissue remodeling and fibrosis will be determined by qPCR, assessing changes in remodeling proteins such as collagen type I and III, MMP2, MMP9, TIMP1, and TIMP4. Increased expression of collagen is indicative of fibrosis. MMP2 and 9 are enzymes that break down the extracellular matrix; TIMP1 and 4 inhibit MMP enzymes. In preliminary data, we found no significant difference in HW:TL in females (WT 1.85 +/- 0.10, KO 2.12 +/- 0.11), but found significant differences in the males (WT 2.38 +/- 0.11, KO 2.78 +/-0.04). This suggests 5-HT is involved in cardiac remodeling in males while females are protected from HF, similar to their protection from HT.

Research Grant: NIH RO1 HL 112998 PI: Emter, AHA 14SDG1856022 PI: Cummings, DHHS 1F31 HL136067-01 PI: Magnusson
Student Support: Dolores Goller Fund for Scholarships and Research in Veterinary Medicine
Roles for the 9-1-1 DNA damage response complex in meiosis

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Due to the volume of endogenous and exogenous stresses encountered by our cells every day, a process known as the DNA damage response (DDR) plays a critical role to help maintain proper genomic integrity. The DDR has been shown to allow germ cells to successfully advance through meiosis, particularly Prophase I, where double-stranded breaks (DSBs) occur to facilitate pairing of homologous chromosomes and crossing over. A central part of the DDR pathway is the RAD9A-RAD1-HUS1 (9-1-1) complex, a heterotrimeric clamp that acts as a molecular scaffold for DNA repair and checkpoint signaling activation, through interaction with several DNA damage response proteins. It has been previously established that testis-specific inactivation of Hus1 or Rad9a leads to; germ cell depletion, and severe meiotic defects. Recently paralogs of 9-1-1 subunits, RAD9A and HUS1, termed RAD9B and HUS1B, have been proposed to form alternative, non-canonical meiotic 9-1-1 complexes (RAD9B-RAD1-HUS1B and RAD9B-RAD1-HUS1), which are still poorly understood. We used Hus1b knockout mice (Hus1b-/-), in conjunction with Hus1 inactivation (hypomorphic Hus1 allele or conditional knockout targeted to the testis) to better understand the roles of these alternative 9-1-1 complexes. We hypothesize that disruption of multiple 9-1-1 complexes with loss of both Hus1b and Hus1 will disrupt proper progression through meiotic Prophase I. Supporting our hypothesis, preliminary results show germ cell loss in both males (increased lumen space) and females (decreased primordial follicle counts). These studies will help elucidate the diverse roles of the 9-1-1 complex on fertility and overall DNA stability.

Research Grant: None
Student Support: Office of Graduate Education – Cornell University College of Veterinary Medicine

In vitro susceptibility of FHV-1 field strains to penciclovir and ganciclovir

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Feline herpesvirus 1 (FHV-1) is the most common cause of feline ocular disease and up to 97% of cats have been exposed to the virus. Oral famciclovir and topical ganciclovir are antiviral drugs used in clinical practice to treat ocular FHV-1 infection. However responses to treatment are variable and published studies of in vitro efficacy of these drugs against FHV-1 have been performed using just a few lab maintained strains. We hypothesized that antiviral susceptibility differs among field strains of FHV-1 from geographically diverse feline populations. To test this hypothesis, yield reduction assays were performed on 10 genetically distinct, PCR-confirmed, FHV-1 field isolates from shelter cats with ocular and/or respiratory disease from around the USA. Viral cultures, on confluent Crandall Rees feline kidney cells, were incubated at a multiplicity of infection of 1 with concentrations from 1.56 - 50 μM penciclovir (the active metabolite of famciclovir) and 0.39 - 25 μM ganciclovir for 24 hours. Assays were run in duplicate and viral yield was averaged between duplicates. Viral yield was determined by plaque assay and EC50 values were calculated by interpolating the drug concentration required to reduce viral plaques to 50% of the zero drug control. It was expected that most isolates of the virus would have similar EC50 values but that some would be resistant (defined as an EC50 value > 2 standard deviations above the average for a known susceptible strain). Initial findings have failed to identify field strains with EC50 values consistent with anti-viral resistance. Knowledge of EC50 values for clinical isolates of FHV-1 will help to guide evidence-based treatment of this disease in veterinary clinical patients.

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Student Support: Boehringer Ingelheim Veterinary Summer Scholars Program
Mutations responsible for Zika virus adaptation to mammalian and insect cells

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Zika virus (ZIKV) is a rapidly spreading mosquito-borne pathogen recently introduced into the Western Hemisphere. It reached epidemic proportions in South America and has been associated with increased risk of birth defects and Guillain-Barre syndrome. A major focus of our lab is to study mosquito-virus-vertebrate host interactions, including ZIKV adaptation to its disparate hosts. We used a Colombian ZIKV strain (ZIKV-FLR), which had been only grown on mosquito cells, and grew up stocks on mammalian (ZIKV-FLR$^{mam}$) and mosquito (ZIKV-FLR$^{mos}$) cells. The stock of ZIKV-FLR$^{mam}$ exhibited a wide range of plaque phenotypes, including a large plaque (LP), and ZIKV-FLR$^{mam}$ grew faster on mammalian cells and slower on mosquito cells compared to ZIKV-FLR$^{mos}$. These results suggest that ZIKV-FLR was adapting to mammalian cells. We hypothesize that the LP phenotype is caused by mutation(s) within the ZIKV genome. LP virus stocks were isolated by three rounds of plaque purification on either mammalian (ZIKV-FLR$^{mam}$-LP) or mosquito (ZIKV-FLR$^{mos}$-LP) cells. After sequencing the LP phenotype viruses, four unique missense mutations were identified in the consensus sequence compared to the parental ZIKV-FLR: two mutations in ZIKV-FLR$^{mam}$-LP and two mutations in ZIKV-FLR$^{mos}$-LP. Using site-directed mutagenesis of an infectious cDNA clone of ZIKV, these mutations were introduced into the parental genome, and the resulting viruses were tested on mammalian and mosquito cells to identify the mutation(s) responsible for the growth kinetics and plaque size phenotypes. Future studies will determine if the ZIKV mutants have altered replication in mice and mosquitoes with the long term goal of identifying potential vaccine candidates.

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Student Support: NIH T35 Short-term Research Training for Veterinary Students in Wisconsin (PI: D. Bjorling)

Genotypic-relatedness and urinary virulence factor prevalence in canine S. pseudintermedius isolates

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Urinary tract infection (UTI) is one of the most common presenting complaints for small animal patients. Staphylococcus pseudintermedius is the second most common cause of UTI in dogs and is linked to struvite urolithiasis. S. pseudintermedius is also the most common cause of pyoderma in dogs, a skin infection associated with allergic and atopic dermatitis. The aim of this study was to evaluate the genetic relatedness of isolates of S. pseudintermedius from the urinary tract and compare them to skin isolates using pulsed-field gel electrophoresis (PFGE). The prevalence of known staphylococcal urinary virulence factors was also determined. The CDC Pulse-Net protocol for S. aureus typing by PFGE was used, and BioNumerics software was then used to identify percentage similarities on a dendrogram. PCR was performed to determine the prevalence of 3 urinary virulence factors that have been identified in the human pathogen S. saprophyticus: D-serine deaminase (DsdA), a hemagglutinin (Aas), and uro-adherence factor A (UafA). 24 urine isolates and 19 skin isolates were included. Two major clusters were identified by PFGE and one cluster contained predominantly urine isolates. For DsdA, 8.3% (2/24) of urine isolates and 0 skin isolates were positive. For Aas, 20.8% (5/24) of urinary isolates and 26.3% (5/19) of skin isolates were positive. For UafA, 41.6% (10/24) of urine isolates and 0 skin isolates were positive (P = 0.001). This suggests that a potential group of S. pseudintermedius isolates may be true uropathogens because of their clonal population structure and the presence of known urinary virulence factors. Understanding S. pseudintermedius as a true uropathogen is important for the prevention and treatment of UTI.

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Student Support: NIH-Merial Veterinary Research Scholars Program
Investigating the differences between ape and human GFAP proteins involved in neurodegeneration

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Advances in medicine have led to increased average life expectancy in humans and an aging society, resulting in a growing importance of age-related diseases, such as Alzheimer’s disease (AD). Unlike many other diseases, the number of deaths due to AD is on the rise primarily due to a lack of understanding of how the disease is caused at the cellular level. The greatest known risk factor for AD is advancing age. It has been reported that non-human primates are not prone to AD. Here, we propose that the interaction between a protein that protects the telomeres and a protein expressed exclusively in astrocytes modulates the accumulation of amyloid deposits, a characteristic of the AD brain. The shelterin protein complex is responsible for maintaining genomic stability by preventing DNA damage to the telomeres. RAP1 is the subunit of the shelterin complex that protects telomeres from illegitimate fusion that leads to genomic instability and cancer. Our lab has recently identified a novel interaction between RAP1 and GFAPδ, a protein associated with neurodegenerative diseases. The GFAPδ isoform also interacts with PS1, the protease responsible for creating the amyloid beta (Aβ) proteins that aggregate into senile plaques characteristic of AD. GFAPδ has several naturally occurring variants in humans. Interestingly, such variation does not occur in non-human primates. We hypothesize that the amino acid sequence differences in the three human variant proteins will correspond to differences in interactions among RAP1, PS1 and GFAPδ, as well as alterations in Aβ.

Research Grant: None
Student Support: Merial Veterinary Research Scholars Program Fellowship

Identifying adaptive mutations in the bacterial pathobiont Escherichia coli LF82

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Gut microbiota play an important role in the immune system and normal digestive functions of their mammalian hosts. While studies have shown that the abundance of bacterial taxa are altered in response to GI inflammation, much less is known about how heritable genetic changes allow bacteria to adapt to the GI environment. To address this, we colonized gnotobiotic altered Schaedler flora mice, colonized with only 8 bacterial species, with the Escherichia coli pathobiont LF82. ASF mice were colonized with LF82 at generation 0 and the mice were allowed to breed for 5 generations. In contrast to conventional mice, LF82 was stably maintained through all of the generations. LF82 was recovered from the mice over the course of each generation and their genomes resequenced to identify single nucleotide polymorphisms (SNPs) that arose over the course of the colonization. To confirm the identity of the genes and to better assess the timing of their occurrence, we developed PCR-based assays to sequence relevant regions of the genes: rpoB (RNA polymerase β subunit), rpoD (RNA polymerase sigma factor), kdgT (2-keto-3-deoxygluconate transporter), prmC (release factor glutamine methyltransferase), proQ (RNA chaperone), and fbaB (fructose-biphosphate aldolase class I). Interestingly, mutations in rpoB and rpoD may reveal a new strategy of LF82 to protect against bacteriophage infection in the mammalian gut. Continued application of this strategy should reveal new insights into how bacteria adapt to new environments, with implications for transmission of a dysbiotic microbiome to offspring, and the emergence of zoonotic pathogens.

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Student Support: NIH T35 Training Grant T35OD012199
**Mycobacterium avium** in table eggs and the relationship to non-tuberculous mycobacterial infections in humans

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*Mycobacterium avium* subsp. *avium* (Maa) is an opportunistic bacterium that can cause disease in humans, especially immunocompromised patients. Maa is commonly found in soil and water, but can be amplified by host species like birds. A steady increase in human *M. avium* subsp. (Ma) infections has been seen in the New River Valley (NRV) since 2012. One possible source may be backyard poultry, since free-range and range-reared flocks are becoming more popular as a source of fresh poultry products. It follows then that poultry products, e.g. eggs, may be contaminated and serve as a source of infection. The NRV has a number of private individuals supplying eggs to consumers via farmers’ markets. The objective of this study is to see if there is a geospatial relationship between human Ma infections and Maa positive eggs. To begin to answer this question, we tested eggs from local markets for the presence Maa genomic material and compared findings with human Ma infection data from the Virginia Department of Health obtained during a previous study. Eggs originating from markets in five different cities/counties around the NRV were tested. The samples were separated into yolk and albumen fractions and frozen at -20°C. Eggs from commercial cage-reared layers were used as negative controls. Positive controls were created by spiking commercial eggs with either whole Maa or a plasmid containing the IS1245 gene, unique to Maa. A TaqMan -based qPCR assay targeting the IS1245 sequence (genomic or plasmid) was performed to determine the presence of Maa genomic material. This data was overlaid on choropleth maps representing the distribution of human Ma cases in the NRV. Results and conclusions are being finalized.

**Research Grant:** Virginia-Maryland College of Veterinary Medicine  
**Student Support:** NIH T35 Training Grant T35OD011887

Immunofluorescent histochemistry procedure to assess the relationship between interleukin-10 and *Eimeria*

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*Eimeria* infection correlates to an increase of Interleukin 10 (IL-10) expression in the lumen of broiler intestines. As an immunosuppressive cytokine, elevated levels of IL-10 aid the proliferation of *Eimeria*. This experiment establishes a method to identify the relationship between *Eimeria* and IL-10 in situ. We developed an Immunofluorescent histochemistry (IFHC) procedure hypothesizing that IL-10 concentration increases throughout intestinal epithelium afflicted with *Eimeria*. Slide sections were obtained from the duodenum, jejunum, and cecum of broilers infected at 20 days of age with 10x dose of Advent coccidia vaccine or sterile saline. Samples were collected at days 3-5 post infection at 12 hour intervals. Paraffin sections were incubated overnight at 60°C, deparaffinized with Xylene, and rehydrated with isopropyl alcohol. Slides underwent heat induced epitope-retrieval (HIER) in Tris Urea solution. To articulate IL-10, tissues were coated in rabbit anti-IL-10 polyclonal antibody at 1:300 dilution in blocking buffer, followed by staining with 1:100 diluted Donkey anti-rabbit Dylight 594. Nuclei were highlighted by Fluorogel with tris buffer and 4’,6-diamidino-2-phenylindole (DAPI) solution. An Olympus BX51 Fluorescent Microscope was used to read the slides under UV (365/10mm), blue (480/20mm), and green (535/15mm) excitation spectrums. At 535/15mm, IL-10 was confirmed to be sparsely present within the intestinal mucosa throughout days 3-5, with increased concentrations at the tips of villi. At days 4.5-5, *Eimeria acervulina* macrogametocytes autofluoresced at 480/20nm, and IL-10 expression increased throughout infection sites. Results suggest that coccidia influences IL-10 up-regulation in microenvironments.

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**Student Support:** NIH T35 Training Grant T35OD011078
Identification of genetic variants associated with myotonia in the horse

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Equine myotonia is a debilitating, likely Mendelian disease. Affected horses have delayed muscle relaxation due to abnormal muscle membrane conduction, often necessitating euthanasia. Historically, identifying the genetic variants associated with diseases like myotonia has been difficult due to the need to sequence potential candidate genes individually. Recently, whole genome sequencing (WGS) of individuals with Mendelian diseases accompanied by a catalog of genetic variation from a healthy population has been effective in identifying disease-causing mutations in humans and cattle. We are developing a similar WGS catalog of 449 horses. We hypothesized that disease-causing mutations for equine myotonia can be identified using this approach. WGS at 12X was performed on DNA from 2 cases of equine myotonia. Raw reads were mapped to EquCab2 and single nucleotide polymorphism (SNP) variants were identified and annotated using publicly available software. SNPs in candidate genes were investigated for potential pathogenicity by predicted functional effect and relative conservation scores. The allele frequency of potential SNPs in a population of 174 horses was established. Two missense variants were identified in SCN4A exon 23 (p.P1810L). One missense variant was identified in RYR1 exon 66 (p.A2816V). The normalized conservation scores at these positions were poorly conserved at 1.853 and 0.893 respectively. No potential pathogenic SNPs were identified in the other candidate genes (ATP2A1, CACNA1S, CLCN1, KCNE3, KCNJ2, STAC3, and TPM3). While a definitive pathogenic variant is yet to be identified, this project demonstrates the utility of WGS methods for ruling out multiple candidate genes for Mendelian diseases in the horse.

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Student Support: Student Support: Morris Animal Foundation, Award D17EQ-600

ECG abnormalities in Trypanosoma cruzi seropositive and negative working dogs across the US-Mexico border

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Trypanosoma cruzi is a vector-borne protozoan parasite that causes Chagas disease in humans, domestic animals, and wildlife. Triatomine insects, the vectors of T. cruzi, inhabit environments where Department of Homeland Security working dogs perform border security functions along the US-Mexico border. Though T. cruzi infection can be asymptomatic, debilitating acute or chronic cardiac disease can develop, characterized by myocarditis, ascites, cardiac dilatation, or sudden death. The clinical and economic importance of T. cruzi in these dogs is unknown, but could be significant given the high value of the working dogs. We aimed to characterize cardiac rate and rhythm abnormalities associated with T. cruzi infection and hypothesized that ECG abnormalities would be more common in T. cruzi seropositive than seronegative dogs. Using a cross-sectional study design, 159 working dogs were tested for anti-T. cruzi antibodies using serological tests and cardiac abnormalities were measured using a non-invasive, short-read AliveCor ECG smartphone app. Additionally, 26 dogs with a two-year serological history of T. cruzi infection were simultaneously tested by a 24-hour constant-read Holter monitor and the AliveCor ECG. In the cross-sectional study, seroprevalence was 6.1% (CI: 2.5-12.2%). A total of 136 AliveCor ECGs, averaging 38s, were found of adequate quality and have ongoing analysis. Preliminary analysis of Holter data shows sinus arrhythmias among all infected dogs. Other findings include supraventricular and ventricular premature beats and atrioventricular block. Clinical assessment of infected dogs will provide a basis for improving the management of working dogs with T. cruzi associated cardiac dysfunction.

Student Support: Boehringer Ingelheim Veterinary Scholars Program & College of Veterinary Medicine, Texas A&M U.
Effects of drug self-administration on neuroinflammatory responses

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Drug abuse is an enduring epidemic plaguing many populations, however women have an increased susceptibility to this problem, both trying drugs at a younger age and experiencing a greater pleasurable response than their male counterparts. Estradiol is thought to be an underlying cause of these changes, influencing the remodeling of the neural synapses in the brain reward pathway. One underlying mechanism through which this occurs is hypothesized to be through microglia activation. Previously unpublished research in this laboratory suggested an increase in the numbers of microglia present in the nucleus accumbens after cocaine administration. The preliminary experiment took the conventional jugular approach to delivering cocaine, though there is an indication that jugular catheterization may affect microglia independently of drug administration. This experiment was designed to test the impact of the route of cocaine administration on microglia proliferation. In order to test this hypothesis, intact female rats received either femoral or jugular catheters. The experimental group was allowed to freely administer cocaine for 6 hours per day for a total of 10 days. The control group also was put in self administration chambers for the same time period but they received the sterile vehicle without cocaine. At the conclusion of the 10 days, brain tissue was collected and analyzed for the total number of microglia present in the nucleus accumbens. This study will help identify the importance of route of cocaine administration on microglia proliferation in the brain as well as lay a foundation for examining a role of estrogen in mitigating these effects of cocaine administration.

Research Grant: National Institutes of Health, Award Number R01 DA035008
Student Support: The Merial Veterinary Scholars Program

Role of butyrate in restoring satiety signaling in rodent model of high-fat diet-induced obesity

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The vagal afferent neural pathway communicates the presence of nutrients in the gut to the brain to induce satiety. However, chronic ingestion of a high-fat diet (HFD) blunts vagal afferent neuron (VAN) sensitivity to gut hormones such as cholecystokinin (CCK), alters gut microbiota, and induces systemic inflammation, resulting in hyperphagia and obesity. Prebiotics can reverse deleterious effects of a HFD, including hyperphagia, weight gain, and increased adiposity. Butyrate, a short-chain fatty acid produced in the gut by fermentation of prebiotic fiber, may be a mechanism through which prebiotics attenuate diet-induced obesity. We sought to determine whether butyrate directly attenuates HFD-induced obesity through a VAN pathway. Mice received a HFD or low-fat diet (LFD) +/- a stable butyrate analogue (monobutryin) for 6 weeks. Inhibition of food intake (FI) in response to exogenous CCK administration was determined to assess VAN sensitivity to satiety-inducing CCK. Hindbrain tissue was harvested for examination of neuronal activation in response to CCK via immunocytochemical localization of the fos protein. Preliminary data from our first cohort showed a reduction in adiposity in butyrate-treated, HFD mice. Adiposity was not significantly different between butyrate-treated HFD and non-butyrate-treated LFD controls. LFD control mice reduced FI in response to exogenous CCK, as expected; butyrate’s effects on CCK-induced FI inhibition are pending further analysis. Continuing analysis with a second cohort should elucidate whether butyrate attenuates HFD-induced obesity, and whether this mechanism involves restoration of VAN function.

Research Grant: National Institutes of Health (NIH)
Student Support: Students Training in Advanced Research (STAR) Fellowship
Evaluation of a nutraceutical for management of lower urinary tract disease in healthy cats

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Idiopathic cystitis and urolithiasis are common causes of feline lower urinary tract signs (LUTS). Prevention and/or alleviation are often accomplished by diluting urine, reducing concentration of calculogenic constituents, and inducing more frequent urination. Traditional therapies are increasingly supplemented with nutraceuticals, although research is limited. We evaluated Tripsy, an herbal supplement recommended for cats with LUTS, in a placebo crossover study of seven healthy male cats aged 10 months to 5 years. We hypothesized that cats would produce larger urine volume, have decreased urine saturation for struvite and calcium oxalate, and have different urine metabolomic profiles when receiving Tripsy when compared with placebo. Cats were randomly assigned in a pairwise fashion to an initial treatment for two weeks, followed by a five-day washout period, then crossed over to the other treatment for two weeks. Urine was collected over a 48-hour span at the end of each treatment period. Samples were analyzed for electrolytes, minerals, and creatinine using an automated chemistry analyzer; citrate and oxalate by ion chromatography; pH by electrode; and ammonia by ion-select electrode. Upper limit of metastability was evaluated by addition of ammonium oxalate to urine and quantified by measuring absorbance using spectrophotometry. Relative supersaturation for calcium oxalate and struvite (an estimate of urolith formation potential) was estimated using an iterative program. Results are pending.

Research Grant: Companion Animal Nutrition and Wellness Institute
Student Support: Boehringer Ingelheim; Veterinary Medical Experiment Station, UGA College of Veterinary Medicine

Gestational intermittent hypoxia induces persistent changes in acute neuroinflammatory responses

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Obstructive sleep apnea (OSA) in pregnant women is a form of sleep disordered breathing characterized by repeated episodes of hypoxemia and reoxygenation during sleep, due to upper airway closure. In rodents, intermittent hypoxia (IH) exposures cause neuroinflammation and central nervous system (CNS) morbidities in areas of the brain important for learning, memory and breathing. Despite emerging evidence of detrimental outcomes in newborns of mothers with OSA, neuroinflammation in newborn rats exposed in utero to IH has not been investigated. Thus, we measured inflammatory gene expression in brain regions involved in breathing in 2-3 day old rat pups exposed to gestational IH (GIH) or gestational normoxia (GNX). We also tested their neuroinflammatory responses to a postnatal immune system challenge (lipopolysaccharide; LPS, 0.1 mg/kg, 3h) because infection is common in high-risk newborns. Timed-pregnant rats (gestational days 10-21) were exposed to alternating 2 min cycles of 21% O2 (normoxia; GNX) or 10.5% O2 and 21% O2 (GIH) for 8 h/day. Total RNA was isolated from the brainstem and cervical spinal cords, and qRT-PCR was used to quantify pro-inflammatory gene expression. Basal neuroinflammation was unchanged in GIH rat pups. However, their neuroinflammatory responses to LPS were impaired in both brain regions, but only in female GIH pups, suggesting that GIH may induce immune tolerance in females. These data demonstrate sexually-dimorphic inflammatory gene responses to LPS in critical respiratory control centers of GIH-exposed newborn female rats. Studies are underway to evaluate the consequences of GIH on neonatal breathing in the presence and absence of acute inflammation.

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Student Support: NIH T35 short-term Research Training for Veterinary Students in Wisconsin
Scoping review of big data, informatics and bioinformatics in animal health and veterinary medical literature

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Big data, informatics and bioinformatics are becoming more important in veterinary medicine as datasets are increasing in size. These tools are new to veterinary medicine and have been under-explored in the context of animal health. The purpose of this study is to characterize how “big data”, “informatics” and “bioinformatics” are used in the animal health and veterinary medical literature. This study uses a scoping review approach, as described by Arksey and O’Malley (2002), with literature searches from the following databases: Web of Science, Medline (via PubMed), Agricola and ProQuest Theses and Dissertations, and Institute of Electronics and Electrical Engineers (IEEE). A relevance screening tool was created and uploaded into DistillerSR. A decision protocol was created by a team of researchers and a kappa above 0.7 was desired. Using the 2 in, 2 out method, article titles and abstracts will be screened for relevant information about a target species and the use big data, informatics or bioinformatics techniques. After an initial pilot of the screening tool, overall kappa for the first 1000 articles was 0.75 and 27.6% of search results were included. The kappa was lower for bioinformatics than non-bioinformatics articles. This led to the production of a decision tree to limit disagreement on article relevance. Following relevance screening, data extraction will be performed to determine information about species, type of research, animal industry and more. We hope that this research will gain insight on what research in animal informatics is being conducted and what more needs to be done.

Research Grant: None
Student Support: Undergraduate Student Research Awards (NSERC)

The use of bacteriophages as a therapy for methicillin resistant Staphylococcus species

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Staphylococcus species are gram positive bacteria that act as opportunistic pathogens. Some species of Staphylococcus have mobile gene elements (MGE) that allow them to share genes with other Staphylococcus species and bacteria. One gene located on an MGE is mecA, which confers resistance to methicillin and other penicillin derived antibiotics. Methicillin resistant Staphylococcus aureus (MRSA) is a notorious infection associated with skin infections, pneumonia, and surgical site infections, which can progress to sepsis and death. The use of antibiotics to treat these infections is increasingly problematic with the continual emergence of antibiotic resistant strains. The use of bacteriophages holds promise as an alternative treatment. The aim of this study was to isolate and characterize phages that could be used as eventual therapeutics against methicillin resistant Staphylococcus species (MRSX). Wild-type bacteriophages were isolated from wastewater collected from local wastewater treatment facilities in the Lafayette area of Indiana. MRSX samples were acquired from the Purdue University Animal Diseases and Diagnostics Laboratory and originally isolated from clinical cases. Two phages (Stps_SAS1, Stps_SAS2) were isolated from the wastewater and found to inhibit bacterial growth against a strain of methicillin sensitive Staphylococcus pseudintermedius (MSSP). These phages, however, had a very narrow spectrum as measured by spot assay against a library of unrelated MSSP and MRSA isolates. While the phages described here may prove beneficial in treating specific MSSP infections, phages with broader spectra will be necessary for effective phage-based treatments when little diagnostic information is available.

Research Grant: Purdue CVM and Boehringer Ingelheim
Student Support: Purdue CVM
Pathogenesis of chikungunya virus in experimentally infected southern toads and leopard frogs

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Chikungunya virus (CHIKV) is a mosquito-borne RNA alphavirus that has recently emerged in new regions such as the Caribbean, Europe, and the Americas. While the virus is maintained by an urban human-mosquito cycle, the sylvatic cycle in these regions remains largely unknown. Previous studies have shown that a variety of birds and mammals experimentally infected with CHIKV failed to develop a viremia, indicating that the virus has few species that act as potential reservoirs. However, experimentally infected ectotherms such as frogs, toads, and snakes can develop a viremia theoretically high enough to transmit the virus to mosquitoes. This study examines the pathogenesis of chikungunya infection in southern toads (Anaxyrus terrestris) and leopard frogs (Lithobates pipiens). Six frogs and six toads were inoculated with a SAH strain of CHIKV, and blood was collected 1, 3, and 5 days post-infection. On days 2, 4, and 7, two frogs and two toads were terminally bled, euthanized with an IP injection of pentobarbital, and necropsied to collect tissue for histopathology and virus isolation. Virus was isolated from the liver and kidney of viremic toads, and from the skeletal muscle, liver, kidney, and lung of viremic frogs. Frogs euthanized on day 2 had high viral titers in the liver and kidney, while frogs euthanized on day 4 had higher viral titers in skeletal muscle. This study will characterize the pathogenesis of CHIKV in potential reservoir hosts and help clarify a possible sylvatic cycle for this virus in North America.

Research Grant: CSU Animal Models Core
Student Support: NIH T35 Training Grant 4T35OD015130-05

Dental pathology of the Grey Fox (Urocyon cinereoargenteus)

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Museum specimens from 637 Grey Foxes (Urocyon cinereoargenteus) were examined macroscopically according to predefined criteria. Of the 637 specimens, 569 were included for further examination. The study population included more males (n=261, 45.9%) than females (n=196, 34.4%) and animals of unknown sex (n=112, 19.7%). Additionally, 481 (84.5%) adults, 67 (11.8%) young adults, and 21 (3.7%) individuals of unknown age comprised the study population with juveniles and neonates excluded from the study. The number of teeth present for examination was 23066 (96.5%) with 624 (2.6%) absent artifactually, 15 (0.06%) absent congenitally, and 193 (0.8%) lost ante mortem through acquired tooth loss. No persistent deciduous teeth or temporomandibular joint osteoarthritis were found in any of the specimens. Ten supernumerary teeth from 9 (1.6%) specimens were encountered. Of the alveoli examined, 1529 (6.4%) displayed bony changes suggestive of periodontitis with 276 (46.5%) of individuals affected. Significantly more adults were affected by bony changes associated with stage 3 periodontitis than young adults. All specimens displaying stage 4 periodontitis were adults. Fractures affected 446 (78.4%) specimens examined and 3554 (15.4%) of teeth present. Almost half (n=10856, 47.1%) of teeth available for examination and most specimens (n=487, 85.6%) displayed some degree of attrition or abrasion. Two individuals (0.4%) exhibited periapical lesions. Teeth with extra roots were found in 61 individuals (10.7%) with 0.4% of all teeth affected. Characterizing the dental pathology in the Grey Fox provides key insight into the ecology of the species and factors contributing to fitness.

Research Grant: Merial Veterinary Scholars Program.
Student Support: None.
Enhancing antibiotic effectiveness by poloxamer 407 gel against *Staphylococcus aureus* biofilms

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A common clinical problem is chronic wound infections with biofilms of *Staphylococcus aureus*. Systemic treatment against *S. aureus* infection is unsuccessful due to lack of wound vascularization, host tissue death, and biofilm defenses. Effective topical antibiotic regimen could increase success of healing in chronic wounds and accompanying infections. We hypothesize that poloxamer 407 gel, a thermoreversible polymer, can be an effective delivery vehicle by slowly releasing antibiotics to extend pharmokinetics of an antibiotic dose at the chronic infection site. The objective of this *in vitro* pilot study was to observe varying methods of biofilm treatment and their effectiveness. First, a successful *in vitro* environment of bovine serum coated coverslips submerged at varying levels of serum broth was achieved. Then *S. aureus* biofilm populations were treated with different concentrations of vancomycin to determine susceptibility via colony forming units. The vancomycin concentrations were incorporated into the poloxamer gel as a vehicle for antibiotic delivery. Success of antibiotics with the poloxamer gel was also determined via colony forming units. To better understand viability of the biofilm, plasmids expressing fluorescent GFP and YFP reporter genes were constructed and transformed to the *S. aureus* strain. Biofilm viability can be determined via fluorescent microscopy and confocal laser microscopy with this gene incorporation. Fluorescent microscopy in addition to colony forming units showed promise in quantification of biofilm viability. Further research is needed for successful study of *S. aureus* biofilms and their susceptibility. The long-term outcome is to integrate studied methods into an *in vivo* application.

**Research Grant:** National Institutes of Health 2T35OD010432-16 and Mississippi State University College of Veterinary Medicine  
**Student Support:** None

Vector capacity of mosquitoes for canine heartworm disease in the UW-Madison Arboretum

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Heartworm disease in dogs causes substantial morbidity, treatment options for infected animals are less than optimal, and there is evidence that the parasites are becoming resistant to existing preventative drugs. There are many species of mosquito implicated in transmission of *Dirofilaria immitis* (*D. immitis*), the etiologic agent of canine heartworm disease. To better understand the specific species involved, we are investigating three suspect vector species, *Aedes vexans*, *Aedes canadensis*, and *Aedes trivittatus*, from the University of Wisconsin-Madison Arboretum in Madison, Wisconsin. This is a site where there is likely active transmission of the parasite because coyotes living in the Arboretum routinely test positive for heartworm infection. In this study, lab-reared progeny from wild-caught individual mosquitoes will be experimentally infected with *D. immitis* to evaluate whether the parasites develop to the infectious stage. Further, PCR for *D. immitis* will be performed on wild-caught individuals to determine the prevalence of infection and further implicate the vector involved in transmission. Data from the literature suggest that these suspect mosquitoes are susceptible to infection and have the flight range to carry the disease outside of the arboretum and into neighboring domestic dog populations. Risk-assessment for heartworm transmission at the wildlife-domestic animal interface will be more accurate as a result of this study.

**Research Grant:** Upper Midwestern Regional Center of Excellence for Vector-Borne Disease  
**Student Support:** NIH T35 Short-Term Research Training for Veterinary Students in Wisconsin
Utility of *Campylobacter jejuni* infected NOD mice with humanized microbiota as a Guillain-Barre model

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*Campylobacter jejuni* is a bacterial pathogen that has been linked with the neuropathy Guillain-Barre syndrome (GBS). GBS is an autoimmune disorder characterized by weakness of the limbs and ascending paralysis. The exact pathogenesis of GBS is unknown but it is thought that molecular mimicry between *C. jejuni* lipooligosaccharide structures and nerve cells gangliosides are a mechanism of anti-ganglioside antibody induction and nerve damage. We hypothesize that *C. jejuni* infected Non-Obese Diabetic (NOD) mice with humanized microbiota will produce more autoantibodies and more nerve lesions similar to those seen in humans with GBS compared to NOD mice with conventional intestinal microbiota. We examined the immune response of NOD mice with conventional intestinal microbiota or humanized intestinal microbiota given several different treatments: orally inoculated with TSB as a control, with *C. jejuni* strain 11168 or with *C. jejuni* strain 260.94. Mice were examined for a neurological phenotype and nerves from these mice were examined for lesions of GBS. The sciatic nerve, brachial plexus, and dorsal root ganglion were dissected, fixed, embedded, sectioned, stained and examined for evidence of pathology. Nerve tissues were analyzed to determine if there was a difference in macrophage infiltration in mice with different microbiota and with different treatments. Counts ranged from 0.66 to 11.44 macrophages per 100,000 pixels squared in the dorsal root ganglia, but no significant differences were detected between treatment groups or microbiota groups based on one-way ANOVA. Available data suggests that we will reject the hypothesis that humanized microbiota exacerbates GBS in NOD mice.

**Research Grant:** NIH-1R21AI121748-01A1  
**Student Support:** Undergraduate Research Office, Michigan State University

Recombinant baculovirus expression of Rift Valley Fever Virus nucleoprotein and use as diagnostic antigen

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Rift Valley Fever Virus (RVFV) is an arbovirus with the potential to cause disease in both humans and animals. It is endemic in Africa and the Arabian Peninsula but has great potential for transboundary spread. Accurate detection is required to contain the spread of the virus. Commercially available serological tests for RVFV mostly utilize E. coli-expressed RVFV nucleoprotein (N). However, some level of cross-reactivity with yet unknown agents has been reported in ruminants in non-endemic areas such as the United States. This demands development of more improved diagnostic tests. The purpose of this study is to produce recombinant RVFV N protein in a baculovirus expression system and assess its use as antigen to detect RVFV antibodies in experimentally infected animals. Using a Bac-to-Bac expression system, a recombinant baculovirus containing the N gene of RVFV strain ZH548 was created and used to infect Spodoptera frugiperda (Sf9) cells. An estimated 30 kDa recombinant protein corresponding to the expected molecular size of RVFV N protein was expressed as demonstrated by western blot analysis and Coomassie blue staining. Immunoblot analysis shows the recombinant N antigen is reactive with mouse anti-RVFV N monoclonal antibody (R3-1D8) and with antisera obtained from sheep and cattle experimentally infected with wild type RVFV. An indirect enzyme-linked immunosorbent assay (ELISA) based on the recombinant N antigen detected the kinetics of RVFV-specific antibody responses in sheep experimentally infected with a wildtype virus. These results suggest recombinant baculovirus-expressed N protein can be used as a suitable antigen for serological diagnosis of RVFV infections in ruminants.

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**Student Support:** NIH T35OD010979
The role of NLRP3 inflammasome in lyme arthritis

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Vector-borne diseases cause more than 1 million deaths annually around the world. Lyme Disease is caused by the spirochete, *Borrelia burgdorferi*, via the bite of an infected tick. Humans with Lyme Disease can develop arthritis, carditis, and neurological conditions, but the mechanisms driving these maladies are unclear. NOD-like receptors (NLRs) are expressed in the cell cytosol and are able to detect intracellular pathogens. They are partly responsible for immune activation leading to production of inflammatory cytokines and inflammation. NLRP3 is the most versatile NLR and likely the most clinically important. Involvement of the NLRP3 inflammasome during infection with *B. burgdorferi* is controversial. Several labs have investigated the role of the NLRP3 inflammasome in Lyme Disease, however, those studies have all used C57BL/6 mice, which are Lyme arthritis resistant and thus do not develop a strong inflammatory response. We will be using C3H mice which develop severe arthritis following a footpad inoculation with *B. burgdorferi*. We hypothesize inflammation in response to *B. burgdorferi* is due to activation of the non-canonical NLRP3 inflammasome. We will be utilizing bone marrow derived macrophages and resident peritoneal macrophages to investigate the inflammatory response to *B. burgdorferi*. Targeting the inflammasome may lead to treatments for inflammasome related inflammatory diseases.

Research Grant: University of Missouri College of Veterinary Medicine COR Grant
Student Support: Boehringer Ingleheim

Urothelial IL-15 receptor transcription in response to acute *Escherichia coli* infection

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Superbugs and their inherent antimicrobial resistance limit a clinician’s ability to treat urinary tract infections (UTIs) with conventionally used antibiotic. This obstacle creates a need for alternative therapies that limit patient morbidity by preventing/repairing urinary bladder damage caused by UTIs. Bacterial induced tight junction destruction allows urine solutes to traverse the bladder epithelium (urothelium) causing inflammation and pain associated with UTIs. Little is known about urothelial tight junction regulation, maintenance and repair, however the interleukin 15 receptor (IL-15R) is critical in forming, maintaining, and repairing intestinal tight junctions via the upregulation of zona occludens and the phosphorylation of claudins. We hypothesize that IL-15R and IL-15 mRNA are upregulated during uropathogenic *E. coli* damage to urothelium in comparison to healthy urothelium. To test our hypothesis intron spanning primers were designed against IL-15Rα and IL-15 genes. RT-qPCR was performed using cDNA from urothelium exposed to uropathogenic *E. coli* and healthy urothelium. We anticipate *E. coli* damaged urothelium will have increased transcription of IL-15Rα and IL-15 genes. These findings will be the first step in proving our overriding hypothesis that during infection IL-15R improves tight junctional integrity by increasing zona occludens expression and claudin phosphorylation alike to what is observed in the intestine. Considering that many of the clinical signs associated with UTIs involve a loss in tight junctional integrity; the ability to modulate the upregulation of these tight junctions could have great clinical implications in the treatment and management of UTIs in both human and veterinary species.

Research Grant: National Institutes of Health K12 Urologic Research Career Development Program: Wood MW.
Student Support: 5T35OD011078-07

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Fluoroscopic kinematic comparison between cranial cruciate ligament-rupture susceptible and stable dogs

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Cranial cruciate ligament (CCL) rupture is the most common cause of hindlimb lameness in dogs. The Labrador is considered an “at risk” breed for CCL rupture, while the Greyhound is considered a “genetically-safe” breed, almost never developing naturally-occurring CCL rupture. We hypothesize that tracking stifle motion during ambulation will demonstrate specific kinematic differences between the two breeds that will help elucidate why Greyhounds are considered a genetically safe breed for CCL disease. Six normal Greyhounds will ambulate on a treadmill while fluoroscopic images of the stifle are acquired at both the walk and the trot. Three-dimensional (3D) bone models of each dog’s femur and tibia, generated from a CT scan of the hindlimbs, are assigned an anatomic coordinate system. Femorotibial kinematics are determined by matching the 3D bone models to the corresponding fluoroscopic images using a 3D to 2D shape-matching technique. These data are then compared to previously described Labrador kinematics. Preliminary results demonstrate that stifle range of motion in flexion and extension is similar between both breeds. Tight coupling between flexion and internal tibial rotation ($r = 0.92$) and between flexion and caudal tibial translation was detected in the Greyhound ($r = 0.94$). This coupling is tighter than what was seen in the Labrador. Interestingly, despite the difference in prevalence of CCL disease between these two breeds, preliminary data suggests that kinematic patterns are markedly similar. Unfortunately, we had to reject our null hypothesis. Significant kinematic differences between these two breeds did not elucidate some of the pathomechanisms behind CCL disease and rupture.

**Research Grant:** None  
**Student Support:** Morris Animal Foundation

UVC radiation bactericidal properties and practical use of handheld device in swine facilities on materials

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Biosecurity at swine farms is of utmost importance to prevent pathogens that may have a significant economic impact on the swine industry. Since supplies and equipment can act as infectious fomites, there is a need to validate biosecurity protocols to decrease the risk of pathogen introduction into farms. Current protocols to safely introduce supplies are time intensive and larger equipment is difficult to disinfect. UVC radiation is an accepted form of microbial inactivation that has been successful in decreasing porcine reproductive and respiratory syndrome virus on common materials and antimicrobial resistant bacteria and problematic bacteria on surfaces in hospitals. Our objective was to evaluate a handheld UVC device for bactericidal properties alongside its applicability of use to disinfect common equipment surfaces for admittance to swine farms. Five materials including plastic, metal, paper, Styrofoam and cardboard, were inoculated with 0.5mL of $10^8$ CFU/mL of a solution of Escherichia coli and treated at 1 second, 10 one second passes and 10 seconds stationary with a UVC wand device (Steril-Aire Steril-Wand; Burbank, California). In order to evaluate the effectiveness of this treatment on soiled surfaces, the materials were also inoculated with Escherichia coli contaminated with sterilized swine fecal material and treated with the same handheld device for the same amounts of time. After treatment samples were cultured and E. coli was quantified. Preliminary results indicated reduction rates at 10 one second passes of 98% and 88% for Styrofoam and cardboard, respectively. Inactivation of paper, plastic and metal was in between these values. There were minor reductions at one second treatments.

**Research Grant:** Swine Disease Eradication Center  
**Student Support:** The University of Minnesota, College of Veterinary Medicine
Genome wide association study of type A pulmonic stenosis in bulldogs

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Pulmonic stenosis (PS) is a common congenital heart defect in dogs. Fusion of the pulmonic valve leaflets, classified as Type A, is the most frequent form observed. Bulldogs are overrepresented for PS leading the authors to suspect a genetic etiology of this condition within the breed. It is hypothesized that Type A PS is caused by variant(s) that disrupt cardiac development. The aim of this study is to identify chromosomal regions associated with Type A PS in Bulldogs using a genome wide association study (GWAS). A GWAS was performed using the Illumina 230k Canine SNP Array on 12 cases and 45 controls. Cases are Bulldogs diagnosed with Type A PS by echocardiography. Controls are Bulldogs with no congenital heart defects or PS. The genotyping data underwent stringent quality control and filtering (call rate < 0.9, MAF < 0.05) using Golden Helix software to identify single nucleotide polymorphisms (SNPs) that are significantly associated with cases when compared to controls. Statistical analyses include Chi-square association tests, Bonferroni correction for multiple testing, and population stratification correction using EMMAX. A genome-wide significant association was present on chromosome 7 (CFA7 praw=2.80x10^-10) after correction for multiple testing and population stratification. Review of candidate genes within the region of association revealed an interesting gene, CFAP53, known to be associated with congenital cardiac abnormalities including PS. Either candidate gene or whole genome sequencing is necessary to identify proposed causal variants. Ultimately the development of a genetic test based on the causal variant(s) may reduce the incidence of this condition in Bulldogs.

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Student Support: AVMA/AVMF 2nd Opportunity Research Scholarship

Gene characterization of biofilm forming Escherichia coli equine reproductive tract isolates

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Biofilms evade the immune system and antibiotics, leading to persistence of infection and increases in antibiotic resistance. Static biofilms form when aggregates of bacteria adhere to a surface and secrete an extracellular polymeric substance. Formation of biofilms in the equine reproductive tract are theorized to be a significant cause of chronic equine endometritis, but there is little research establishing causality. The purpose of this study is to improve understanding of genes involved with biofilm formation by E. coli colonizing the equine reproductive tract. We hypothesize that biofilm-forming E.coli isolates possess genes demonstrated to be important for biofilm adhesion: fimH (type 1 fimbriae); sfa (S-fimbriae); pgaA and pgaC (matrix polysaccharide adhesion); and csgA and csgD (curli fimbriae). The DNA from 26 strong biofilm forming E.coli reproductive tract(15 clitoral fossa, 11 uterine) isolates (based on crystal violet assay) were evaluated by PCR analysis; 16s PCR confirmed all samples were E.coli. Control isolates (MG1655, J96, 25922, and 8739) were positive for all genes of interest except MG1655 and 8739, which were negative for sfa. All sample isolates were positive for the genes, fimH, pgaA, pgaC, csgA, csgD. Only two clitoral fossa isolates were positive for sfa: ecf49 and ecf7. Gene sequencing to establish authenticity is underway. This is the first report on gene characterization of equine reproductive tract E. coli isolates. Future studies will compare these isolates to those of weak and moderate biofilm forming isolates, as well as investigate additional genes pertinent to biofilm formation.

Research Grant: Department of Clinical Sciences
Student Support: CVM Veterinary Scholars Program, Merial Grant, Fund for Discovery, Herbert Benjamin Endowment
Radiographic sizing for canine meniscal transplantation

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In veterinary literature, information regarding the utility of meniscal allograft transplantation is sparse. Currently partial meniscectomy while leaving as much normal meniscus intact as possible is commonly performed in dogs. This procedure is associated with a poor long term outcome. In humans meniscal transplantation is frequently performed with good outcome. In humans meniscal size can reliably be determined from standard anterio-posterior and lateral knee (stifle) radiographs. To our knowledge there is still no standard protocol available to determine meniscal allograft size in dogs which is needed for a successful outcome of meniscal transplants. Therefore, the purpose of our study was to determine the correlation between standard radiographic bony landmarks and anatomical meniscal dimensions in dogs so that veterinary surgeons can order size-specific meniscal allografts. Twenty two hind limbs were obtained from 11 canine cadavers which provided 22 medial menisci. After transecting the medial joint capsule and medial collateral and cranial cruciate ligaments, the medial meniscus was painted with a radiopaque mixture, the capsule and ligaments were repaired and radiographs of stifles were obtained. Radiographic measurements (tibial plateau length and width) were acquired by 4 investigators. The radiopaque mixture from the medial meniscus was then removed and stifles were completely disarticulated and anatomical meniscal measurements (meniscal length and width) were performed using digital calipers. Currently statistical analysis is being performed based on the ICC (intra-class correlation coefficient) to compare the meniscal anatomic and radiographic measurements to establish a relationship between the two.

Research Grant: Summer Scholar Grant, LSU
Student Support: NIH T35-OD011151

Synthesis and analysis of elephant endotheliotropic herpes virus gene expression in elephant cells

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Elephant endotheliotropic herpes virus (EEHV) is a ubiquitous infection found in Asian and African elephants. This virus causes a hemorrhagic disease with few prodromal signs and death within hours to 7 days. There have been 7 different species of EEHV identified and all are capable of leading to hemorrhagic disease, although with different degrees of pathogenicity. Of the 46 confirmed cases of EEHV in the United States and Europe only 10 elephants survived. All but five of these cases involved Asian elephants. EEHV has also been proven lethal in Asian elephant wild ranges with up to 15 confirmed cases and many more anecdotal reports. Clinical symptoms include lethargy, lameness, colic, anemia, thrombocytopenia, edematous swellings of the head and thoracic limbs, oral ulceration and cyanosis of the tongue. Currently the most effective therapy is early detection and immediate intervention with 24-hour supportive care along with the administration of the human antiviral medications famciclovir and ganciclovir for a week or more; however, treatment is costly and the use of antivirals have yet to be proven effective. New vaccine and treatment development have been limited by the inability to propagate EEHV in culture. To address this challenge, our goal is to synthetically assemble the genome of the EEHV1A subtype using DNA assembly methods. The EEHV1A genome has been sequenced and is associated with more fatalities than any other EEHV subtype. In addition, an artificial chromosome is added to the EEHV1A viral genome to facilitate propagation and study. This work will allow for the design of novel treatment strategies for EEHV and facilitate elephant conservation.

Research Grant: None
Student Support: NIH T35 Training Grant
Characterization of 5 newly generated canine osteosarcoma cell lines

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Canine and human osteosarcomas are notably similar, and have a high rate of metastasis. There is a poor understanding of the tumor development process, predisposing causes, and varying levels of aggression among different cell lines. By characterizing newly developed canine osteosarcoma cell lines, treatments for people and pets can be developed. Of the seven subtypes of OS, three are represented in this group: osteoblastic (the most common), fibroblastic, and giant cell variant. To our knowledge, there are no other giant cell variant canine OS cell lines in the published literature and only one canine fibroblastic osteosarcoma cell line. Understanding the differences between the histologic subtypes in dogs will help to guide comparative research. This study characterized five primary canine osteosarcoma cell lines: Booza, Kayden, Leibniz, Molly, and Tatianna. For characterization a cell proliferation assay, Boyden chamber invasion assay, alkaline phosphatase staining, cisplatin sensitivity, phosphorylated Y-H2AX immunohistochemistry, oxidative damage assay, differentiation media assay, and single flank injections in athymic nude mice were performed. Thus far, Alkaline phosphatase expression and invasive-ness appear to be positively linked. Invasiveness appears to have a negative correlation with in vivo growth rate and flank injections of Tatianna have resulted in the fastest growth rate in vivo. Further comparisons of these cell lines may identify a variety of characteristics valuable for understanding the disease process and developing treatments for osteosarcoma.

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Student Support: Student Support: National Institutes of Health #5T35OD010991

Effects of social status and periodontal disease on the severity of post traumatic osteoarthritis in mice

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Osteoarthritis (OA) affects over 27 million Americans, and knee OA is the most common joint affected. OA causes progressive breakdown of articular cartilage leading to disability, decreased quality of life and substantial economic burden. Social stress identified by low socioeconomic status (SES) is a risk factor for worse OA, and periodontitis is correlated with both SES and OA, but neither causal relationship nor mechanism have been established. The aim of the study was to evaluate if chronic social stress or periodontitis change the progression of post-traumatic OA in mice. Chronic social stress was modeled using the resident-intruder chronic social defeat (SD) paradigm, and periodontitis was induced with periodontal ligature (PL). Destabilization of the medial meniscus (DMM) induced OA with additional SD or PL were hypothesized to exacerbate OA compared to DMM alone. With IACUC approval, 14 week old male C57BL6/J mice were divided into 4 groups: 1) sham surgery control, 2) DMM alone, 3) DMM+PL and 4) DMM+ PL 8 weeks of SD. DMM and PL were performed at 16 weeks, and mice were sacrificed at 24 weeks of age. Knees were scanned by micro-computed tomography and the following parameters quantified: total joint bone volume (TJBV), subchondral bone thickness, subchondral bone volume, subchondral bone density, trabecular bone mineral density, trabecular bone volume, and bone fraction (BV/TV). Based on previous studies, these values are expected to be increased in groups with worse OA, particularly in the medial tibia and medial femur, due to bone remodeling from altered weight bearing. Evaluating risk factors such as periodontitis and chronic social stress will increase the understanding of the complex phenotype of OA.

Research Grant: National Institute of Health; Duke University; Purdue University
Student Support: Boehringer Ingelheim Veterinary Research Scholars Program
Detection of fetal microchimerism in the mare

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Fetal microchimerism is the presence of fetal cells circulating in maternal blood during and following pregnancy. It has been observed in humans, rodents, dogs, and cows. In humans, studies have shown a relationship between the presence of fetal microchimerism and protection from cancer. The presence of male DNA can also indicate early-term fetal sex. Our lab has generated primers to detect a segment of the equine Y-chromosome. The purpose of this study will be to optimize a detection protocol, analyze banked samples, and determine whether fetal microchimerism occurs in pregnant and parous mares. Further, we will observe the short and long term presence of fetal cells in the mare. We hypothesize that a polymerase chain reaction (PCR) assay can be used to identify the presence of male fetal DNA circulating in mare maternal blood both prior to and post-partum. Previously isolated DNA samples from blood collected at two different breeding farms will be used in this study. Each sample will be tested using a two-step nested PCR to increase sensitivity and prevent contamination. DNA from male horses will serve as a positive control and DNA from nulliparous mares will serve as a negative control. We anticipate that Y-chromosomal bands will be detected in mares that are pregnant with colts and persistent in some mares from prior colts. These results would indicate an ability to detect male fetal genetic material in mares, and offer the possibility of a non-invasive method of early fetal sex determination that is simpler than current methods practiced in the equine industry.

Research Grant: Tom and Betty Scott Endowed Program in Veterinary Oncology
Student Support: Mizzou Advantage initiative in One Health / One Medicine

Crate training shelter dogs using a computer assisted training system


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At least 10% of dogs adopted from shelters are returned. Over 50% of these returns are due to behavior problems. Training programs may increase adoption rates and decrease return rates. Crate training helps dogs to accept confinement to a crate, which can aid in addressing common behavior problems such as house soiling and destructive chewing. Crate training may therefore reduce shelter returns. However, many organizations lack adequate employee or volunteer time to provide this. The purpose of this study is to use the Computer Assisted Training System for Dogs (CATS) to crate train shelter dogs, largely without the need for a human trainer. Over the course of five experimental phases: two phases of classical conditioning and three of operant conditioning, dogs learn to lie down quietly in the crate. The CATS is used for the entirety of the latter four phases. Thus far, five of nine dogs have successfully completed phase one, which requires them to enter and remain in the open crate for 150 consecutive seconds. Three of three dogs have successfully completed phase two, which requires subjects to remain in the closed crate while the CATS dispensed food reinforcers at increasing intervals. Dogs have to eat all treats and remain below the set limit for vocalizations, demonstrating they are positively classically conditioned to the crate and the CATS. This study has the potential to provide a method for shelters to efficiently crate train dogs and reduce returns.

Research Grant: NSF Cyber Physical Systems Program Grant CNS-1329738
Student Support: Merial Grant, The Fund for Discovery, and Herbert Benjamin Endowment
WBC differential counts in healthy bats and those with white-nose syndrome

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Bats play important roles in their ecosystems, including insect control and pollination. In recent years, white-nose syndrome has been devastating to many bat populations in the US, particularly those in the genus Myotis. This disease is caused by a fungus known as Pseudogymnoascus destructans, but is not fully understood yet. As it continues to spread west, it is important for us to learn more about the disease in order to preserve the remaining bat populations. For many species, white blood cell differentials can reveal whether or not an animal has an infection, and how their immune system is reacting. Blood smears have been made from a number healthy bats, as well as many bats infected with white-nose syndrome. We are performing WBC differential counts on each sample, starting with the little brown bats (Myotis lucifugus), to obtain the relative percentages of each leukocyte type. Bats have all the typical leukocytes: neutrophils, eosinophils, basophils, lymphocytes, and monocytes. We expect to find a difference in the present leukocytes between the healthy bats and those fighting white-nose syndrome. We are also working on methods to measure WBC counts and other blood parameters. Not only will this establish baseline data for healthy bats, but it could also provide a new way to diagnose white-nose syndrome as well as reveal more information about the mechanism behind this fatal disease.

Research Grant: Unknown
Student Support: Endowment established by IDEXX-BioResearch

Is sex a biological variable in corneal wound healing?

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The cornea, a transparent tissue of the eye, is vulnerable to damage from the external environment. Following insult, the cornea undergoes a complex healing process affected by several factors, such as age and stress. The role of sex in corneal wound healing is poorly understood. The purpose of this study was to determine the role of sex in corneal wound healing using a rabbit model. The hypothesis that sex plays a minimal role in corneal wound healing was tested using male (n=6) and female (n=6) New Zealand White rabbits. The Institutional Animal Care and Use Committee approved the animal study. Procedures and treatments in animals were performed in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Visual Research. A well-established protocol for wounding of the rabbit cornea was utilized. Clinical stereo- and slit-lamp examination and imaging and intraocular pressure (IOP) measurements were done prior to and on days 0, 3, 7, and 14 after wounding. On day 14, rabbit corneal tissues were collected after humane euthanasia to investigate biological parameters of wound healing. RNA levels of alpha-smooth muscle actin (α-SMA), transforming growth factor-beta (TGF-β), and extracellular modeling proteins were measured with qPCR. Protein expression and localization were analyzed with immunohistochemistry (IHC). Quantification and statistical analyses are underway. The clinical imaging (Fantes: male = 1, female = 1), IOP (male = 9.5 mmHg, female = 9.5 mmHg), mRNA (α-SMA: male = 12.4-fold, female = 11.9-fold; TGF-β: male = 10.4-fold, female = 10.9-fold), and IHC (comparative analysis pending) data collected thus far suggest sex has limited impact on corneal wound healing. More studies are warranted.

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Student Support: Stipend is supported by the Mizzou Advantage initiative in One Health / One Medicine.
Development and evaluation of a new app to assess risk and exposure to antimicrobial resistant bacteria

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Introduction: Antimicrobial resistant bacteria (AMRB) are being transmitted from animals to humans and vice versa through a magnitude of known and unknown pathways. To better quantify human exposure to spatially defined biohazards, a new app (i.e., FarmQuestion) was developed and tested in a pilot study. Farmers downloaded the app on their smartphone to more accurately measure exposures to spatially explicit biohazards and to collect biosecurity behavioral data. Behavioral questions were cued randomly in time or when farmers were near on-farm biohazards. Via location tracking and geofencing, the app recorded farmers‘ duration of exposure to bio-hazardous areas. A pilot study was conducted to identify the feasibility of using the app to measure exposures spatially. Methods: Participants selected for the study had to be involved in commercial animal husbandry within 150 miles of Lansing, Michigan. During enrollment, a biosecurity beliefs and behaviors survey was administered, and participants were assisted in initializing the app. The app collected 2 weeks of data in 15 second intervals. Chi-Square tests were used to analyze numerical responses from the questionnaire and the app. Thematic analysis was used to evaluate free response questions. Farmers‘ exposure levels to AMRB were quantified using time exposure recorded in the app. Results: There are significant inconsistencies across multiple sectors of animal production on what biosecurity means and how it is being implemented. Conclusion: The app is an effective method of quantifying human exposure to biohazards on farms, but participant compliance with downloading and answering questions posed difficulty.

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The prevalence of Baylisascaris procyonis and Trypanosoma cruzi in raccoons from New Orleans, LA

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Infection with the raccoon roundworm, Baylisascaris procyonis, causes severe and often fatal eosinophilic meningitis in humans. While this roundworm has a wide geographic distribution, there is no published data indicating raccoons in New Orleans carry B. procyonis. Further, it is not well understood if raccoons contribute to the transmission of Chagas Disease (Trypanosoma cruzi), another relevant zoonotic disease. The aim of this study is to determine the prevalence of Baylisascaris procyonis and Trypanosoma cruzi in raccoons from New Orleans, LA. 62 raccoons from Orleans and Jefferson Parish were examined. Adult roundworms were removed from the intestines. They were identified morphologically using a scanning electron microscope and molecularly using PCR. Double-spin fecal flotations were done to determine prevalence of Baylisascaris eggs. Heart and colon samples were tested for T. cruzi by diagnostic PCR using primers TcZ1/TcZ2 for genomic satellite DNA. Results showed a prevalence of 34% for adult roundworms and 28% for Baylisascaris eggs. This difference may be attributed to immature worm populations or single-gender populations. Preliminary T. cruzi results showed a prevalence of 43%. Results were consistent with Baylisascaris prevalence data recorded from other urban areas. Additionally, there is a greater prevalence of T. cruzi throughout the city of New Orleans than was previously known. Since many positive samples were collected from parks throughout the city, there is a greater chance of animals and humans being infected by these parasites. As the first study in New Orleans to demonstrate this data, these results are critical for public education and disease prevention.

Research Grant: Faculty Resources Grant Louisiana State University School of Public Health
Student Support: NIH T35 Training Grant T35OD011151
Cyanidin stimulates insulin secretion and pancreatic β-cell gene expression

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Cyanidin, a flavonoid found in dark-colored fruits and vegetables (such as blueberries and blackberries), is an anti-oxidant and anti-inflammatory molecule. It also has anti-diabetic properties, including the ability to lower blood sugar and increase insulin levels in patients. However, the mechanism by which cyanidin stimulates insulin secretion from pancreatic β-cells remains unclear. This study was performed to elucidate the mechanism of cyanidin and to determine whether it controls the expression of genes involved in the glucose-induced insulin secretion pathway. In the first experiment, we utilized the static incubation technique to measure insulin secretion from INS-1 cells. In the second experiment, cells were stimulated with cyanidin and RNA collected at various time points to quantify gene expression of proteins in the glucose pathway. Stimulation with cyanidin increased insulin secretion, but was inhibited by nimodipine, a voltage-dependent Ca\(^{2+}\) channel (VDCC) blocker. In the absence of extracellular Ca\(^{2+}\), cyanidin failed to increase insulin secretion, but not after depletion of intracellular Ca\(^{2+}\) stores in the endoplasmic reticulum. In addition, cyanidin up-regulated the expression of the glucose transporter GLUT-2, ATP-sensitive K\(^{+}\) channel, and VDCC genes. Our results revealed that cyanidin stimulates insulin secretion by activating VDCCs, which promotes Ca\(^{2+}\) influx. Furthermore, several genes involved in the glucose response in pancreatic β-cells were up-regulated. These findings suggest that cyanidin could be used as an alternative treatment for reducing hyperglycemia in diabetic patients.

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Effects of altered weight bearing on digital perfusion in horses

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The pathophysiology involved in the development of support limb laminitis (SLL) has yet been elucidated; however, vascular occlusion associated with increased weight bearing has been proposed. Support (or contralateral) limb laminitis is known to occur in horses treated with cast application and duration of casting has been positively associated with increased risk of developing SLL. The objectives of this study were 1) to determine if placement of a distal limb cast would alter weight bearing and change vascular perfusion to the hoof and 2) to determine if mechanical foot support on the contralateral limb could be used to help prevent vascular changes associated with the development of SLL. Eight horses were placed in a distal limb cast on one forelimb for 48h to evaluate the effect of altered weight bearing on digital venous perfusion of the contralateral limb. Digital venograms of the contralateral limb were performed without casting (control) and with a cast applied, both without contralateral foot support (cast/no shoe) and with contralateral foot support (cast/shoe). Pedometers were placed on the contralateral limb for 8hrs to determine the frequency of weight shifting / bearing. Application of a cast without a support shoe resulted in a significant difference (P < 0.05) between the casted and contralateral limb. Comfort scores were significantly (P < 0.05) higher in the casted horses. No difference was noted in frequency of weight shifting between groups. Venograms were graded and vascular perfusion patterns described. Data analysis is ongoing at this time to compare differences between the treatment group.

Research Grant: Equine Health Studies Program, Louisiana State University School of Veterinary Medicine
Student Support: National Institute of Health T35- OD011151
Antigenicity of xenogeneic heart valves determined by a novel immunoproteomic approach

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American Heart Association estimates the prevalence of valvular heart disease to be 2.5% in the United States. Biological heart valve replacements are considered the current standard of care. The NHLBI xenotransplantation working group identified xenoantigenicity as the barrier for use of xenogeneic tissues. We have developed an affinity chromatography method that can offer an innovative shotgun proteomic approach to antigen identification, and aim to test it with human serum. Protein was extracted from BP and two groups were obtained from the Mayo Clinic BioBank, six control patients with mechanical valve implants, and six post-implant patients with glutaraldehyde-fixed bovine pericardium (GF-BP) implants. Antibodies were cross-linked to Protein G HP SpinTrap columns and protein run through the column. Antigenic proteins were trapped and non-antigenic proteins were washed through the column. These antigenic proteins were eluted off the column and identified using LC-MS/MS. Both the mechanical implant patients and the GF-BP implant patients had antibodies toward proteins from the bovine pericardial extract. This could be due to the cross-reactivity of antibodies as 1% of IgG in human serum is toward galactose-alpha-1,3-galactose, which are present on BP proteins and could result in protein capture on the column even though the antibodies are not specific to the protein epitopes. However 104 proteins were found to be significantly elevated in the bovine pericardial implant group. This work therefore represents the first high throughput method of antigen identification that can now be used to monitor currently implanted patients as well as inform the development of BP-based biomaterials in the future.

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Student Support: 5T35OD010956-18

Dermatophagoides farinae-specific IgG in atopic dogs receiving sublingual immunotherapy

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Canine Atopic Dermatitis is a skin disease characterized by an imbalance in the response of the immune system upon allergen-recognition, in which IgE antibody is inappropriately produced leading to mast cell degranulation and pruritic clinical signs. House dust mite Dermatophagoides farinae (Df) has been identified as the most common allergen in dogs. Sublingual immunotherapy (SLIT) involves administration of patient-specific allergen extract leading to the induction of allergen-specific IgG antibodies, which block allergen binding to IgE. SLIT has been adopted as a common treatment in dogs, but there are no established biomarkers for determining its efficacy. This is important as SLIT takes several months to manifest improvement in clinical signs and veterinarians are limited by purely subjective assessment of therapeutic response. In people receiving immunotherapy, it has been established that a rise in allergen-specific IgG can be used as a biomarker for monitoring treatment success. We hypothesize that in atopic dogs receiving SLIT for hypersensitivity to house dust mite, Df-specific IgG will increase over time. To test this, we used ELISA for Df-specific IgG on paired sera, pretreatment and 6-18 months into treatment from 14 atopic dogs being treated with SLIT. Three dogs that showed an excellent-good therapeutic response to SLIT had a 19.9% average increase in u/mL Df-specific IgG, whereas 11 dogs that showed a poor-fair response had a 3.2% average decrease in u/mL Df-specific IgG. This trend in increased allergen-specific IgG with positive therapeutic response to SLIT has the potential to revolutionize the way that SLIT is monitored in dogs-allowing therapeutic efficacy to be determined faster and more reliably.

Research Grant: None
Student Support: School of Veterinary Medicine, Office of Academic Affairs
Characterizing the conventional outflow pathways in felines with primary congenital glaucoma (PCG)

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Primary congenital glaucoma (PCG) due to increased intraocular pressure (IOP) is an important cause of blindness in children. Conventional aqueous humor outflow pathways, including the angular aqueous plexus (AAP), collector channels (CC) and scleral venous plexus (SVP), play an important role in regulating IOP. Although it is believed malformation of these pathways leads to IOP elevation in children and animals with PCG, disease mechanisms remain poorly understood. Therefore, improved understanding of PCG pathophysiology is needed to better target treatment of this disease. However, ocular tissues from human patients are seldom available for histopathology. We have identified a genetic form of PCG in cats that is essentially identical to human PCG due to LTBP2 mutation. The aim of this study was to investigate anatomical abnormalities in the conventional outflow pathways in eyes of cats with inherited PCG. Eyes from 3 PCG and 3 normal, adult felines, were fixed with 4% PFA, embedded in OCT compound, 10um-cryosectioned and immunofluorescent labeled using markers for endothelial cells (CD31) and pericytes (alpha-SMA). Images were captured by epifluorescence and confocal microscopy. As in the equivalent human structure (Schlemm’s canal), feline AAP is CD31-positive, but is alpha-SMA-negative, whereas CCs and SVP were positive for both CD31 and alpha-SMA. Furthermore, the AAP is present in both PCG and normal feline eyes, suggesting that AAP may not be an important site for increased resistance to aqueous outflow in PCG. However, additional histomorphometric studies will be important in determining whether anatomic relationships in this region are altered in PCG and are ongoing.

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Student Support: NIH T35 Short-term Research Training for Veterinary Students in Wisconsin (PI: Dale Bjorling)

Cryosurvival and fertility of mouse cumulus oocyte complexes by using a Cryoloop method

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Embryo and gamete cryopreservation is important to preserving rodent strains used as models for animal and human disease research. However, cryopreservation of mammalian oocytes is less successful than that of sperm and embryos. Increased oocyte cryopreservation success would provide more complete genome banking of genetically modified rodent strains. This study’s objective is to provide information to improve oocyte cryopreservation success by comparing mouse oocyte cumulus complexes (COCs) cryo-survival and post-thaw fertility rates between a vitrification procedure with a Cryoloop versus a 0.25 mL French straw. COCs from superovulated outbred CD-1 mice were vitrified with either a Cryoloop or French straw method. Vitrified COCs were thawed and cumulus cells were removed to record oocytes with intact and damaged oolemma. Cryosurvival rates of COCs vitrified with 0.25 mL French straws (19%) were significantly lower than those using a Cryoloop (75%) (P < 0.05). An in-vitro fertilization (IVF) procedure was performed to compare fertility of COCs vitrified by Cryoloop and freshly collected COCs. IVF rates of COCs vitrified by Cryoloop (71%) were lower than freshly fertilized COCs (78%) (P < 0.05). In-vitro embryo culture was performed to determine developmental competence of Cryoloop-vitrified COCs up to the blastocyst stage. embryo development rates following IVF of Cryoloop-vitrified mouse COCs (56%) were lower than freshly collected COCs (90%) (P < 0.05). This shows, despite some reduction, acceptable in-vitro fertility and embryo development rates can be achieved following cryopreservation of mouse COCs with a Cryoloop vitrification method and this method may be a successful way to preserve mouse strains for genome banking.

Research Grant: The Mutant Mouse Research and Resource Center
Student Support: The University of Missouri Mutant Mouse Resource and Research Center (U42OD010918)
The effect of the probiotic Enterococcus faecium SF-68 on cats with chronic kidney disease

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Current recommendations for the treatment of chronic kidney disease (CKD) in cats include minimizing uremic toxins, maintaining energy requirements, and decreasing acid-base imbalance. However, no study in cats has explored the effect of probiotics on clinical abnormalities or biochemical abnormalities associated with CKD. The commercially available probiotic Enterococcus faecium SF-68 (FortiFlora; Nestle Purina PetCare; SF-68) is known to be palatable and has immunomodulatory effects in cats and dogs. As cats with CKD usually have interstitial nephritis with infiltrates of lymphocytes, immune modulation could have potential benefits. The primary hypothesis of this pilot study is that feeding SF-68 to cats with CKD will improve their wellness scores, appetite, water intake, and renal function when compared to a placebo. To evaluate this hypothesis, 16 cats diagnosed with stable CKD will be randomized to be fed either SF-68 (n = 8) or the product’s chicken based palatability enhancer without SF-68 as a placebo (n = 8) over an 8-week period. If the cats fed SF-68 show improved clinical and laboratory outcomes compared to the placebo group, it will suggest the immunomodulatory properties of SF68 had an effect on interstitial nephritis. To date, 12 cats have entered the study and of the 3 cats with at least 2 weeks of follow-up data, the SF-68 or placebo has been ingested consistently. The data from this pilot study will be used in a power calculation to design a larger study if indicated.

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Student Support: Nestle Purina PetCare

Mathematical modeling of Newcastle disease virus in double-crested cormorants

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Newcastle disease virus (NDV) is the causative agent of Newcastle disease, and is capable of infecting more than 250 bird species in 27 orders. While most NDV infections are subclinical cases caused by lentogenic (low pathogenicity) viruses, in the United States, pigeons and double-crested cormorants (DCCO) are natural reservoirs for virulent NDV. In fact, outbreaks of virulent NDV are frequently reported in DCCO, and have historically posed a threat to the commercial poultry industry. These DCCO outbreaks are typically detected every few years, and while many hypotheses for the cause of this cyclicality exist, none have been thoroughly tested. Mathematical modeling provides a unique opportunity to test hypotheses to further understand the driving forces behind the pattern of NDV outbreaks in DCCO. The development of such a model, however, requires data with which to parameterize the model, and some types of data are difficult to obtain. We therefore sought to develop a conceptual model for NDV in DCCO, and, using what data exists in the literature, conducted a sensitivity analysis to identify components of the model that would most benefit from further research. For this first-pass investigation, we focused on a model of only juvenile DCCO, as these birds appear to drive NDV dynamics in DCCO populations. Our model identified mortality rates due to NDV, peak prevalence during an outbreak, and seroprevalence following an outbreak as particularly important empirical data to collect to help understand the dynamics of NDV in DCCO.

Research Grant: None
Student Support: None
The human airway as a site of active HIV replication during long-term antiretroviral therapy (ART)

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Human immunodeficiency virus (HIV) remains the dominant global health crisis, affecting tens of millions of people worldwide. While modern antiretroviral therapy (ART) has largely controlled the HIV pandemic in the United States, sub-Saharan Africa remains severely affected. Treatment failure due to poor compliance or emergent resistance has stimulated significant interest in therapies that target the virus within reservoir cells, which harbor HIV even during effective antiretroviral therapy. Our prior work demonstrated the presence of HIV mRNA in alveolar macrophages of adults in Malawi, Africa, suggesting these cells may be viral reservoirs. Using robust data pertaining to the HIV infection status of individual cells, we are currently studying HIV that persists in the macrophages in the lung of adults during antiretroviral treatment, and are defining the human transcripts and viral adaptations that facilitate this persistence. To probe for the presence of infectious HIV in alveolar macrophages, I developed several novel reporter cell lines to be deployed at the point of care in Blantyre, Malawi. We have combined these cell co-culture approaches with our newest data obtained from single cell sequencing to characterize the virus present in alveolar macrophages and to discern it from HIV in T-lymphocytes, the primary target of current therapies. Our overarching objective is to contribute to new HIV therapies aimed at eliminating specific tissue reservoirs with the ultimate goal of a functional, durable HIV cure.

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Examining the effect of sorafenib on radiation-induced dermatitis in a novel mouse model

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Radiation therapy (RT) is prescribed in ~50% of cancer patients in North America. Radiation-induced dermatitis (RID) is a common side effect of RT, affecting up to 95% of patients. The effects of RID range from mild to severe and can lead to pain, disfigurement and may impede completion of cancer treatment. While the pathophysiology of RID is partially known, a complete understanding is lacking and there are no targeted therapeutic strategies. The objective of this study was to characterize the microscopic features of RID in a novel hairless mouse model and to determine the effect of sorafenib, a tyrosine kinase inhibitor, on RID clinically and microscopically. To define the dose-response effect in skin of SKH1-Elite mice following RT, a dose escalation (15 Gy, 20Gy, 25Gy, 30Gy) study was performed. To characterize the progressive pathology of irradiated SKH-1 mice and examine the efficacy of sorafenib, 2 groups (sorafenib+vehicle and vehicle only, n=5 / group) were irradiated. To evaluate the sequential effects of RT +/- treatment, biopsies were collected at 4 time points (2hr, 10d, 12d, 18d post RT). Mice were sacrificed at 24d post RT. Tissues were collected for light microscopic and IHC analysis (VEGFR2, CD34, CD31 and TGFβ-1). Histopathologic evaluation revealed progressive epithelial thickening and loss of sebaceous and follicular structures, and IHC demonstrated a dramatic increase in the intensity and distribution of VEGFR2 expression at d10 in the vehicle group. Additional details on expression of TGFβ-1, CD-31 and CD-34 are pending. The SKH1-Elite mice appear to be an adequate model for RID. Sorafenib was effective at mitigating VEGFR2 expression, but did not overtly alter the clinical course of RID.

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Student Support: The National Institutes Of Health, Award Number T35OD011118
Cat adoption in families of children with autism: Impact on cat stress and child’s social skills/anxiety

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The incidence rate of children with Autism Spectrum Disorder (ASD), 1/68, represents a significant health issue. Human-animal interaction may promote better social skills and decrease anxiety in children with ASD. Cats are a common companion animal within these families. No previous research has studied cats as interventions nor stress levels of cats in these homes. The purpose of this study is to test if the pairing of shelter cats with families of children with autism would have an effect on the cat’s stress and children’s social skills and anxiety. We hypothesize that shelter cats will have no significant increase in stress levels after introduction into a family of a child with ASD. We also hypothesize that children with ASD living with cats will have more social skills and less anxiety than those without cats. This will be an 18-week randomized controlled trial with a delayed treatment control. The Cat Stress Score, fecal cortisol concentrations, and body weight will assess cat stress. Social skills and anxiety of children with ASD will be measured via the Social Skills Improvement System Rating Scale, Screen for Child Anxiety Related Emotional Disorders, and qualitative surveys. Descriptive statistics and Analysis of Variance will be used to study within and between group comparisons of cat stress and child social skills/anxiety. We expect that cats will have no significant increase in stress. We also expect children with ASD living with cats will have more social skills and less anxiety than those living without cats. Exploring the impact of cats living with families of children with ASD will provide critical information for families with such challenges and may increase shelter cat adoption.

Research Grant: Winn Feline Foundation
Student Support: Dolores Goller Fund for Scholarships and Research in Veterinary Medicine

Analysis of changes in ISC biomarkers to determine tissue viability in horses with intestinal strangulation

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Background: Colic is a major cause of morbidity and mortality in horses. Strangulating lesions, in which loss of intestinal blood supply occurs, often necessitates resection of the compromised intestine due to extensive cell death. Currently there is no method to objectively determine intestine viability at time of surgery. Intestinal stem cells (ISC) are critical to mucosal repair following injury and their presence is likely associated with tissue viability. We aim to evaluate changes in relative gene expression of different biomarkers indicative of ISC activity from horses presenting with strangulating colic to identify a biomarker associated with intestinal viability. Hypothesis: We hypothesize that increased relative gene expression of biological markers associated with ISC will be associated with improved intestinal viability. Methods: Mucosal scrapings were obtained from 10 surgical cases of small intestinal strangulation. RNA was extracted from the proximal and distal resection sites at time of surgery, and converted to cDNA. Primers Lrig1, Lgr5, Sox9, HopX targeted ISC biological markers versus Muc2, β-actin, Sucrose Isomaltase, PCNA, EpCAM, CGA, and Lyz targeted post-mitotic cell biological markers. Analysis relative to a pooled control sample was performed via the ΔΔCt method and a one-way ANOVA. Results: When compared to the pooled control, samples collected from proximal and distal resection sites appeared to show a decreased gene expression of ISC and post-mitotic cell biomarkers. Conclusion: This information may help to determine intestinal viability in horses and aid surgeons to determine the extent of intestinal resection necessary to decrease morbidity and improve patient prognosis.

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Student Support: Merial Veterinary Scholars Program and Comparative Medicine Institute
Characterization of parasitic and free-living nematodes in feces and enclosure substrate of poison dart frogs

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Differentiating between the free-living and parasitic nematodes living in the enclosures of poison dart frogs under managed care is important to frog health because nematode species differ in their pathogenic potential. While the presence of free-living nematodes in the enclosure substrate of these frogs is typically copacetic, parasites like that of Rhabdias species can have adverse affects on the health, growth, and survival of frog populations. Frogs living in closed environments are particularly at-risk for infection, as substrates are not fully changed regularly and total disinfection of the exhibit occurs semiannually. Without proactive surveillance, these enclosures can quickly become infested with Rhabdias species, as this nematode has both parasitic and free-living stages in its lifecycle, putting frogs at risk for a potentially fatal parasitic pneumonia. The objective of this study was to determine the location of parasitic nematodes, either throughout the enclosure substrate or solely within the frogs’ fecal matter, so as to facilitate progressive husbandry practices and reduce morbidity and mortality in the poison dart frog population. Nematodes consistent with parasitic Rhabdias species were found only in the frogs’ isolated fecal samples, while diverse populations of free-living nematodes (orders included Aphelenchida, Dorylaimida, Enoplida, Mononchida, Rhabditida, and Tylenchida) were found in the enclosure substrate samples. In order to improve the welfare of poison dart frogs under managed care, these findings suggest that husbandry efforts should focus on the partial cleaning of areas of the exhibit with the greatest load of fecal matter.

Research Grant: None
Student Support: Disney’s Animal Kingdom; Florida Veterinary Scholarship Program

Dysregulated splenic monoamine metabolism in a Gulf War Illness model: modulation by a neoglycoconjugate

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Gulf War Illness (GWI) is a chronic multisymptom illness affecting > 25% of the 1990-1991 GW veterans of unknown etiology, but likely caused by deployment-related chemical exposures, i.e., pyridosigmine bromide (PB, a nerve agent prophylactic), numerous pesticides, including DEET, sprayed regularly on the grounds and on uniforms, and the nerve agent sarin (by personnel stationed near the Khamisiya burn pits). Additionally, GW soldiers were subjected to the stressful war environment, manifested as increased corticosteroid levels. Some of the GWI symptoms might be related to autonomic dysfunction and resultant immune dysregulation due to altered peripheral monoamine, i.e., norepinephrine (NE) and serotonin (5-HT), homeostasis. Using a mouse model of GWI where mice were exposed to a combination of PB, DEET and corticosterone followed by a challenge with the sarin surrogate diisopropyl fluorophosphate (DFP), the effects of these GWI chemicals on splenic NE and 5-HT metabolism and the potential protective effects of a novel therapeutic, the neoglycoconjugate LNFPIII, were investigated 6 or 48h after the DFP challenge. Using high performance liquid chromatography splenic NE, its metabolite MHPG, 5-HT and its metabolite 5-HIAA were measured. GWI treatment increased 5-HT and NE at 6 and 48h independent of LNFPIII; 5-HIAA (statistically) and MHPG (numerically) were increased by both GWI treatment and LNFPIII at 6h, but not 48h, with the greatest metabolite increases seen in the GWI treatment/LNFPIII combination. Thus, it appears that the GWI treatment leads to lasting increased demands for splenic NE and 5-HT that are compensated by LNFPIII via increased monoamine metabolism at the earlier time point.

Research Grant: GWI150195 (Department of Defense; CDMRP)
Student Support: NIH Office of Research Infrastructure Programs, Grant Number 2T35OD010433-11
Functional role of the multicopy single-stranded DNA loop nucleotide sequence in *Salmonella Typhimurium*

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*Salmonella enterica* is the leading cause of bacterial foodborne illness and death worldwide. Serotype Typhimurium (STm) is one of the leading serotypes associated with human infections. Our laboratory discovered that multicopy single-stranded DNA (msDNA), a hybrid molecule containing a single-stranded DNA covalently linked to RNA, is essential for *Salmonella* intestinal colonization. The DNA portion of msDNA contains a loop of 4 unpaired nucleotides (GACT) atop a 29-base-pair stem. We hypothesized that the sequence of the unpaired nucleotides in the DNA loop would confer function. To test our hypothesis, we made 4 mutants, each containing a single nucleotide in the loop. We analyzed anaerobic growth, msDNA abundance, and relative fitness during infection in the murine colitis model. Our data demonstrate that the mutant containing only adenine (AAAA) has stunted anaerobic growth. In contrast, there was a small but insignificant reduction in anaerobic growth for the mutants containing all cytosines (CCCC) or all guanines (GGGG). We were unable to detect msDNA for the adenine mutant only, suggesting that our anaerobic growth phenotype was due to absence of msDNA. Finally, we demonstrate a significant reduction in fitness during infection for the mutant containing all cytosines. Together our data suggest that the sequence of the DNA loop of msDNA is important for function. These data provide insight into how msDNA functions. Our work to understand msDNA function will contribute to the development of novel therapeutics that capitalize on the importance of msDNA in the gut to reduce the occurrence of STm infections worldwide.

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**Student Support:** NIH T35OD011070

Comparative evolutionary genetics of the mtDNA genome and select nuclear genes of two lamnid sharks

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Sharks (*Elasmobranchii*) are marine apex predators that are of major conservation concern and represent an important group for understanding early vertebrate evolution. To explore aspects of molecular evolution in sharks, we examined both comparative mitochondrial and selected nuclear gene sequence evolution of a mako and white shark, respectively. The mitochondrial genome of an Atlantic Ocean specimen of a shortfin mako (*Isurus oxyrinchus: Lamnidae*), was assembled from NextGen genome sequence reads. The mtDNA genome was 16,700 bp long with 13 protein-coding genes, 2 rRNA genes, and 22 tRNA genes. The base composition was: 28.8% A, 28.0% C, 15.2% G, and 28.0% T. We compared this sequence to a published *I. oxyrinchus* mtDNA sequence taken from a Pacific Ocean specimen, to gain insight on the level of divergence between these two populations. Eighty SNPs were found and the Atlantic specimen contained one single nucleotide deletion, in the s-rRNA region. These polymorphisms may be useful genetic markers for distinguishing the two different populations in future studies of population genetics and conservation management. We also studied the evolution of nucleotide excision repair (NER) genes in the white shark (*Charcharodon carcharias: Lamnidae*) by comparing the predicted genes from an ongoing project on the white shark genome, with NER genes of eight different fish species. Using the program PAML, we identified sites with a history of positive selection in the different taxa, thereby identifying potential molecular adaptations in the NER genes of sharks. In turn, these may be related to the evolution of large shark genome sizes, possible resistance to cancer, and aging.

**Research Grant:** Save Our Seas Foundation  
**Student Support:** Cornell College of Veterinary Medicine, Office of Graduate Education
Natural history and long-term clinical outcomes in dogs with cervical spondylomyelopathy

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Cervical spondylomyelopathy (CSM), also known as wobbler syndrome, is the most common disease affecting the cervical spine of large and giant breed dogs. CSM is characterized by static and dynamic compression of the spinal cord, nerve roots, or both in the cervical region. Current treatment options include surgery, of which there are over 30 techniques reported, or medical management. Holistic treatments, such as acupuncture, are frequently sought after by owners as well. No consensus currently exists on the best treatment for dogs with CSM. Owners of previous CSM patients seen at the Ohio State University Veterinary Medical Center in the last 8 years were telephoned, and interviews were conducted with regard to the dog’s current status, overall quality of life, and date and cause of death. The objective of this study is to gain a better understanding of canine CSM patients’ long-term welfare across various treatment modalities. Because canine CSM is the natural model for cervical spondylotic myelopathy in people, this study can assist both medicine and veterinary medicine in developing the best methods to manage and treat these diseases.

Research Grant: None
Student Support: Rohovsky Research Grant, NIH T35 Training Grant

Measuring force production and myosin expression in hopping muscles of the kangaroo rat

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Effective locomotion is dependent on the interplay of skeletal muscles contracting and relaxing during shortening and lengthening. The kangaroo rat represents the extreme of mammalian hind-limb function, as these animals are capable of hopping upwards of three vertical feet. As the kangaroo rat hops, the lateral gastrocnemius muscle contracts, and, like a motor, extends the tarsus to propel the animal into the air. As the rat lands, the vastus lateralis muscle is stretched during active contraction, and, like a brake, opposes the downward force of the falling body. We measured biomechanical properties of skinned single cells (or fibers) of the lateral gastrocnemius and vastus lateralis muscle in the kangaroo rat. We compare the absolute force production, calcium-sensitivity of force production, and myosin cross-bridge kinetics as calcium activation varied for both muscle types. Initial measurements of contractile strength and calcium-activated fiber dynamics were largely similar between these two muscle types. These results suggest that the specialized dynamic contributions of these muscles to hopping may be due to differences at the neuronal level. In addition, SDS-PAGE gels of lateral gastrocnemius, vastus lateralis, extensor digitorum longus, plantaris, and soleus muscle samples reveal a heterogeneous myosin-heavy chain isoform distribution, specific to these different muscle types. This distribution of myosin heavy chain isoforms may provide insight into the specialized role these muscles play in facilitating the extreme hind-limb function of the kangaroo rat.

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Student Support: Boehringer Ingelheim-VSP. WSU-CVM Darden Memorial Research Endowment. WSU-CVM Office of Dean.
Characterization of *Dirofilaria immitis* amphids by fluorescent staining

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Macrocyclic lactone (ML) resistance to canine heartworm (*Dirofilaria immitis*) has been documented. Heartworms arrive in the heart and pulmonary artery after a lengthy migration through host tissues, and while the mechanism of parasite killing by MLs is still poorly understood, it is possible the parasite’s ability to migrate normally is interrupted in this process. Amphids are sensory neurons in nematodes used to navigate the environment and respond to stimuli. The purpose of this study is to test the hypothesis that *D. immitis* amphid structures are altered in ML-resistant parasites, as previously observed in other species. To test this hypothesis, *D. immitis* third-stage larvae were stained with DiO and DiI. Then, amphid staining was assessed visually using fluorescence microscopy. *Caenorhabditis elegans* served as a positive control, as its amphids were successfully stained using standard procedures. While established methods were unsuccessful in staining *D. immitis*, the procedures were modified in attempt to obtain clear amphid staining. Collagenase treatment, molting to fourth-stage larvae, and incubation in different media with EDTA did not improve stain uptake. However, the most successful procedure involved staining *D. immitis* during overnight incubation with DiO at 37°C, which yielded fluorescent staining localized at the amphids. Further development of an amphid staining procedure in *D. immitis* will allow for better characterization of amphid structure between susceptible and resistant isolates. This information could aid in determining the role of amphids and migration in the ML mode of action.

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Applied ethology methods for miniswine

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Applied ethology is the study of animal behavior in their home environments. This field serves both the animal agriculture and biomedical fields. The objective was to synergize automated (AUTO) technologies with traditional video timestamping (TS) of miniswine behaviors. The TS-ethogram focused on mainly non-nutritive oral behaviors (NNOB), as limit-fed pigs will spend most of their active hours performing these behaviors. In addition, AUTO-accelerometers were attached to the ear tags and an AUTO-event logger also tracked the use of a novel environmental enrichment device (EED). The first step was to visualize the TS-data and identify pigs that did not perform a normal rate of NNOB. Three out of 28 pigs had low NNOB expression. These pigs paced instead of performing NNOB. Excessive pacing is considered a stereotypy, which influences the variation within an experiment. Mini-pigs spent about 62% of their time budget during daylight hours performing NNOB, with a CV of 54%. For future experiments, if a 50 or 75% difference of NNOB between treatments was expected (α = 0.05 ; = 0.20), 19 and 8 pigs would be needed, respectively. Some behaviors in the ethogram were not worth noting. For example, sitting only occurred 0.06% of the time (400 recorded pig hours). There was correlation (P < 0.01) between NNOB and the ear tag accelerometer and the EED; however, the R2 values were low. This led us to suspect that data were not aligned. The next step is to review the video recording protocol and import the automated data into the TS video.

**Research Grant**: Applied Research Associates contract  
**Student Support**: NIH T35 Training Grant T335OD012199
Antimicrobial hydrogel dressings for chronic wounds

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Chronic wound infections are a major problem for both human and equine health. The profound health and economic impacts of chronic wounds create a critical need for more effective dressings. Gallium maltolate (GaM) is a metallic compound that exhibits antimicrobial activity against several pathogenic bacteria associated with chronic wounds. Our long-term objective is to create a GaM-infused hydrogel matrix as an antimicrobial dressing to treat chronic wounds. The objective of this study is to develop a matrix with a dual release system, exhibiting both burst and sustained GaM release to immediately treat infection and prevent further colonization. The hydrogels were fabricated by first dissolving poly(ethylene glycol) diacrylate (PEGDA) and Irgacure in water, and then photopolymerizing with UV light. The hydrogels were dried and loaded with a 10% GaM solution. The loaded hydrogels were soaked in water, and the GaM concentration was determined by UV-VIS spectroscopy. Significant (P < 0.05) burst release of GaM was observed after 1 hour with complete release occurring by 6 hours. The bactericidal activity of the released GaM was determined by a microdilution antimicrobial susceptibility technique against strains of *Staphylococcus aureus*, including methicillin-resistant *Staphylococcus aureus* (MRSA). The hydrogel releasate significantly (P < 0.05) inhibited bacterial growth of both strains similarly to both a GaM concentration of 4 mg/ml and the negative controls. Development of microspheres for sustained antimicrobial release is underway. This study supports further investigation of the in vivo use of this novel antimicrobial hydrogel dressing as a treatment for chronic wounds.

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Student Support: National Institutes of Health #5T35OD010991

Comparison of human and canine hypomorphic mutations in the FANC complex by cisplatin sensitivity

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The FANC core complex that facilitates homology directed repair during replication. Mutations in any one of 19 components of this pathway result in Fanconi anemia (FA): an autosomal recessive anemia that presents with bone marrow failure and an increased risk of acute myeloid leukemia (AML). It has been shown that an L71P missense mutation in FANCG results in milder clinical symptoms. This mutation destabilizes FANCG and prevents it from forming a complex with FANCA to generate the FANC core complex. No FA-like diseases have been reported in domestic animals. Recently, a missense variant in dogs has been discovered. The dog had no FA-like symptoms reported prior to development of a sarcoma. However, fibroblast cells derived from this animal display extreme sensitivity to drugs that induce DNA cross-links, a characteristic of FA deficient human cells. This mutation was initially studied by mimicking this mutation in human 293T cells and showed that this mutant represents a hypomorphic allele. It will be determined whether the loss of function in the canine allele behaves similarly to the human hypomorphic mutation. A Crispr/Cas9 strategy will be used to knockin the L71P mutation in human 293T cells. The cellular phenotypes of the canine variant will then be compared to L71P. This will help address whether the lack of FA phenotype in the affected dogs is due to an inherent difference in susceptibility or if the canine mutation retains more function than the human hypomorphic allele. This work will hopefully facilitate understanding of how FA failure contributes to AML in humans and to sarcomas in canines.

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Comparative anatomy and the kinematic analysis of the atlantoaxial joint in feline and human computer Models

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Instability or subluxation of the atlantoaxial joint in humans can be due to congenital, idiopathic, inflammatory, or traumatic reasons. The aim of this study is to better understand the interaction between the two bones of the atlantoaxial joint, the axis (C1) and atlas (C2), by creating an accurate representation of the joint movement through the pivot point at the dens. The dens is a bony projection of C2 that provides vital attachment points for ligaments limiting and protecting the movement of the atlantoaxial joint. Using the Autodesk MAYA, three-dimensional modeling and animation program, we created a 3D kinematic model from CT data of a cat skeleton and placed it in a 3D coordinate system (i.e., with an x, y, and z axis); so movement in the three views (i.e., dorsal, frontal, and lateral) could be analyzed. The greatest degrees of movement were expected to be in the flexion/extension of the joint; however, the greatest range of motion (~20 degrees) was observed in lateral flexion and rotation. Additionally, we analyzed models with the dorsal atlantoaxial and apical ligaments removed and found there were significant increases in rotational movement in all axes. This is most likely due to the key roles the two ligaments play in joint dislocation. The findings can be extrapolated to the functions of the human atlantoaxial joint based on structural and functional similarities. While our model is useful in understanding the possible movements of the joint, it currently does not account for the effect of other soft tissues (e.g., muscles and connective tissues) on joint movement. In order to make the model more anatomically accurate, future work on the analysis of soft tissues is needed.

Research Grant: Unknown
Student Support: LSU School of Veterinary Medicine; Merial Veterinary Scholars Program

Fate of second immunization of an attenuated Salmonella vaccine relative to maximizing protective immunity

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Recombinant attenuated Salmonella vaccines (RASV) have been studied and utilized as bacterial vectors to elicit strong cellular and humoral immune responses against S. pneumoniae for decades. One of the main challenges of using Salmonella vectors is perfecting the balance between attenuation and colonization efficacy of deep lymphoid tissue while inducing long-term protective immunity. RASV strain χ11281 is comprised of regulated delayed attenuation mutations allowing for the retention of wild-type characteristics at time of inoculation and colonization while gradually losing virulence to avoid disease symptoms in the host. Plasmid pYA4088 has been shown to produce high quantities of Pneumococcal surface protein A (PspA), a significant virulence factor expressed by all clinical S. pneumoniae. In this study, we evaluated the ability of strain χ11281(pYA4088) to colonize Peyer’s patches and spleens after oral inoculation in BALB/c mice. Prior to inoculation, plasmid stability, strain growth kinetics, and pspA expression were evaluated. Following primary oral immunizations, secondary immunizations were completed at days 4, 7, and 11. Quantitative colonization titers were assessed at days 3, 7, and 11 for both primary and secondary immunizations. Preliminary colonization data is inconclusive due to low sampling numbers. However, we hypothesize that enhanced colonization of internal lymphoid tissues will be observed when mucosal immunity induced by primary immunization is present at the time of secondary inoculation.

Research Grant: National Institutes of Health United States Department of Agriculture
Student Support: Boehringer Ingelheim Veterinary Scholars Program
Development of a cell culture system to optimize B cell proliferation and function

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B cells are a critical component of the adaptive immune system in animals. Following activation by an antigen, B cells will go down one of two pathways. Many B cells become activated and produce antibodies that are specific for a single epitope on a certain pathogen. A small number of B cells will differentiate into long-lived memory B cells that are activated when the antigen is encountered a second time. This memory and specificity is the basis behind vaccination. Avirulent antigen of a specific pathogen is introduced to the animal, then the animal will produce memory B cells that are activated if and when exposed to the virulent form of the pathogen, resulting in protection against disease. The aim of this study is to produce a lymphocyte culture system that maximally expands specific memory B cells by adding various cytokines and receptor agonists to an in vitro culture system, so that key protective memory B cells can be characterized. B cells were isolated from porcine spleen. IL-2, a cytokine produced by T cells in vivo and known to cause B cell proliferation, was added along with various other proliferation and differentiation factors. B cells were cultured in plates with round bottom or flat bottom wells, and proliferation and functional antibody secretion were measured after 6 days. Interestingly, results showed that the flat bottom wells allowed for increased production of antibodies compared with the round bottom wells. The findings from this study will be applied to culturing and cloning of memory B cells for receptor and RNA analysis.

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Student Support: Merial Veterinary Scholars Program

Tumor-derived exosomes downregulate type I interferon signaling to promote pre-metastatic niche formation

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Metastases are the major cause of cancer morbidity and mortality among patients. The metastatic process involves complex mechanisms necessitating the formation of a premetastatic niche. These mechanisms rely on cell-to-cell communication, partly mediated by tumor exosomes (TEX). Exosomes are small extracellular vesicles (30-150 nm) made from late endosomes and plasma membrane, containing plasma membrane proteins, cytoplasmic proteins, DNA and different RNAs (mRNA, miRNA…). Normally, they are produced by all kind of cells and maintain homeostasis, however TEX alter non-cancer cells and tissues. Evidence suggests that TEX are involved in formation of the pre-metastatic niche. Preliminary evidence from our laboratory suggests TEX, lead to loss of type 1 interferon receptor subunit 1 (IFNAR1) on the cell surface. Loss of IFNAR1 results in insensitivity to type 1 interferons (IFN) and cancer progression. Therefore, we hypothesized that IFN signaling through IFNAR1 could be an intrinsic defense mechanism against formation of the pre-metastatic niche. To test this hypothesis, we used our unique knock-in model in which the IFNAR1 Serine 526 is mutated to Alanine (SA) in order to evade ligand and non-ligand induced phosphorylation, ubiquitination, and protein degradation. We also utilized drugs that mimic the effects of IFN signaling via IFNAR1 to suppress TEX-mediated generation of the pre-metastatic niche. This study will, therefore, function to study alternative therapies to cancer patients at risk of metastatic progression who would be irresponsive to IFN adjuvant therapy.

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Student Support: Boehringer Ingelheim Veterinary Scholars Program
Quantitative evaluation of AAV vector genome biodistribution by real time PCR

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Gene therapy is a robust approach being explored to treat a wide variety of genetic diseases. Adeno-associated virus (AAV) is a leading viral vector in gene therapy. The goal of genetic therapy is to deliver normal genes to replace missing or defective genes. An important issue in gene therapy is knowing the biodistribution of the viral vector after therapy. Quantitative real time polymerase chain reaction (qPCR) is a highly sensitive technology for quick and precise quantification of viral genome using fluorescent signals. Here, we studied AAV genome distribution in a mouse model of Duchenne muscular dystrophy (DMD). Specifically, an AAV vector was injected via the tail vein to 16 diseased mice. Tissues including the gastrocnemius muscle, diaphragm, biceps, triceps, quadriceps, heart, spleen, liver, and kidney were harvested by snap frozen following the therapy. We also collected tissues from 2 untreated mice as the negative control. We extracted DNA from these samples and then diluted the DNA to a concentration of 0.5 ng/μL. We quantified the viral genome and then using TaqMan Assay technology, we designed six different assays based on the information of the vector genome. These Assays were designed to be specific for the viral DNA. We are going to perform qPCR on our collected samples with each of the TaqMan assays we designed. We expect the qPCR to accurately inform us of the AAV vector genome in different tissues. This data will suggest that using qPCR may be a good tool for measuring the efficiency of delivering an AAV in gene therapy.

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Developing a hypoxia model of dormancy in the model organism Mycobacterium smegmatis

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Therapy for Mycobacterium tuberculosis (Mtb) infection requires at least six months of antibiotic treatment. During an Mtb infection, granulomas are formed as part of the immune response, in which bacteria are exposed to hypoxic conditions. Two membrane proteins in Mtb, DosS and DosT, are activated during hypoxia and in turn activate a transcription regulator, DosR, which turns on transcription for a number of genes which induce dormancy by modulating metabolism. A hypoxia model will be developed using the fast-growing non-pathogenic bacterium Mycobacterium smegmatis (Msm). Msm relies on DosS to sense hypoxia and activate DosR and the dormancy regulon. To study the activation of the dormancy regulon, a Msm strain containing the hspX'::GFP plasmid was developed. The hspX promoter binds DosR and has been shown to be induced by hypoxia in both Mtb and Msm. Therefore, fluorescence can serve as a reporter for hypoxia- and DosR-dependent induction of the dormancy regulon. Differing methods of generating hypoxic conditions will be compared to determine optimal conditions for induction of fluorescence in Msm. Should the Msm model recapitulate the Mtb data, efforts will be undertaken to isolate Msm mutants resistant to previously discovered DosRST inhibitors. This hypoxia model will accelerate mechanism of action studies for new Mtb therapies that target dormant bacteria.

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Student Support: Steven Arnoczky Fellowship at Michigan State University
Effect of acute iNSC transplantation on BBB leakage in a novel porcine controlled cortical impact TBI model

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Traumatic brain injury (TBI) is a major cause of disability and death in the United States, with an estimated 5.3 million Americans living with long-term disability from TBI. TBIs are a contributing factor in ~30% of all injury related deaths, and the CDC estimates that 153 people die each day from TBI-related injuries. TBI pathophysiology is complex, including the breakdown of the blood brain barrier (BBB) and secondary inflammatory insults. When the BBB is damaged, it becomes more permeable due to a decrease in tight junction proteins and the death of endothelial cells. This makes the BBB susceptible to infiltration of inflammatory cells that can cause even more long-term damage. It’s been demonstrated by our lab previously that human induced pluripotent stem cell-derived neural stem cells (iNSCs) may improve this damage long-term by producing neuroprotective and regenerative signaling factors. The aim of this study was to characterize BBB breach after TBI, survival of iNSCs post-transplant, and the effect of iNSCs on BBB breach and the inflammatory response in a novel porcine controlled cortical impact TBI model. We hypothesized that acutely transplanted iNSCs will lessen the damage caused by a TBI by decreasing BBB leakage and the release of inflammatory cytokines. BBB leakage was confirmed with Evans Blue Dye. The survival of iNSCs was confirmed by gross histological assessment of DiR-cell labeling, demonstrating robust cell numbers. Collectively, the results demonstrate that TBI leads to significant BBB breach, and iNSCs can survive in a cytotoxic environment. Ongoing assessments will determine if the transplanted iNSCs have immediate beneficial effects in a novel porcine controlled cortical impact TBI model.

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Student Support: 2017 AVMA/AVMF 2nd Opportunity Research Scholarship

Comparing prevalence and strain diversity of A. phagocytophilum between vector life-stages in Ft. McCoy, WI

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Anaplasma phagocytophilum is a gram negative intracellular bacterium that causes human granulocytic anaplasmosis. The main vector of A. phagocytophilum in the eastern and northern United States, Ixodes scapularis, harbors different strains of A. phagocytophilum. The two major strains are the human active strain (Ap-ha) and variant 1 (Ap-v1), which does not infect humans. We are interested in comparing the prevalence of the two strains in questing nymphal and adult I. scapularis. Because A. phagocytophilum is not passed on transovarially, larvae were not investigated. We hypothesize that the infection prevalence will be higher in adult I. scapularis based on existing data and because adults have had one more blood meal, or chance to become infected. Questing I. scapularis were collected by drag cloth on three 1-ha grids in Fort McCoy, WI, an area chosen for its long-established tick population. DNA was extracted from ticks and then screened by quantitative PCR targeting a fragment of the A. phagocytophilum msp2 gene. To differentiate strains, we subjected positive samples to a nested PCR targeting a 546 bp fragment of the 16s gene, which was then sequenced. Prevalence, and density, of infected ticks with the two major strains of A. phagocytophilum in I. scapularis separated by nymphs and adults will give a more accurate risk assessment of human disease. The data collected will also indicate which hosts are more often used for blood feeding by the different life-stages of I. scapularis. Small mammals are reservoirs for Ap-ha while white tailed deer are reservoirs for Ap-v1. The strain with a larger prevalence would indicate which hosts are of greater use to larvae and nymphs.

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Student Support: NIH Grant No T35OD016477 to Michigan State University
Optimal transfection of corneal transplant buttons after ex-vivo AAV-GFP incubation

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A rise in human corneal disease has led to a staggering increase of individuals that are in need of a corneal transplant. However, some corneal transplants can have high rejection rates based on the ocular condition of the patient. Adeno-associated virus (AAV) HLA-G therapy has been shown to decrease the risk of possible rejection by increasing immune tolerance and decreasing vascularization in the cornea. By utilizing this gene addition therapy, the hope is to reduce rejection rates in high-risk corneal transplant patients by transfecting corneal donor tissue (“corneal button”) with HLA-G. The aim of this project is to determine the appropriate AAV-GFP concentration and ex-vivo incubation time for effective transduction of the transgene product into a corneal button. The concentration of AAV-GFP is comparable to the effective amount of HLA-G. Porcine corneal buttons were incubated at 37°C in high and low concentrations of AAV-GFP. The buttons were then placed in DMEM culture media after 1, 3, 6, and 24-hour time periods of incubation and in-vivo imaged for GFP expression at 24 hours, 72 hours and 7 days. Distribution and expression of the AAV-GFP was evaluated in the corneal epithelium, stroma, and endothelium. The results show excellent GFP expression that peaked after 5 days of culture and that there is no statistical difference between the different incubation time periods. Thus, an incubation time of 1 hour should allow enough transfect of HLA-G therapy within the corneal button. The results of this study will be utilized in upcoming corneal transplant experiments.

Research Grant: UNC TraCS Translational Team Science Award
Student Support: Veterinary Scholars Program, Merial grant, Fund for Discovery, the Herbert Benjamin Endowment

The effect of diethylhexyl phthalate exposure on gene expression and histopathology in the gut of zebrafish

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Diethylhexyl phthalate (DEHP) is an endocrine disrupting chemical used in the production of plastics. It is considered a ubiquitous contaminant in the environment and is associated with adverse health effects on reproduction and development at low exposure concentrations in mammals and aquatic wildlife. DEHP is also proposed to act as an obesogen, a chemical that promotes adiposity. However, additional studies are required to clarify any relationship between DEHP and obesity and to determine the underlying mechanisms that are involved. Interactions between DEHP exposure and the gut may be a mechanism by which this chemical acts as an endocrine disruptor and obesogen. This study aimed to better understand the impact of DEHP in zebrafish by assessing histopathological changes in the gut and liver tissue and by measuring the expression of transcripts related to hormone signaling and nutrient transport. A two month feeding trial was conducted; male and female zebrafish were exposed to DEHP (3 ppm) via dietary exposure. Fish were collected at 0, 1, and 2 months for histopathology and gene expression analysis. Gut and liver tissue stained with hematoxylin & eosin are being evaluated for histopathological changes. Preliminary data suggest that there are no significant morphologic changes between control and treatment groups. The expression levels of gut hormones are currently being analyzed. This study clarifies the effects of DEHP in a vertebrate model to better understand how environmental contaminates impact lipid-related processes and metabolism.

Research Grant: European Commission’s Programme through the Marie Sklodowska-Curie actions - Global Fellowship Programme (no.707241) and the College of Veterinary Medicine Seed Grant 2016
Student Support: Florida Veterinary Student Scholars Program
Preconception and prenatal exposures to e-cigarette vapor decrease birth weight and length in mice offspring

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The use of electronic nicotine delivery systems has drastically increased since it was released in America in 2006. There has been a societal trend, mostly in young adults, to move from conventional cigarettes towards the believed healthier option, electronic cigarettes (e-cigs). Compared to the known effects of cigarette smoking during pregnancy, such as premature births and low birth weights, little is known about the effects of e-cigs, particularly on neonates. We hypothesized that prenatal exposure to e-cig vapor impairs pregnancy outcomes and damages the respiratory health of neonates. To test our hypothesis, female BALB/c mice (n= 11-12/group) were exposed to cinnamon flavored e-cig vapors for 2 hours a day for either, 12 days before mating and during gestation or from gestational days 6 to 19. Control mice were exposed to filtered-air for these same periods. At birth, offspring were counted, weighed, and measured. Lungs were harvested for histopathology and gene expression analysis. Compared to respective air-exposed controls, both preconception and prenatal exposures to e-cig vapor significantly decreased the pregnancy rate (50.0% vs 90.9% and 66.7% vs 91.7%, respectively), the offspring birth weight (1.35g vs 1.55g and 1.33g vs 1.51g) and length (2.84 cm vs 3.01 cm and 2.79 cm vs 2.97 cm). Gene expression analysis of the preconception-exposed group revealed down-regulation of lung development related genes, including Tgf-β1, Igf1, Igf2, Wnt3a, Wnt7a, Shh, Muc5ac, and Mmp12, suggesting impairment of lung growth and maturation processes. In conclusion, our study demonstrates that preconception and prenatal e-cig vapor exposure is an adverse biological risk to pregnancy outcomes and neonatal lung development.

Research Grant: Louisiana State University School of Veterinary Medicine start-up funds for Dr. A. Noël.
Student Support: Boehringer-Ingelheim

The in vitro effects of demethylating agents decitabine, 6-thioguanine and zebularine on canine osteosarcoma

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Osteosarcoma is a prevalent and aggressive disease; it accounts for up to 85% of all primary bone tumors in dogs and is the most prevalent bone cancer in children and young adults. Only 60% of people survive five years after diagnosis; this drops to 15-20% if visible metastasis is seen at presentation. In veterinary and human medicine, the treatment of choice for osteosarcoma is surgical removal of the tumor followed by cytotoxic chemotherapy. Even with the addition of chemotherapy, approximately 50% of dogs will die from metastasis within one year. Epigenetic changes have recently become a focus of investigation in carcinogenesis. DNA methylation has been shown to occur at CpG islands, important areas near promoter regions. Hypermethylation of these islands causes gene silencing, while hypomethylated regions allow transcription of genes. Dysregulation of these methylation patterns can lead to abnormal proliferation, migration, and cell invasion. Previous studies in both murine and human osteosarcoma cell lines have shown evidence that demethylating agents have beneficial effects: decreasing proliferation, migration, and making cells more susceptible to chemotherapeutics and radiation. However, no study to date has been performed in canine osteosarcoma cells. We evaluated 3 demethylating agents, decitabine (DAC), 6-thioguainine (6-TG), and zebularine (Zeb), for their effects on cell viability, cytotoxicity, and apoptosis at high and low physiologic doses using an ApoTox-Glo Triplex Assay. 6-TG significantly reduced cell viability in two cell lines tested. These results indicate demethylating agents should be further investigated as a potential therapy in canine osteosarcoma.

Research Grant: University of Missouri chapter of Phi Zeta
Student Support: Endowment Established by IDEXX-BioResearch
Effects of osteosarcoma on IL-2 and IFN-γ production by peripheral blood mononuclear cells

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Osteosarcoma (OSA) is a devastating disease in both humans and dogs. In humans, it primarily affects juveniles with a high incidence of metastases and fatality. Due to its similar clinical presentation, dogs are a useful model to understand aspects of the disease in humans. Previous studies have shown OSA is a candidate for immunotherapy, however, the complex interaction between OSA and the immune system requires further investigation. The primary aim of this study was to establish methodology for examining the cytokine response of peripheral blood mononuclear cells (PBMCs) to autologous OSA cells by first examining the response to allogeneic OSA cells. For methodology development, allo-reactivity was expected to yield more robust cytokine activation due to possible PBMC tolerance to autologous cells. PBMCs isolated from healthy dogs were assessed for IL-2 and IFN-γ production via ELISpot assay under various conditions, including unstimulated, stimulation with PHA and following incubation with allogeneic OSA cells, allogeneic OSA cell supernatant, or allogeneic fibroblasts. Preliminary results show PBMCs incubated both with OSA cells and with fibroblasts produced greater levels of IFN-γ and IL-2 compared to unstimulated PBMCs and PBMCs stimulated with PHA. These results indicate that PBMCs increase IFN-γ production as part of the immune response induced by OSA. Given the immunosuppressive nature of Treg cells, one hypothesis is that OSA induces an increase in IL-2 production leading to an increase in Treg cells, and a subsequent decrease in antitumor immunity. These findings support examining the response of PBMCs to autologous OSA cells for further understanding of the immune response to OSA.

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Student Support: Stan Skadron Summer Scholar Fund & The University of Minnesota College of Veterinary Medicine.

A systematic review of the literature on health outcomes in wild and captive wolf populations worldwide

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The diseases that affect wolves are diverse and the impacts varied. Disease in wolves can affect ecosystem, livestock and human health, give insight into the genetic background of dogs, and assist in conservation planning and implementation. As a keystone predator, wolves have a large impact on the health and diversity of the surrounding habitat and disease that impacts wolf survival will, in turn, affect the entire ecosystem. Infectious and parasitic diseases carried by wolves can be transmitted to other wildlife species, livestock, and humans. Also, conservation and re-population efforts may be impacted by the presence of heritable congenital defects and it is therefore important to report the prevalence of their occurrence within wolf populations. Systematic review methods were utilized to identify published reports of health outcomes in either grey (canis lupus) or red (canis rufus) wolf populations worldwide. Search terms included pertained to both wolf populations as well as multiple health outcomes including infectious, parasitic, neoplastic, congenital, and metabolic diseases. Relevant data were extracted from manuscripts included in the review. A total of 3718 articles met the initial search requirements and 301 articles were retained after the first relevance screening. Health outcomes were stratified based on species, population type, and geographic regions. The majority of health outcomes described in the literature concerned parasitic infections; other outcomes described include infectious diseases, neoplasia, congenital disorders, trauma and others. To the authors’ knowledge, this is the first comprehensive systematic review of all health outcomes in wolf populations.

Research Grant: None

Student Support: Student Support grant funded by Merial Veterinary Research Scholars Program
Active surveillance of Lyme disease pathogen in its questing vector in southeastern Michigan

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Lyme disease is endemic in areas of the Northeast and Midwest United States, but Lyme disease continues to emerge in Michigan, in large part due to the emergence of the vector. Evidence from Lyme disease risk maps, citizen submission of ticks, and veterinarian submission of ticks from canines suggest that both the Lyme disease vector, *Ixodes scapularis*, and the Lyme disease causative agent, *Borrelia burgdorferi*, have spread further into southeastern Michigan than previously known, calling for increased active surveillance. As *B. burgdorferi* is a zoonotic agent and *I. scapularis* is an opportunistic parasite, active surveillance is of public health importance. Over half of the state’s population lives in southeastern Michigan, ~4.6 million in this region, making it a high-risk area if and/or when *B. burgdorferi* invades. We hypothesized that active surveillance for the tick and pathogen would result in detection of previously unknown populations of *I. scapularis* and *B. burgdorferi* in southeastern Michigan, whose counties had previously been classified as low to unknown risk by the Department of Health and Human Services. We sampled for host-seeking ticks by dragging a 0.75m² white drag cloth across leaf litter for ~1300m at one or more parks in each of the 12 southeastern counties. All *I. scapularis* ticks obtained were then assayed for *B. burgdorferi* by qPCR targeting the 16S rDNA gene. *Ixodes scapularis* ticks were detected in 4 counties of low or unknown risk and 1 county of unknown risk. Results on *B. burgdorferi* detection and *I. scapularis* infection prevalence are forthcoming, but the increase in *I. scapularis* populations in southeastern Michigan suggests the need for increased active surveillance of the vector.

**Research Grant**: Centers for Disease Control and Prevention Vector Biology Fellowship grant RC107-252 and the Michigan Lyme Disease Association

**Student Support**: Midwest Center of Excellence in Vector-Borne Disease

Characterization of HaPV coinfection in hamster model of ZIKV pathogenesis

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The ongoing Zika virus (ZIKV) epidemic has produced unique and severe clinical outcomes including neurological diseases and birth defects. This has brought about the urgent need for an animal model that replicates human ZIKV infection and has comparable reproductive anatomy. Preliminary trials were conducted on STAT2 KO hamsters, which are deficient in type 1 interferon responses, and the data suggested that these hamsters responded to the virus in a way comparable to humans. However, some ZIKV infected and uninfected hamsters developed and succumbed to tumors that presented in a way similar to hamster polyomavirus (HaPV). HaPV, a DNA virus that can integrate into the genome of the host animal, is seen almost exclusively in research colonies. It is speculated that HaPV can be transmitted vertically through breast milk or by integration into a heritable portion of the host genome. If the latter is true, it is possible that most, if not all, research hamsters carry HaPV. To better determine if HaPV coinfection was the cause of the tumors found in the ZIKV infected hamsters, we developed a PCR detection assay against HaPV. Primer sets were designed against the 5’ end of the HaPV sequence and tested in conjunction with a previously published primer set against the 3’ end, where random deletions often occur in the virus. The PCR detection assay will be used to test the tumors, livers and terminal blood from the hamsters used in the Zika trials. Upon evaluation of these results, we will access the consequences of HaPV coinfection and determine if engineering an HaPV free hamster would be necessary to utilize the STAT2 KO hamster as a model for ZIKV infection.

**Research Grant**: Startup Funds Adamovicz DM812

**Student Support**: Department of Veterinary Pathobiology, University of Missouri College of Veterinary Medicine
Evaluation of a vaccine against *Lepeophtheirus salmonis*, an ectoparasite of salmonids

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*Lepeophtheirus salmonis*, commonly known as the salmon louse, is an important parasitic copepod that primarily infects Atlantic salmon (*Salmo salar*). These lice feed on the mucus, skin, and blood of the fish host, resulting in lesions on the surface of the fish that can become large enough to cause osmoregulatory failure and increased susceptibility to secondary infection. Colonization by *L. salmonis* can affect the market value of fish by reducing feed conversion capability, decreasing growth rate and downgrading the final product. There are a number of commercial drugs available to treat *L. salmonis* infections; however, in recent years the majority of these treatments have been rendered ineffective due to drug resistance. This study aims to test the efficacy of a novel prototype vaccine using a challenge model that closely mimics the natural infection of sea lice. Salmon were divided into three treatment groups: (1) control, (2) single, and (3) triple vaccine dose. Vaccine and placebo were administered by intraperitoneal injection prior to lice exposure. Vaccine efficacy will be determined through comparisons of lice numbers on vaccinated fish versus unvaccinated controls, as well as by comparing the gene expression profiles of immune relevant genes using qPCR.

**Research Grant:** Natural Sciences and Engineering Research Council of Canada Undergraduate Student Research Award (NSERC USRA)
**Student Support:** Atlantic Veterinary College Veterinary Student Research Awards (AVC VetSRA)

Assessing plasma zinc concentrations as a reflection of zinc status in aging rhesus macaques

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Ongoing research in human and animal populations indicates that aging greatly increases the likelihood of zinc deficiency. Individuals deficient in zinc exhibit a wide variety of symptoms including decreased immune function, delayed wound healing, dermatitis, alopecia, enhanced inflammatory response and loss of appetite. The remarkable similarities between the signs of zinc deficiency and the common health dysfunctions associated with the aged population often enables zinc deficiency to go undetected while continuously contributing to age related maladies. Currently little data exists regarding the prevalence of zinc status and deficiency in rhesus macaques. This pilot study aims to establish plasma zinc concentrations in healthy adult and geriatric rhesus macaques and subsequently compare these values between age groups. The hypothesis of this study is that geriatric rhesus macaques at the California National Primate Research Center will have lower plasma concentrations than their younger adult counterparts, thus putting them at a higher risk for marginal or possibly overt zinc deficiency. 24 geriatric macaques (> 16 yr) and 24 sex-matched control adult macaques (8-16 yr) were enrolled in the study. Subjects were fasted, sedated and had 6ml blood collected by routine venipuncture. Plasma zinc concentrations will be analyzed via inductively coupled plasma mass spectrometry.

**Research Grant:** Unknown
**Student Support:** NIH Students Training in Advanced Research T35RR0067
Inhibition of biofilm formation and antibacterial potentiation by 2-aminoimidazole compounds

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Biofilm formation is important in the pathogenesis of many bacterial infections of both humans and animals. Coagulase-negative staphylococci (CNS) are significant biofilm-producing pathogens found in human foreign-body infections and ruminant mastitis. We have previously shown differences in biofilm production by representatives of various genotypes of Staphylococcus aureus causing bovine mastitis. We further demonstrated that 2-aminoimidazole compounds have anti-biofilm and antibacterial potentiation properties when tested in vitro using these isolates. In a recent study, we isolated 9 different species of CNS from the milks of a sample of North Carolina goats. The CNS are the bacteria most commonly isolated from goat milk. Our purpose was to evaluate the biofilm-forming potential of representatives of genotypes of the most common CNS we found in goat mastitis. We hypothesized differences in biofilm-producing potential among goat CNS isolates and that biofilm formation may reflect pathogenic potential. Using the most prolific biofilm-forming CNS isolate, we hypothesized that 2-aminoimidazole compounds would inhibit biofilm production and potentiate antibacterial activity. Our in vitro results show a range of biofilm-producing potential across 15 CNS isolates tested, with six isolates forming markedly robust biofilms. One of the most prolific was tested in vitro with the 2-aminoimidazole compound, and the compound showed anti-biofilm activity. Preliminary results indicate that the compound has antibacterial potentiation activity with three antibiotics when tested in vitro on a multi-drug resistant goat mastitis CNS isolate. The 2-aminoimidazole compounds have potential in the effective treatment of CNS infections.

Research Grant: American Dairy Goat Association Foundation
Student Support: CVM Veterinary Scholars Program, Merial Grant, Fund for Discovery, Herbert Benjamin Endowment

Biochemical analysis of tears in healthy cats and in cats affected with corneal sequestrum

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Corneal sequestrum is a brown to black corneal lesion resulting from chronic corneal ulceration, irritation, or infection with feline herpesvirus-1. Clinical signs and possible sequelae include ocular discharge, pain, visual impediment and corneal perforation. Understanding the pathogenesis of sequestrum formation and the nature of its black discoloration could lead to less invasive therapies or potentially prevention strategies. Previous studies have hypothesized the pigment to be melanin, porphyrin or iron, but to date, the source of sequestra coloration remains an enigma. We aim to determine the nature of corneal sequestrum discoloration by comparing the biochemical composition of tears from cats with sequestra to those of unaffected cats. Using Schirmer strips and polyvinyl acetal sponges, tears were collected from 8 cats with either historical or active corneal sequestrum and from 8 unaffected cats that were breed and age-matched. The samples were evaluated using a non-targeted approach with gas chromatography with mass spectrometry (GC-MS) and liquid chromatography with mass spectrometry (LC-MS). The GC-MS data was analyzed: 51 unique compounds and 485 unknown compounds were identified across all the affected eye tear samples. Of the 51 unique compounds identified, the most prevalent were urea, citric acid, scylo-inositol, malic acid, phosphoric acid, and α-alanine. Analysis of the LC-MS data is yet to be performed. Statistical analysis between the affected and unaffected groups will determine what compounds are up-regulated or down-regulated with corneal sequestrum.

Research Grant: None
Student Support: This project was supported by Morris Animal Foundation Award #D17FE-601
Determining anthelmintic efficacy against persistent *Ancylostoma caninum* infections and shedding

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Monitoring the efficacy of anthelmintic treatments is an important aspect of small animal practice to ensure that treatments are effective and to help monitor the possibility of drug resistance in small animal nematodes such as *Ancylostoma caninum*. Drug resistance in livestock and equine nematodes is well recognized and is a significant problem. Drug resistant nematodes are not thought to be as common in small animals. It is unknown how frequent or widespread drug treatment failure is in dogs because there is a lack of subsequent routine follow-up fecal analysis after normal deworming procedures. Deworming dogs is an important public health measure as both *A. caninum* and *Toxocara canis* are zoonotic parasites. The study aimed to determine the efficacy of anthelmintic treatments and the potential of drug resistant *A. caninum*. Feces were collected pre-treatment and 7-10 days post-treatment. Samples were evaluated for parasite ova. If positive for *A. caninum*, fecal egg counts and larval cultures were performed. In the absence and presence of drug, an *in vitro* egg hatch assay and larvae assays were analyzed. PCR-RFLP confirmed *A. caninum* identification. Study results will help to determine if drug resistance is present and which treatments are effective. With this evidenced-based information, veterinarians will be able to choose the most efficacious treatment regimens for canine hookworm infections, particularly ones that are difficult to clear. This information could be especially significant for greyhounds, which may be more susceptible to resistant hookworm infections since they may have difficulty achieving adequate steady-state anthelmintic drug levels due to their naturally lean body condition.

Research Grant: None
Student Support: NIH T35 Training Grant 5T35OD010911-09

Analysis of American black bear retinal cone photoreceptor distribution

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The distribution and subtypes of cone photoreceptors (important for color and quality vision) varies widely in different carnivore species, but there have been limited studies on bear (ursid) cone distribution. Polar bears (*ursus maritimus*) have dichromatic vision (can distinguish between two colors) and a previous behavioral study suggests that American black bears (*ursus americanus*) are also dichromatic, indicating that they possess 2 cone subtypes. The purpose of this study was to examine the subtype and topography of cones in American black bear retinas to further predict the nature of their color vision and image resolution. Seventeen eyes from 9 individuals were collected from black bears in northeastern North Carolina and frozen in liquid nitrogen. Methods were developed to examine frozen eye sections and retinal wholemounts using antibodies targeting two cone opsin subtypes: long/medium (L/M) wavelength sensitive and short (S) wavelength sensitive. Fluorescent microscopy was used to create density maps of cone opsin subtypes by systemically imaging across each wholemount. Retinas contained both cone subtypes, with L/M cones outnumbering S cones by at least 3:1, a finding confirmed in retinal frozen sections. A cone-dense visual streak was present directly around the optic nerve, similar to that found in other carnivores. These conclusions confirm that American black bears are predicted to have dichromatic vision with high acuity indicated by the presence of the dense visual streak. Since they corroborate the previous findings about American black bears, these results can be used in the future to further understand bear behavior and also be compared to investigations of the visual ability of other carnivores.

Research Grant: none
Student Support: Merial grant, the Fund for Discovery, and the Herbert Benjamin Endowment
Epidermal metaplasia and endoplasmic reticulum stress in Thoroughbred horses with supporting limb laminitis

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Equine supporting limb laminitis (SLL) is a debilitating and poorly understood condition associated with non-weight-bearing lameness. Pain from the primary injury discourages normal weight-shifting in the contralateral limb which is proposed to limit blood flow, thus interfering with cellular homeostasis and organelle function. We hypothesize that endoplasmic reticulum (ER) stress contributes to SLL pathogenesis. ER stress activates the unfolded protein response (UPR), an adaptive mechanism to maintain homeostasis that becomes overwhelmed in several degenerative diseases in humans, leading to apoptosis and tissue damage. In addition to histologic evidence of lamellar tissue stress in SLL feet, epidermal cells display metaplasia, based on morphology and Periodic acid-Schiff (PAS) staining patterns. Our aim was to determine the association between the up-regulation of the ER stress and UPR reporter, spliced X-box binding protein 1 (XBP1s), and the degree of epidermal metaplasia in affected and unaffected feet from Thoroughbred SLL cases (N=16) relative to control feet (N=7). Levels of XBP1s were determined by semi-quantitative immunoblotting and densimetry of proteins extracted from snap-frozen archived lamellar tissue. Metaplastic cells were scored on PAS-stained slides from SLL cases and controls. PAS+ epidermal cells were counted manually in three high-power (40x) fields at three anatomical locations relative to the skeletal axis of the digit. Outcomes were compared by ANOVA and post-ANOVA multiple comparison tests based on the severity of laminitis in each foot. The association between epidermal metaplasia and XBP1s expression was determined by Pearson’s correlation coefficient calculation.

Research Grant: American Association of Equine Practitioners Foundation
Student Support: NIH-Merial Veterinary Research Scholars Program (T35 RR07065)

Evaluating microneedles for precise corneal drug delivery and gene therapy

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Many ocular diseases would benefit from a precise method for drug delivery to the corneal stroma. Current ocular injection methods using standard needles are technically difficult and imprecise, whereas using microneedles in clinical settings would be easier and more accurate. For diseases like mucopolysaccharidosis type 1 (MPS-1), microneedle treatments could be an alternative to unsuccessful corneal transplants. In MPS-1, the body lacks an enzyme that metabolizes glycosaminoglycans, leading to corneal clouding and blindness despite systemic cell and gene therapy. The objective of this study was to evaluate a commercially available dermal microneedle (the NanoPass microneedle) for efficient and accurate intrastromal delivery of gene therapy in porcine cadaver corneas. To ensure the safety of the NanoPass microneedle, lesion size and depth of needle penetration were measured using confocal microscopy and optical coherence tomography respectively. Porcine cadaver eyes were injected with fluorescein dye to monitor distribution within the corneal stroma over time. In later studies, porcine eyes were injected with different volumes and concentrations of AAV8G9-GFP. Using the Xenogen in vivo imager, eyes were evaluated for GFP concentration at 24 hours, 3 days, 5 days, and 7 days following AAV8G9-GFP injection. Results demonstrated that intrastromal fluorescein injection of 50 μL covers up to 99% of the cornea within 24 hours. Preliminary results for AAV8G9-GFP treatments showed that microneedle injection treatments transfected stromal fibroblasts successfully. Future studies will evaluate immunofluorescence histologically and live animal models to assess microneedle treatment success for eventual use in MPS-1 children.

Research Grant: UNC TraCS Translational Team Science Award
Student Support: CVM Veterinary Scholars Program
Age-related expression of Group II mGluRs in the primary auditory cortex

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Age-related hearing loss is a serious medical problem, causing decreased quality of life in seniors. While excitatory glutamatergic and inhibitory GABAergic receptors have been well studied in the auditory neural pathways, metabotropic glutamate receptors 2 and 3 (Group II mGluRs), which provide additional inhibition in this pathway, have received little attention. Group II mGluRs attenuate transmission of unwanted stimuli in the auditory pathway and their expression has been found to decrease with age in layer IV of the visual cortex. We hypothesize that Group II mGluR expression will decrease similarly with age in layer IV of the primary auditory cortex, which may underlie several age-related auditory perceptual deficits, such as the inability to filter unwanted auditory stimuli. To investigate the age-related expression of Group II mGluRs, we utilized immunofluorescence, western blot, and autofluorescence imaging on three age groups of BALB/c mice: neonatal (2-3 weeks), juvenile (9-10 weeks), and adult (9 months). Expression of Group II mGluRs were qualitatively and quantitatively analyzed in the primary auditory cortex. These data are expected to help identify the critical time course for the progression of Group II mGluR expression with age in the auditory cortex.

Research Grant: NIH R03AG052120
Student Support: NIH T35OD011151

Phenotypic and transcriptomic characterization of canine myeloid-derived suppressor cells

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Myeloid-derived suppressor cells (MDSCs) are key players in immune evasion, facilitating tumor growth and metastasis. MDSCs accumulate under various pathological states, adopting one of two recognized phenotypes: monocytic (M)-MDSCs and polymorphonuclear (PMN)-MDSCs. Increased MDSC frequencies in the peripheral blood of cancer patients predict a negative prognosis. Studying the function of these cells in mice is not ideal, since murine models often do not reliably recapitulate human disease. Dogs develop spontaneous tumors that share many features of human cancers, making them an excellent model for cancer research. Our study aimed to characterize the phenotypic and transcriptomic signatures of MDSCs in the dog, defining for the first time monocytic and polymorphonuclear subsets in this species. MDSCs in the peripheral blood of tumor-bearing and control dogs were defined as hypodense MHC class II-CD5-CD21-CD11b+ cells, with M-MDSCs defined as CADO48A-CD14+ cells, and PMN-MDSCs defined as CADO48A+CD14- cells. In common with human studies, peripheral frequencies of PMN-MDSCs were increased in dogs with various histotypes of cancer compared to controls, higher frequencies correlating with bulkier tumors. Bioinformatic analyses have revealed that the transcriptomic signatures of M-MDSCs and PMN-MDSCs are distinct from each other and from those of monocytes and polymorphonuclear cells respectively, but similar to the respective human populations. Our findings demonstrate for the first time that dogs have two distinct populations of MDSCs, characterized by specific phenotypic and transcriptomic signatures that share features of human MDSC subsets, validating the dog as a model for studying these cells in the context of cancer.

Research Grant: Petplan Charitable Trust
Student Support: NIH T35 Training Grant OD010919 and the NIH/Merial Program at the University of Pennsylvania
Effects of degenerative myelopathy on the canine genioglossus muscle

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Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease of motor neurons causing progressive muscle atrophy. Clinical signs eventually evolve into difficulty swallowing and speaking due to tongue muscle atrophy. Many ALS patients die from respiratory failure attributed to dysphagia-related aspiration pneumonia in the end stages of the disease, which makes it difficult to study tissues during disease progression. Canine degenerative myelopathy (DM) parallels the clinical signs of some forms of ALS, thus offering a suitable translational model. In latter stage disease, DM affected dogs develop dysphagia and difficulty moving the tongue. The tongue muscle has not been studied in DM. The genioglossus muscle is of particular interest since it is necessary for grabbing and swallowing food and drink in dogs. This muscle is composed of predominantly Type 2 myofibers. Based on findings that intercostal muscles of DM-affected dogs developed a type 1 myofiber predominance corresponding with muscle atrophy, we expect to find a similar pattern in the genioglossus. Therefore, we are investigating post-mortem genioglossus samples from age- and breed size-matched controls (n=11) and DM-affected dogs spanning all disease stages (n=16). Cross sections of paraffin-embedded samples are being analyzed using immunohistochemical methods for characterization of markers of muscle atrophy. Compared to controls, we hypothesize that DM-affected genioglossus will have: 1) reduced abundance of type 2 fibers, 2) SOD1 protein aggregation, and 3) reduced myofiber diameters. Results of this study may provide novel evidence of tongue muscle pathology in DM to parallel findings in ALS patients, thus further strengthening this model.

Research Grant: American Boxer Charitable Foundation
Student Support: IDEXX-BioResearch

A pilot study in the establishment of canine urothelial primary cell cultures

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Chronic cystitis is a common affliction in both human and veterinary medicine. This research team aims to prove that canine models of disease are appropriate for developing treatments for human chronic cystitis. This study served as the first stepping stone in the model’s development, in that this team sought to demonstrate the capability of establishing a primary cell culture for future use in testing potential chronic cystitis treatment options. The approach to this study involved two methods for cell collection - isolating urothelial cells from free catch urine samples and enzymatically digesting the tissue of a bladder harvested from a recently euthanized animal. A total of 33 free-catch urine samples were collected from 11 dogs - 5 castrated males, 3 intact males, 2 spayed females, and 1 intact female. For purposes of refining technique, 1 intact male rat bladder was harvested before harvesting the 2 spayed female canine bladders included in the study. Following cell isolation from both sources, the cells were incubated in 1mL of complete culture media in a cell culture plate. A heterogenous cell population, including epithelial-like cells, was noted on all cultures. The viability of the cell population was assessed using a LIVE/DEAD fluorescence stain. A portion of cells were incubated on a poly-L-lysine coated coverslip as a specimen for scanning electron microscopy to characterize the urothelial cells’ morphology. Despite a visibly appreciable increase in the number of cells attached to the culture surface, a complete monolayer was not achieved from the free-catch urine sample cultures. Complete data acquisition from the canine bladder harvests has not yet been achieved due to the timing of the bladder harvest.

Research Grant: Mississippi State University College of Veterinary Medicine
Student Support: Boehringer Ingelheim Veterinary Scholars Program
Genetic characterization and comparative genome analysis of vesicular stomatitis virus isolates from Colorado

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Vesicular stomatitis virus (VSV) is an economically important pathogen of ruminants, horses, and pigs. It results in low mortality, high morbidity, and significant financial losses due to testing and quarantine measures as it is clinically indistinguishable in cloven hooved animals from foot-and-mouth disease. The evolution of VSV has been well characterized within an in vitro system; however, the genetic determinants of viral adaptation that may impact spread and sporadic epidemics of VSV remain very poorly characterized. During a statewide VSV epidemic in 2014 and 2015, 495 and 155 horses tested positive for VSV via qRT-PCR in Colorado, respectively. Given recent changes in the distribution and incidence of VSV infection, we initiated two studies: 1) a cross-sectional study of banked equine serum samples to identify the seroprevalence of VSV among Colorado horses; and 2) a retrospective phylogenetic analysis of field strains submitted to the Colorado State University Veterinary Diagnostic Lab during the 2015 epidemic. Preliminary results indicate that 21% of horses have neutralizing antibodies to VSV (primarily New Jersey strain). Genetic characterization of the hypervariable phosphoprotein (P) region of the genome was conducted using Sanger sequencing on samples that tested positive via VSV qRT-PCR. Data generated from these studies provide unique information regarding the genomic diversity and evolution of VSV field isolates from Colorado compared to isolates previously submitted to GenBank.

Research Grant: Young Investigator Grant, Center for Companion Animal Studies, Department of Clinical Sciences, College of Veterinary Medicine & Biomedical Sciences, Colorado State University

Student Support: USDA-NIFA Animal Health & Disease Research Program Funding 2017-36100-06008

A VE 0991 inhibition of meconium-induced apoptosis in human lung epithelial

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Meconium Aspiration Syndrome is a low incidence fetal respiratory condition caused by the inhalation of meconium, an inherently sterile dark-green mixture of lanugo, mucus, bile, intestinal epithelial cells, water, and amniotic fluid. Meconium does not present a direct bacterial threat but may result in pneumonia, hypoxia, and scarring of the lungs due to its apoptotic-inducing effects in alveolar epithelial cells. Previous studies have shown that the angiotensin pathway may provide insight into inhibiting apoptosis in human epithelial cells. Prior research has shown the upregulation of ANG1-7 (angiotensin 1-7, the product of the protective enzyme ACE-2) inhibits phosphorylation of c-Jun N-terminal kinases (JNK), through activation of the mas receptor, thus inhibiting apoptosis. We hypothesize that using the synthetic mas receptor agonist, AVE 0991, will inhibit meconium induced apoptosis in human alveolar epithelial cells. A549 cells, a line of human adenocarcinomic alveolar epithelial cells, were cultured to 50% confluence in F-12 media. The media was aspirated and replaced with serum-free F-12 media containing 1% penicillin streptomycin (pen-strep) antibiotic for 20 hours. The media was removed and selected wells (2 columns) were treated with 2.5% meconium and serum-free (+1% pen-strep) F-12 media. Selected wells also received a treatment of 10-7 M of AVE 0991. After another 20-hour incubation period, cells were fixed with 70% ethanol at 4°C. Fluorescent microscopy using a propidium iodide solution was used to determine apoptotic cells based on altered nuclear morphology. Results were then analyzed using a GraphPad Instat t-test and Student Newman Keuls post hoc test.

Research Grant: None

Student Support: NIH-5R25HL103156-07
Deciphering the functional role of enhancers as gene regulatory elements

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Enhancers are distal control elements that play a key role in establishing gene expression patterns. Although genome-wide studies have identified hundreds-of-thousands of candidate enhancers in Metazoan genomes, these elements have not been systematically tested, and their target genes remain unknown. We aim to characterize the effect of enhancers on transcription through systematic inhibition of regulatory elements, in conjunction with a genome-wide readout of their effects on gene expression. We will use CRISPR interference (CRISPRi) screening, which uses catalytically-dead Cas9 (dCas9) fused to Kruppel associated box (KRAB) domain, to repress regulatory elements in chronic myelogenous leukemic (K562) cells. The effects of each enhancer knockdown will be analyzed using PRO-seq, which maps the location of RNA polymerase genome-wide. A power analysis indicates that transfecting two sgRNAs per enhancer will increase the throughput of the screening method, by increasing the likelihood that each experiment will have an effect on gene expression. Short-term goals are to successfully clone two sgRNAs, scaffolding, and promoter sequences into a BsmBI-sgRNA expression vector. We will create a lentivirus to infect stable K562 inducible dCas9-KRAB cells. We will select stable cell lines expressing our paired sgRNAs using Hygromycin B. Changes in gene expression in these stable cell lines will be measured with PRO-seq. After developing a strategy for repressing the desired regulatory elements, we will design a library to target enhancers with varying functional properties. This systematic inhibition of enhancers with differing properties will provide evidence of in vivo contextual transcriptional activities of enhancers.

Research Grant: National Human Genome Research Institute – R01 HG009309-01
Student Support: NIH T35 Training Grant – OD010941

Innovative approaches to the treatment of Staphylococcus pseudintermedius infections

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There is an urgent need for discovery of effective antimicrobial drugs and therapeutic strategies to combat important microbial pathogens of animals and humans. Staphylococcus pseudintermedius is a gram-positive bacterium that is a predominant cause of skin and soft tissue infections (SSTI) of animals including pyoderma, otitis, surgical site infections, and urinary tract infections. Emergence of S. pseudintermedius clinical isolates resistant to beta lactam antibiotics (methicillin-resistant S. pseudintermedius (MRSP)) and/or many other antibiotic classes (multiple drug resistance), underscores the critical need for effective treatments that do not induce antimicrobial resistance. The hypothesis tested was that novel antimicrobial compounds will result in significant reduction of Staphylococcus replication and survival in planktonic culture and biofilm. A panel of 68 compounds was screened against planktonic bacteria; 16 compounds with high efficacy were evaluated further. Bacterial isolates used were obtained from the Indiana Animal Disease Diagnostic Laboratory; isolates were cultured from animals treated at Purdue University Veterinary Teaching Hospital. Minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) were tested using Clinical and Laboratory Standards Institute (CLSI) methods. Efficacy against biofilm was tested in 96 well plates via previously published methods. Compounds were initially screened using 1 MSRP and 1 methicillin-susceptible (MSSP) isolate; those with MIC of ≥2 mM or 2 mg/ml were further tested against a total of 8 isolates. Highly effective compounds will be studied further including evaluation of toxicity for mammalian cell lines and efficacy in infected animals.

Research Grant: Purdue College of Veterinary Medicine
Student Support: Morris Animal Foundation
Biomechanical comparison of two implant configurations for feline tibial fracture repair

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There is limited scientific information in the literature describing long bone fractures in cats. Few articles describe locking plate technology, which has shifted the goal of fracture repair from anatomic reduction to bridging plate osteosynthesis, and may be advantageous in certain clinical situations. There are many types of locking plate systems available in veterinary medicine, including the locking compression plate (LCP) and conical coupling plate. The objective of this study was to biomechanically compare stiffness and strength of LCP and conical coupling plates used as single plate locking constructs for fracture repair in the feline tibia. 20 hind limbs were harvested from 10 feline cadavers, and the tibia were stripped of all soft tissues. Tibia pairs from each cadaver were randomly assigned to the LCP or conical coupling group. An 8 hole, 2.7 mm LCP or 6 hole, 2.5 mm conical coupling plate of similar overall length was applied to the medial surface of the tibia. A 1 cm fracture gap was centrally placed in the tibial diaphysis. The constructs were tested in four-point bending, non-destructive axial compression, and axial compression to failure. Preliminary data analysis suggests that both plates are stiffer in craniocaudal bending compared to mediolateral bending, and that there may be a statistically significant difference in axial stiffness and failure load between the two plates. Further analysis may suggest that one plate may be a more suitable single implant choice in feline tibial fracture repairs. Further investigation in the clinical setting is recommended.

Research Grant: Departmental Funds - Small Animal Clinical Sciences, University of Florida College of Veterinary Medicine
Student Support: Boehringer Ingelheim Veterinary Scholars Program

Effects of diet and a stress relieving supplement on upper respiratory disease and diarrhea in shelter cats

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Managing stress-related illnesses in shelter cats is a common challenge for high volume animal shelters. Identifying cost-effective methods for minimizing diarrhea and upper respiratory infection (URI) in shelter cats potentially can improve animal welfare, reduce average length of stay, and reduce costs associated with the housing and medical management of sick cats in shelters worldwide. Feeding a consistent diet or supplements with natural stress relieving properties may lessen diarrhea and URI. In Experiment 1 of this study, the hypothesis is that diarrhea and URI will be less in cats fed a consistent, high quality diet (3 weeks duration) when compared to cats fed the shelter facility diet (3 weeks duration) which is a mixture of donated products of variable quality. In Experiment 2, the hypothesis is that diarrhea and URI will be less in cats fed a consistent high quality diet and a stress relieving supplement (alpha-casozepine; Zylkene; Vetoquinol) when compared to cats fed the high quality diet and no supplement. Standardized clinical score rubrics for diarrhea and URI are applied daily by trained observers to each of the individually caged cats housed in a single room of the shelter in both Experiments. In Experiment 2, the observers are masked to which cats have been randomized into the supplement or no supplement groups. The potential stress-reducing effects of the supplement in Experiment 2 will also be assessed by comparing fecal cortisol concentrations on entry and exit from the study. In Experiment 1, no significant differences in diarrhea or URI rates were detected between cats fed the variable facility diet or a consistent high quality diet. Experiment 2 is ongoing.

Research Grant: Supported by the Center for Companion Animal Studies
Student Support: Petsmart Charities Fellowship
A syngeneic rat model allows for the study of osteosarcoma metastasis in patients with intact immune systems

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Osteosarcoma is the most common bone cancer in children and teens. In approximately 20% of these patients, metastasis has already occurred before tumor diagnosis. In order to better understand factors that determine metastasis, the development of an animal model that closely replicates the events that take place in these patients is critical. Many animal models use immunocompromised mice to grow human osteosarcoma. Here, we established a syngeneic osteosarcoma Sprague Dawley (SD) rat model with an intact immune system. Juvenile Sprague Dawley (SD) rats were orthotopically implanted with rat osteosarcoma cell line UMR-106 (ATCC), originally isolated from a SD rat. We transfected UMR-106 cells with Td Tomato red fluorescent protein, allowing potential metastases to be identified with in vivo whole animal imaging. Using aseptic technique, a 22 gauge needle was used to make a small hole in the tibial plateau of three week old rat pups. The UMR-106 cells (150,000) were then injected into the diaphysis through this opening using a Hamilton syringe. Significant tumor formation in the injected tibias was observed within three weeks by CT scans and IVIS optical fluorescence imaging. When pups reached six weeks of age, the hind limbs with the primary tumor were amputated by coxofemoral joint disarticulation and were examined histologically for osteosarcoma. Metastasis was evaluated in a time course experiment. In parallel to the in vivo experiments, western blots from lysates of UMR-106 cells demonstrated the expression of ErbB2 and EGFR proteins, allowing for future therapies using tyrosine kinase inhibitors. This will allow us to also investigate immunotherapy treatment for osteosarcoma using rats with intact immune systems.

Research Grant: American Heart Association Grant in Aid
Student Support: Charles River Laboratories

The role of disseminated tumor cells in recurrent glioblastoma multiforme

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Glioblastoma multiforme (GBM) is one of the most common and aggressive forms of primary brain cancer in humans. Invasion by GBM cells lead to recurrence and a median survival rate of 12-14 months. Tumor recurrence is classically viewed as outgrowth of localized, radio- and chemoresistant cells. This study examines a novel mechanism of recurrence involving migration and proliferation of distant, disseminated tumor cells (DTCs) that repopulate the original tumor site. Glioma stem cells (GSCs) were isolated from a patient’s primary, untreated tumor (0203) and from various locations of tumor tissue at the time of death (T2-T7). Whole exome sequencing identifies ablation of the original 0203 signature following treatment, and indicates that the recurrent tumor (T3-T4) is most similar to tumor subpopulations in the distant, contralateral lobe (T6-T7). These data suggest the recurrent tumor originated from the T7 subpopulation, rather than transformation of the original 0203. To test this, we initiated mouse xenograft studies to analyze GSC migration and interaction between these subpopulations, mimicking the pre- and post-treatment environment. Single cell RNA-sequencing has also been performed on 0203 and recurrent subpopulations to evaluate tumor heterogeneity. Identifying a role for DTCs in tumor recurrence may lead to more effective therapies, aimed at prolonging disease-free intervals following initial treatment in GBM patients.

Research Grant: Elsa U. Pardee Foundation Research Grant
Student Support: NIH T35 Summer Biomedical Research Fellowship
Evaluating a veterinary specific digital refractometer measuring urine specific gravity & plasma total protein

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Objectives- 1) To evaluate the relationship between urine osmolality and urine specific gravity as measured with a veterinary specific digital refractometer in canine patients, and to determine how commonly measured urine solutes may affect it. 2) To examine the statistical association between total protein as measured by a veterinary specific digital refractometer to total protein reported on a serum chemistry, and how this compares to a traditional optical refractometer.

Animals- Dogs presented to the Midwestern University Companion Animal Clinic and requiring urinalysis or hemanalysis as part of their diagnostic plan. No attempt was made to screen candidates based on health, age, breed or sex.

Procedures- Urine and blood samples were collected by veterinarians, veterinary technicians or supervised students via cystocentesis and phlebotomy respectively. Urine samples were divided, and one aliquot was used to measure specific gravity with a veterinary specific digital refractometer. A second aliquot was frozen at -80°C for future determination of osmolality via freezing point depression. A portion of each blood sample was centrifuged and the plasma total protein measured with a veterinary specific digital refractometer by one researcher while a second researcher measured plasma total protein with a light refractometer. The remainder of all blood and urine samples were submitted to a veterinary diagnostic lab for further analysis. No blood or urine samples were obtained solely for the purpose of this study, but were collected from samples ordered by the attending veterinarian as a part of the patient’s diagnostic plan.

Results- Results will be presented at the National Veterinary Scholars Symposium.

Research Grant: None
Student Support: Merial

Surveying the chemosensory system of filarial nematodes

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Lymphatic filariasis (LF) is a Neglected Tropical Disease caused by filarial nematodes including Brugia malayi, infecting approximately 120 million people in 73 endemic countries. 39 million of these people suffer clinical symptoms, with the most extreme being elephantiasis, a gross swelling of the extremities. Despite orchestrated elimination efforts, LF remains a global health concern; therefore, there is a dire need for new control strategies. Parasitic nematodes rely on acute perception of their environment to establish infection within the host, such that chemosensory systems are attractive targets for novel therapeutic intervention. However, the chemosensory systems of parasitic nematodes are poorly understood. Here we begin to describe chemosensory pathways in the filarial nematode, B. malayi, using a PCR approach to define the temporal expression patterns of chemosensory genes. Via a BLAST search of the B. malayi genome, we identified Brugia homologs of known nematode chemosensory genes. RT-PCR analysis showed expression of Bm-osm-9, Bm-tax-4, Bm-daf-11, Bm-gpc-3 in L3 larvae, adult male, adult female and microfilaria stages. Unexpectedly, Bm-odr-3, a highly conserved odorant receptor, was not expressed at any stage. Quantitative PCR analysis indicated no significant differences in stage specific expression of these genes with the exception of Bm-gpc-3, which was most highly expressed in adult female parasites. These data suggest a relatively conserved chemosensory apparatus in B. malayi at the genetic level both between different life cycle stages and in comparison to other nematode species. Functional studies are now required build on these data and understand how filarial nematodes perceive their environment.

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Student Support: NIH T35 OD 012199-15
Comet assay to compare biological effectiveness of various radiation sources in canine bladder cancer cells

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Radiation therapy and surgery are the primary treatments for tumors in both humans and dogs. The main goal of radiation therapy is to kill tumor cells via DNA damage, while causing minimal damage to normal cells. DNA damage occurs as single or double stranded breaks. Single stranded breaks are more likely to be repaired by intracellular mechanisms. Different types of radiation may interact with tissues in dissimilar ways. Despite the common use of radiation therapy in dogs, DNA strand breakage in regards to radiation source, has not been directly studied in these patients. In the present study, to test the effect of different radiation source, we are using canine bladder cancer cells (Transitional cell carcinoma, TCC). To observe the difference in relative biologic effectiveness, which will be analyzed by studying the quantity of single and double stranded DNA breaks using a comet assay after being exposed to 8 Gy of radiation. We hypothesize that low linear energy transfer (LET) radiation, such as photons and high energy electrons, will cause less DNA damage than high LET radiation, such as neutrons or alpha particles. DNA strand breaks will be compared amongst the modalities using the comet assay. In our study, we will be using high and low energy photons, high and low energy electrons, alpha particles, and neutrons. While validating the comet assay and generating a dose response curve, we expect to see an increase in DNA damage as the dose of radiation increases from 0 Gy to 9 Gy. We will attempt to more accurately quantify the relative biologic effect of these different radiation sources in canine bladder cancer cells.

Research Grant: Richard Wallace Faculty Incentive Grant, University of Missouri Alumni Association.
Student Support: Department of Veterinary Medicine and Surgery, University of Missouri CVM

Discovery of novel viruses in mosquitoes from the Midwestern United States and Mexico

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Viral metagenomics was used to detect novel and recognized viruses in mosquitoes from the Midwestern United States and the Yucatan Peninsula of Mexico. To facilitate the identification of viruses in the Midwestern U.S., 7041 mosquitoes from 24 species and 8 genera that had been collected in Iowa were sorted into 54 pools, homogenized, filtered and inoculated onto monolayers of Aedes albopictus (C6/36) cells. Another 17 pools, representing 684 mosquitoes (2 species) from Mexico, were processed as described above. Cell cultures were monitored regularly for cytopathic effect (CPE). A second blind passage was performed using all samples that caused CPE and a subset that did not. Cell monolayers were harvested and total RNA was extracted and analyzed by unbiased high throughput sequencing. Two novel viruses and four recognized viruses were detected. One novel virus, discovered in Aedes trivittatus from Iowa, belongs to the genus Orbivirus (family Reoviridae). Our initial analysis indicates that the virus contains 10 genomic segments and that the predicted amino acid sequences contain no more than 63% amino acid identity to the corresponding regions of its closest known relatives. The other novel virus, discovered in Ochlerotatus taeniorhynchus from Mexico, belongs to a newly proposed taxon known as Negevirus. The virus contains a single-stranded RNA genome that contains no more than 76% nucleotide identity to its closest known relatives. Recognized viruses identified in this study are as follows: Houston virus (genus Alphamesonivirus, family Mesoniviridae), Koyoma Hill virus (genus Orbivirus, family Reoviridae), Umatilla virus (genus Orbivirus, family Reoviridae) and Culex flavivirus (genus Flavivirus, family Flaviridae).

Research Grant: Iowa State University College of Veterinary Medicine
Student Support: NIH T35 Training Grant T335OD012199
Evaluation of *Salmonella* Typhimurium mutant growth in the presence of reactive oxygen species

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Non-typhoidal Salmonellae cause acute infectious gastroenteritis characterized by neutrophilic inflammation. To kill pathogens, neutrophils (PMNs) generate a respiratory burst producing reactive oxygen species (ROS). Neutrophil ROS kill most bacteria, however, *Salmonella* thrives in these conditions. Our prior work identified 33 *Salmonella* Typhimurium (STm) mutants that influence the PMN respiratory burst. Two of these mutants, deleted for STM1213 and STM1690, increase the PMN respiratory burst. The purpose of this project is to establish the reason for the observed alteration in PMN respiratory burst. We hypothesize that the ΔSTM1213 and ΔSTM1690 mutants will be sensitive to ROS, have altered motility, and have reduced fitness during infection. We tested the growth of our STm mutants in the presence of two different ROS: hydrogen peroxide and hypochlorite. Our data demonstrate that neither of the mutants display sensitivity to hydrogen peroxide. Preliminary work suggests that the ΔSTM1690 mutant is sensitive to hypochlorite although further experiments are needed. We established that both ΔSTM1690 and ΔSTM1213 have adequate motility on semi-solid agar. Finally, we demonstrate that ΔSTM1690 has a fitness defect in the murine colitis model. Our data suggest that neither altered motility nor hydrogen peroxide sensitivity contribute to the increased neutrophil ROS in response to our mutants. However, sensitivity to hypochlorite may be the mechanism for the ΔSTM1690 fitness defect during infection and for increased neutrophil ROS production. Future experiments will establish the fitness of ΔSTM1213 during infection. This work will improve our understanding of how STm interacts with neutrophils to benefit from inflammation.

**Research Grant:** NCSU CVM Internal Grant  
**Student Support:** NIH- T-35 OD011070; NIH- T-32 OD011130

Serum histamine and tryptase levels in dogs presenting with anaphylaxis: an emergency department study

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The current diagnosis of anaphylaxis is based upon patient history in combination with presenting symptoms. In veterinary medicine, however, getting an accurate history for the patient is often difficult. It is for this reason that identifying measurable biomarkers of anaphylaxis in veterinary patients would be particularly valuable. The goal of this study is to establish if local and systemic anaphylaxis in dogs is associated with systemic increased histamine and tryptase, two biomarkers that have been evaluated in human medicine. The levels of these potential markers are to be compared among three groups of dogs, including healthy dogs, dogs with anaphylaxis or local urticaria, and dogs with mast cell tumors. The hypothesis of this study is that dogs with anaphylaxis and dogs with mast cell tumors will have elevated levels of serum histamine and tryptase compared to healthy dogs. 16 dogs in each of the three categories-- anaphylaxis, healthy, and mast cell tumor-- are being recruited to the study. Serum samples are being collected and frozen for batch analysis using a validated commercial ELISA test.

**Research Grant:** Cummings School of Veterinary Medicine Summer Programs for Veterinary Students Fund  
**Student Support:** Merial Veterinary Research Scholars Program
Ambient vapor-phase pollutants suppress the innate immune response of dendritic cells

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Particulate matter (PM) coexists in the ambient atmosphere with volatile/semi-volatile organic compounds in the gaseous phase (vapor-phase pollutants, aka vapor). Studies over the last few decades have shown that oxidative stress is a major mechanism by which PM contributes to asthma pathogenesis. A loss of transcription factor Nrf2, which protects cells from oxidant injuries, leads to increased susceptibility of antigen-presenting dendritic cells (DC) to oxidative stress. The effects of vapor on DC has not been studied. We hypothesized that ambient vapor-phase pollutants suppress lipopolysaccharide (LPS)-induced DC response and that this effect is lost in the absence of Nrf2. Our results show that, while LPS alone induced significant release of IL-6, IL-12p40, TNFα from DC (Balb/c), vapor alone did not have any effect. LPS-induced innate cytokine response was suppressed by the presence of vapor and this was accompanied by an increase in HO-1 protein expression. To determine the role of Nrf2, wild-type (WT) and Nrf2 knockout (KO) DC on C57Bl/6 background were also tested. While untreated WT and KO DC had similar levels of these cytokines, they responded differently to LPS. Levels of WT DC showed higher levels of IL-6 and TNFα and lower levels in IL-12p(40) in LPS-induced response compared to KO. The suppressive effect of vapor on LPS-induced IL-12p(40) and IL-6 responses was weakened in Nrf2 KO DC. Vapor had no significant effect on LPS-induced TNFα. This study is the first to show the effect of ambient vapor-phase pollutants on DC, suggesting that these pollutants could contribute to asthma pathogenesis. Future studies are needed to understand the health effects of vapors and their effects in conjunction with PM.

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Evaluation of Plasmodium clonality in children undergoing ivermectin mass drug administration for malaria

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Malaria continues to be a major cause of morbidity and mortality in endemic areas such as sub-saharan Africa because the gains from malaria control efforts over the last decade, such as bed net use and combination drug therapies, are stalling due widespread emergence of resistant mosquitoes and parasites. A recent clinical trial in Burkina Faso (RIMDAMAL: NCT02509481), which tested a new malaria control strategy of repeated ivermectin mass drug administration for prematurely kill biting mosquito vectors, resulted in significantly reduced malaria episodes in village children from the intervention arm. Unexpectedly, malaria incidence was further reduced in a subset of older children, meeting the minimum height inclusion criterium, who were repeatedly treated with ivermectin, suggesting a direct effect of ivermectin treatment on clinical malaria episodes. Our study evaluated the hypothesis that the repeated ivermectin treatment of older children affected the parasitemia and/or clonal structure of Plasmodium populations in their blood, which may explain their reduced malaria episode incidence. To test this hypothesis, we have examined and compared the parasitemia data from blood smears taken from these children and their controls when they presented with malaria and are further examining the clonal structure (multiplicity of infection: MOI and molecular force of infection: mFOI) of these parasite samples. Preliminary data suggests children who received repeated ivermectin mass drug administrations may have a reduced mFOI compared to children in the control arm who received a single treatment. We expect the results of this study to aid in the understanding and development of a novel control strategy for malaria.

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Student Support: National Institutes of Health T35OD015130
Identifying MHC class I alleles associated with resistance to *M. ovipneumonia* infection in bighorn sheep

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Bighorn sheep are a charismatic megafauna that are a species of concern throughout their range due to small population sizes, and are federally endangered in the Peninsular ranges of California. Bighorn sheep are highly susceptible to a variety of infectious diseases, such as *Mycoplasma ovipneumonia*, which can lead to deadly pneumonia. To aid in conservation efforts, it is necessary to understand the immunogenetics of bighorn sheep, especially alleles which may increase or decrease protection to *M. ovipneumonia* infection. Class I major histocompatibility complex (MHC I) genes are highly polymorphic genes which are necessary for presenting foreign antigens to cytotoxic T lymphocytes and MHC genetic diversity at both the individual and population level is necessary to protect vertebrate animal populations from infectious diseases. The aim of this study is to identify MHC class I genes expressed in different populations of desert bighorn sheep and to use this information to determine if particular alleles are expressed in certain populations. Additionally, we will develop experimental protocols to adapt next generation sequencing technologies to rapidly identify MHC class I genetic diversity from hundreds of individual animals sampled over a period of four years during an *M. ovipneumonia* outbreak in southwestern United States. Our long-term goals are to use this data to determine if particular MHC class I alleles are associated with either disease resistance or susceptibility using previous diagnosis of disease made at the time of sample collection.

**Research Grant:** Unknown  
**Student Support:** Merial Veterinary Research Scholars Program

Design of a technique for patient-specific rapid prototyped surgical cutting guides for canine cranial tumors

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Canine cranial tumors are a rare and challenging tumor to treat due to the complexities associated with removal of a portion of the cranial vault and reconstruction. The most common cranial tumors include osteosarcoma, multilobular osteochondrosarcoma and osteoma. In many cases, excellent long-term local control or cure can be achieved with good surgical margins but the accurate identification and achievement of these margins can be challenging due to the local anatomic variations and various structures present. The emergence of rapid prototyping technology has allowed for the development of patient-specific implants and cutting guides to assist in both the pre and intraoperative phases. Previous application of this technology in orthopedic procedures has demonstrated that cutting guides improve the accuracy of the procedure and implant placement, while reducing surgical times. The purpose of this feasibility study was to determine whether a patient specific cutting guide could be developed for dogs with cranial tumors and to assess the user experience and impact on corresponding implant placement. The hypothesis is that a patient-specific cutting guide can be manufactured in a time-sensitive and cost-effective manner and will result in a predictable defect that will allow for accurate placement of the implant. Dogs with skull tumors and diagnostic computed tomography scans were considered and patient-specific cutting guides were designed and manufactured. Material properties, including sterilization potential, cost and ease of use were considered. Based on this work, it appears that patient-specific rapid prototyped surgical cutting guides for cranial tumors are both feasible and cost effective in dogs.

**Research Grant:** Boehringer Ingelheim Veterinary Research Scholars Program  
**Student Support:** None
Diabetic nephropathy in nonhuman primates

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Roughly 40% of human patients with diabetes will develop diabetic nephropathy. Nonhuman primates (NHP) spontaneously develop type 2 diabetes mellitus (T2DM). This study aims to describe the histological and morphological changes associated with later stage diabetic nephropathy in NHP. In this retrospective study, kidney samples were collected from animals with diagnosed diabetes as well as age matched controls, from cynomolgus macaques (Macaca fascicularis-MF), rhesus macaques (Macaca mulatta-MM), and African green monkeys (Chlorocebus aethiops sabaeus-CAS). Qualitative analysis was performed by two board certified pathologists who were blinded to diabetic status. Animals were classified using a scale developed by the Renal Pathology Society based on mesangial expansion, presence of nodular lesions, as well as interstitial and vascular lesions. Quantitative analysis was performed by digitizing and measuring the glomerular tuft and Bowman’s capsule using Visiopharm software. Mesangial thickening was seen in all species, but nodular lesions were rare. In two species (MF and CAS), diabetic animals had substantially greater volume of solid glomerular tuft tissue (5-7 fold; p < 0.001), but in rhesus monkeys this was not the case.

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Detection of blue-green algal scum accumulations on lake shorelines using small unmanned aircraft systems

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Small unmanned aircraft systems (sUAS) have the ability to perform ultra-high resolution remote sensing at a relatively low cost. We applied sUAS equipped with visible light and color-infrared sensors to detect shoreline scum accumulations of blue-green algae scums during cyanobacterial harmful algal blooms (cHABs). Such scums represent a significant poisoning risk to dogs. Traditional methods of water sampling and testing typically do not account for risks posed by scums on the shore—a significant threat to dogs due to its accessibility. Generally, higher flight altitudes result in better efficiency due to larger areas covered per unit time. Three sUAS-borne sensors were used: 6.6 mm x 8.8 mm 12 MP and 8.8 mm x 13.2 mm 20 MP visible light sensors, and a 16 mm x 24 mm 24 MP color infrared (CIR) sensor, at altitudes of 10 m, 20 m, 30 m, 50 m, and 100 m, to gauge the maximum heights needed for detection of Microcystis aeruginosa scums. Scum locations were confirmed with ground truthing. Results indicated that sUAS equipped with a CIR sensor had the best efficiency for detecting shoreline algal scums, being effective at altitudes of at least 100 m. High reflectance values in the near infrared range contributed to detection efficiency. Visible light sensor efficiency was related to sensor size and resolution. The 20 MP sensor was effective up to 50 m, and the 12 MP sensor up to 30 m, respectively. Increased dynamic range contributed to the higher efficiency of the larger sensor. We concluded that sUAS-borne sensors could be used to scan local areas of lake shorelines for scum accumulations. Sensors with larger surface areas, and the use of the CIR sensors, increased detection efficiency.

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Student Support: Merial Veterinary Research Scholars Program
Impact of intralingual AAVrh10-miRSOD1 injection on respiratory function in SOD1\textsuperscript{G93A} mice

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Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease in which patients normally succumb to the disease within 5 years of onset. Death is usually a result of impaired respiratory function due to loss of motor neurons that control upper airway muscles and/or the diaphragm. The motor neurons that control upper airway muscles are found in the brainstem in a region called the hypoglossal motor nucleus. One cause of ALS is a mutation in the superoxide dismutase-1 (SOD1) gene, and rodent models with this mutation have been developed and are being used to explore treatment options. The purpose of this study is to determine if a microRNA against SOD1 (miRSOD1) can be used to increase respiratory function (e.g. tidal volume, frequency, and minute ventilation). We hypothesize that intralingual injection of miRSOD1 into SOD1\textsuperscript{G93A} mice will knockdown mutant SOD1 in hypoglossal motor neurons and improve respiration. AAVrh10-miRSOD1 or vehicle (phosphate buffered saline) will be intralingually injected at 6 weeks of age. At 13 weeks of age, respiratory function at baseline and in response to hypoxia (11% O\textsubscript{2}) + hypercapnia (7% CO\textsubscript{2}) will be studied in miRSOD1 injected SOD1\textsuperscript{G93A} mice (n=6), vehicle injected SOD1\textsuperscript{G93A} mice (n=6), and non-transgenic mice (n=9) via whole-body plethysmography every other week until SOD1\textsuperscript{G93A} mice reach end-stage (20% body weight loss). We expect that tidal volume, frequency and minute ventilation will be increased in miRSOD1 injected SOD1\textsuperscript{G93A} mice compared to vehicle injected SOD1\textsuperscript{G93A} mice, and not different vs. non-transgenic mice. This result would indicate that miRSOD1 was beneficial and should be studied further as a potential treatment for respiratory deficits associated with ALS.

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Student Support: University of Missouri College of Veterinary Medicine Office of Research

Influence of butyrate on murine intestinal epithelial cells under inflammatory conditions

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Ovarian hormone deficiency induces bone loss in humans as well as in murine models. Dietary supplementation with dried plum (DP) has been shown to prevent and reverse this bone loss. Recent studies have shown the carbohydrate component of DP may be a responsible factor. The intestinal microbiota produce a variety of metabolites that are absorbed by the intestinal epithelium. Butyrate, a short chain fatty acid, is an end product of fiber digestion by microbes. Butyrate has been shown to aid intestinal barrier function and may also have direct or indirect immunologic effects, influencing cell differentiation and gene expression in mucosal associated lymphoid tissue. This study examined in vitro gene expression in intestinal epithelial cells treated with sodium butyrate under normal and inflammatory conditions. The MODE-K murine intestinal epithelial cell line was used. Cell culture was performed in RPMI+GlutMAX media supplemented with 10% FBS, 1% sodium pyruvate, 1% non-essential amino acids, 1% HEPES, and 0.1% β-mercaptoethanol and incubated in 5% CO\textsubscript{2} at 37°C. Effects of butyrate (0, 0.25, 0.5, 1, 2, 4, 8, and 16 mM) on cell proliferation and viability were measured over 12, 24, and 48 hours using the methyl-thiazolyldiphenyl-tetrazolium (MTT) and trypan blue exclusion assays. Significant decreases in cell proliferation were observed in cells receiving doses higher than 2 mM butyrate. At 12 and 24 hours, cells treated with 0.5 and 1 mM butyrate exhibited a significant increase in proliferation. There were no significant differences in cell viability at any time point observed for NaBu (0-2 mM). Further experiments will examine changes in gene expression in MODE-K cells under inflammatory and non-inflammatory conditions.

Research Grant: Unknown
Student Support: Unknown
Non-viral DNA-delivery system for familial adenomatous polyposis therapy in a rat model of human colon cancer

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Familial adenomatous polyposis (FAP) is a heterozygous dominant inherited disease causing colorectal cancer in 100% of patients. Mutations in the adenomatous polyposis coli (APC) gene lead to development of colorectal cancer (CRC) in patients, with prophylactic treatment being resection of the colonic segments. Recent studies in model systems have shown that re-established APC expression can induce CRC regression. We hypothesized that a functional APC gene replacement will lead to existing polyp regression and prevent adenomagenesis. To test our hypothesis, we investigated the efficiency and effect of human wild type APC gene reintroduction comparing two liposomal based delivery systems in the F344-Ap-cam1137/+ PIRC rat model. Rats ranging from 120-210 days were divided into 3 groups (n=5), viz. Lipofectamine+APC (positive control), DNALite+APC (test group) and DNALite+GFP (to monitor the functionality of the proprietary DNALite system). Pre- and post- treatment colonic adenoma burden will be monitored longitudinally by colonoscopy and image analysis. Blood draws will be taken in parallel to evaluate the complete blood count (CBC) and biochemistry panel to detect changes due to treatment. At 240 days, post-mortem tumor size will be assessed grossly and histologically, and GFP uptake will be visualized through immunohistochemistry. Upon completion of the trial, we expect a greater regression of adenoma size in the DNALite+APC group compared to the others. If successful, the DNALite delivery system may provide gene therapy options for FAP patients to improve and extend quality of life in this often-debilitating disease.

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Intestinal inflammatory responses to antibiotics in male and female RAG-knockout mice

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Antibiotics are widely used for the prevention and treatment of various bacterial infections. They also have been shown to have adverse side effects, such as disruption of the intestinal immune system. Previous experiments from the lab have shown that males and females respond differently to the antibiotics treatment. The purpose of this experiment is to determine how oral antibiotics affect inflammatory gene expression in the large and small intestine in the absence of an adaptive immune system. We hypothesize that the inflammatory markers will increase in response to the antibiotic treatment and this would be diminished in the RAG knockout mice. RAG-1 knockout (lack mature T and B lymphocytes) male and female mice and their corresponding wild-type controls received antibiotic treatments for two weeks (ampicillin and neomycin) in the drinking water. After treatment, the intestinal segments were harvested and RNA extraction performed with Trizol. The cDNA underwent a polymerase chain reaction to determine the differences in the inflammatory and anti-inflammatory genes: tumor necrosis factor alpha, interleukin-6, and interleukin-10. Males and females responded differently to the antibiotics especially in the absence of an adaptive immune system. Understanding the relationship between the response to antibiotics in the gut of male and female mice will lead to effective methods to specifically prevent unwanted side effects.

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Student Support: NIH grant 5R25HL103156-0
Mice and cockroaches as carriers of Staphylococcus aureus in homes of inner-city children with asthma

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Respiratory microbes cause infections and can exacerbate asthma in people. Emerging literature points to a role for insects and mammals to serve as mechanical vectors or reservoirs for these potential pathogens. However, little work has evaluated the risk from household pests, specifically cockroaches and mice. This study aims to determine the prevalence of mechanical contamination and carriage of Staphylococcus aureus (SA) and other respiratory microbes by household cockroaches and mice in the homes of inner-city children with asthma. We evaluated a subset of households in a randomized, controlled trial that tests whether removal of pests among children sensitized to pest allergen improves asthma control. Mice and cockroaches were obtained on a home visit that coincided with Pest Management (IPM) service or via hotline. The pests were then tested for external and internal presence of respiratory microbes, including SA, Moraxella catarrhalis, and Group A Streptococcus via culture-based methods. 53 homes (47% of 112) were randomized to IPM. From these homes, a fresh cockroach or mouse was received from 11 (20%). 20 of the pests trapped were cockroaches (all Blattella germanica) and 8 were mice (all Apodemus sylvaticus). 50% of the 4 tested pests were positive for SA. Of 13 pests tested for other respiratory pathogens, no pathogens (beyond SA) were detected. Incidentally, Escherichia coli was detected from 3 (75% of 4) mice tested and Enterococcus faecali and non-target gram negative bacilli were identified in two separate mouse specimens. These findings demonstrate that mice and cockroaches in inner city homes have the potential to carry SA and suggests that pest management should be considered in the control of asthma.

Research Grant: Unknown
Student Support: 1. Boehringer Ingelheim 2. Department of Molecular and Comparative Pathobiology JHU Med School

Molecular characterization of the proventricular microbiota of Nymphicus hollandicus and Myiopsitta monachus

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In all species, the normal microbiota of the gastrointestinal tract is an essential factor in maintaining health and preventing disease. While now widely accepted, mammals have largely composed the population studied for microbiome research. The data available on companion avian species, specifically psittacines, is limited to fecal analysis. The aim of this study was to characterize the proventricular microbiota of two common companion bird species, cockatiels (Nymphicus hollandicus) and quaker parrots (Myiopsitta monachus). Swabs of the luminal surface of the proventriculus were taken from ten apparently healthy birds, five cockatiels and five quakers. DNA was extracted, isolated and purified, and 16S rRNA genes sequenced using the Illumina MiSeq platform and analyzed using Quantitative Insights into Microbial Ecology (QIIME). Firmicutes was the most abundant phylum for both bird species, followed by Proteobacteria. Tenericutes was the third most abundant phylum in cockatiels while Actinobacteria was the third most abundant for quakers and fourth most abundant for cockatiels. Lactobacillaceae (phylum Firmicutes), important in lactic acid production, was the most abundant family in both cockatiels and quakers. Mycoplasmataceae (phylum Tenericutes) was the second most abundant family in cockatiels only. Pseudomonadaceae and Comamonadaceae (both phylum Proteobacteria) were the next most abundant families in both species. There was no significant difference in intestinal bacterial diversity between cockatiels and quakers (P > 0.05), though PCoA plots of UniFrac distances suggest a slight clustering of microbial communities by bird species. Given a larger sample size, it is possible this clustering may become more prominent.

Research Grant: Schubot Exotic Bird Health Center.
Student Support: College of Veterinary Medicine & Biomedical Sciences, Texas A&M University.
Epidemiology and genomic characterization of MDR *Salmonella* from domestic animals and wildlife

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As human populations expand, the gap between natural and anthropogenic landscapes disappears bringing wild and human populations into closer contact. Antimicrobial resistant *Salmonella* strains identified in Ethiopian livestock are known to spread to humans via consumption of contaminated water and food. Resistant *Salmonella* strains may be similarly transmitted between wild and domestic animals. Existing research on the distribution of *Salmonella* in Ethiopia has primarily focused on livestock. Consequently, the prevalence of multi-drug resistant (MDR) *Salmonella* strains among Ethiopian wildlife populations has not been investigated and the role of wildlife in transmission of these strains to humans remains unknown. The objective of this study was to determine the prevalence of MDR *Salmonella* in Ethiopian wildlife to identify the role they play in the transmission cycle. A cross-sectional study was conducted to assess the prevalence and antimicrobial resistance profiles of *Salmonella* identified in Ethiopian wild and domestic species. *Salmonella* is suspected in 13 of 22 samples. Once confirmed, all isolates will be tested for MDR using the Kirby-Bauer disk diffusion method and will undergo whole genome sequencing. Results will be compared to previous data from domestic and wild species as well as from human origin to determine the extent of phenotypic and genotypic similarity. The findings of this study will help inform future research and ultimately improve our understanding of MDR *Salmonella* transmission among these populations. Such information will be vital for the development of management strategies that can interrupt the transmission of MDR strains when animal and human health could be at risk.

**Research Grant:** BETHA  
**Student Support:** Boehringer Ingelheim

Exploring the beneficial effects of blueberries in horses

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The use of blueberries (BB) in human health has attracted a large number of nutraceutical/feed industries to market BB in pet foods and as a nutritional supplement. However, the majority of these claims in regards to animal health have no strong scientific basis. More importantly, many of the supplements on the market are difficult to judge due to a lack of scientific evidence regarding the efficacy of these products. In many instances, there is no understanding of how the supplements function or the effects on the body. Even worse, one cannot be sure when the proposed supplement is ingested that it is absorbed into the bloodstream to produce a response. In addition, results from studies in other species, i.e. humans and rats, are often used to support claims regarding the efficacy of a supplement intended for use in horses. This study’s results provide a scientific basis for use of BB as beneficial supplements for horses. This objective will be studied under two aims: (i) determine the palatability, route of administration, dosing, and absorption of BB in horses (ii) determine the effect of BB on exercise adaptation and endurance in thoroughbred horses. Of the 17 horses used, they were either sedentary or underwent exercise testing, were put into either treatment or control groups, and the following were measured: echocardiogram exam values, blood packed cell volume (PCV), plasma lactate, plasma total protein (TP), heart rate (HR), and redox balance. The hypotheses of the study are that BB are absorbed into the bloodstream when ingested, and that they have a beneficial effect on the cardiovascular system in regards to exercise adaptation and endurance.

**Research Grant:** United States Highbush Blueberry Council  
**Student Support:** Boehringer-Ingelheim Veterinary Research Scholars Program
Admixture between historically isolated orang-utan lineages in North American zoos

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Orang-utans comprise two critically endangered species on the islands of Borneo (Pongo pygmaeus) and Sumatra (P. abelii), each with multiple subpopulations or subspecies that have been geographically, genetically, and reproductively isolated to varying degrees over time. To maintain genetically viable orang-utan populations, zoos in North America participate in a captive breeding program, which aims to prevent inbreeding by pairing the least related individuals. However, interbreeding individuals from naturally isolated subpopulations could result in outbreeding depression, which may seriously impact orang-utan health. The ancestral geographic origins of orang-utans in North American zoos are unknown; consequently, there is potential for unintentional hybridization of naturally isolated lineages. Determining the maternal ancestral origins of captive orang-utans is therefore a key preliminary step to assessing the degree of hybridization and the potential for outbreeding depression. I am extracting, amplifying, and sequencing the complete mitochondrial DNA control region from one orang-utan from each matriline within the captive population, and comparing the sequences to those published from orang-utans of known geographic origin. I predict that the captive orang-utan population derives ancestrally from all recognized subspecies and subpopulations of Bornean and Sumatran orang-utans. The results of this study, along with known pedigree data, will clarify the degree of hybridization and the possibility of outbreeding depression within the captive orang-utan population. Should evidence of outbreeding depression be found, zoos may need to refine breeding practices to prevent further hybridization of captive orang-utans.

Research Grant: The Chinese Academy of Sciences, The National Natural Science Foundation of China, Henry Vilas Zoo, Henry Vilas Zoological Society
Student Support: Morris Animal Foundation Fellowship

Efficacy of a novel interferon inducing PRRSV vaccine candidate against atypical PRRSV challenge

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Currently available vaccines do not consistently provide protection against porcine reproductive and respiratory syndrome virus (PRRSV). An interferon inducing PRRSV vaccine candidate A2MC2 was passaged 90 times (A2P90) and attenuated. A2P90 conferred protection against clinical disease in pigs challenged with moderately virulent PRRSV strain VR-2385 in a previous study. This study evaluated the efficacy of adjuvanted live A2P90 vaccine formulation, administered by intranasal or intramuscular routes, against a highly virulent atypical PRRSV strain MN184. Forty-five, 3-week-old pigs were randomly assigned to five groups including NEG-CONTROL (no vaccine; no challenge), POS-CONTROL (no vaccine, challenge with MN184), A2P90 IM (intramuscular vaccine, challenge with MN184), A2P90 IN (intranasal vaccine, challenge with MN184), and BIVI MLV group (commercial modified live PRRSV intramuscular vaccine by intramuscular route, challenge with MN184). Pigs were vaccinated at 3 weeks of age and challenged at 8 weeks of age. The pigs were euthanized on day 10 post challenge to assess the vaccine mediated protection. At the time of challenge 4/9 A2P90 IN, 6/9 A2P90 IM, and 9/9 BIVI MLV pigs seroconverted. Fluorescent focus neutralization assay will be performed to determine PRRSV-specific neutralizing antibodies at the time of challenge. Macroscopic lung lesions were assessed at necropsy and lung samples were collected for histopathology to assess microscopic lung lesions and to quantify PRRSV antigen in tissues using immunohistochemistry. Reverse-transcriptase quantitative PCR will be performed to assess viremia and nasal shedding levels.

Research Grant: Iowa Livestock Health Advisory Council
Student Support: Iowa Livestock Health Advisory Council
Comparison of ELISA and qPCR screening for FFV infection in Colorado mountain lions (*Puma concolor*)

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Feline Foamy Virus is an apathogenic virus found in felids throughout the world. Due to its mode of transmission, its detection among apex predators can be used as a tool to model contact-dependent virus transmission. ELISA and qPCR have been used to detect FFV. qPCR detects viral genome in blood cells or tissues while ELISA detects seroconversion after viral exposure. There is no comparative data on their relative sensitivities and no published literature describing FFV infection in free-ranging felid populations. 134 Colorado mountain lion (*Puma concolor*) samples from the Front Range and Western Slope were screened for FFV using qPCR and ELISA. 60% were qPCR positive (n=81) while 77% were ELISA positive (n=104). 57% were qPCR/ELISA positive (n=76) and 18% were qPCR/ELISA negative (n=25). 0.04% were qPCR positive but ELISA negative (n=5). Using ELISA as the Gold Standard as determined through comparative testing of experimentally infected domestic cats, the FFV qPCR had a sensitivity of 73% and specificity of 83% in Colorado mountain lion populations. The data illustrate that ELISA is a more effective test for FFV detection in cats and the infection rate among free-ranging animals is very high (prevalence = 77%). This analysis suggests antibody testing can be used to determine infection rate. Future studies will include modeling of FFV transmission among mountain lions to inform management programs to better predict and control pathogenic contact-dependent viruses.

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**Student Support:** Boehringer Ingelheim

Characterizing immune cell infiltrates in the tumor microenvironment of canine oral melanoma

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Understanding the tumor microenvironment is crucial for developing potential therapeutics against cancer. Due to similarities between spontaneous canine oral melanoma tumors and a subset of human melanoma tumors, the dog is a suitable model for translational research for this tumor type. One of the emerging concepts in cancer therapeutics is the development of targeted immunotherapies for both humans and animals. As part of the Canine Comparative Oncology and Genomics Consortium (CCOGC), the aim of this study was to characterize the immune cell infiltrates (ICIs) in canine oral melanoma tumors. For patients with known history, the average survival time was 194.3 ± 45.3 days. Out of 25 cases, 19 developed metastases to either lung or lymph node, 8 received chemotherapy, 10 received radiation, and 15 received at least one dose of the melanoma vaccine. The ICIs were identified via immunohistochemical techniques and included cytotoxic T cells (CD8+), T helper cells (CD4+), activated T cells (CD3+), plasma cells (Mum1+), regulatory T cells (FoxP3+), M2 macrophages (CD163+), and an inhibitory checkpoint antigen (CTLA4+). The most abundant ICIs were CD4+ and CD8+ T cells and lowest level of ICIs was FoxP3+ cells. CD3+ cells were lower than both CD4+ and CD8+ cells, suggesting that T helper and cytotoxic T cells were present in the tumor microenvironment but some were not activated. CD163+ and CTLA4+ cells were present at low levels. This study provides the initial characterization necessary for comprehending the complex microenvironment in canine oral melanoma tumors and is the first step in developing targeted immunotherapeutics for both canines and humans.

**Research Grant:** P30CA0106058
**Student Support:** Busey Research Fellow, Ohio State University College of Veterinary Medicine

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Volumetric analysis of the equine hoof using magnetic resonance imaging

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Lamenesses originating from the hoof have been reported to be up to 80% of all lamenesses. Accurate interpretation of a hoof disease, or injury predisposition, and its pathophysiology, requires information of the healthy internal and external anatomy of the hoof. Existing knowledge of the range attributing to a healthy hoof and the degree of deviations that constitute a pathology, has yet to be defined. Volumetric evaluation is necessary to fully characterize and understand the morphological properties of the hoof. Our objectives were to provide morphogeometric data as a means of characterizing the three-dimensional hoof’s structure in horses with healthy hooves using MRI technology, and to investigate the correlation between the internal and external anatomy of the hoof. The T1-weighted MR images from 18 Standardbred horses with no known hoof pathologies were examined. All measurements were performed using Image J Software. Pairwise correlations among measurements were examined using Pearson’s product moment correlation coefficient and P values < 0.05 were considered significant. We found extensive correlations among internal and external hoof measurements which provides an insight into the normal hoof architecture and predisposition to pathological changes. Our volumetric data and ratio analyses of the hoof showed considerable congruency amongst our subjects. Our study has established that weight may be another indicator of hoof size. This study, for the first time, provided a reference on the 3D morphology of the healthy equine hoof. This data provides a reference benchmark for identifying pathological changes in the hoof anatomy which may be correlated with poor conformation and predispose the horses to injuries.

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IL-4 reverses bone loss by impacting bone turnover in a novel murine model of wear particle disease

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Total joint replacement is an excellent treatment for end-stage arthritis. The main long-term complication of the operation is osteolysis (bone loss) around the implant, resulting in aseptic implant loosening. Peri-implant osteolysis is driven by macrophage-mediated inflammation triggered by wear particles that are formed due to wear at the implant bearing surface. We have previously demonstrated that interleukin-4 (IL-4) prevents this particle-induced macrophage activation and peri-implant osteolysis. The aim of this study was to evaluate the efficacy and mechanisms of IL-4 in treating peri-implant osteolysis in a murine model of wear particle disease. Wear particles were continuously delivered into mouse femur for 4 weeks using a subcutaneously implanted osmotic pump, tubing, and hollow titanium rod that was press-fit in the right distal femur. After establishment of osteolysis, IL-4 was added to the particle infusion in select groups by changing the pump and the experiment continued for 4 additional weeks. This delayed IL-4 treatment was compared to continuous IL-4 delivery initiated at beginning of the experiment. It was found that both IL-4 treatments prevented and even reversed particle-induced osteolysis as assessed with μCT imaging. We hypothesized that IL-4 has an effect on bone resorbing osteoclasts & bone forming osteoblasts and assessed the number of these cells in histological sections. Both IL-4 treatments decreased the number of TRAP<sup>+</sup> osteoclasts and increased the number of ALP<sup>+</sup> active osteoblasts compared to the particle treated samples alone. In conclusion, IL-4 prevented and even reversed particle-induced bone loss and these effects were in part due to its impact on markers of bone turnover.

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Clinicopathologic and echocardiographic effects of anti-inflammatory glucocorticoids in healthy cats

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Administration of long-acting injectable glucocorticoids has been reported to precipitate congestive heart failure in cats. This prospective clinical trial aimed to investigate mechanisms by which oral intermediate-acting glucocorticoids could predispose cats to progression of heart disease. Systemically healthy cats with allergic dermatitis (n=10) were given oral prednisolone at anti-inflammatory doses (1-2mg/kg) once daily for 14 days followed by taper and washout. Clinicopathologic, echocardiographic, and hemodynamic variables were measured prior to and 1 hour post prednisolone administration on day 0 (timepoints [TP] 1 & 2) and day 7 (TP3 & 4). Measurements were repeated on days 14 (TP5) and 35 (post-washout, TP6). Paired t-tests were used to compare variables at baseline (TP1) to TP2-6, with significance level p < 0.05. No significant changes in blood glucose, blood pressure (BP), sodium, potassium, or cardiac biomarkers occurred at any timepoint. Expected hematologic and biochemical changes occurred in prednisolone-treated cats, including increased neutrophils, monocytes, platelets, cholesterol and triglycerides, and decreased eosinophils. Statistically significant changes from TP1 were noted in fructosamine (increased at TP5), BUN and creatinine (decreased at TP2 & 4), left ventricular dimension (increased at TP4 & 5), and indices of myocardial relaxation (decreased at TP4 & 5). However, all measurements remained within reference range at all timepoints. Overall, these results suggest that anti-inflammatory prednisolone does not cause acute changes in BP or diabetogenic effects in healthy cats, though may impact diastolic myocardial function.

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Student Support: Summer scholar research stipend support provided by Dr. Ward.

Effects of lymphodepleting agents on follicular T cells in different organs

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Recent clinical successes with Chimeric Antigen Receptor (CAR) T cell therapy have generated tremendous hope for the previous incurable diseases including cancers and HIV/AIDS. Lymphodepletion preconditioning is a proven procedure increasing the survival and function of the transferred CAR T-cells in patients, but the potential toxicity of the procedure warrants a careful risk-vs-benefit analysis. In particular, preconditioning for the treatment of HIV/AIDS or T-cell follicular lymphoma may require an optimization of regimen as recent studies including our own preliminary data have suggested that current lymphodepleting agents are limited in killing follicular T-cells. Here, we evaluate several lymphodepleting agents, including cyclophosphamide (CTX), fludarabine (FLU), and monoclonal antibodies, for their effect on various organs in particular focused on the depletion of CXCR5+ follicular T-cells (Tfh) using mouse models. C57B/6J mice were injected IP with either CTX or FLU. The lymphocytes were isolated from various organs including bone marrow, lymph nodes, and blood, and the cells were stained with a mixture of fluorescent antibodies for flow cytometry analysis. Efficacy of the agents on T cell depletion was compared against the lymphocytes from the CD4iDTR mice that were treated with Diphtheria toxin (DT) as a control. The cytotoxic agents led to varying amounts of lymphodepletion among the lymphoid organs. Both CTX and FLU reduced follicular T cells expressing CXCR-5 and PD-1, but a significant number of these cells remained while DT completely removed these cells in CD4iDTR mice. Both CTX and FLU failed to eliminate Tfh. A combination drug treatment may be needed for the efficient depletion of Tfh.

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Student Support: NIH T35 Training Grant
Mouse models for Typhoid Fever research using bioengineered *Salmonella* Javiana and Typhimurium

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Having convenient laboratory animal models is critical in infectious disease research. However, this can be challenging for human-adapted pathogens. One exemplary pathogen is *Salmonella* Typhi, the causative agent for typhoid fever resulting in approximately 21 million illnesses and 200,000 deaths annually throughout the world. This human-adapted pathogen *S*. Typhi necessitates collaboration with laboratory animal veterinarians to create effective animal models that are useful for studying the pathogenesis of typhoid fever, but also testing new therapeutic and vaccine candidates. Here, we aim to test two promising strategies using bioengineered *Salmonella* serovars Javiana and Typhimurium that infect MyD88 knockout and wild-type C57BL/6J mice respectively, and produce bacterial determinants important for recapitulating many of the characteristic signs of typhoid fever. If successful, this scientific endeavor would bring significant impacts in typhoid fever research.

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**Student Support:** Cornell Leadership Program for Veterinary Students

Effects of hypertonicity on canine erythrocyte size and osmotic fragility in an in vitro diabetes model

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Hypertonicity caused by increased effective osmoles in plasma causes cellular dysfunction. Canine erythrocytes are an ideal model to study the effects of hypertonicity that accompanies diabetes because of their ability to respond to incremental changes in tonicity. The study examined the in vitro effects of hypertonic glucose, sucrose, and 2-Deoxy-D-glucose (2-DG) on canine erythrocyte osmotic fragility (OF) and mean cell diameter (MCD) after hypotonic challenge. Erythrocytes incubated for 48-hr in conditions that mimic moderate (333 mOsm) or severe (366 mOsm) hyperglycemia had reduced OF after hypotonic challenge in 250 mOsm NaCl compared with those in a normoglycemic (305 mOsm) condition. Erythrocytes incubated in 333 and 366 mOsm sucrose, which is excluded by the erythrocyte membrane, also showed decreased OF compared to 305 mOsm sucrose. The change in MCD after hypotonic challenge increased with increasing glucose concentration. In contrast, the change in MCD was decreased with increasing sucrose concentrations. The role of glucose in erythrocyte adaptation to hypertonicity was investigated using 2-DG, a non-metabolizable glucose analogue. Erythrocytes incubated with 366 mOsm 2-DG showed more than 2-fold increase in OF after hypotonic challenge when compared to erythrocytes incubated with 366 mOsm glucose. The findings show that OF and MCD of erythrocytes maintained in vitro under diabetic conditions vary depending on the extracellular osmole (glucose vs. sucrose) responsible for the hypertonic stimulus and that glucose does not act as purely effective osmole in this system. The results also demonstrate a requirement for glucose metabolism in the erythrocyte response to hypotonic challenge.

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Leptospirosis in shelter dogs and cats in the tristate area of Kentucky, Tennessee, and Virginia

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Leptospirosis, a worldwide zoonotic infection that affects dogs and many other mammalian species, including man, is caused by infection with pathogenic members of the genus *Leptospira*. Pathogenic leptospires live in the proximal renal tubules of asymptomatic carrier animals and are shed in the urine. Virtually any mammalian species can act as asymptomatic reservoir, characterized by chronic renal carriage and shedding of a host-adapted leptospiral serovar. Environmental contamination by these chronic shedders results in acquisition of infection by susceptible animals. In this study, we investigated if clinically normal shelter dogs and cats harbor leptospires in their kidneys by screening urine samples for the presence of *Leptospira* spp. Additionally, we measured *Leptospira*-specific serum antibodies to test correlation between seroprevalence and urinary shedding. The results showed that approximately 17% of the 133 shelter dogs and cats screened by qPCR were positive for leptospiral DNA in urine and 21 of the 145 animals screened with microscopic agglutination test (MAT) had a titer level greater than 1:100 across five tested *Leptospira* serovars. Nineteen animals in the study showed positive results for both qPCR and MAT. Twelve animals were positive with qPCR but not with MAT. These findings have significant implications regarding animal and public health in the area and possibly outside where these animals may be adopted.

Research Grant: LMU-CVM Intramural Grant
Student Support: Merial Veterinary Research Scholars Program

Itchy eyes no more: the effects of Zaditor on the healthy canine eye

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The precorneal tear film consists of multiple components that contribute to vision as well as ocular health and nutrition. Previous research demonstrated that the tear film of humans can be negatively affected by certain topical and oral medications; however, such phenomenon has not been determined in dogs. Zaditor is an over-the-counter antihistamine drop frequently prescribed to dogs that have irritated eyes due to allergies. At this time, it is unknown if Zaditor has a detrimental effect on the canine tear film. The purpose of this study is to determine if Zaditor alters the quantity or quality of tears produced in healthy dogs when administered twice daily. We hypothesize that the use of Zaditor will not influence the tear quantity and quality. Healthy dogs were enrolled, and ocular examination and tear production and quality tests performed, including Schirmer tear test (STT), tear osmolality, tear ferning, and meibometry. All parameters were evaluated at baseline, on days 7 and 14 of treatment, and on day 30 of the study (2-week washout period). To date, baseline values from 25 dogs were obtained. Analysis of variance was used to verify any differences between right (OD) and left (OS) eyes. Mean STT ± SD (mm/min) were 22.3 ± 2.9 (OD) and 21.8 ± 3.9 (OS). Mean osmolarity ± SD (mOsm/L) were 305.4 ± 35.3 (OD) and 304.2 ± 33.0 (OS). Mean tear ferning grades ± SD were 2.1 ± 0.8 (OD) and 2.0 ± 0.8 (OS). Mean meibometry ± SD (MU) were 115.5 ± 56.7 (OD) and 173.7 ± 139.3 (OS). No significant differences between eyes were observed at baseline day for any test (p > 0.05). The results of this work will contribute to better understanding the safety of this topical drug in dogs.

Research Grant: University of Illinois College of Veterinary Medicine
Student Support: Boehringer Ingelheim Veterinary Scholars Program
Investigation of the hippo signaling pathway in zebrafish nf2 gene mutants

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Neurofibromatosis Type II (NFII) is an autosomal dominant human genetic disease, characterized by the growth of tumors in the nervous system, such as vestibular schwannoma, meningioma, ependymomas, astrocytomas, and neurofibromas. Mutations of the NF2 gene, which encode for the cytoskeletal protein neurofibromin 2, or merlin, lead to the NFII syndrome. Moreover, mutations of NF2 are often found in several types of human cancer, suggesting it acts as a tumor suppressor gene. The tumor suppression mechanism of this gene has been difficult to delineate, partly due to the lack of a model that closely resembles human NFII. Hippo signaling is known to play important roles in animal organ size regulation and tumorigenesis, and NF2 was found to be an important regulator for this pathway. We recently created zebrafish models of NFII. Zebrafish have two homologs of NF2, nf2a and nf2b, and they develop malignant peripheral nerve sheath tumors when either gene is mutated. We hypothesize the downstream genes of the hippo signaling pathway will be altered in the zebrafish nf2 mutants. Using whole mount in situ hybridization, we found cgtfa and yap1 genes are upregulated in nf2a mutants compared to wildtype zebrafish embryos (1 day post fertilization). Results of these genes in zebrafish embryos 2 days post fertilization were inconclusive. Our results demonstrate that nf2 may regulate hippo signaling in our new zebrafish NFII models. More experiments are needed to explore the relationship of nf2 and the hippo signaling pathway. Experiments on other pathways, such as RAC-PAK signaling, may be helpful in better characterizing our zebrafish models.

Research Grant: Hayward Foundation
Student Support: Boehringer Ingelheim Veterinary Scholars Program and Purdue College of Veterinary Medicine

Prazosin disrupts hemangiosarcoma and angiosarcoma cell metabolism and undermines cell viability

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Human angiosarcoma (AS) and canine hemangiosarcoma (HSA) are aggressive malignancies of vascular origin with nearly identical pathologies and clinical presentations. Current therapies do not effectively prevent recurrence or limit metastasis, and long-term prognoses for human and canine patients remain poor. Propranolol, a beta-adrenergic receptor (AR) antagonist, has been shown to alter key metabolic pathways and induce cell death in AS and HSA tumor cells, and AS patients treated with propranolol demonstrated 100% response to the drug (complete and partial responses). While promising, tumors eventually progressed or recurred in these patients. We found that AS and HSA cells also express alpha1-ARs, and hypothesized that inhibition of alpha1-AR signaling would induce cell death and metabolic changes detrimental to HSA and AS cell viability. To test this idea, we examined the effects of prazosin, an alpha1-AR antagonist commonly used in veterinary medicine, on HSA and AS cell viability and metabolism. The human AS cell line, AS-5, and canine HSA cell lines, COSB and 1426, were used in our studies. Prazosin treatment induced cell death in AS and HSA cells more effectively than propranolol (EC50 of 30 μM for prazosin versus EC50 of 150-200 μM for propranolol). Additionally, prazosin increased mitochondrial coupling and modulated the expression of regulators controlling cholesterol and fatty acid synthesis. These data suggest that prazosin may alter cellular energy production and drive cell metabolism toward anabolic pathways, leading to metabolic catastrophe and cell death. Preliminary studies suggest that prazosin may also synergize with chemotherapy, offering a valuable addition to AS and HSA treatment regimens.

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Do fast and slow muscle fibers have dedicated stem cell populations?

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Three types of muscle are present in the body: smooth, cardiac, and skeletal. This lab focuses on skeletal muscle. It is attached to the skeleton with functions including voluntary limb movement, posture retention, and respiration. Skeletal muscle is composed of two types of myofibers, fast and slow. Fast fibers are more common overall, functioning in rapid strong contracting muscles. Slow fibers are in muscle sustaining less forceful contractions such as maintaining stability. Each skeletal muscle has a unique composition of fast and slow fibers. The lab studies adult stem cells of skeletal muscle, termed satellite cells, responsible for regeneration of injured muscle. Satellite cells are found on both fast and slow fibers and are quiescent until activated by injury. The pattern of slow and fast fibers after satellite cells regenerate injured muscle is maintained in the same composition present prior to injury - how? Recently this lab showed that the cell surface repulsive ligand ephrin-A3 is specific to slow myofibers. This suggested the possibility that a receptor for ephrin-A3 may be expressed by fast satellite cells, which could let them differentiate between the two populations of muscle fibers and thus preserve the fiber type patterning after regeneration. I am learning muscle and satellite cell biology as well as technical skills including fiber isolation, immunostaining, and culture. I am collaborating with lab member Jacqueline Ihnat to test this hypothesis: we are designing experiments to ask a series of questions, give possible answers, and create a stepwise decision tree to come to experimental conclusions based on data as it is collected.

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Faecalibacterium prausnitzii increases insulin sensitivity in diet induced obese mice

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It is widely accepted that beneficial microbes can play a role in improving human health. Faecalibacterium prausnitzii is a butyrate producing gut bacterium that exhibits anti-inflammatory properties and is protective against intestinal inflammation. Low abundance of F. prausnitzii in the human gut has been associated with obesity and type two diabetes. The objective of this study was to evaluate the effects of administering a live culture of F. prausnitzii on insulin sensitivity in obese mice. Mice were orally treated for 10 or 20 days with a cocktail of four F. prausnitzii isolates from our culture collection. Before sacrifice an oral glucose tolerance test (OGTT) was performed and blood samples collected for insulin concentration. The microbiome of feces, small intestine and colon samples was characterized by sequencing of the 16S rRNA gene using the MiSeq platform (results pending). Results of the OGTT showed that after 10 days of treatment, mice had lower glucose AUC (P=0.09) and lower serum insulin AUC (P=0.11) following oral glucose administration, compared to controls. After 20 days of treatment, glucose AUC did not differ between treatment and control groups, however, treatment mice had lower serum insulin AUC than controls (P = 0.06). Overall these findings demonstrate that F. prausnitzii increases insulin sensitivity in diet induced obese mice and may have potential therapeutic use in diabetes patients.

Research Grant: Unknown
Student Support: NIH T35 Training Grant - OD010941
Characterizing the role of TRIM9, a ubiquitin ligase, in macrophage motility

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Tripartite motif containing (TRIM) genes encode a large family of E3 ubiquitin ligases which mediate the ubiquitination of a wide range of substrates and are highly conserved across vertebrate species. Although TRIM9 expression is best characterized in neurons where it is highly expressed and plays a role in regulating axonal migration, TRIM9 expression has been recently reported in immune cells. Transcript levels of Trim9 increase in macrophages in response to various toll-like receptor (TLR) agonists and our lab has shown its importance in macrophage motility using a dominant negative transgenic zebrafish (Danio rerio) model. We have demonstrated that expression of a truncated version of Trim9 in vivo in zebrafish macrophages results in abnormal cellular morphology and decreased motility. The goal of the current research is to determine if the role of Trim9 in macrophage motility is conserved in mammalian species as well as other innate immune cells, such as neutrophils. To further characterize this role, the TRIM9 protein network, including ubiquitination substrates, will be investigated in mammalian innate immune cells. Lastly, we hypothesize that TRIM9 is essential for additional cellular functions that require cellular architectural restructuring such as phagocytosis and exocytosis. Defining the role of TRIM9 and its interacting partners in innate immune cells will provide insight into the functions of these proteins during infection. Furthermore, this research may lead to new therapeutic targets in diseases where local tissue damage is caused by over-stimulated inflammatory processes.

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De novo exploration of MHC class I genes in the Arabian horse

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The major histocompatibility complex (MHC) class I molecules are transmembrane glycoproteins that play an important role in immune surveillance against intracellular pathogens and in the regulation of innate immunity. The MHC genomic region, located on horse chromosome 20, is very gene-dense and highly polymorphic. In humans and mice, the best studied species, most individuals carry the same number of MHC class I genes in their MHC haplotypes. In the horse, however, many MHC class I genes appear to be located in different loci between haplotypes. This factor, in addition to their shared sequence motifs, makes characterizing new MHC class I alleles challenging. Previous studies using serology and microsatellites identified about 50 equine MHC haplotypes. Two haplotypes, COR007 and COR008, are notably common in Arabian horses. The aim of this study is to identify the MHC class I genes in these Arabian horse haplotypes. Primers were designed using a targeted approach to amplify cDNA from lymphocytes obtained from MHC homozygous horses for cloning and sequencing. Final sequences were compared to nucleotide sequence databases using the National Center for Biotechnology Information’s (NCBI) basic local alignment search tool (BLAST). Sequences with the highest and statistically significant identity matches will be annotated and mapped to the equine genome. Determination of the MHC class I genes of several distinct equine MHC haplotypes may yield clues to the evolutionary forces that resulted in the very complicated MHC haplotypes of the horse, and may also help explain the function of the many equine MHC class I genes.

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Student Support: NIH Grant 4T35AI007227-29
Do levels of DNA-PK alter cisplatin sensitivity in FANCG deficient HEK293T cells in a dose dependent manner?

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All organisms have two predominate, competing DNA double-strand break repair (DSBR) pathways: homologous recombination (HR) and non-homologous end joining (NHEJ). Proteins encoded by genes in the Fanconi anemia (FA) pathway comprise a complex that helps ensure faithful DNA replication; part of this function is to facilitate DSBR that is mediated by HR. Mutations in these FANC proteins of the FA pathway produce the phenotypes characteristic of FA: birth defects, cancer, and bone marrow failure. Additionally, FANC deficient cells are sensitive to interstrand cross-linking agents. The severe distinguishing phenotypes of FA are only seen in primate species. In comparison to other species, primates express high levels of the NHEJ pathway factor complex that initiates NHEJ, the DNA-dependent protein kinase (DNA-PK). Lower levels of DNA-PK in non-primate species may provide an explanation as to why FA does not develop as these levels would allow a crippled HR pathway to repair breaks over NHEJ. To address whether DNA-PK levels promote the dramatic FA phenotypes observed in humans, NHEJ factors: DNA-PK or XRCC4 were targeted in HEK293T FANCG knockouts via CRISPR/CAS9 to produce knockouts and hypomorphic mutants of each protein. These mutants were confirmed by western and were tested for sensitivity to the cross-linking agent cisplatin. Understanding the mechanisms leading to the harsh phenotype observed in humans will facilitate development of therapeutic strategies for FA patients.

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Fibular osteotomy to allow tibial plateau rotation during TPLO: indications, effectiveness and complications

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Cranial Cruciate Ligament (CCL) rupture is a common cause of hindlimb lameness in the dog. Tibial plateau leveling osteotomy (TPLO) is a frequently performed geometry altering procedure to treat CCL rupture. The success of this procedure depends on proper positioning, rotation, and fixation of the tibial plateau segment. Occasionally, the fibula prevents proper rotation of the proximal tibial segment, and this restraint to rotation must be addressed. There is currently no published literature regarding the procedure of fibular osteotomy. This retrospective study aims to identify factors in dogs undergoing TPLO that increase the risk of requiring a fibular osteotomy, and document whether fibular osteotomy has any effect on TPLO outcome. Medical records of dogs receiving TPLO between 2005 and 2017 at The Ohio State University CVM and Veterinary Specialty and Emergency Center were reviewed. We found that the following breeds were more likely to require a fibular osteotomy: Great Dane, German Shepherd, and Doberman Pinscher. In addition, heavier dogs and dogs with a larger fibular diameter relative to that of the tibia were more likely to require a fibular osteotomy. Fibular osteotomy was effective in allowing appropriate rotation of the tibial plateau. However, dogs with a fibular osteotomy had significantly more postoperative TPLO instability (rockback and valgus deformity) than dogs that had undergone an uncomplicated TPLO procedure. Data suggests that augmenting the fixation using a second bone plate can mitigate instability, but there is not enough data to confirm this hypothesis at this time. This study should help surgeons predict the requirement for fibular osteotomy and to improve the surgical planning of TPLO.

Research Grant: Boehringer Ingelheim
Student Support: Boehringer Ingelheim
Evaluation of an in clinic test for detection of Leptospira spp. antibodies in cats

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Multiple Leptospira spp. are associated with clinical disease in dogs and people. The agents are rarely recognized as cause of acute clinical disease in cats but whether infection is associated with chronic kidney disease (CKD) has not been widely studied. Leptospira spp. antibodies historically are detected with the microscopic agglutination test (MAT) which is highly subjective, requires the maintenance of viable leptospiral colonies, highly trained staff members, and results are not rapidly available. In this study, it was hypothesized that a recently commercialized in-clinic ELISA optimized for canine sera would detect anti-Leptospira spp. antibodies in cat sera and cats with suspected CKD (n = 69) would be more likely to have antibodies than cats without CKD (n = 25). Sera from 2 purpose-bred research cats inoculated with a quadrivalent Leptospira spp. vaccine for dogs to induce antibodies were positive in the ELISA. A total of 3 of the 94 client owned cats were positive for anti-Leptospira spp. antibodies, each of which had suspected CKD. These pilot results suggest that the ELISA can detect anti-Leptospira spp. antibodies in cat sera. These results have led to a prospective research plan to further validate the assay for use with cat sera and then the ELISA will be used in a larger seroepidemiological study of cats with and without CKD.

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Student Support: Boehringer Ingelheim Fellowship

Defining the role of endothelial cells in controlling dissemination of Toxoplasma gondii

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Toxoplasma gondii is an intracellular apicomplexan parasite that is a prominent veterinary and human pathogen, affecting nearly one-third of the world’s population. Infection with T. gondii typically causes clinical disease in immunocompromised subjects who can develop severe encephalitis, retinitis and respiratory disease. A strong and persistent Th1 immune response with production of inflammatory cytokines IFN-γ and TNF-α is needed to control parasite replication in vivo. Due to the clinical relevance of the presence of T. gondii in the brain, there has been a general interest in understanding how T. gondii can cross the blood-brain barrier and cause disease. Previous research in the Hunter laboratory has suggested that endothelial cells may possess a mechanism to limit the spread of T. gondii into the brain parenchyma, representing an important bottleneck for parasite dissemination. To examine this hypothesis in vitro, mouse brain microvascular endothelial cells were isolated, cultured and infected with T. gondii in various experimental environments including stimulation with IFN-γ and TNF-α, as well as activated CD8+ T-cells. Using these experiments, parasite burden was assessed using flow cytometry and fluorescence microscopy in order to quantify infected cells and endothelial cells that were successful in controlling parasite replication.

Research Grant: NIH/Boehringer-Ingelheim Summer Veterinary Research Scholars Program
Student Support: NIH T35 Training grant
Identification of biofilm in healthy canid uteri and pyometra

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Biofilms, a complex community of microorganisms and other substances that adhere to favorable surfaces have recently been shown to be a source of persistent pathology. However, the presence and effect of biofilm production in the reproductive tract of many domestic species is unclear as it can be difficult to reliably detect in standard histologic sections. In this study, we investigated the ability of different histochemical stains to detect biofilms in archived formalin fixed paraffin embedded canine reproductive tissues and correlate the thickness and bacterial content to the presence of pyometra. Three beagle pyometra cases and nine beagle non-pyometra cases in various estrus stages were selected from archived specimens. Six stains (Alcian Methylene Blue, Vierhoff van Gieson, Mucicarmine, PAS, Steiner Silver, and Gram stain) were applied to uterine tissue samples. Each stain was assessed by light microscopy. Morphometric analysis (using Image-Pro Plus) was used to evaluate the density of biofilm areas and bacterial content. A two-tailed paired sample t-test was used to compare pyometra cases to non-pyometra cases in regards to biofilm characteristics. Subjectively, the Alcian blue stain highlights the biofilm and the Steiner silver stain demonstrates bacteria most effectively in all samples. Further objective measurement and statistical comparisons are pending.

Research Grant: American Association of Zoo Veterinarians, the Association of Zoos and Aquariums Reproductive Management Center and the Reproductive Health Surveillance Program
Student Support: Boehringer-Ingelheim and MSU College of Veterinary Medicine and Graduate School

Susceptibility of meadow voles (Microtus pennsylvanicus) to elk (Cervus canadensis) chronic wasting disease

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Chronic wasting disease (CWD) is a fatal, neurodegenerative prion disease that affects wild and captive cervids. The increasing prevalence and geographic distribution of CWD, coupled with its exceptional environmental stability, raises concerns about transmission to other species. Most prion diseases transmit in a species specific manner, however, the “mad-cow” disease outbreak that led to human infection upon beef consumption demonstrated that the species barrier may not provide absolute protection against cross-species prion transmission. Rodents sympatric with current CWD epizootics are candidates for possible interspecies transmission of CWD due to their widespread distribution, relative abundance, and opportunistic scavenging behavior. In this study, we assessed the susceptibility of meadow voles to elk CWD via bioassay by i.c. inoculation. Initial challenge resulted in a median survival time (days) of 335±30.1 and 328±82.5 for elk CWD strain 1 and 2, respectively, and shortened to 165.5±57.9 and 171±52.3 upon second passage, suggesting prion adaptation to the vole host. Immunoblot analysis demonstrated presence of disease-associated prion protein (PrPTSE) in brain tissue in 96.2% of the challenged voles, and indicated stability of glycoform ratios as di>mono>unglycosylated, consistent with the elk CWD inocula. The molecular mass of PK-cleaved PrPTSE was indistinguishable throughout both passages in voles. Lesion profiling on CWD infected vole brains will be performed to resolve possible strain-level differences. These results demonstrate that elk CWD can be i.c. transmitted and adapted to meadow voles, suggesting potential roles for this species in CWD disease ecology and as small animal models for CWD research.

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Student Support: Boehringer Ingelheim Veterinary Scholars Program
Flow cytometric analysis of canine small B-cell lymphoma

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In people, small B-cell lymphomas can often be categorized with flow cytometry (FC) into distinct diseases which can present with blood and/or tissue phases. Dogs have similar types of small B-cell lymphomas comprised of small cell lymphoma (SLL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL) and follicular lymphoma, but specific subtyping currently requires lymph node histopathology. Even then, the histologic distinction between certain forms remains difficult. Retrospective analysis of standard FC data from canine lymph node aspirates with a histologic diagnosis of SLL, MCL or MZL was performed to investigate immunophenotypic distinctions. Additionally, peripheral blood samples with a B-cell lymphocytosis were prospectively analyzed by FC with an expanded panel of antibodies that were selected based on previous gene expression data and review of the human literature. After determining species cross reactivity, this secondary panel consisted of monoclonal antibodies against the following surface markers: CD9, CXCR4, CD21, CD22, CD48 and CD49d. The FC data from histologically categorized cases demonstrated that cell size and CD21 staining intensity were significantly greater in MZL compared to MCL/SLL. When subdivided based on cell size, the B-cell lymphocytosis cases demonstrated significant differences in expression intensity of CD21, CD9 and CXCR4. Taken together, this data suggests that we may be able to differentiate certain forms of canine small B-cell lymphoma using FC. Availability of improved immunophenotypic profiling of canine lymphoma subtypes would provide a minimally invasive diagnostic tool and allow for the collection of specific prognostic data, both of which could inform treatment decisions.

Research Grant: None
Student Support: NIH T35OD015130

Folate-p53 interactions in the development of neural tube defects

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Neural tube defects (NTDs) are deleterious birth defects that result in herniation and exposure of nervous tissue during embryogenesis when the neural tube fails to close. Folate deficiency causes failure of neural tube closure and 70% of all NTDs are folate responsive. However, the mechanism of this rescue effect remains to be elucidated. The tumor suppressor protein p53 plays an important role in development and both its loss or overexpression can lead to NTDs in mouse models. Studies in vitro demonstrate interactions between p53 and folate one-carbon metabolism pathways, specifically the de novo thymidylate (dTMP) biosynthesis pathway. Mouse models with impaired de novo dTMP synthesis have increased rates of NTDs that are responsive to folate supplementation. The aim of this project was to determine if folate supplementation could rescue p53−/− induced NTDs. This study determined that folate deficiency does not have an affect on p53−/− NTD incidence. Interestingly, p53−/− mouse embryonic fibroblasts have higher rates of de novo dTMP and purine biosynthesis and decreased levels of genomic instability. These results suggest that p53−/− embryos may have an innate protective effect against folate deficiency, and thus develop NTDs that are not responsive to folate supplementation.

Research Grant: NIH National Institute of Child Health and Human Development HD059120
Student Support: None
Enteric resistome analysis via targeted amplicon sequencing: effects of the route of antibiotic administration


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The use of antimicrobials in animal agriculture is necessary to maintain the health and well-being of livestock; however, any such use leads to the propagation of antimicrobial-resistant (AMR) bacteria. These bacteria pose a threat both to animal and human health. Historically, quantitative analysis of the effects of antimicrobials on the enteric microbiome has been restricted by the intrinsic limitations of traditional approaches to genomic analysis, which are insensitive to low-copy - yet clinically significant - resistance genes and to shifts in microbial community composition. The objective of this study was to observe the effects of the route of antibiotic (tylosin) administration on the expansion of AMR in the enteric microbiome of production swine comparing traditional (qPCR) and next generation sequencing methods. Eighty healthy finisher swine were randomized to groups receiving tylosin by injection, orally in water, orally in feed, or to a control group receiving no antibiotic. Fecal samples were collected from each pig on day 21 of the trial. DNA extracted from the fecal samples was analyzed for changes in bacterial community composition using 16S metagenomics, and for the prevalence of AMR genes using qPCR versus targeted amplicon sequencing of 6 resistance genes representative of high and low copy numbers (tet(A), tet(B), tet(M), erm(B), bla_{CMY-2}, and bla_{CTX-M}). Preliminary findings show a difference both in bacterial community composition and in AMR gene prevalence between treatment groups. In the future, these approaches can be used to choose antimicrobial administration routes that reduce selection pressures for resistance by targeting AMR genes of clinical importance with greater sensitivity.

Research Grant: National Pork Board Pork Checkoff 16-053
Student Support: National Institutes of Health #5T35OD010991

The role of inflammation in vaginal Simian Immunodeficiency Virus (SIV) transmission

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Although rare, multiply HIV-exposed, seronegative women exist, however there are currently no immunologic correlates of protection that have been found to explain their apparent resistance to vaginal HIV transmission. Due to the difficulty and limiting nature of HIV studies in humans, multiply SIV/SHIV-exposed, seronegative (MESN) rhesus macaques are the current research model for the above women. Recent advances in mucosal immunity suggest pre-existing vaginal inflammation and infiltrations of inflammatory CD3+CD4+ T cells in vaginal tissues may play a role in the susceptibility to infection with these viruses. This study was performed to test the hypothesis that pre-existing vaginal inflammation (increased CD3+CD4+ T cells) will be associated with a greater risk of vaginal SIV transmission; i.e., monkeys that get infected after a single vaginal SIV challenge have higher numbers of T cells in the vaginal mucosa compared to animals that resist infection. Since viral challenges also contain other factors that may trigger inflammation, we also tested whether a sham inoculation resulted in increases in T cells in the vagina. To test this, 6 MESN macaques were vaginally challenged with a single high dose of pathogenic SIVmac251, along with 4 normal naive macaques that received only sham inoculations. Vaginal biopsies were collected twice before inoculation (at least 2 weeks prior to challenge to ensure complete healing at time of challenge), and after challenge at day 2, 3, 7, 14 and 21. Slides were imaged under fluorescence microscopy for CD3 to obtain absolute counts of CD3+ T cells per mm² of tissue. Vaginal fluids were also assessed for chemokines and cytokines to detect levels of inflammation before and after challenge.

Research Grant: National Institutes of Health Simian Vaccine Evaluation Units (SVEU) Project P187 (Veazey PI).
Student Support: NIH T35-OD011151; LSU School of Veterinary Medicine Summer Scholars Program.
Role of oxytocin in the black rhinoceros following human and animal interactions

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Often termed the “love hormone” in humans, oxytocin is a neuroendocrine hormone that has been associated with pair bonding and maternal behavior in both humans and animals. Recent studies have investigated the importance of oxytocin in human-animal interactions, specifically measuring the oxytocin response in animals following interaction with a human counterpart. Studies thus far have demonstrated the role of oxytocin in domestic animals, yet none has investigated the role in exotic species under human care, such as the black rhinoceros (Diceros bicornis). We wish to explore the role of oxytocin in the black rhinoceros in a variety of pair settings, with both fellow members of the species and with humans, compared to solitary settings. Saliva samples will be collected at various timepoints throughout the day and under a variety of social circumstances (solitary, housed with same species, and interacting with a keeper). Salivary oxytocin levels will be measured using an oxytocin ELISA, which will be validated for use with black rhinoceros saliva. We hypothesize that there will be a correlation between social situations and increases in salivary oxytocin levels. We also hypothesize that there will be an increase in salivary oxytocin levels in the black rhinoceros following a training session with a familiar keeper. Understanding the role of oxytocin in an exotic species in a zoological setting could provide insight into zoo animal welfare and human-animal bonding. In addition, with an increasing emphasis on the One Health initiative, these results could provide insight into the relationships between zoo animals and human keepers.

Research Grant: Cleveland Metroparks Zoo Conservation Medicine program
Student Support: The Monahan Family, The Ohio State University Veterinary Research Scholars Program

Growing feline regulatory T cells for adoptive immunotherapy

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Feline regulatory T cells have been well characterized and available reagents for their study have been previously validated. Naturally occurring immune mediated diseases that would benefit from Treg therapy are common in feline patients, making the cat a suitable animal model. While there is evidence to suggest feline regulatory T cells can be induced in-vitro, the maintenance of their phenotype and function has not yet been studied. To determine if feline cell lines can be transformed in-vitro into functional regulatory T cells, we will grow cells in different growth media with conditions previously shown to induce regulatory function in mouse and human cells. The work we complete in our research will establish an in vitro model for the expansion of regulatory T cells using commercially available feline cell lines. The first goal is to determine the intrinsic phenotype and function of a feline T cell line. Our second goal is to determine if the cell line can be transformed into regulatory T cells and if these cells can retain their regulatory function. Cell lines will be evaluated before and after culture for the expression of surface and intracellular markers known to be expressed in regulatory T cells. Their regulatory function will be tested in suppression and cytokine production assays. We hypothesize that feline regulatory T cells transformed or expanded in-vitro will maintain regulatory phenotype and function serving as a model for the study of this elusive T cell subset. This work will contribute to our overall knowledge of Treg cell subsets and has the potential to expand our knowledge of mechanisms involved in regulatory function.

Research Grant: College of Veterinary Medicine Academic Research Enhancement Award, 2017
Student Support: Merial; Summer Research Fellows Program - CVM, Midwestern University
Anaplasma platys, ticks and dogs: unraveling the infection dynamics

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Anaplasma platys, the etiology of canine infectious cyclic thrombocytopenia is the only known pathogen that colonizes canine platelets. The pathogenesis of A. platys infection and the role of the brown dog tick, Rhipicephalus sanguineus as a vector for its transmission is ambiguous. In our initiative to better understand this pathogen, a study was conducted to establish the overall prevalence of A. platys infection in dogs and ticks. Fifty four out of 158 (34.2%) blood samples tested were positive for A. platys DNA and 58/158 (36.7%) were positive for E. canis DNA by real-time PCR. Coinfections were observed in 35/158 (22.2%) samples and a strong association between A. platys and E. canis PCR results was observed (p-value < 0.05). Among 119 samples for which, the SNAP 4Dx test results were available, 31/119 (26.1 %) were positive for Anaplasma antibodies, and 70/119 (58.8 %) were positive for Ehrlichia antibodies whereas 50/119 (42%) were positive for A. platys PCR, and 51/119 (42.9%) were for E. canis PCR. There was no significant association between A. platys PCR and the Anaplasma antibody test results (p-value > 0.05). Out of tick samples collected from 21 dogs, 10 (47.6%) were positive for A. platys PCR and 15 (71.4%) were positive for E. canis PCR and 8 (38%) of the samples were positive for both. Based on our findings, we conclude that; the role of ticks as a biological vector of A. platys infection needs further evaluation and the negative antibody test results for A. platys infection must be interpreted with caution. Future studies will be targeted to improve the diagnostic tests, to identify the role of ticks in transmission and to define the conditions leading to fatal illness in A. platys infected dogs.

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Student Support: Merial Veterinary Research Scholarship
RUSVM Dean’s Scholarship

Surface decontamination using cold plasma device

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Plasma or ionized gas is classified as the fourth state of matter. Generation of plasma in a non-thermal or near room temperature environment, also known as cold plasma, has been used in multiple applications including medical sterilization and decontamination. In this study we used a novel portable surface dielectric barrier discharge (SDBD) device for cold plasma generation and decontamination of glass, plastic and metal surfaces contaminated with Staphylococcus aureus and Pseudomonas aeruginosa, common pathogens involved in hospital acquired infections. Bacterial viability studies conducted to evaluate efficacy of cold plasma exposure on the different surface types showed a reduction of >/=7 logs of viable bacteria based on standard culture methods. In addition to bacterial viability, the impact of cold plasma treatment on bacterial cell morphology was also analyzed using electron microscopy. Cell walls of the bacteria appeared to rupture and degrade, with leakage of cytoplasmic contents. Results from this study indicate that SDBD cold plasma is a promising technology for surface decontamination of various substrates.

Research Grant: Research Grant: Technology Business Development Program supported by Oklahoma State University
Student Support: Student Support: Oklahoma State University CVHS 2017 Summer Research Training Program
Effects of in utero exposure to a mixture of hydraulic fracturing chemicals on spermatogenesis in mice

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Hydraulic fracturing, a practice done by some oil and natural gas operations, can result in the contamination of ground and surface water with endocrine-disrupting chemicals that influence estrogen, androgen, glucocorticoid, progesterone, and thyroid receptors. Previous studies found that male mice exposed in utero to a mixture of these chemicals experienced a decrease in sperm count and pituitary hormone concentrations (most notably FSH, which is critical in maintaining spermatogenesis in the adult), and an increase in testis weights and serum testosterone concentrations. In this study, PAS-stained testicular sections from male mice whose dams were exposed during gestation to vehicle only or one of several different doses of a mixture of chemicals commonly utilized in hydraulic fracturing were examined and staged to evaluate the potential effects of these chemicals on spermatogenesis. The stage of spermatogenesis (I-XII) was identified and recorded for 200 individual seminiferous tubules for each belonging to each treatment group. The mean percentage of tubules in each of the stages of the seminiferous epithelium for each treatment group will be compared to evaluate what effect, if any, different doses of this mixture of chemicals might have on spermatogenesis in the male offspring of exposed dams.

Research Grant: Unknown
Student Support: University of Missouri, College of Veterinary Medicine Office of Research

Effects of 12- and 13-Hydroxyoctadecadienoic Acid on Lipid Mobilization in Bovine and Rodent Adipose Tissue

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From three weeks before to three weeks after parturition, dairy cows undergo drastic metabolic changes driven by intense energy demands to support fetal growth and lactogenesis. At the same time, cows experience decreased dry matter intake, leading to a state of negative energy (NE) where energy expenditure exceeds energy intake. In response to NE, lipolysis releases non-esterified fatty acids (NEFA) from adipocytes to be used as sources of energy. Typically, lipolysis rates decrease as lactation progresses. However, some cattle continue to experience intense lipolysis, leading to adipose tissue inflammation, which further enhances lipolysis and can result in periparturient metabolic diseases. Linoleic acid is a common FA that is released in large quantities during lipolysis. In the presence of reactive oxygen species, linoleic acid yields 9-, 10-, 12-, and 13-hydroxyoctadecadienoic acids (HODE). 12- and 13-HODE become more abundant during excessive lipolysis. These HODEs are pro-inflammatory, however, their effects on adipocyte responses to lipolytic stimuli are unknown. Our study has shown that 13-HODE may physiologically hinder the lipolytic capacities of adipocytes. Future research will more closely examine the effects of 12-HODE on bovine and rodent primary adipocytes.

Research Grant: USDA-NIFA AFRI competitive program grant 2015-6705-23207.
Student Support: NIH T35 training grant.
Analysis of phagocytic activity of adenylyl cyclase type 7 knockout macrophages

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Cyclic AMP (cAMP) is a second messenger that has a suppressive effect on the body’s immune response. Because adenylyl cyclase (AC) is the enzyme responsible for generating cAMP, it is an important regulatory component that can potentially be targeted by drugs. The aim of this study is to examine the role of the type 7 isoform of adenylyl cyclase (AC7) in the phagocytic innate immune responses of macrophages. 2 types of macrophages were isolated from the bone marrow of mice and cultured: AC7 knockout (KO) macrophages, which lack expression of AC7, and wild-type (WT) macrophages. A phagocytosis assay will be carried out to compare the phagocytic activity of the AC7 KO macrophages and the WT macrophages. Staphylococcus aureus labeled with Alexa Fluor 647, a green fluorescent dye, will be phagocytized by the macrophages, and fluorescence-activated cell sorting (FACS) flow cytometry will be used to measure phagocytosis levels. It is expected that the AC7 KO macrophages will experience a decrease in cAMP levels, therefore resulting in an increased level of phagocytic activity as compared to the WT macrophages.

Research Grant: LSU Biomedical Collaborative Research Program
Student Support: Dr. Kenneth F. Burns Lectureship and Clinical Clerkship Foundation

Characterizing microbial load and composition in hummingbird feeders: implications for best practice

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Hummingbirds, one of the world’s few avian pollinators, are vulnerable to extinction: nearly 15% of hummingbird species are threatened or endangered. Consequently, understanding drivers of population dynamics and health may be key to conservation efforts. One likely but poorly studied threat to hummingbird populations is disease. Microbial pathogens have been documented in captive hummingbird populations, where they are associated with high levels of mortality. However, little is known about disease prevalence or transmission amongst individuals, particularly in wild populations. We hypothesize that hummingbirds exchange microbiota, including pathogens, through shared food resources and that these resources differ in their ability to harbor microbiota. The primary aim of this study is to characterize sugar water from hummingbird feeders as a potential reservoir of microorganisms, focusing on pathogenic bacteria and fungi. Experimental feeders were set up at two sites in Winters, CA, representing different bird population densities. Feeders were subject to treatments that (1) allowed free access, (2) restricted access to birds, and (3) restricted access to both birds and insects. Sugar-water solution samples were taken at set timepoints and cultured on differential media types. Microbial cultures are currently undergoing identification via MALDI-TOF (Biotyper) and bacterial 16S metagenomic sequencing. Ultimately, we aim to compare microbes isolated from birds to floral nectar and sugar solutions from hummingbird feeders to characterize the overlap of microbial species, evaluate the potential for pathogen transmission via shared food resources and better inform current recommendations for backyard hummingbird health.

Research Grant: UC Davis Programmatic Initiative
Student Support: Merial Veterinary Scholars Program
Prevalence of *Haemoproteus* spp. infections in blood samples from Allen’s hummingbirds

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Avian haemoparasite infections have been reported to be pathogenic and to reduce the survival of wild bird populations. The most common avian haemoparasites, Haemosporidian parasites are transmitted by blood-sucking insects (order Diptera), and they negatively affect host fitness and force selective pressures on natural host populations. In the hummingbird family *Trochilidae*, the presence of haemoparasites is rare; however, microscopy and nested polymerase chain reaction based methods have identified three *Haemoproteus* spp. (*H. archilochus, H. trochili* and *H. witti*). A coastal species of California hummingbird, Allen’s (*Selasphorus sasin*) hummingbird was sampled for blood and screened for *Haemoproteus* spp. using PCR primers specific for the mtDNA cytochrome *b* gene. Preliminary results show that 46 Allen’s hummingbirds samples (100 birds sampled and 46 samples tested so far) were PCR negative for *Haemoproteus* spp. Compared to previously published data for other California hummingbirds (Anna’s 2.5% and Black-chinned hummingbirds 17.3% prevalence and four distinct *H. archilochus* cyt *b* lineages), the Allen’s hummingbird results are interesting. The prevalence of *Haemoproteus* is suspected to vary between hummingbird species due to habitat differences in the avian hosts and dipteran vectors. While Allen’s hummingbirds are found mostly along the California coast, Anna’s and Black-chinned hummingbirds gravitate to riparian forest areas. Riparian habitats are potentially better suited for vectors to fly, reproduce, and land on hosts due to the presence of freshwater and lack of wind compared to the coast. The preliminary results suggest that future work investigating vector populations and feeding behavior on hosts is warranted.

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Student Support: SVM Endowment Funds from the STAR Fellowship and SVM Office of Research & Graduate Education

Canine Distemper Virus and Parvovirus: How long does immune memory last and are we over vaccinating?

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The current standard of veterinary practice is to administer canine core vaccines including Canine Distemper Virus (CDV) and Canine Parvovirus (CPV-2) every three years. Adverse effects due to over vaccination are an increasing concern in both human and animal health. A growing number of veterinarians utilize antibody testing to determine the need for revaccination. Therefore, the duration of immunity engendered by canine core vaccines has been subject to investigation. The current study aims to determine if revaccination intervals greater than three years can be successful. 31 beagles were held in a virus-free environment; 16 were last vaccinated three years prior and 15 nine years prior. 18 dogs received a commercial modified live vaccine containing CDV and CPV-2, 9 dogs received recombinant CDV and killed CPV-2 vaccine, and 4 dogs received killed CPV-2 vaccine only. Sera were collected at predetermined time points. Serum Virus Neutralization (SVN) for CDV and Hemagglutination Inhibition (HI) for CPV-2 were performed. Immune responses were compared between the groups based on time and vaccine administered. Of the dogs that were vaccinated nine years prior, 93% retained protective titers for CDV and 42% for CPV-2. In the absence of protective titer, immune memory was maintained for up to nine years. Immune response to revaccination is correlated with antibody titer at day 0; high titers neutralize modified live vaccine virus. In conclusion, dogs maintain immune memory to CDV and CPV-2 for up to nine years. Therefore, titer testing continues to be an excellent tool to determine the need for revaccination. Lastly, geriatric dogs may benefit from boosting if their titers are below protective levels.

Research Grant: None

Student Support: Boehringer Ingelheim Veterinary Scholars Program
Newly recognized retinopathy in standard poodles: clinical phenotype and genetic basis

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Inherited retinal degenerations (IRDs) represent the leading cause of blindness in humans and dogs. Many of these vision-threatening disorders remain poorly characterized and are still considered incurable. To date, naturally occurring IRDs in different dog breeds are best explored and constitute important translational models to develop therapies for human IRDs. The aim of this study is to characterize the clinical and molecular aspects of a newly recognized form of retinopathy segregating in Standard Poodle (SP) breed and in SP-based crosses/backcrosses used to produce “Doodles”. The onset, course, and progression of the SP-associated retinopathy were analyzed based on clinical records collected at UPenn School of Vet Medicine and across the country. Based on preliminary review, this IRD differs in clinical presentation from that described in other breeds and resembles Leber’s congenital amaurosis in humans. To identify the gene and mutation underlying this IRD, a genome wide association study, homozygosity mapping, and candidate gene analysis were performed. The SP-IRD-associated ~4Mb region was fine-mapped to canine chromosome 8, which contains 3 Expressed Sequence Tags expressed in the retina. The goal of the current research is to characterize the functional and positional candidate genes in the region of interest, and investigate its association with the disease phenotype. Preliminary screening of the first candidate gene encoding Protein-Tyrosine Phosphatase D1 confirmed association of this locus with the disease phenotype. Once characterized on a phenotypic and molecular level, this new animal model will serve as a platform for developing therapeutic approaches that can be clinically applied to human patients.

Research Grant: Van Sloun Fund for Canine Genetic Research
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FFB Center grant
Student Support: Merial Veterinary Research Scholars Program

Probing the role of the aging brain in brain metastases in vivo

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The mechanical properties of the local tissue environment are known to influence gene expression, cell signaling, and motility. The role of tissue mechanics on cancers that originate in the brain have been studied where an increase in tissue stiffness has been associated with progressive grades of gliomas. However, the effect on infiltrating tumor cells remain largely unknown. There can be a long latency up to decades between presentation of primary tumor and the detection of a brain lesion. One missing factor may be the effect of the mechanical properties of the brain on tumor progression and drug efficacy. Disease and aging may modulate both the mechanical environment and cellular composition of the brain. Using both in vitro and in vivo models, we explored the correlation between the aging and brain metastases. Tumor cells were injected into the hindbrain of immune competent and immunocompromised zebrafish. Cells where visualized using fluorescence microscopy to determine metastatic spread. We then modeled the in vivo brain parenchyma and evaluated drug efficacy as a function of modulating the stiffness of the microenvironment. Finally, we designed in vitro culture systems to incorporate protein aggregates associated with neurodegenerative diseases. Neurodegenerative diseases are thought to be due to the abnormal aggregation of proteins such as Tau and FUS that accumulate over the courses of decades. Here we co-cultured tumor cells with FUS and Tau proteins and studied drug efficacy in the presence and absence of protein aggregates. We then evaluated modulation of gene expression in response to drug treatment as a function of tissue microenvironment.

Research Grant: none
Student Support: National Cancer Institute
Equine procedural site preparation with an alcohol-based hand antiseptic

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Surgical site infections (SSI) are a leading cause of health-care associated morbidity in both human medicine and veterinary medicine. In human medicine, alcohol-based products have been implemented into surgical hand preparation in attempts to reduce the risk of SSI. The purpose of this study is to determine if an alcohol-based hand antiseptic is effective at reducing bacterial counts on equine skin, as well as the appropriate contact time, without causing any adverse skin reactions. Samples were collected pre- and post-preparation from clipped sites over both jugular veins of horses and were plated on 3M Petrifilm Aerobic Count Plates in duplicate. Trial 1 tested an alcohol-based product PRO (45% 2-propanol/30% 1-propanol mixture) against a sterile saline control both at 180s contact time. Trial 2 tested two different wet contact times of PRO - 90s and 180s. All samples were assessed for a change in log CFU/mL. Data were analyzed using the Kruskal-Wallis Test and significance was set to p≤0.05. PRO had a mean reduction of 2.9 log CFU/mL between pre- and post-preparation. A significant difference in the reduction of log CFU/mL between PRO and sterile saline was observed (p=0.003). There was no difference in the log CFU/mL reduction between the two contact times (p=0.75). Mild skin reaction was observed in both treatment (27%) and control (36%) groups. These findings demonstrate that PRO is effective for reducing bacterial counts on equine skin and could be used for preparation of neck or trunk procedures at contact time of 90s. Future study will be performed to determine the efficacy of PRO on equine limbs, where bacterial counts are presumably higher.

Research Grant: None
Student Support: Boehringer Ingelheim Veterinary Scholar and AVC Veterinary Student Research Award

Development of a femtosecond infrared laser neurosurgical approach to treat chronic focal neocortical epilepsy

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Epilepsy affects about 5% of dogs and 3% of humans. In focal epilepsy, seizures initiate at one location in the brain and propagate to other regions. About 30% of such cases are not responsive to anticonvulsants and resective neurosurgery, which may impact brain function, is the only current alternative. One potentially less invasive approach would be to sever neural connections seizures propagate along rather than resecting the seizure-prone tissue, but this would require the capability to make precise cuts inside the cortex without causing extensive collateral damage (for example, to the blood vessels on the brain surface). Tightly-focused femtosecond infrared laser pulses can provide a laser scalpel with the capacity to ablate tissue in a micrometer-sized focal region located up to ~2 mm into the brain while leaving surrounding structures intact. Previous rodent studies from our lab showed that severing lateral connections within the supragranular layers of the neocortex with a laser cut that surrounded an acutely induced seizure focus resulted in a 63% reduction in the number of seizures that propagated beyond the cut and abolished seizure propagation in some animals. These cuts largely preserved the health and function of the neurons located inside the cut. In ongoing work, we aim to test the longer-term efficacy of this approach. Nano injections of iron chloride into the neocortex are used to induce chronic focal epilepsy and electrodes are implanted to measure local field potential at different distances from the resulting seizure initiation site. We will then determine whether femtosecond laser cuts surrounding the injection site reduces the propagation of seizures from the initiation site to distant electrodes.

Research Grant: NS078644
Student Support: NIH T35 Training Grant – OD010941
Chronic *Salmonella* mouse infection: looking for correlations between granulomas and fecal shedding levels

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Typhoid fever is a life-threatening infection caused by *Salmonella* Typhi that affects about 21.5 million people every year, particularly those from developing countries. Without treatment, this infection has up to 20% mortality rate. However, 1-6% of infected individuals become chronic carriers, some of whom periodically shed high amounts of bacteria. Presently, little is known about the mechanism of *Salmonella* Typhi persistence within chronic carriers and how granulomas impact the lifelong carrier status. To study the asymptomatic carrier state, we used a mouse model of typhoid fever in which we orally infected mice with a related serovar, *Salmonella* Typhimurium. The aim of this work was to determine whether granuloma number and size in the liver and spleen correlate with *Salmonella* fecal levels. Feces of *Salmonella*-infected Diversity Out-bred (DO) and 129X1/SvJ mice were collected and dilutions were plated during the course of the infection. Mice were humanely euthanized on day 28 and the liver and spleen were collected for both bacterial count and histology. Interestingly, in one mouse that is considered to be systemic tolerant (no bacterial shedding in the feces, but high levels of bacteria in spleen and liver), the liver contained 324 granulomas, which is significantly higher than the numbers counted in the other mice (average: ~26 granulomas/liver). Further study into possible mechanisms behind this phenotype will need to be conducted. The number and size of granulomas in the livers of the remaining mice did not significantly correlate with *Salmonella* fecal shedding. However, more liver samples will need to be counted to reveal any possible associations. Results in the spleen have yet to be determined.

Research Grant: Defense Advanced Research Project Agency (DARPA)
Student Support: NIH T35 Training Grant

Characterization of TRAF3 and MCC in canine and human B-cell lymphoma

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Pet dogs are a valuable clinical model of cancer, and lymphoma--a common cancer in both humans and canines--is no exception. In canine B cell lymphoma (cBCL) and human diffuse large B cell lymphoma (DLBCL), the tumor necrosis factor receptor-associated factor 3 (TRAF3) gene is commonly mutated and deleted, respectively. TRAF3 is a negative regulator of the alternative NF-κB pathway, inhibiting lymphoid development and B cell maturation, thereby acting as a tumor suppressor in B lymphocytes. The gene mutated in colorectal cancer (MCC), a known tumor suppressor in colorectal cancer, acts as an oncogene in B cells--increasing its expression in response to malignant transformation of TRAF3 knockout B cells. A recent genome-wide association study revealed a single nucleotide polymorphism (SNP) in an MCC intron to be significantly associated with lymphoma in dogs. This present study sought to elucidate the mutation status and expression profile of TRAF3 and MCC in DLBCL and cBCL, through SNP genotyping, qPCR and Western blotting. Primers were designed to identify SNPs and amplify mRNA in both canine and human samples. To measure protein levels, we identified antibodies that recognized both species based on epitope similarity. Genotyping of the MCC SNP (rs24083535) in 66 cBCL patients revealed a disease-associated allele frequency of 90%. We are measuring the gene and protein expression of TRAF3 and MCC in DLBCL and cBCL cell lines and cBCL patient-derived xenografts. With this project, we hope to validate pet dogs with TRAF3/MCC mutated cBCL as a representative model of human DLBCL with TRAF3 deletion and/or MCC overexpression to allow for more precise and efficient clinical trials that target the consequences of TRAF3 loss.

Research Grant: LLS SCOR Grant 7012-16
Student Support: NIH T35 Training Grant OD010941
Pervasive decline in muscle mass and function is a universal facet of mammalian aging. In skeletal muscle, a hallmark of age-related decline is loss of resident muscle stem cells (MuSCs) or satellite cells ability to repair muscle when injury occurs. Age-dependent defects in MuSCs have been shown to have the capability to rejuvenate in a model of heterochronic parabiosis, suggesting both cell intrinsic and host environment alter MuSCs. It has been hypothesized that cell extrinsic factors mediate the regenerative properties of MuSCs in a youthful state and these factors are amenable to rejuvenation in the old. To study satellite muscle regeneration in vivo, a transplantation model was established in which bone marrow from young mice was transplanted into aged mice. Aged mice received a hind limb muscle injury. 5 days post-injury, muscles will be analyzed for indices of regeneration and nascent myotube formation by conventional and immunohistological analysis. In addition, to test for evidence of proliferation, 5-ethynyl-2′-deoxyuridine (EdU) incorporation into myocytes will be quantified. Histologic evidence of regeneration and EdU+ incorporation in injured old mice support the notion that exposing old mice to factors in young serum restores regenerative and proliferative capacity of aged MuSCs. Additionally, it may suggest that a subset of MuSCs retain intrinsic proliferative potential with age and the cell extrinsic environment of the MuSC niche precludes regeneration. Though molecular mechanisms of this process remain elusive, this in vivo model provides a tool to study how cell extrinsic factors regulate MuSC differentiation and may act as a tool to develop novel therapeutic approaches for diseases of muscle wasting.

Research Grant: Glenn Foundation for Medical Research (Feldman)
Student Support: NIH T35 Training Grant 5T35OD010989-16; Merial Veterinary Research Scholars Program

Acetaminophen (APAP) overdose is the leading cause of acute liver failure and treatment options are limited. Previous experimental studies assessing the role of inflammation in experimental APAP hepatotoxicity have been unable to consistently reproduce key findings, for unknown reasons. To identify factors contributing to experimental variability, this pilot study was designed to assess background pathogen status in laboratory mice prior to and after liver injury. Routine surveillance of mice in colonies dedicated to APAP studies identified the presence of Helicobacter ganmani and H. hepaticus. Helicobacter is common in laboratory mouse colonies and can cause sub-clinical disease in the GI tract and liver. We hypothesized that the presence of Helicobacter could impact the mechanism of APAP hepatotoxicity and lead to variable outcomes of liver injury. C57BL/6J mice (n=20) with Helicobacter-free health status were housed under identical husbandry conditions. One group (n=10) received an oral gavage of Helicobacter-positive fecal slurry, and controls (n=10) were gavaged with saline. After seven days, mice from each group received either APAP (300 mg/kg) or saline vehicle by intraperitoneal injection. APAP-induced hepatotoxicity was similar in mice receiving both gavages, as indicated by serum alanine aminotransferase, a biomarker for liver injury. However, fecal analysis of gavaged mice at the time of euthanasia demonstrated that the direct fecal transfer was unsuccessful in transmitting detectable Helicobacter. The results indicate that even direct fecal transplant is insufficient to recolonize Helicobacter and affect APAP hepatotoxicity within one week.

Research Grant: NIH R01 DK105099
Student Support: Nathan Brewer Endowment Fund for Laboratory Animal Medicine
Placental mesenchymal stromal cells for the treatment of canine neurological disorders

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Background: Spinal cord injury (SCI) is a devastating disorder that affects humans and their canine companions. The prognosis of SCI depends on the severity of the injury and can include varying levels of motor and sensory deficits including devastating paraplegia and quadriplegia. Placental mesenchymal stromal cells (PMSCs) have been shown to improve wound healing and possess neuroprotective and immunomodulatory capabilities, but have not yet been clinically tested for the treatment of SCI.

Results: In this study, we developed a protocol to isolate PMSCs from canine placentas and characterized their therapeutic potential in vitro to determine their potential as a treatment option for neurological disorders in dogs. Canine PMSCs (cPMSCs) were plastic adherent, were capable of trilineage differentiation, and expressed typical MSC markers. Genotyping of cPMSCs revealed a fetal origin of these cells with no evidence of maternal contamination. cPMSCs were viable and expansive in a collagen hydrogel delivery vehicle, and they secreted the immunomodulatory and neurotrophic paracrine factors interleukin (IL)-6, IL-8, monocyte chemoattractant protein 1 (MCP-1), and vascular endothelial growth factor (VEGF). cPMSCs were also found to be neuroprotective and stimulated neuron proliferation when co-cultured with SH-SY5Y cells, a neuroblastoma cell line commonly used to model neuron growth in vitro.

Conclusions: cPMSCs meet the criteria to be defined as MSCs and represent a potential regenerative therapy option for neurological disorders in dogs with their robust growth in collagen hydrogel, secretion of potent paracrine factors, and neuroproliferative and neuroprotective capabilities.

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Student Support: UC Davis School of Veterinary Medicine Endowment Funds

Using California sea lions to test a mechanism of human temporal lobe epileptogenesis

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Seizures caused by temporal lobe epilepsy (TLE), a common form of human epilepsy, usually initiate in the hippocampus. In TLE, inhibition of hippocampal granule cells is reduced, but the underlying mechanism is unclear. Parvalbumin (PV)-expressing interneurons synapse on excitatory granule cells and normally provide reliable, powerful inhibition. Reduced inhibition may be caused by fewer PV synapses with granule cells. To test whether the number of PV synaptic boutons per granule cell is reduced, we evaluated hippocampi from California sea lions that developed TLE after natural exposure to the neurotoxin domoic acid, which enters the marine food web during algal blooms. Sea lions were intracardially perfused with formaldehyde immediately upon euthanasia after failed response to treatment and poor prognosis. Unbiased stereology was used to estimate the number of PV-immunoreactive boutons and Nissl-stained granule cells per hippocampus. Hippocampi of control sea lions (n=12) contained 2.31±0.10 million granule cells (mean ± sem). Epileptic hippocampi (n=17) contained an average of only 31% of controls (p < 0.001, t test), demonstrating granule cell loss similar to that of human patients. Control hippocampi contained 34.1±2.0 million PV boutons per hippocampus. Epileptic hippocampi contained an average of only 37% of controls (p < 0.001). Therefore, there is loss of PV boutons in epileptic hippocampi but to a degree comparable to granule cell loss. The median number of PV boutons per granule cell in epileptic hippocampi (18) was not reduced compared to that of controls (13). These findings suggest, contrary to the hypothesis, that decreased inhibition of granule cells in TLE is not attributable to PV synapse loss.

Research Grant: NSF & NIH
Student Support: NIH T35 Training Grant
Genotyping for physical traits and hereditary conditions of *Felis catus*

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Precision medicine in our companion animals includes state-of-the-art methods for DNA profiling. DNA profiles of known diseases and traits causing variants will help with the management of breeding programs and the healthcare of the individual cats. Over 70 variants are known for 40 traits and diseases in cats. Effective DNA profiling uses simple and efficient methods to obtain accurate results. Herein is a description and analysis of a new method to perform DNA profiling in cats. The hypothesis is that DNA profiling methods will be able to accurately predict the cat’s phenotype and health status. Samples were taken from the cat colony that segregates for different traits and health status using buccal swabs. DNA was isolated and agarose-electrophoresis was used to confirm quality and quantity. MALDI-TOF was used to assay 29 genes in which the cat colony segregated for potentially 53 variants. The 53 variants were multiplexed into two different assays that were genotyped on an Agena MassArray instrument. Overall, 18 colony cats were genotyped including 8 males and 10 females. The colony cats segregated for variants in 15 genes that cause phenotypic traits and health concerns. Most of the assays worked perfectly since they correlate with the known cats’ phenotypes although some assays need improvement, such as the four assays required for the blotched tabby locus. These results demonstrate that MassArray techniques are accurate, efficient, and cost effective for performing DNA testing in cats. Therefore, these assays could aid veterinary practices to address cats to confirm breed, physical traits and hereditary conditions in order to improve their healthcare.

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**Student Support**: Stipend for José F. López is supported by an endowment established by IDEXX-BioResearch

Effects of developmental exposure to bisphenol A on the gut microbiome of California mice in the F1 generation

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Bisphenol A (BPA) is an industrial chemical used to produce many commonly used household items. Developmental exposure to BPA may affect the gut microbiome and this may contribute to neurobehavioral disorders affecting behavioral domains disrupted in ASD children. In utero exposure to environmental chemicals may increase the risk of neurobehavioral disorders. It is uncertain whether developmental exposure to BPA leads to ASD-like behaviors in California mice. Furthermore, it is undetermined if exposure of BPA during periconception and weaning leads to gut dysbiosis. The purpose of the present study was to test whether developmental exposure to BPA induces gut microbiome changes in California mice at different life stages and whether potential gut microbiome changes are associated to behavioral changes. Female P0 mice were exposed to BPA two weeks prior to breeding, during gestation, and lactation. Barnes maze, reverse Barnes maze, and elevated maze will be performed to evaluate various behavioral domains. Social interactions will be evaluated by recordings of mice exposed to stranger mice and communication will be assessed by analyzing their audible and ultrasonic vocalizations. Fecal microbiome will be examined with 16SrRNA sequencing at various ages in the F1 to determine whether gut microbiome changes are associated with behavioral deficits. Our hypothesis is that California mice developmentally exposed to BPA will demonstrate impairments in social, communication, learning, and memory behaviors. This group is expected to demonstrate increased anxiety-like behaviors. We predict that gut dysbiosis will result in neurobehavioral disorders. This work might open therapeutic strategies for ASD patients.

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**Student Support**: IDEXX-BioResearch
**Clostridium difficile** toxin detection by MALDI-TOF mass spectrometry

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Around 30,000 human deaths are associated with *Clostridium difficile* infections each year. In addition, virulent *C. difficile* has been implicated in causing diarrhea and colitis in a wide array of mammals including dogs, horses, pigs and non-human primates. The main virulence factors produced by *C. difficile* are two large toxins: toxin A and toxin B. Accurate detection of these toxins is necessary to differentiate between non-toxigenic strains and disease causing strains. Current detection methods include cytotoxicity assays (CTA) and enzyme-linked immunosorbent assays (ELISA) which are both labor-intensive and expensive. The aim of this study is to develop a novel method of *C. difficile* toxin detection using MALDI-TOF Mass Spectrometry. Commercially available, purified *C. difficile* toxin A and concentrated supernatants from bacterial isolates underwent proteolytic digestion to generate fragments small enough to be recognized by MALDI-TOF MS. Toxin production by the bacterial isolates was verified using ELISA prior to being ran on MALDI-TOF MS. Mass to charge (m/z) ratios and spectra for the purified toxin A were compared to the bacterial isolates. Results showed no matching spectra between purified toxin A and toxigenic bacterial isolates. Additionally, toxigenic and non-toxigenic strains generated congruent spectra and m/z ratios. These findings suggest that the proteolytic digestion was unsuccessful in generating fragments that were detected by MALDI-TOF MS.

**Research Grant:** Indiana Animal Disease Diagnostic Laboratory  
**Student Support:** Boehringer Ingelheim and Purdue Veterinary Medicine

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**Assessing impacts of antibiotic therapy in neonatal dairy calves on gut and animal health**

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Diarrhea and pneumonia are commonly observed in pre-weaned calves on dairy farms and account for > 50% of all calf deaths. There is evidence that these diseases are over treated with antibiotics and their use may disrupt colonization of gastrointestinal tract (GIT) microbiota. The aim of this study is to better understand the impacts of intramuscular antibiotics on dairy calves’ growth rate, health and microbiotic density of beneficial bacteria in the GIT. One hundred and twenty-one pre-weaned dairy calves were enrolled into groups according to their health status (sick vs. healthy) and half of the calves in each group were randomly treated with antibiotics. Daily health scores were recorded twice daily before, during and post treatment to determine probability of treated animals recovering compared to controls. *Bifidobacteria*, an anaerobic Gram-negative bacteria associated with decreased *E. Coli* and overall good health was extracted from fecal samples before, during and after treatment and quantified using qPCR. The focus of our analysis will be on clinical outcomes, productivity based on weight gain, and quantified *Bifidobacteria* variation.

**Research Grant:** USDA: NIFA 2016-11586  
**Student Support:** Boehringer Ingelheim-VSP, WSU-CVM Darden Memorial Research Endowment
b-cell glucagon-like peptide-1 receptor regulates α-cell proglucagon processing in mice

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Vertical sleeve gastrectomy (VSG) causes type 2 diabetes remission in human patients, but the mechanism is undefined. Post-prandial glucagon-like peptide 1 (GLP-1) secretion increases after VSG. GLP-1 is a hormone that enhances glucose-stimulated insulin secretion. We’ve reported that the b-cell GLP-1 receptor (GLP-1R) contributes to improved glucose regulation and islet function in mice after VSG. Accordingly, we investigated the role of the b-cell GLP-1R in islet protein expression after VSG. Using a b-cell specific tamoxifen-inducible GLP-1R knockout mouse model, male Glp-1r^b-cell+/+ (WT) and Glp-1r^b-cell-/-(KO) littermates on tamoxifen supplemented HFD underwent VSG or sham surgery (Study groups: sham WT (S WT), sham KO (S KO), VSG WT, VSG KO; n=3-6). 1.5 months after surgery, pancreas was collected and fluorescently stained for insulin, glucagon, and GLP-1. We found that increased b-cell GLP-1R signaling decreased b-cell area per islet and increased α-cell area per islet after VSG. Also, the percentage of islets with central α-cells was lower in WT than KO mice (S WT = 7±3, S KO = 26±5%; P<0.05 S WT vs S KO). Furthermore, VSG increased islet GLP-1 expression in WT mice (S WT = 47±8, VSG WT = 133±39 μm^2; P<0.05 S WT vs VSG WT), but this effect was lost in the KO mice (S KO = 63±14, VSG KO = 81±13 μm^2). PC1/3 is required to convert proglucagon to GLP-1, so we stained for PC1/3 and glucagon. VSG increased α-cell PC1/3 expression in WT mice (Pearson’s correlation coefficient: S WT = 0.11±0.03, VSG WT = 0.31±0.04; P<0.05 S WT vs VSG WT), but not KO mice (S KO = 0.15±0.07, VSG KO = 0.02±0.03). Together, these data reveal a novel role for the b-cell GLP-1R in regulating α-cell location and α-cell proglucagon processing.

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Student Support: NIH T35 Training Grant 4T35AI007227-29

Combined autophagy inhibition and chemotherapy treatment of canine osteosarcoma cell lines

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Appendicular osteosarcoma (OSA) is the most common bone tumour in dogs and humans and is highly malignant and resistant to chemotherapy. An important contributor to chemoresistance of cancer cells is autophagy, a reversible process where cells selectively digest organelles and other internal structures to survive during stressful conditions. We hypothesized that a combined treatment of an autophagy inhibitor and chemotherapy drug would reduce autophagy in canine OSA cell lines. Cell lines derived from either primary or metastatic tumours, and non-transformed control cells were pre-treated with Spautin-1, an autophagy inhibitor, followed by doxorubicin (doxo). Protein was collected and run on Western blots to identify key autophagy markers; beclin-1, pS6RP, and LC3, with β-actin as a loading control. In non-transformed control cells, Spautin-1 treatment alone led to decreased autophagy as expected. However, pre-treatment with Spautin-1 followed by doxo led to increased autophagy as measured by LC3 conversion. pS6RP was increased in the Spautin-1 alone group confirming a decrease in autophagy with this treatment. In metastatic OSA cell lines, Spautin-1 decreased beclin-1 but had variable effects on LC3 conversion and pS6RP expression, both with and without doxo. In contrast, OSA cells from primary tumours showed consistent increases in LC3 conversion when treated with Spautin-1 and doxo but were variable with Spautin-1 alone. Our results show that a combination of Spautin-1 and doxo can reduce some autophagy markers in canine OSA cells, (e.g. beclin-1 in metastatic cells) but expression of other markers is variable or even increased. Future work will examine combination therapy and clonogenic survival of canine OSA cells.

Research Grant: OVC Pet Trust
Student Support: OVC Andrea Leger Dunbar Summer Research Assistantship
Examining the influence of the microbiome on asthma in a mouse model

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Asthma affects over 300 million people. The condition runs in families but is currently increasing at a rate too fast to be explained solely by genetic shifts. The microbiome, which is influenced by our early life exposures, is a potential contributing factor to the development of asthma. It has been shown that developing gut microbiota in infants is influenced by many factors that are also known to raise asthma risk such as mode of delivery or antibiotic exposure. In mice, infection with Campylobacter jejuni has been demonstrated to cause a shift to a TH2 immune response. We hypothesized that composition of the gut microbiome modifies the risk of asthma and allergic sensitization. Germ-free C57BL/6 mice were gavaged with a human fecal slurry to colonize their gut with human microbes while control mice maintained a conventional mouse microbiota. Mice were then gavaged with C. jejuni or sham inoculum and subsequently intranasally sensitized with House Dust Mite (HDM) or sham inoculum. Allergic immune responses are being quantified via plasma IgE concentrations measured by ELISA and bronchoalveolar lavage cell enumeration and differentials. We anticipate that mice with human microbiota that have been sensitized to HDM will have higher IgE concentrations than mice with conventional microbiota, and that infection with C. jejuni will further exacerbate the allergic response. If results show elevated allergic sensitization in humanized mice, this mouse model can be further used to investigate how difference in the human microbiome may predispose or protect individuals from asthma and other allergic diseases.

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Student Support: NIH R25HL103156

Characterization of epidermal microbiota in swine in locations relevant to auto- and alloimmune diseases

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Porcine and human skin share many structural and physiological qualities. Examples include dermal vasculature, collagen arrangement, cell turnover, follicular density, lipid composition, rete ridges, and dermal papillae. Hence, swine are uniquely positioned as models of auto- and alloimmune skin conditions, allo- and self-skin grafts, and wound healing. The skin forms an environmental barrier and is colonized by mostly non-pathogenic bacteria, fungi, and viruses. Changes in microbiota have been linked to autoimmune diseases such as psoriasis. Yet there is a gap in knowledge of the swine skin microbiota. Thus, better understanding the healthy swine skin microbiome will develop this clinically relevant model of wound healing, skin graft-versus-host disease (GVHD), and other skin-related conditions. To this end, our study aims to characterize the skin microbiome in (mini)pigs at the University of Pennsylvania Philadelphia campus. We hypothesize that the swine skin microbiome will differ between moist, sebaceous, and dry sites similarly to humans and will be stable over one month. We also hypothesize that microbial profiles will vary by the pig’s farm of origin. We will study pigs up to six months of age and of both sexes. Anatomical regions targeted by autoimmunity and GVHD will be swabbled and include the retroauricular, axillary, and inguinal creases. The shoulder will be used as a commonly unaffected region. Pigs will be swabbed upon arrival at the University and at weeks 1, 2, and 4. Sequencing of the 16S ribosomal RNA gene will be used to characterize the bacterial microbiota. To date, we have collected over 100 samples from 14 pigs. This study’s results will be instrumental for future skin studies using the pig model.

Research Grant: University Laboratory Animal Resources Resident Research Funds.
Student Support: NIH T35 OD010919
Development of a harmonized integrative epidemiological model for Rift Valley Fever

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Rift Valley Fever (RVF) is a mosquito-borne viral zoonosis endemic in many countries in Africa and the Arabian Peninsula, which epidemics result in significant losses in livestock and human illness and deaths. Although important research has been done on the epidemiology of RVF, there is still a lack of harmonized information on the disease in the affected countries. The aim of this study is to develop a harmonized model for the epidemiological evaluation of RVF infection and estimation of the risk in African countries. Firstly, a database was elaborated collecting information on RVF outbreaks from official data health repositories as the World Organization for Animal Health (OIE), World Health Organization (WHO), Food and Agriculture Organization (FAO) and Centers for Disease Control and Prevention (CDC). A quantitative stochastic model was developed by integrating the results of a climatic/ecological forecast model (RVF monitor, USDA-ARS&NASA) with the previously created database and other input parameters from relevant publications on RVF. The model was developed and run using @Risk 7.5 in Microsoft Excel with 10,000 iterations. Spatial analysis was done in QGIS. The database contained detailed information from RVF outbreaks in humans (2000-2016) and animals (2005-2017). The risk model identified Botswana as the currently highest risk country, with a mean of 41 and 90% CI of (3, 121) potentially RVF infected humans per month; followed by Namibia, South Africa and Zimbabwe all with a mean of 19 and 90% CI of (1, 56). The standardized database and quantitative model developed here will be easily updated and serve to perform numerous epidemiological analysis as the quantitative risk of RVF introduction into the US.

Student Support: Center for Outcomes Research and Epidemiology (CORE)

Co-localization of unkempt and HECA proteins in HEK cells

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Unkempt is a RNA-binding protein that regulates the early morphology of neuronal cell. To understand the mechanisms underlying Unkempt induced neuronal cell morphology changes, we identified a protein HECA (the human homologue of Drosophila Headcase), that physically interacts with Unkempt. To further investigate whether HECA has functional relevance with Unkempt, we explored the localization of these two proteins in human embryonic kidney (HEK293) cells. For this purpose, we generated GFP tagged HECA and RFP tagged Unkempt, respectively. We found that when individually transfected in HEK293 cells, both HECA and Unkempt were often localized near the nuclear periphery, with Unkempt occasionally exhibited a punctuate structure. Interestingly, co-expression of HECA and Unkempt revealed that the two proteins were co-localized near the nuclear periphery with a strong punctuate structure. Immunostaining with the Golgi markers indicated that Unkempt and HECA co-localize within the Golgi apparatus. Our study would therefore suggest that, HECA may have similar functions as Unkempt in regulating gene translation and neuronal cell polarity. This should be further investigated in following research.

Research Grant: Kansas State University Johnson Cancer Research Center
Student Support: NIH T35OD020979
The identification of transglutaminases in perivascular adipose tissue

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Norepinephrine (NE) is a signaling molecule of the sympathetic nervous system that functions to mediate many physiological processes throughout the body, including maintaining normal vascular tone. Transglutaminases (TGs) are a family of enzymes that act as a glue, forming a bond between a free amine group on one molecule (e.g. lysine) and a glutamine substrate protein. In the presence of TGs, NE can become attached to a protein in the process of amidation, a posttranslational modification that may alter the function of the protein. Because NE is located in the perivascular adipose tissue (PVAT) of blood vessels, we are curious if any of the eight mammalian TGs [TGs 1-7 and Factor XIII (FXIII)] are also present and actively functioning in PVAT. We hypothesize that TGs are found in the PVAT of rat arteries. To identify if any of the TGs listed above are found in PVAT, immunohistochemistry (IHC) was performed on rat tissue samples from the aorta, superior mesenteric artery, and mesenteric resistance vessels using primary antibodies from transglutaminases. IHC results showed that TG1, TG2, TG4, and FXIII were found in PVAT of the tissues above. Further experimentation using peptides derived from the transglutaminases will test the active functioning of these enzymes in the tissues they are found.

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The effects of oral Bisphenol exposure on ovary and egg development in adult chickens

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Understanding the impacts of endocrine disrupting chemicals (EDCs) on synthesis, secretion, transport, and metabolism of natural hormones is essential in determining the risks posed by these compounds on human, animal and environmental health. Bisphenol analogues, including Bisphenol A (BPA) and S (BPS), are among the most common commercial EDCs. BPA is used in polycarbonate plastics, dental resins, and the lining of metal food cans; it is also one of the most potent environmental xenoestrogens. BPS has emerged as an alternative to BPA in the midst of rising consumer health concerns and has proven to be even less biodegradable. Few studies have been completed concerning the endocrine disrupting potential of BPS. Chickens serve as an ideal and commercially relevant animal model for endocrine disruption due to their well characterized genome and physiology. After oral exposure to 50 μg/kg body weight of bisphenols or the vehicle (corn oil) over a 10-week period, egg quality characteristics including shell thickness, weight, calcium concentration and appearance were determined. RNA isolation was performed on ovarian follicular tissues, and RNA sequencing will be conducted to determine dynamic gene expression. Preliminary results suggested significant differences in egg shell thickness between the BPA treated group and the other treatments. BPA treatment also produced more shell deformities, including ridges and pimples, than BPS and the vehicle. Further studies will be conducted to determine the distinct effects of BPA and BPS at key developmental stages and their genotoxic potential.

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Immunogenicity of candidate rotavirus vaccine P-VP8* in a gnotobiotic pig model of human rotavirus infection

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Live oral human rotavirus (HRV) vaccines have lower than expected efficacy in low-income countries. One of the likely causes is the interference by gut microbiota from these populations. Parenteral, non-replicating vaccines may perform better by avoiding such interference. The chimeric P-VP8* particle, a vaccine candidate which uses the norovirus P particle to present the VP8* subunit of the rotavirus spike protein VP4, has been shown to induce a strong immune response and decrease viral shedding in mice. The purpose of this study was to evaluate the immunogenicity and protective efficacy of this vaccine in the gnotobiotic (Gn) pig model of HRV infection and disease. Gn pigs were intramuscularly inoculated with either 200 µg P-VP8* [with Al(OH)3 adjuvant] or PBS (mock) at 5, 15, and 26 days of age. A subset of these pigs was challenged with the homotypic virulent Wa strain HRV at 33 days of age. Following challenge, rectal swabs were collected daily to determine fecal consistency scores and virus shedding by CCIF and ELISA. Serum samples were collected weekly to determine HRV-specific IgA and IgG antibody titers by ELISA. Historical serum samples from Gn pigs vaccinated with either an attenuated, live HRV (AttHRV) or a P2-VP8* vaccine (fusion protein of VP8* and P2 universal CD4+ T cell epitope) were tested together for comparison. The P-VP8* vaccine induced serum IgG and IgA responses that are slightly lower than that of the P2-VP8*, but markedly lower than that of AttHRV. In association with the weak antibody response, there was only a slight reduction in virus shedding and diarrhea scores compared to the mock group. Further study is needed to increase the immunogenicity and protective efficacy of the P-VP8* vaccine.

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Genotyping and subgenotyping of Cryptosporidium spp. isolates to identify zoonotic transmission

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Cryptosporidium is a common protozoan parasite that causes diarrheal disease with the associated complications: dehydration, electrolyte imbalance, weakness, lethargy and destruction of intestinal villi leading to malabsorption of nutrients. In 2009 and 2016, students at the Atlantic Veterinary College experienced outbreaks of Cryptosporidium spp. In 2009, 14 suspect cases of human infection with Cryptosporidium spp. were identified, with laboratory confirmation in 5 of 8 students tested. Significant epidemiological risk factors were being in the 3rd year class, had been in contact with beagles in a medical exercise on a specific week and/or surgery lab. The calves and beagles used in teaching labs were tested. No calves were positive whereas 65% of the beagles tested positive for Cryptosporidium spp. and were sequenced as C. parvum. The latter outbreak in 2016 was likely transmitted to the students via calves in the teaching barn. Of the 10 students who became ill, 6 had contact with calves in the teaching barn. Three were then tested using ELISA and confirmed positive for Cryptosporidium spp. The purpose of this study is to use genotyping at the HSP70 gene and subgenotyping at the GP60 gene to determine the zoonotic source tracking of the particular isolates in the outbreak from different hosts (beagles, calves and humans). From the 2009 outbreak, 3 students had PCR bands suggestive of Cryptosporidium spp. and were sequenced as C. parvum. One student was successfully sub-genotyped as C. parvum IIaA15G2R1. The results of genotyping and subgenotyping of the Cryptosporidium spp. from the animals and the students from 2016 are currently being performed.

Research Grant: Term Research-SJG
Student Support: VetSRA [or] Merial Veterinary Research Scholars Program
Hypoxia induced chondrogenesis of equine-synovial membrane-derived stem cells

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The equine athlete is prone to joint and articular cartilage injury. Unfortunately, the ability of articular cartilage to repair and regenerate is limited, and the subsequent fibrocartilaginous repair tissue leads to further degeneration. Mesenchymal stem cells (MSCs) are a potential cell-based therapeutic to bolster healing. MSCs are found in several tissues, including bone marrow and synovium both of which are easily harvested with little harm to the equine patient and can be culture expanded in the laboratory. BM-MSCs have had disappointing chondrogenic differentiation; therefore, SD-MSCs are being investigated as an alternative source. There is literature to support SD-MSCs for cartilage repair in other species. Currently, the potential benefit of SD-MSCs is unknown. We hypothesize that SD-MSCs will display higher chondrogenic potential in vivo compared to BM-MSCs, and that SD-MSCs will have superior chondrogenesis in a hypoxic environment compared to a physoxic environment. The aim of this experiment is to compare the osteogenic and adipogenic potential of synovial membrane-derived mesenchymal stem cells (SD-MSCs) and bone marrow-derived mesenchymal (BM-MSCs), and to evaluate their chondrogenic potential in both normoxic and hypoxic environments. Stem cells were isolated from the bone marrow and synovium tissues of equine patients, and the cells’ ability to differentiate were evaluated using a trilineage differentiation assay. MSCs were then evaluated by histology, qRT-PCR, immunohistochemistry, GAG content, and total DNA content.

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Student Support: NIH/Merial Summer Research Program

Comparative stiffness of 3.5mm versus 4.5mm cortical bone screws for repair of equine navicular bone fractures

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Sagittal fractures of the equine navicular bone are surgically repaired using cortical bone screws in lag fixation. Use of a 3.5mm screw provides easier insertion due to smaller screw head, core diameter, and thread length. However, larger 4.5mm screws may better withstand compressive loads. Understanding differences in biomechanical strength of the two screw sizes will better assist implant choice by surgeons. Our hypothesis is that a 4.5mm bone screw is stiffer compared to a 3.5mm screw when repairing fractured navicular bones. Twenty-eight navicular bones (14 left/right pairs) were obtained from 11 thoroughbreds. Paired bones were randomly allocated to 3.5mm or 4.5mm groups. Bones were fractured sagittally using a band saw. Screws were inserted in lag position according to AO standard. Specimens were tested in four-point bending using a material testing machine according to ASTM standard. A single cycle test under position control formed a load-deformation curve of specimen elasticity. The slope of the linear portion of the curve equaled specimen stiffness. Stiffness was statistically compared using a paired t-test, with significance set at p < 0.05. Mean (±SD) stiffness was 522.49 N/mm ± 168.21 for the 4.5mm group, and 408.46 N/mm ± 131.13 for the 3.5mm group. The 4.5mm screw implant was significantly stiffer than the 3.5mm screw group (p = 0.047). These findings suggest that a 4.5mm cortical screw better resists bending forces when used for this specific fracture configuration. As horses impart large compressive loads on the bone during anesthetic recovery and during normal weight bearing, the 4.5mm screw may better withstand construct failure clinically. Future directions include cyclic and torsional testing.

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Identification of novel Brucella canis antigens for improved diagnostic testing

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Current diagnostic tests for Brucella canis are difficult to interpret, slow to run, and have high cross reactivity. Antibiotic treatment is often ineffective, and breeding kennels euthanize animals that test positive. The end goal of our study is to produce a rapid and reliable serologic test for detection of infected dogs. Previously, two B. canis proteins were identified as immune-reactive by western blotting with infected dog sera. These proteins were identified by mass spectrometry and NCBI database analysis, with four other immune-reactive proteins identified through the database. One antigen, BP26, has demonstrated some utility in a diagnostic test. This study analyzed the other B. canis proteins for use with BP26 in a poly-antigenic test. Each gene was cloned onto a plasmid (pQE60) with a lac promoter for inducing gene expression, and a carboxyl-terminal His tag for identification and purification of expressed protein. These clones were then transformed into an E. coli strain that harbors a plasmid (pREP4) containing the lacI repressor. This dual plasmid system allows for controlled gene expression. IPTG-induced expression will be verified by Coomassie stain and western blotting with anti-His antibody. Each protein will then be tested against serum from an infected dog, with antibody binding indicating the antigen has potential for use in a diagnostic test. The proteins will then be purified and tested using a Luminex assay. Positive results would warrant further examination of these antigens for use in a commercially available diagnostic test. Using isolated proteins from B. canis should offer higher sensitivity and limit cross-reactivity making diagnosis of canine brucellosis more efficient.

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Student Support: Merial Veterinary Research Scholars Program

Effect of air quality on mild equine asthma in Ontario horses

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Mild Equine Asthma (MEA) in horses is similar to mild to moderate persistent asthma in people. The clinical signs of MEA include decreased athletic performance and cough in association with exercise lasting for at least four weeks. Because clinical signs are nonspecific, MEA is often diagnosed using bronchoalveolar lavage. With this technique, a small amount of sterile saline is instilled and retrieved from the lungs by aspiration. This “wash” recovers both cellular and non-cellular secretions of the lower airways and alveoli, and the secretions are analyzed. Although MEA is a relatively common disease, the exact cause has not been found; occurrences are suspected to correlate with increased air pollution as measured by the Air Quality Health Index (AQHI). This is a daily measurement of the following components of air quality; nitrogen dioxide, ozone and particulate matter less than 2.5nm. These values are combined to yield a number on a scale of 1-10, 1 being the best and 10 being the poorest air quality. The aim of this study is to analyze AQHI data and data collected from bronchoalveolar lavages performed at the Ontario Veterinary College on 168 horses between the years of 2007 and 2017 to determine if there is a correlation between poor air quality and a diagnosis of MEA. The hypothesis is that an increase of even one point on the AQHI scale will increase the relative risk of developing MEA. Conditional logistic regression will be used to assess whether there is a correlation between a 1 point increase in AQHI and the incidence of MEA. As data are still being compiled, statistics have not been run, however, results will be available for presentation at the National Veterinary Scholars Symposium.

Research Grant: None
Student Support: Ontario Veterinary College’s Andrea Leger Dunbar Summer Research Studentship
Utility of immunohistochemistry to better define canine soft-tissue sarcomas

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Soft-tissue sarcomas (STSs) are tumors of mesenchymal origin that represent 10-15% of tumors in the dermis and subcutis of dogs. Traditionally, they have been grouped by histologic grade to predict biologic behavior and guide treatment. However, data suggest that the grading scheme is incomplete in predicting outcome. The aim of this study was to assess immunoreactivity for collagen IV, laminin, calretinin, and Ki67 in canine STSs samples to determine if these refine the histologic diagnosis or correlate to histologic grade. Cases from the New York State Animal Health Diagnostic Center were graded per intensity of the immunohistochemical reaction, or number of positive cells/HPF for Ki67. Sixty-one cases were analyzed representing 21 grade I, 20 grade II, and 20 grade III. For collagen IV, immunoreactivity was strong in 20 (33%), moderate in 24 (39%), weak in 9 (15%), and negative in 8 (13%). For laminin, immunoreactivity was strong in 14 (23%), moderate in 23 (38%), weak in 14 (23%), and negative in 10 (16%). For calretinin, immunoreactivity was strong in 7/30 (23%), moderate in 7/30 (23%), weak in 13/30 (43%) and negative in 3/30 (10%). For Ki67, 8 cases had <5 positive cells/HPF, 32 had 5-15 positive cells/HPF, and 21 had >15 positive cells/HPF. Ki67 correlated with histologic grade (r = 0.543; p-value < 0.00001). Immunohistochemistry for collagen IV and laminin indicates that most of these tumors possess basal lamina, but is not sensitive in further classifying canine STSs. We suggest supplanting mitotic count with Ki67 immunohistochemistry for more accurate assessment. Future studies will be aimed at using genetic analysis to determine novel mutations in canine STSs that drive tumor progression and may predict outcome.

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Student Support: NIH T35 Training Grant OD010941

X-linked gene expression in splenic B-cells of a murine model of systemic lupus erythematous

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Systemic lupus erythematous (SLE) is a severe autoimmune disease that affects women at a rate nine times higher than men. The genetic basis for this bias is the X-chromosome, where the greatest concentration of immunity related genes on any chromosome can be found. Females have two X-chromosomes (XX), and through a process, known as X-chromosome inactivation (XCI), silence one of their X-chromosomes randomly to have a similar level of X-linked gene expression as males (XY). Previous research has shown that human SLE patient B cells exhibit altered localization of XIST RNA, a long non-coding RNA that coats the inactive X (Xi) and further recruits heterochromatin modifiers to condense it, thus indicating that they have partial reactivation of the Xi. The purpose of this study was to determine if there is a difference in the expression of X-linked genes between wild type (WT) and NZBWF1 mice, which are a murine model of SLE. The hypothesis of this study is that the expression of X-linked genes is increased in splenic B-cells of NZBWF1 mice due to improper Xist RNA localization. qPCR was performed using cDNA from splenic B-cells taken from female 3 and 7 month WT (n=1 each) and 3, 7, and 9 month NZBWF1 mice (N=1, 2, and 2 respectively). Preliminary results indicate that the expression of TLR7 and CXCR3, two x-linked genes, are increased in naive B-cells in comparison to stimulated B-cells after 24 hours. This decrease in expression aligns with the observation that Xist RNA is not localized to the Xi in naive B-cells, but is localized to the Xi in 24 hour stimulated B-cells. Additionally, the 7 and 9 month old NZBWF1 mice appear to have higher expression of TLR7 and CXCR3 in their splenic B-cells than the 7 month old WT.

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Student Support: Howard Hughes Medical Institute-Burroughs Wellcome Fund Medical Research Fellows Program
Investigation of the role of the aryl hydrocarbon receptor in the mechanism of NSAID-induced enteropathy

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NSAID-induced enteropathy is associated with a high morbidity and mortality rate, yet the pathophysiology of the disease remains unclear. Previous work from our laboratory indicates that the aryl hydrocarbon receptor (AhR) is a major upstream regulator of this disease. AhR has been shown to have both harmful and beneficial effects on other GI diseases. In addition, NSAIDs have been shown to activate AhR in vitro. Thus, we aim to investigate the role of AhR in NSAID-induced enteropathy in vivo and in vitro. We will evaluate if AhR manipulation affects NSAID-induced cell death in vitro by administering NSAIDs, in the presence or absence of AhR agonists or antagonist, to intestinal epithelial cell lines. We will also determine if NSAIDs activate AhR through a murine model of NSAID-induced enteropathy by administering increasing doses of NSAIDs and measuring the expression of AhR-dependent downstream targets (e.g. CYP1A1) in the intestinal mucosa. We hypothesize that manipulation of AhR will affect NSAID-induced cell death in vitro and that administration of NSAIDs to a murine model will activate AhR in vivo. We expect that these results will provide insight into the role of AhR in the pathophysiology of NSAID-induced enteropathy and aid in the development of novel prevention and therapeutic strategies.

Research Grant: None
Student Support: Boehringer Ingelheim Veterinary Scholars Program, College of Veterinary Medicine Texas A&M U.

Immunophenotyping of lymphocytes in a minipig model of vascularized composite allotransplantation rejection

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Vascularized composite allotransplants (VCAs) are compound transplants that include multiple distinct tissue types, including skin, muscle, bone and other associated tissues. With rigorous immunosuppressive therapy, successful transplantation can be maintained in both animal models and human patients with VCAs with low rates of acute rejection. Clinically, the main target of rejection appears to be the skin, and although the exact immunologic mechanism remains unclear, clinicopathologic monitoring of the skin provides a useful metric for the rejection status of the graft as a whole. A stifle VCA rejection model is achieved with MHC class 1 and 2-mismatched Massachusetts General Hospital (MGH) minipigs, a model with similar dermohistomorphology to humans. However, more detailed studies of the pathology of porcine dermal tissues in acute VCA rejection are necessary. The aims of this project include developing a scoring system based on the human system of the dermatohistopathology of acute rejection in the minipig model and characterizing the lymphocytic infiltrate of the skin in VCA rejection controls using immunohistochemical (IHC) staining. The overarching goals of IHC analysis include optimization of CD3+, CD20+, and FoxP3+ primary antibodies in control lymphoid tissues, and quantification of the amount of CD3+, CD20+, or FoxP3+ inflammation in acute graft rejection. Based on observations in human VCA rejection, we hypothesize that the inflammation will be predominantly CD3+ T cells with significantly fewer CD20+ B cells and FoxP3+ regulatory T cells. These studies will set the groundwork for future immunologic characterization of VCA rejection using the MGH minipig model under a variety of immunomodulatory therapies.

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Student Support: Department of Molecular and Comparative Pathobiology, School of Medicine, JHU
Radiographic evaluation of thoracic girdle fractures in wild birds after presumptive window collisions

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Window collisions represent a common cause of injury for both wild and companion birds. These collisions commonly result in fractures or luxations of the bones of the thoracic girdle, which include the coracoid, clavicle, and scapula. Clinical diagnosis of these fractures can be difficult, as the bird may show few clinical signs and usually requires radiographic evaluation. This project sought to compare the diagnostic value of different radiographic views, including 45° oblique views, to postmortem examination as the gold standard. Radiographs and necropsies were performed on 103 presumptive window collision cadavers. Lincoln’s sparrows were the most frequently represented species (n=25), followed by painted buntings (n=13), and 31 other passerine species with fewer than eight individuals each (n=65). The average weight of these birds was 14.9 grams (range: 5-46g). On gross necropsy, 14/103 birds had at least one coracoid fracture or luxation, 18/103 had at least one clavicle fracture or luxation, and 41/103 birds had at least one scapula fracture. Overall, approximately 54% of the cadavers had at least one injury to the thoracic girdle bones. However, these cadavers are presumptive natural fatalities, therefore we cannot rule out that some of the fractures were the result of postmortem trauma. Image collection has been completed and radiographic evaluation is pending. Postmortem results will be compared to radiographic findings and correlations will be determined.

Research Grant: None
Student Support: Morris Animal Foundation

Systemic effects of aerosolized ammonia in laboratory mice housed in static isolation cages

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Currently acceptable practices, as described in the Guide for the Care and Use of Laboratory Animals, aim to reduce environmentally sourced effects on mice and provide healthy animals for research. Our previous studies demonstrated a positive correlation between intra-cage ammonia levels and nasal pathology, suggesting that these practices could have detrimental effects in the respiratory tract of mice. To evaluate if the effects of high ammonia levels are associated with systemic inflammatory effects, we propose to measure cytokine concentrations in blood samples from mice using the Multiplex Cytokine Assay (MILLIPLEX Mouse High Sensitivity T Cell Magnetic Bead Panel). We aim to determine if cytokine levels correlate with ammonia exposure and nasal pathology. Using pooled plasma samples from our previous study we ran the Multiplex Cytokine Assay and compared the concentrations of 18 separate cytokines in each specimen with average nasohistopathology scores and average ammonia levels at day 7, post-cage change. To directly evaluate the correlation between nasal pathology and systemic cytokine levels in individual mice, we plan to conduct a prospective experiment hoping to replicate previously seen effects on nasal pathology in the face of elevated ammonia concentrations. These experiments will help us to understand if current housing protocols are sufficient to maintain the health of laboratory mice housed in static microisolator cages. The results may have possible implications on studies that use laboratory mice to evaluate inflammation for other experimental reasons.

Research Grant: College of Veterinary Medicine Intramural Funds
Student Support: Merial Fellowship Program Scholarship
An evaluation of body condition scoring in three species of wild raptors

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Body condition reflects long term nutritional status, physical activity and overall health of an animal. Systems of scoring body condition are an important tool for determining individual prognoses, and assessing population health trends. A subjective pectoral muscle and keel palpation determines a body condition score (BCS) in most avian species, including wild raptors admitted to the Gabbert Raptor Center, of the University of Minnesota. This system is lacking a full assessment of its reliability and accuracy for use with raptor species. Without such, its use could hinder the quality and standardization of wildlife health data. This research seeks to address that problem, and to begin exploring an objective BCS system using size-adjusted mass. We investigated the use of BCS for three raptor species: Bald Eagle (Haliaeetus leucocephalus), Red-tailed Hawk (Buteo jamaicensis), and Great Horned Owl (Bubo virginianus). We collected blinded BCS data from multiple clinicians and rehabilitators to investigate inter-rater reliability. Eight morphometric size indices were collected with admission weight to create a size-adjusted mass. We validated and compared these methods with a post-mortem assessment of internal body condition with qualitative and quantitative measurements. Our results showed a significant relationship between weight and BCS for each species, with intraspecies sex differences. Keel BCS variability differs significantly between species, indicating there may be a need for species specific scoring systems. Keel BCS explained more variation in internal condition than size-adjusted mass residuals. Adapting the current BCS system to improve reliability across species could be a viable option for the future.

Research Grant: None
Student Support: The Department of Veterinary Population Medicine, University of Minnesota

Making a list and checking it twice - the effects of implementing a surgical checklist in veterinary medicine

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Following development by WHO, surgical checklists have become an adopted standard in human hospitals, and studies have shown that they reduce intra-operative and post-operative complications. Despite the proven benefits in human medicine, there has yet to be comprehensive evaluation in veterinary medicine. The objective of this study was to evaluate the impact of adopting a surgical safety checklist in a veterinary medical academic center. We hypothesized that implementing a surgical checklist would decrease the number of perioperative errors and post-operative complications. To begin this study, we looked retrospectively at the orthopedic, neurology, oncology, and soft tissue surgeries that took place in our hospital between March 2017 and May 2017. Of the 301 surgeries that occurred, 21.6% had intra-operative complications and 36.2% had post-operative complications. Next, we observed three weeks of surgeries to observe any perioperative complications prospectively. During this time, a sample checklist was drafted and reviewed by surgeons, anesthesiologists, and technicians so that a final customized file could be constructed. This final checklist was then implemented for three weeks, during which time surgeries were also observed and perioperative error rates were determined. The number and type of surgical complications associated with the pre-checklist surgeries will be compared to those that used the checklist. We will then extend the study over another three-month period to collect more data and compare results to the retrospective data. The aim of this study is to provide information that veterinarians can use to assess the impact of checklists and whether they should institute one in their practice.

Research Grant: None
Student Support: Boehringer Ingelheim Veterinary Scholars Program
Urban backyard poultry flocks in Massachusetts: evaluating Salmonella prevalence and antimicrobial resistance

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Through the increasing popularity of backyard poultry flocks, more people now have close contact with poultry and poultry coops, which researchers attribute to an increase in poultry-associated salmonellosis. However, to date, there have been very limited studies assessing prevalence of Salmonella in backyard chickens (BYC). The aim of this study is to understand this public health risk associated with BYC ownership by assessing the flock-level prevalence of Salmonella and by comparing it with published prevalence reports in commercial poultry flocks. The hypothesis of this study is that prevalence will be higher in BYC due to a lack of regulation, owners’ unfamiliarity with zoonotic diseases, and owners’ viewing BYC as pets, not production animals. A convenience sample of 50 flocks have been enrolled, 50% of which are from the greater Boston area, and 50% of which are from more rural locations. Average flock size is six birds (range 2-21). Composite fecal material, cloacal swabs, and dust samples from each flock/coop were tested for Salmonella using established culture techniques for isolation followed by molecular confirmation at the Cornell Animal Health Diagnostic Center. Currently, suspect Salmonella has been isolated from 3 out of 42 flocks with their genotypic confirmation pending. Upon confirmation, phenotypic antimicrobial resistance profiles will be assessed using a Sensititre NARMS Gram Negative plate. Flock owners have been surveyed about their demographics, husbandry, handling, and biosecurity practices, in hopes the findings will allow for an understanding of the relationship between these variables and the presence of Salmonella.

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Student Support: NIH Summer Research Training Program

Rapid development of diagnostic PCRs for emerging arthropod-borne viruses

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Arthropod-borne viruses (arboviruses), including Zika virus (ZIKV) and Mayaro virus (MAYV), are a major global health concern. ZIKV, from the Flaviviridae family, can be transmitted through mosquito bites or sexual activities. ZIKV symptoms are usually mild, consisting of fever, conjunctivitis, headache, myalgia, and pruritus, but early term fetal infections cause severe birth defects including microcephaly. MAYV, of the Togaviridae family, is an emerging virus and imminent public health concern. Acute symptoms consist of fever, cutaneous rash, and arthralgia that may persist for months or years. As seen with past and recent ZIKV and MAYV epidemics, arboviruses can spread rapidly worldwide leading to severe impacts on public health. Thus, there is a significant need for novel methods to rapidly develop specific and sensitive diagnostic tests. Here, we report the development of RIGEL as a unique computational tool to scan genomic information and identify conserved and virus-specific regions within the ZIKV and MAYV genome. These nucleotide segments were used to develop primers for one-step reverse transcriptase-PCR (RT-PCR) using both real-time and gel-based detection. ZIKV diagnostics were developed using synthetic RNA and RNA derived from ZIKV/COL/2015 infected Vero cells. While the sensitivity of the ZIKV real-time RT-PCR assay ranged from 20 to 200 viral RNA copies, gel based detection was one log less sensitive. At present, the MAYV-specific RT-PCR assay is under development using the RIGEL analytical platform. Our results show the feasibility of using RIGEL to facilitate the rapid development of a diagnostic PCR for various arboviruses.

Research Grant: Center of Excellence for Emerging and Zoonotic Animal Diseases

Student Support: Center of Excellence for Emerging and Zoonotic Animal Diseases
Assessment of bacterial biofilm development on 3D printed materials used for patient-specific implants in dogs

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Methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) is one of the most common causes of surgical site infections in canines. It produces surface-coating biofilms composed of extracellular polymeric substance matrix. This matrix confers resistance to antibiotics, disinfectants, and the host’s immune system, and facilitates exchange of resistance genes thereby promoting chronic infections. Human medicine has seen an increase in both the frequency of implant associated surgical procedures and the use of 3D printing to manufacture these implants. The availability and use of 3D printing in both human and veterinary medicine necessitates investigation of the sterility of materials used to 3D print implants, including biofilm formation on their surface. Fifteen small disks were created of each of the following materials: titanium alloy (Ti64), stainless steel, cobalt chrome, Polyjet, Ultem 1010, SLA standard and dental resins; in different resolutions and surface finishes. MRSP was used to form a biofilm on the disks following a previously established protocol. Disks were sonicated to remove biofilm bacteria and serial dilutions were performed to a maximum of 10^{-7} and plated to quantify bacterial biofilm formation on each different type of disk. Two disks from each material group underwent preservation with 2% glutaraldehyde both pre-sonication and post-sonication for scanning electron microscopy to confirm biofilm presence and assess surface features. The goal of this study is to determine which 3D printed materials may be better suited for implants in dogs by choosing materials that minimize bacterial biofilm formation.

Research Grant: Pet Trust
Student Support: Unknown

The meningeal compartment supports tertiary lymphoid organogenesis in a natural model of multiple sclerosis

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Multiple sclerosis (MS) is an idiopathic demyelinating disease in which meningeal immune cell infiltrates resembling tertiary lymphoid organs (TLOs) correlate with accelerated clinical disease. TLOs are highly organized lymphoid aggregates arising from the interaction of distinct immune cell subsets and resident stromal/endothelial cells at sites of chronic inflammation. The study of MS is restricted due to limited access to specimens, long disease course and confounding factors of experimental models. Naturally occurring models offer an opportunity to understand MS immunopathogenesis and provide a framework for translational research. We propose granulomatous meningoencephalomyelitis (GME) as a natural model to study MS. GME is an idiopathic inflammatory disease of dogs characterized by perivascular lymphohistiocytic infiltration in the cortex and white matter associated with demyelination and axonal pathology. The subarachnoid space, an important niche supporting immunological activity, displayed areas of gadolinium enhancement that correlated with heavy lymphocytic infiltration. The infiltrates had discrete collections of proliferating B cells contained in a conduit-like collagen fiber network and were associated with expression of the lymphorganogenic chemokines CXCL13 and CCL21. T cells in the periphery of TLOs were characterized by low density of T regulatory cells. Although parenchymal infiltrates contained B cell clusters, they lack the TLO signatures found in the meninges. Our findings indicate that the meningeal microenvironment sustains the development of TLO-like structures during chronic neuroinflammation and suggest GME as a novel naturally occurring model to study meningeal and B cell driven inflammation.

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Investigating the role of exosomal miR-9 in canine and human osteosarcoma

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Osteosarcoma (OS) is the most common malignant bone tumor in children and dogs and remains a fatal disease for 30% of children and over 90% of affected dogs. MicroRNAs (miRs) are non-protein coding RNAs that regulate gene expression and their dysregulation is well documented in cancer. Circulating miRs embedded in small (30-100 nm) membrane-derived vesicles called exosomes are detectable in body fluids such as serum and plasma and recent studies demonstrate that tumor-specific exosomal miRs are capable of mediating tumorigenesis and metastasis. Our laboratory recently found that overexpression of miR-9 in OS cells promotes cell motility and invasiveness, consistent with data implicating miR-9 as a key player in promoting metastasis in human cancer cells. We hypothesize that high levels of miR-9 will be detected in exosomes derived from canine and human OS cell lines. We further hypothesize that serum exosome miR-9 will be increased in dogs with OS compared to healthy controls and that tumor-associated miR-9 levels will decrease following therapeutic intervention. Exosomes were isolated from conditioned media from canine and human OS cell lines and canine serum and analyzed with NanoSight imaging and Western blotting for exosomal marker expression. Real time PCR demonstrated that exosomal miR-9 expression is higher in canine and human OS cells compared to normal osteoblasts, suggesting that OS cell-derived exosomal miR-9 may play a role in mediating tumor-stroma cross-talk. MiR-9 is detectable in canine serum-derived exosomes; however, studies are underway to evaluate serum exosome miR-9 levels in healthy dogs and dogs with OS to determine the feasibility of circulating miR-9 as a non-invasive biomarker in canine OS.

Research Grant: Unknown
Student Support: NIH T35 Training Grant

Coccidiosis decreases bacteremia and spinal lesions caused by pathogenic Enterococcus cecorum


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Pathogenic strains of the bacterium Enterococcus cecorum (EC) cause the disease Enterococcal Spondylitis which is responsible for significant morbidity and mortality in broiler chickens. In this disease, pathogenic E. cecorum infect the spine at the free thoracic vertebra (FTV) resulting in paralysis. Only birds with both osteochondrosis dissecans lesions in the FTV and bacteremia develop the disease. In prior work, we demonstrated that gut colonization precedes bacteremia and spinal lesion development. However, it is unclear how pathogenic E. cecorum escape the gut niche and enter the circulation. One potential mechanism is that damage to intestinal barrier caused by common infections like Eimeria spp. potentiates translocation of E. cecorum. In this study we test this hypothesis by modifying our oral E. cecorum challenge model to include coccidian co-infection. A total of 1,440 male Cobb 500 broilers were divided into 3 treatment groups: EC (E. cecorum only); EC:Cocci (Dual E. cecorum and Eimeria spp. infection) or sham. Outcome measurements were spleen cultures for E. cecorum, histologic evaluation of the spine for lesions of Enterococcal spondylitis; live performance parameters; and histologic evaluation of the intestine. While EC and co-infection negatively impacted broiler performance, co-infection with Eimeria spp. significantly decreased the prevalence of E. cecorum bacteremia and FTV lesions. The mechanism for this finding is unclear; however, potential explanations include increased surveillance by the immune system, decreased transit time (diarrhea), or decreased attachment of pathogenic EC. Clearly, additional work is needed to understand how pathogenic EC escape the gut niche.

Research Grant: NCSU Veterinary Scholars Program, Merial Inc. and Zoetis Poultry Inc.
Student Support: NCSU Veterinary Scholars Program and Merial
Mammary tumor cells and macrophages may affect the formation of a metastatic niche in murine lungs

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Obesity in dogs lowers the mean age of mammary cancer development, increases the incidence of tumor formation, and enhances tumor progression. To model the effects of obesity on tumor growth and progression, we utilized a high fat diet to induce obesity in C57BL/6 female mice and transplanted the immortalized mammary tumor cell line, EO771 cells, into their inguinal mammary glands. Compared with mice fed the control diet, obese C57BL/6 mice demonstrated decreased latency to tumor formation and larger end stage tumor volumes. Histologic examination of the lungs suggested that lung metastases occurred with greater frequency in obese mice. Using immunohistochemistry, we evaluated the recruitment of reactive fibroblasts within lung tissue using smooth muscle actin (SMA). SMA+ fibroblasts were detected surrounding metastases, suggesting that the tumor cells recruited reactive stromal cells to the metastatic microenvironment. Based on these findings, we hypothesized that cytokines secreted by inflammatory cells and tumor cells facilitate the formation of a metastatic niche within the lung parenchyma. To investigate this hypothesis in vitro, primary murine lung cells were exposed to conditioned media collected from two tumor cell lines (EO771 and MET1) and a macrophage cell line (RAW 264.7). After exposure to conditioned media for one week, RNA was extracted from the lung cells and qPCR was used to detect changes in stromal cell gene expression, including SMA, fibroblast specific protein 1 (FSP1), vimentin, fibroblast activating protein (FAP), S100A8, and S100A9. These studies suggest that interactions among tumor cells, macrophages, and lung stromal cells enhance the microenvironment for metastatic growth within the lungs.

Research Grant: Susan G. Komen CCR15332611
Student Support: AVMA/AVMF 2nd Opportunity Summer Research Scholarship

Identification and characterization of Grenadian freshwater fish species through DNA barcoding

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Identifying and cataloging fish species is important to understanding Grenada’s freshwater ecosystem. DNA barcoding creates a clearer picture of fish diversity of the species present. DNA isolated from muscle samples collected from teleost species from various freshwater bodies was sequenced for the mitochondrial cytochrome c oxidase 1 gene to provide species-level identification and to elucidate community-level patterns. Results to date have characterized greater than ten distinct teleost species from eight water bodies that likely represent both native and introduced species. Further sampling is planned that will more comprehensively examine the island’s fish population. These results create a representation of the island’s ecosystem and provide the framework for managing Grenada’s fisheries.

Research Grant: None
Student Support: Boehringer Ingelheim Veterinary Scholars Program
Environmental decontamination techniques for *Syphacia obvelata* infections in laboratory mice

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Murine pinworm infections in mice are frequently subclinical, but can cause clinical signs such as rectal prolapse, intussusception and enteritis in susceptible mice. Infections can impact research, such as modulating immune responses and causing changes in behavioral test paradigms. As such, it is undesirable to have infected mice in research colonies. One challenge in the eradication of pinworm infections is the resiliency of the ova, which can be easily aerosolized causing extensive environmental contamination. The ova are also adhesive, resistant to common disinfectants, and can be viable in the environment for several months. Here, efficacy of environmental decontamination methods to render *Syphacia obvelata* ova nonviable was investigated. Specifically, exposure of harvested ova to steam at various pressure settings and times and dry heat at varying temperatures for 24 hours were tested. Our results showed that steam treatment at setting 0 for 30 seconds and dry heat at 45°C, 55°C, and 60°C reduced ova viability significantly. Based on these findings, dry heat and steam treatments can be used in conjunction with other decontamination procedures to reduce the viability of pinworm ova in the environment. Effective decontamination methods are vital to eradicate challenging infections in mice in order to maintain the highest standards of research and laboratory animal welfare.

**Research Grant:** Unit for Laboratory Animal Medicine  
**Student Support:** Boehringer-Ingelheim

Evolution of respiratory and enteric coronaviruses in captive ruminants

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Members of the family coronaviridae have been associated with emerging diseases such as Severe Acute Respiratory Syndrome (SARS) in 2002, which was traced to coronaviruses transmitted from animals to humans. Coronaviruses are positive-sense, single-stranded RNA viruses that form nested transcripts during replication. The poor proof-reading activity of the viral RNA transcriptase leads to viral variants with disparate cell tropism and host range during replication, producing infection in new host species and inducing pathology in unexpected organ systems. These viral variants are associated with mutations in the spike protein that mediates viral entry into host cells through receptor binding or membrane fusion. Ruminants, such as cows, are susceptible to bovine coronavirus (BCoV). Previous *in vitro* research demonstrated that an insertion in the spike protein gene enabled BCoV to infect human and bovine macrophages. However, there is paucity of information on whether such mutations occur following BCoV infection of a new host *in vivo*. Our study will use an outbreak of BCoV in captive ruminants from the Saint Louis and Kansas City Zoo as an *in vivo* model of BCoV evolution during host switch events. We hypothesize that the mutations responsible for enabling infection of zoo ruminant species with BCoV will localize to the viral spike protein genes. We will purify viral RNA and assemble full-length nucleotide sequences of BCoV spike protein from stool samples of infected ruminants through Next Generation Sequencing. This study may provide information on the genetic bases of host-switching events and may guide the design of new therapeutics for coronavirus-induced diseases.

**Research Grant:** None.  
**Student Support:** Missouri College of Veterinary Medicine Office of Research.
STING agonists: potential novel immunotherapy for canine osteosarcoma

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Osteosarcoma (OSA) occurs in both humans and dogs with an annual incidence of 450 and 25,000 cases, respectively, making dogs a useful comparative oncology model for the development of immunotherapies for people. The current standard of care treatment for OSA is amputation, or amputation followed by chemotherapy. However, the vast majority of dogs will succumb to metastatic disease. Cancer immunotherapy holds the promise of more effective treatment of the primary OSA as well as distant micrometastases. One such novel immunotherapy is STING (stimulator of interferon genes) agonists, which upregulate inflammatory cytokines such as IFN-β, inducing T cell priming to tumor antigens. STING agonists have been studied extensively in mice and are now in early human clinical trials, but have never been tested in dogs. Unlike humans, where multiple STING alleles influence STING agonist responses, we have found evidence for only a single canine allele. To determine if STING agonists trigger the same inflammatory pathway in dogs, peripheral blood was acquired from 13 canine patients. Peripheral blood mononuclear cells (PBMCs) were isolated and incubated with the STING agonist. Induction of IFN-β (as measured using quantitative reverse transcription PCR) indicated STING agonist activity. When compared with untreated PBMCs, 12 of 13 dogs responded with an average of 133-fold induction of IFN-β expression (range of 10-fold to 395-fold). These data show robust in vitro activity of STING agonists in canine samples establishing their potential use as immunotherapies in canine patients with OSA.

Research Grant: Center for Image-Guided Animal Therapy Gift Fund
Student Support: Department of Molecular and Comparative Pathobiology, Johns Hopkins School of Medicine

Effect of enteric glial cell factors on in vivo recovery of ischemic-injured neonatal porcine jejunum

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Intestinal ischemia causes sloughing of the epithelial barrier, allowing influx of toxic luminal contents into the bloodstream. Epithelial restitution post-ischemic injury involves migration of remaining epithelial cells over the defect and restoration of tight junctions. We have previously demonstrated that restitution is reduced in neonatal pigs when compared to juveniles, and recent studies show enteric glial cells (EGC), whose network matures in the postnatal period, have important paracrine signaling mechanisms to promote barrier maintenance and repair. We hypothesize that introduction of EGC-conditioned media into the jejunum of neonatal pigs at the time of surgically-induced ischemia will increase restitution of the epithelial barrier during in vivo recovery due to the presence of currently unknown EGC factors. 30 minutes of reversible ischemia followed by 120 minutes of in vivo recovery was induced in the jejunum of four 2-week-old Yorkshire-cross piglets with and without infusion of rat EGC-conditioned-medium (GCM). Mucosal transepithelial resistance (TER) was collected as a measure of barrier function and tissues fixed for histological scoring. Unexpectedly, TER values were elevated across all treatment groups. Histomorphometry revealed 100%±0 epithelialization in the recovered GCM-treated villi compared to 87%±9.27 in the ischemia-only group and 99%±1.15 in the recovered control media-treated group. Sources of error including inconsistency in ischemic injury using bulldog clamps and possibly measuring villus cross-sections rather than villus tips may have influenced the measured outcomes. Further data collection is needed to assess the effect of GCM on in vivo mucosal repair in neonates.

Research Grant: College of Veterinary Medicine Veterinary Scholars Program
Student Support: NIH T35 Interdisciplinary Biomedical Research Training Program (IBRTP) – T35OD011070
Day to day variation in a sample of equine heart rate variability estimates

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Heart rate variability (HRV) is defined as irregularity in R-R intervals between heartbeats, which can be used as an indicator of autonomic nervous system function. The balance between vagal parasympathetic cardiac tone and sympathetic cardiac tone are estimated within the frequency domain of standardized heart rate monitor measurements. The purpose of this study was to determine the consistency of HRV measurements between test days separated by at least a two day interval. Establishing the consistency of measurements of HRV is an important first step in determining the applicability of HRV for subsequent equine behavior studies. The hypothesis of this study is that HRV measurements obtained with portable heart rate monitors will provide accurate and consistent data from day to day (test to retest). This study obtained HRV measurements for 31 horses both free in a stall and restrained on cross ties, with HRV recorded under set conditions, at the same time of day, 48 hours apart. Results were determined by a comparison of means and variances using a general linear model. Results indicated that there were no significant differences in the day to day variations for the sub-measurements of HRV (eg. mean heart rate, low frequency power nu_AR, high frequency power nu_AR, low frequency to high frequency ratio) within the total sample of horses. These results support the hypothesis that HRV measurements from portable heart rate monitors will be consistent from day to day.

Research Grant: None
Student Support: Atlantic Veterinary College Veterinary Summer Research Award (VetSRA)

The role of BMP signaling in the maintenance of intestinal stem cell quiescence

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The cells of the intestinal epithelium have a high turnover rate, which necessitates intestinal stem cells (ISC) that are capable of rapidly generating large numbers of progeny. In order to meet these demands, the intestine utilizes a dual stem cell system, consisting of both active and reserve ISCs. The active ISCs are responsible for the majority of proliferative output during homeostasis. These cells are characterized by high Wnt activity, but also a high sensitivity to DNA damaging agents, such as radiation. In contrast, a second population of reserve ISCs are radiation-resistant, and serve to replenish the population of active ISCs. These cells remain in the quiescent G0 phase of the cell cycle, but can be activated in response to intestinal damage. Reserve ISCs will also exit from quiescence and form organoids in vitro when exposed to BMP inhibitors and Wnt agonists. In this study, we investigate the signaling events that allow reserve ISCs to exit from quiescence and enter an active, Wnt-responsive state. Previous research in the Lengner lab has shown that the activity of Musashi (Msi) RNA binding proteins are necessary to drive reserve ISCs out of quiescence. Msi is also known to bind to the mRNA encoding the BMP receptor Bmpr1a, further implicating the BMP signaling pathway in the maintenance of stem cell quiescence. We propose that the BMP pathway acts to maintain reserve ISC quiescence, and that BMP inhibition is crucial for the activation of reserve ISCs. By utilizing an in vitro organoid culture system, and through genetic manipulation in vivo, we seek to determine the role of the BMP pathway in maintaining stem cell quiescence.

Research Grant: NIH/NIDDK
Student Support: NIH Veterinary Research Scholars Program
Improving the IVF efficacy of porcine embryos through the alteration of IVF protocol and medium selection

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In Vivo Fertilization, or IVF, has become an important technology in animal agriculture, particularly in the dairy and beef industries. Although it has played less of a role in the swine industry, it is a necessary technology for introducing direct genetic modifications into animals. The technology requires, however, high quality, competent, in vitro-derived oocytes for its success. In particular, specialized media are needed to allow the immature oocytes to complete meiosis and be fertilized in vitro, and for the resulting zygotes to develop to blastocysts and provide offspring. Recent developments have led to significant increases in the efficiency of producing in vitro-derived piglets. In particular, this laboratory has described a chemically defined maturation medium containing 3 cytokines (FGF2, LIF, and IGF-1) called FLI medium, which doubled the overall efficiency of nuclear maturation of oocytes in cumulus-oocyte complexes (COC’s) and their development to blastocysts in vitro. Nevertheless aspects of this technology have not been thoroughly explored. The objective of our present study is to compare the efficacy of producing blastocysts after maturing the COC in FLI medium and control medium. At the end of the 44h maturation in medium, half the oocytes in each group will be denuded of their cumulus cells and subjected to IVF (the conventional method) while the remainder will retain these cells and undergo IVF (the modified method). This is the first study to investigate the most efficient combination of these factors during IVF protocol. We hypothesize that using modified IVF in the presence of FLI medium will lead to an increase in blastocyst number, thereby increasing overall IVF success.

Research Grant: Boehringer Ingelheim.
Student Support: None.

How does reproduction affect the personality of female threespined sticklebacks (Gasterosteus aculeatus)?

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Evidence has shown that the personality of an animal impacts its life history traits and fitness, but we know little about how life history events like reproduction affect personality. Reproduction is one of the most important events for any individual to experience. The aim of this project is to investigate how personality changes after reproduction in female threespined sticklebacks (Gasterosteus aculeatus). We hypothesize that females will be bolder and more risk-prone post reproduction, because the life history theory predicts a trade-off between current and future reproduction. We tested the personality of females before and after reproduction (control: did not reproduce) using three personality assays. The first assay assessed the females’ activity level in a new environment, the second assessed how females reacted to conspecifics, and the final assay was a trade-off between resource acquisition (i.e. food) and risk of predation (i.e. wooden bird). All three personality assays were performed on the same experimental and control fish for three consecutive days prior to reproduction. After the final personality assay on day 3, a water sample was obtained for a hormonal assay to evaluate stress and sex hormone levels. Once the “before” assays were complete, the gravid experimental females were placed in a tank with a male for courtship. The females and their controls were then evaluated again using the same assays. The data from the “before” and “after” assays will be compiled and compared to determine if the experience of reproduction changes the personality of females. The results should show that life history could impact personality and provide more evidence about the proximate mechanism for personality change.

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Student Support: Office of the Director, NIH, T35 OD011145
The effect of OTM diet on fecal microbiome in association with reduction of DD and EHEC0157 shed in cattle

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Lameness in beef cattle is predominantly due to digital dermatitis (DD). (Zinicola et al.) Also, beef cattle are known for shedding Escherichia coli 0157(EHEC0157). Both, DD and EHEC0157 continue to be a concern for consumers in the US. The results of the current study will be used to highlight and improve food safety regarding with beef cattle by understanding the fecal microbiomes of beef cattle related to the shedding of EHEC0157. Analysis of fecal microbiome data will establish an association within the supplementation of OTM and the significant reduction of the prevalence of DD and the shedding of EHEC0157 in beef cattle. We found significant relationships between the OTM diet with the shedding of EHEC0157 through evaluation of the alpha diversity of the fecal microbiome. Once we looked at the beta diversity of our data set we did not find significant relationships between the shedding of EHEC0157 and the treatment versus control diet. This study reflects implications for improved food safety and cattle welfare. Effective prevention and control of DD breaks the transmission cycle of EHEC0157 resulting in reduced shedding. This break leads to improved food safety through risk factor control in cattle pre-harvest.

Research Grant: Walter and Martha Renk Endowed Laboratory for Food Safety
Student Support: Unknown

Development of a new and rapid fixation/sterilization protocol for high-risk infected tissue

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Fixation is a process involving placing tissues in solutions to prevent degradation and autolysis. After fixation, the tissues are rendered aseptic. The goal is reproducible tissue morphology and cellular detail preservation. Fixed tissues are used for histopathological evaluation as well as molecular diagnostics. Current protocol, when working with high-risk infected tissue (viral and bacterial primarily), involves fixing infected tissues for 3 weeks or more in formaldehyde. However, it has been demonstrated that over fixation results in increased damage to biomolecules (DNA, RNA and protein). This study aims to develop a new and rapid protocol for fixing/sterilizing tissues in various fixative solutions and autoclaving conditions, producing optimal histology and biomolecular integrity.

Research Grant: Intramural Research Program of the National Institutes of Health, National Cancer Institute, Center for Cancer Research.
Student Support: National Cancer Institute
Neoplastic diseases in captive psittacine birds submitted to the Ontario Veterinary College

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Psittacine birds are becoming increasingly popular in households, with a growing reliance on pathologists to formulate accurate diagnoses. Concerning tumor diagnostics, pathologists have the challenge of determining prognosis and contributing to possible therapeutic options. Unfortunately, comprehensive information about neoplastic diseases in birds, including grading algorithms, is often limited. In this study, we conducted a retrospective analysis of diagnostic data from psittacine birds diagnosed with cancer (necropsy and biopsy) at the Ontario Veterinary College and Animal Health Laboratory from 1997 to present. This study aimed to review the prevalence of neoplastic lesions, describe disease presentation, and possibly determine risk factors. A database was created including, for each case, signalment (e.g., species, genus, age), history, and the type of cancer. Neoplastic lesions were characterized by body system and classified as epithelial (e.g., carcinoma), mesenchymal (e.g., sarcoma), round cell (e.g., lymphoma), neuroectodermal, or tumor-like lesions (e.g., cysts). A total of 161 cases with a diagnosis of neoplasia were retrieved. Highest prevalence of neoplasia was observed in the genus *Ara* (16%), *Nymphicus* (11.8%) and *Melopsittacus* (11.8%). The most commonly represented age class was mature (46.6%) and geriatric (21.7%), with only 4.3% represented by immature birds. Carcinoma (38.5%) and sarcoma (14.3%) were the most commonly diagnosed neoplasia. Regardless of tumor type, the most commonly affected systems were alimentary (26.1%), integument (24.2%) and multi-systemic (16.8%). These findings will prove useful to optimize algorithms for accurate diagnosis and grading of neoplastic diseases in these species.

Research Grant: Pet Trust Fund
Student Support: Andrea Leger Scholarship

Using differences in gene expression to differentiate histiocytic sarcoma from soft tissue sarcoma

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Histiocytic sarcoma (HS) is a notoriously difficult disease to definitively diagnose, and carries a grave prognosis for canine patients. The difficulty in obtaining a definitive diagnosis is an obstacle in developing effective therapies. Our study aims to provide pilot data for developing a clinical test for definitively diagnosing HS. Preliminary data from our lab a four gene expression signature (LMNB1, HAUS2, ERBB4, EHHADH) that can differentiate HS from other Soft Tissue Sarcomas (STS). We hypothesize that the protein levels of these four gene products, assessed via immunohistochemistry (IHC), will allow us to differentiate between HS and STS. More specifically, we expected to detect increased protein expression of LMNB1 and HAUS2 in HS samples, and increased protein expression of ERRB4 and EHHADH in STS samples. We used 6 HS and 10 STS fresh frozen samples for Western blot (WB) and RT-PCR experiments, and 20 independent tumor samples (10 HS and 10 STS) for IHC experiments. Positive controls for WB were DH82 cells, while positive controls for IHC experiments were HeLa cells, normal canine liver and kidney. The WB experiments demonstrated 10/15 STS and 0/6 HS positive for ERBB4, 12/15 STS and 0/6 HS samples positive for EHHADH, all STS and HS samples positive for LMNB1, 10/15 STS and all HS samples positive for HAUS2 gene products. Thus far, our initial results support our hypothesis, pending the results of RT-PCR and ongoing IHC experiments.

Research Grant: Grayton Friedlander Memorial Fund and Virginia-Maryland College of Veterinary Medicine
Student Support: 2017 Merial Veterinary Scholars Program (PO 1075449)
The effect of vagotomy and sympathectomy on feeding behaviors evoked by intra-aortic infusion of GRP-29

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Gastrin releasing peptide-29 (GRP-29) or the large molecular form of GRP in rats, given intraperitoneally (ip), has been shown to reduce meal size (MS), prolong the intermeal interval (IMI) and increase the satiety ratio (SR=IMI/MS) via vagal and sympathetic pathways. Here, we investigated the neuronal pathway by which GRP-29 (0.5 nm/kg), given in the aorta at the specific gastrointestinal site of action, elicits these responses (MS, IMI and SR) in free feeding vagotomized (VGX) and sympathectomized (SYMPX) male Sprague Dawley rats. We expect that VGX and SYMPX will attenuate reduction of MS, prolongation of the IMI and an increase in SR by GRP-29. This expectation is based on the facts that: the peptide is secreted by the gut, the GRP receptors responsible for reduction of food intake by GRP are located in the gut, and vagal and sympathetic afferents that carry the satiety signals of GRP from the gut to the brain are located in the gut.

Research Grant: National Institute of Health
Student Support: NIH T35 Grant

Cyclic-GMP values in plasma from canines with progressive retinal atrophy: assay development

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Progressive retinal atrophy (PRA) is a disease characterized by degeneration of the photoreceptors leading to loss of vision and eventual blindness. Studies have shown PRA in canines can serve as a useful model for Retinitis Pigmentosa (RP) in humans. Both diseases can be caused by a recessively inherited mutation in the rod specific cyclic guanosine monophosphate (cGMP) phosphodiesterase gene (PDE6A), altering phototransduction and causing an increase in cGMP in the retina. Recent studies in human patients have suggested that an increased level of cGMP could be detected in the plasma of individuals affected with RP, with one reference specifically for those affected due to a mutation in PDE6A gene. We have a colony of dogs with autosomal recessive PRA due to a mutation in Pde6a. This colony of dogs will allow us to investigate if the same results occur in the canine model. This study aimed to optimize the cGMP direct immunoassay kit (abcam, ab65356) for the use in our lab to determine if there is a relationship between plasma cGMP levels and the genotype of the individual. Initial experiments using canine plasma showed that there was an assay inhibitor in the plasma. To develop a protocol to remove the inhibitor we first tried 10 kd spin columns (abcam, ab93349). The spin columns were clogged by sample and found to be unsuitable for use with canine plasma. We next used a TCA protein precipitation protocol (abcam, ab204708) to deproteinize the sample. This latter protocol removed the protein assay inhibitor allowing us to next investigate a suitable plasma dilution to place the sample cGMP level within the accurate detection range of the kit.

Research Grant: Myers-Dunlap Endowment for Canine Health
Student Support: NIH T35 Training Grant No T35OD016477
Clinical and histopathologic evaluation of intraocular and periocular melanomas in dogs and cats

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Ocular melanomas and melanocytomas are problematic neoplasms of melanin-containing cells found within or around the eye. Unfortunately, there is currently a lack of data concerning metastatic rates and long-term survival of canine and feline patients with ocular and periocular melanomas. Prognosis and recommendations for treatment have been determined based on anecdotal experience with melanomas from distant sites, which may not accurately represent the behavior and prognosis for these neoplasms. This retrospective study was done to determine the rates of metastasis and disease-free intervals for ocular and periocular melanomas in dogs and cats following diagnosis and initial treatment. Cases were included if they had a confirmed histopathologic diagnosis of melanoma or melanocytoma in the eye or periocular tissues. Data was mined from the UFVH patient medical records system and included signalment, site of disease, results of imaging studies performed, survival time, and cause of death. If survival time was not apparent from the medical record, additional data was gathered via telephone interviews with owners and referring veterinarians. This study also aimed to determine if histopathologic characteristics could be used to predict clinical behavior and prognosis. Samples for each case were re-evaluated for specific traits. The characteristics evaluated included mitotic index, degree of pigmentation, tumor size, depth of cells, margins, percent of necrosis, vascular invasion, and nuclear characteristics. At this point in time, data has been collected and results are currently under analysis.

Research Grant: None
Student Support: Boehringer Ingelheim Veterinary Scholars Program and Departmental Funds

Providing veterinary care to companion animals in northern Canada

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Due to the small size of most northern Canadian communities, there is little to no access to veterinary care in most communities in the Canadian territories. There are only five veterinary clinics in total across all three territories. Volunteer initiatives have proven successful in offering veterinary care and education to low-access communities in these three territories. This study aims to better understand how to address this lack of veterinary care by mapping the current five veterinary clinic locations as well as the 54 low-access communities identified via a literature review. Currently, there are a small number of organizations and some veterinary colleges providing voluntary veterinary care to some of the low-access communities in a piecemeal manner. However, there has been no systematic survey of the potential interest or support for these volunteer activities across Canada. Therefore, interest among veterinary professionals and students in participating or supporting volunteer initiatives in northern Canada was evaluated via a survey. This information describes the demographic that should be targeted for future volunteer initiatives in northern Canada, and it assesses awareness about this important issue among veterinarians, veterinary technicians, and veterinary students in Canada. The preliminary findings have demonstrated willingness from the majority of survey respondents in supporting such initiatives by donating either time, money, or supplies. A coordinated program for improving veterinary care to low-access northern Canadian communities would result in better animal health and welfare, animal population control, and public health, since many diseases are shared among people and their pets.

Research Grant: VetSRA and Elanco
Student Support: None
Developing an optimized vector for muscular dystrophy gene therapy

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Duchenne muscular dystrophy (DMD) is a muscle-wasting disorder caused by a mutation of the dystrophin gene. Because dystrophin provides structural support of the muscle cell sarcolemma, using a viral vector to promote exogenous dystrophin expression, or functionally related μ-Utrophin expression, may provide a viable therapeutic option for DMD. Previous work in the lab has shown that viral vector AA V9 can be used to express μ-Utrophin in virtually all striated muscles of dystrophic mice and dogs. The purpose of this study was to determine if Anc80, a synthetic vector designed to recapitulate the structure of a putative ancestor to AAVs1-9, can likewise deliver μ-Utrophin to striated muscle throughout the body. In this study, we compared the biodistribution of AA V9 and Anc80 in dystrophic (mdx) mice following intraperitoneal (IP) administration in neonates. We injected 7-day-old mdx mice with Anc80 and AA V9 vectors, and used western blots to screen for μ-Utrophin expression in murine tissue samples beginning 2 weeks post injection. The purpose was to determine if Anc80 can be used in place of AA V9 in future clinical trials. Because AA V9 is an extant virus, a large subset of the population will have pre-existing neutralizing antibodies to vectors that share the native virus’s capsid structure, excluding such patients from participating in clinical trials. By contrast, Anc80 was reconstructed from aligned sequences of extant AV genomes, to minimize recognition by pre-existing neutralizing antibodies. Minimizing the risk of immunity associated with vector delivery is critical before transitioning to human studies, and thus, this project may provide a foundation for selecting an optimal vector for future clinical trials.

Research Grant: 5R01NS094705-02
Student Support: NIH T35 OD010919
University of Pennsylvania School of Veterinary Medicine

Identification of a predominant Campylobacter coli clone in feedlot cattle in the United States

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Campylobacter is a major foodborne pathogen and a leading cause of human gastroenteritis in the U.S. and other countries. Campylobacter is commonly present in food-producing animals, and ruminants are important reservoirs. To determine the epidemiology of C. coli in cattle, we collected 3,184 fecal samples from 35 feedlots in five different states and conducted isolation of Campylobacter from the samples. In total, 356 C. coli isolates were obtained. To determine the genetic relationship of the isolates, 120 C. coli isolates were randomly chosen for genotyping using pulsed-field gel electrophoresis (PFGE), multi-locus sequence typing (MLST) and whole genome sequencing. Based on the 88% similarity level, the isolates were grouped into 15 clusters by PFGE. Notably, the majority (75%) of the PFGE-typed C. coli isolates were grouped into three clusters of high genetic similarity, and MLST revealed they belong to a single sequence type (ST-1068). Of the 116 isolates tested, 91 (78.4%) were found to be resistant to tetracycline, 96 (82.7%) were resistant to ciprofloxacin, 95 (81.9%) were resistant to nalidixic acid, 17 (14.7%) were resistant to clindamycin and 19 (16.4%) were resistant to florfenicol. None of the isolates were resistant to azithromycin, erythromycin, gentamicin or telithromycin. These results revealed the dissemination of a predominant C. coli clone on different cattle farms in the U.S., and the C. coli isolates were highly resistant to fluoroquinolone and tetracycline.

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Student Support: NIH grant 5 T35 OD 012199-15
Validating detection methods for porcine teschovirus and porcine sapelovirus using qPCR and nested RT-PCR

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Porcine Teschovirus (PTV) and Porcine Sapelovirus (PSV) are two closely related viruses from the family Picornaviridae and are both known to cause neurologic disorders in swine. PTV and PSV are commonly transmitted through a fecal-oral route and traces of the viruses have been found in the feces of otherwise healthy swine. Strains of these viruses have been documented in Asia, Europe, South America, and recently in North America. Detection of PTV and PSV is often employed through real-time PCR (qPCR), reverse transcriptase PCR (RT-PCR), or nested RT-PCR. Nested RT-PCR is prone to cross-contamination, is less efficient, and less sensitive than qPCR, but is still used in some laboratories due to lower cost of equipment and reagents, compared to those for qPCR. The purpose of this study was to compare published nested RT-PCR assays for PTV and PSV with qPCR assays for those agents. By comparing results from the assays and using serial dilutions of viral or genomic copy standards of known concentration, we can evaluate effectiveness and sensitivity, and determine the limit of detection of the various assays. Eight ten-fold dilutions of each virus will undergo nested RT-PCR and qPCR to determine the sensitivity. Known positive and negative samples, as well as samples of unknown status will be tested for PTV and PSV by nested RT-PCR and qPCR and the results will be compared to show efficacy of each PCR method. A subset of samples yielding positive results will be sequenced to confirm the presence of the virus. This comparison data will be useful for making decisions on the most appropriate assay to use for testing for these two agents.

Research Grant: Swine Health Information Center
Student Support: Boehringer Ingelheim Vetmedica, Inc.

Bovine viral diarrhea virus in Maritime dairy cattle herds

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Bovine viral diarrhea virus (BVDV) is one of the most important pathogens to affect the cattle industry. Infection may be sub-clinical and show no clinical signs, however it can also lead to severe enteric problems including mucosal disease. Dairy cattle infected with BVDV present with lowered milk production, immune suppression, difficulty maintaining pregnancy, and most importantly, the development of persistently infected calves when infected in utero. Persistently infected animals are lifelong carriers and the largest source of virus shed into their environment. Controlling the persistently infected animals is crucial to eliminating the spread of the virus and subsequent infection throughout the herd. Based on previous bulk tank milk screening of all dairy farms in the Maritime provinces, 71 farms were included in this study, and of those, 41 showed a positive result. Individual sampling is currently being done on positive farms to determine (via RT-PCR and/or antigen capture ELISA) which animals were infected. On both positive and negative farms, sentinel animal sampling is conducted in order to assess the efficacy of swabs as a method of collection to detect the virus in feed bunks and water troughs. At each farm, 6 consumption surface swab samples are collected and tested using RT-PCR. Blood samples from 6 random, unvaccinated animals are taken and tested using antigen capture ELISA to serve as a basis by which the swabs were to be compared. Further sampling and testing is underway and expected to provide more conclusive results.

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Student Support: Atlantic Veterinary College Veterinary Student Research Award
Maritime Quality Milk
Testing the role of fibroblast growth factor signaling in ovarian cancer using zebrafish

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Ovarian cancer is the fifth leading cause of cancer deaths in women and the most lethal of the gynecological cancers. Currently, there are few ovarian cancer models that arise from the outer epithelial or stromal tissue. In vertebrates, the adult ovary and testis develop from a bipotential gonad that consists of primordial germ cells and somatic gonad precursors. Our lab has shown that Fgf24 is required for proliferation, morphogenesis, and differentiation of the early somatic gonad. In many cases, inappropriate activation of developmental pathways in adult tissues can promote a cancerous phenotype. For example, Fgf receptor overexpression correlates with poor ovarian cancer prognosis. Given the role of Fgf24 in gonad development in zebrafish and the potential role in cancer, our hypothesis is that overactivation of Fgf signaling in ovarian somatic cells will lead to a cancer phenotype. During normal zebrafish development, fgf24 is expressed in an epithelial layer that surrounds the early gonad. In response to Fgf24 signaling, the MAPK pathway is activated in mesenchymal cells in the interior of the gonad, leading to the expression of the transcription factor Etv4. Importantly, MAPK activation and Etv4 overexpression are correlated with various cancers, including ovarian cancer. We are generating transgenic zebrafish that inappropriately express Fgf24 in a subset of early somatic gonad cells using a Tol2 transposon-base system and the gonadal soma-derived factor promoter. Using histology and gene expression analysis, we will compare the development of wildtype and Fgf24-overexpressing gonads. We predict that Fgf24 overexpression will alter gonadal development and result in ovarian tumors.

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Student Support: NIH

Binding of p53 and SAF-1/MAZ to the EGFR promoter controls breast cancer cell growth

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Breast cancer is the most common cancer occurring in women and has the second highest death rate among cancers in people. Tumor microenvironment (TME) determines tumor growth, invasion and metastasis. A number of cellular processes regulate different elements of the TME and determine the status of the tumor ranging from dormancy to aggressive growth. Epidermal growth factor receptor (EGFR) family members which include HER1, HER2, HER3 and HER4 perform key roles in determining aggressive growth of breast cancer due to the abnormal expression of these genes. Overexpression of EGFR/HER1 in aggressive breast cancer implicates a cancer cell-specific transcriptional induction mechanism. We have detected that Ras-activated transcription factor, SAF-1/MAZ, promotes EGFR expression in breast cancer cells. A tumor suppressor protein, p53, and its derivatives which are abundantly present in normal breast epithelial cells suppress SAF-1/MAZ function by binding to the EGFR promoter. In contrary, high level of SAF-1/MAZ in breast cancer cells likely prevents p53 binding resulting in an increased expression of EGFR and therefore, growth of breast cancer. In this study the binding of p53 and SAF-1/MAZ to the EGFR promoter was examined using four different cell lines: normal breast epithelial cells (MCF-10A), and breast carcinoma cells (MCF-7, MDA-MB-231, and MDA-MB-468). To assess any potential interaction between p53 and SAF-1/MAZ, co-immunoprecipitation assay was performed. Results show a protein:protein binding between p53 and SAF-1/MAZ and suggest that this action is, at least partly, responsible for the sequestration of p53 and loss of suppressor function in breast cancer cells leading to high level of EGFR expression.

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Student Support: The student stipend is supported by an endowment established by IDEXX-BioResearch.
Interaction of Artemisinin-like compounds with Mtb sensor kinases

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*Mycobacterium tuberculosis* (Mtb) is an airborne pathogen that infects more than 1/3 of the human population. It is phagocytized by lung alveolar macrophages and triggers an immune response that leads to the formation of a granuloma. The granuloma depletes the oxygen available to Mtb and prevents replication, leading to a condition known as non-replicating persistence (NRP). NRP allows Mtb to main a chronic, latent infection. The DosRST two-component regulatory system is essential in the establishment of NRP in Mtb. DosS and DosT sensor kinases are activated in response to hypoxic conditions, carbon monoxide, or nitric oxide, and phosphorylate the DosR response regulator to induce the DosRST regulon. In an effort to inhibit NRP, we previously performed a high throughput screen of >540,000 small molecules to target DosRST pathway. Novel DosRST inhibitors, such as Artemisinin, have been identified and characterized. We showed that Artemisinin targets the heme of DosST by modulating heme redox status and alkylating heme. Here, we characterize Artemisinin analogs and synthetic endoperoxides, novel molecules carrying an endoperoxide bridge, for their ability to modulate the heme of the DosST proteins; they are hypothesized to have the same effect as the parent compound Artemisinin. To conduct this experiment, the DosST proteins are expressed and purified from *E.coli*. Then, using UV-vis spectroscopy, the redox states of DosST heme are studied in response to compounds. The compound GC003 can modulate the redox status of DosS as Artemisinin, however, the synthetic endoperoxide does not modulate heme redox. Further testing with mass spectrometry, will be necessary to determine if the synthetic endoperoxide alkylates the DosST heme.

Research Grant: OPP1119065
Student Support: NIH R25HL103156

Use of a population-guided approach to identify novel genetic modulators of TCDD-induced liver toxicity

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2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is a persistent and pervasive environmental toxicant that has been linked to wide array of disease states including cancer, immunosuppression, diabetes, and metabolic syndrome. TCDD-induced toxicity is mediated through the aryl hydrocarbon-receptor (AHR), a ligand-activated transcription factor. Previous studies have indicated that individuals respond differently to TCDD. This study aims to identify potential genetic variations that are associated with an individual’s susceptibility to TCDD-induced toxicity. We are using a genetically diverse mouse panel to model the human population. 15 strains of inbred mice were dosed with 0, 10 or 100 ng/kg of TCDD for 8 consecutive days. Liver samples were collected following the dosing regime. RNA was extracted using Trizol per the manufacturer’s instructions. RNA quality was assessed using an ND-1000 spectrophotometer. A Nanostring nCounter will be used to measure the expression levels of 9 AHR-target genes for each strain and dose. We expect to see varying levels of AHR-target gene expression amongst the 15 differing strains. Such differences will be used to scan for quantitative trait loci (QTL) which may indicate regions of the mouse strains genome associated with the differing AHR-mediated response. The results from this study have the potential to identify genetic variants within the population that explain an individual’s susceptibility to TCDD-induced toxicity. Thus, the results will likely have direct implications within risk-assessment. Furthermore, this model is at the heart of precision medicine and can be extrapolated to identify safe levels of other chemical exposures within the human population.

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Student Support: Michigan State University, BRUSH Program [NIH R25 HL 103156]
Delivery of Jagged1 Notch ligand to repair critical-sized craniofacial defects

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Current techniques for repairing significant craniofacial bone injuries include the use of autogenous, allogenic, or prosthetic grafts, and the delivery of a single-class of osteogenic molecules, bone morphogenetic proteins (BMP). However, drawbacks to these techniques include a narrow window of time for graft placement, donor-site rejection, infection potential, and ectopic bone formation with BMP. Thus, there is a need for improvement. Notch signaling is a developmentally conserved pathway and plays a role in bone development. The Notch ligand Jag1 has previously been investigated for its role in craniofacial development, and the Hankenson laboratory has shown that Jag1 is potently osteogenic. To study the effect of Jag1 in a craniofacial defect, a square critical defect of 7x7mm was created in the calvaria of male rats. A 1.1x1.1x0.5cm collagen sponge with either 50μg Jag1, 5μg BMP, or PBS was then placed into the defect. Rats were sacrificed on day 5 and day 60. Day 5 samples were processed for decalcified histology and quantitative PCR. Day 60 samples were scanned using microCT (Bruker-SkyScan, 65 kVp, 381 μA, 1 μm Aluminum). Scans were reconstructed, re-oriented, then analyzed for bone formation within the defect using Bruker software programs NRecon, DataViewer, and CT-An, respectively. In PBS negative controls 1.9% bone was formed, in BMP positive controls 35.9% was formed, and in Jag1 samples 17.6% bone was formed. These results implicate the possible use of Jag1 in promoting bone formation in significant craniofacial injuries. Future studies will include a dose-response curve for optimal Jag1 delivery, and a time curve to investigate the optimal time of delivery post-injury.

Research Grant: None
Student Support: None

Bacterial shifts in the feline microbiome during Toxoplasma gondii sexual differentiation

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Toxoplasma gondii, a common parasite known to cause toxoplasmosis in mammals, infects approximately 1/3 of the human population, may cause serious congenital infections, and is the leading cause of infectious uveitis globally. The parasite replicates asexually in all warm-blooded vertebrates, and undergoes sexual replication in the definitive feline host. In mice, T. gondii replication induces a profound outgrowth of γ-proteobacteria after oral infection. Recently, it was shown that products derived from the bacterium Vibrio fisheri induce the protist Salpingoeca rosetta to undergo sexual replication. Based on these observations, we hypothesize that specific bacterial species in the cat gut trigger T. gondii bradyzoites to commit to sexual cycle differentiation. We isolated DNA from fecal samples of two uninfected littermate control cats and three T. gondii-infected cats sequentially over 15 days, and analyzed microbial population density and diversity changes via 16S rRNA quantitative PCR using Eubacteria, Bacteroides, E. coli, Enterobacteriaceae, EREC, Lactobacillus, and Segmented filamentous primer sets. In infected cats, Bacteroides populations demonstrated an approximate 90% decrease during oocyst production 10 days post-infection, and later returned to pre-infection values. However, overall population abundance detected by the Eubacteria-specific primer remained relatively static over time; raw CT values ranged between 13.5 and 16.5, indicating that the sexual cycle leads to a bacterial outgrowth undetected by qPCR. Because these primers are insufficient to capture total diversity and bacterial outgrowth, metagenomic analysis will be conducted to identify specific populations altered over the infection period.

Research Grant: Intramural Research Program, National Institute of Allergy and Infectious Diseases, National Institutes of Health
Student Support: Comparative Biomedical Scientist Training Program, NCI, National Institutes of Health
Ovulatory and luteal response in 3-month old calves after kisspeptin-10 and GnRH treatment

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Kisspeptin binds to its receptor GPR54 located on the hypothalamic neurons to trigger the secretion of GnRH and the associated rise in LH and FSH resulting in ovulation in adult animals. Kisspeptin is also involved with the onset of puberty. The aim of this study was to understand the development of the hypothalamic-pituitary-gonadal axis in 3-month old heifers and whether kisspeptin or GnRH can induce ovulation at this age. We tested the hypothesis that kisspeptin-10 (kp10) and GnRH would result in LH release in 3-month old calves and alter the growth rate of the dominant follicle and/or induce ovulations. Fifteen Hereford-cross calves weighed 138±17 kg and 81±2.5 days of age were used. Transrectal ultrasonography of ovaries was performed daily to record the number, size, and location of follicles >3mm. The day of follicular wave emergence (Day 0) was defined as the day on which the dominant follicle was first detected between 4 to 5mm in diameter with a concurrent increase in the number of 4mm follicles. Calves were treated on Day 4 with a single IV treatment of 90 μg Fertagyl, a GnRH analog (n=7), or 3 IV injections of 15mg human Kp10 at 0, 60 and 120 min (0 min= first treatment; n=7). Plasma samples were obtained at 0, 15, 30, 60, 75, 90, 120, 135, 150, and 180 minutes from 5 calves in each group. Preliminary results show that both GnRH and kp10 did not result in ovulations. Currently, blood samples are being assayed to determine the levels of plasma LH in order to determine whether the hypothalamic-pituitary-gonadal axis was able to respond to the injected hormones or if the dominant follicle was not expressing LH receptors.

Research Grant: Research supported by the Natural Sciences and Engineering Council of Canada and the Merial Veterinary Research Scholars Program

Student Support: None

Levels of SDC4 and an endogenous retroviral element in variably prion permissive sheep microglia

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Prion disease results from the misfolding of normal, cellular prion protein (PrP\(^{C}\)) into pathologic, protease-resistant prion protein (PrP\(^{RES}\)). The first of these misfolded proteins to be identified was the scrapie prion protein (PrP\(^{Sc}\)). While some factors of permissibility and resistance have been identified, such as the amino acid sequence of the prion protein gene (PRNP), a growing body of evidence implicates other factors. For example, a transcriptomic analysis between a pair of prion permissive and non-permissive ovine microglial cells revealed that permissive cells have increased transcript levels of putative endogenous retroviral (ERV) elements and decreased transcript levels of extracellular matrical genes involved in fibronectin binding. For this study, the ERV Loc105604082 was selected along with syndecan-4 (SDC4), a binding partner of fibronectin that has not been fully analyzed in this system, for comparison beyond the original permissive/non-permissive pairing. The transcript levels for these two genes were assessed using reverse-transcriptase quantitative PCR (RT-qPCR) with 5 ovine microglial clones of varying prion permissibility. The results validate the usefulness and efficiency of these primers in amplifying the target sequences.

Research Grant: Department of Veterinary Pathology and the College of Veterinary Medicine, University of Georgia, Athens, GA

Student Support: NIH Office of Research Infrastructure Programs, Grant Number 2T35OD010433-11
Identification and preliminary evaluation of *Anaplasma phagocytophilum* mutant vaccine candidates

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*Anaplasma phagocytophilum* (*Ap*) is an emerging tick-borne zoonosis that infects a variety of domestic and wild animals. In humans, it is the causative agent of human granulocytic anaplasmosis (HGA), the second most commonly diagnosed tick-borne disease in humans in the United States. In humans and most domestic animals, it causes high fever, leukopenia, and thrombocytopenia. *Ap* is maintained in the environment by cycling through mammals and *Ixodes* ticks. Tetracycline antibiotics are the primary treatment for HGA and there is no vaccine available. Nearly half of the predicted open reading frames encode hypothetical proteins with no significant homology with known proteins. A Himar1 transposon mutant library consisting of 857 isolates has been generated and can be used to investigate gene function and mechanisms of *Ap* pathogenesis. HGE1_03162 (APH_0720) is a large hypothetical protein containing a predicted SMC (structural maintenance of chromosomes) domain and is highly expressed in infected tick cells. Three mutations were chosen at different sites within the protein to evaluate its importance to infection of both tick cells and human cells. Through PCR and cell culture these mutants were isolated and purified. Mutants were inoculated onto tick and human cells and samples were collected every other day or daily, respectively, to determine growth curves. Control growth curves were generated using wild type *Ap* and an intergenic *Ap* mutant. The first mutant successfully infects tick and human cells. The study is on-going and preliminary results will be reported at the National Veterinary Scholars Symposium.

**Research Grant**: NIH/NIAID R01AI042792 (Munderloh PI)

**Student Support**: The National Institutes of Health, Award Number T35OD011118

Injury and *S. aureus*-induced inflammation and invasion of osteoclasts and neutrophils during bone healing

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Osteomyelitis is a serious bone infection typically caused by *Staphylococcus aureus*, the pathogenesis of which is poorly understood. We determined the time course of inflammation, osteoclast (OCL) development, and neutrophil invasion during the onset of bone healing at 3, 7, and 14 days following infection of a unicortical femoral midshaft defect in 8wk old female mice treated with vehicle (Con) or a clinical *S. aureus* isolate, UAMS1. MicroCT of injured bones showed normal bone healing and low bone destruction within 14d in Con mice, with progressive increases in serum P1NP (marker of bone formation) and no change in CTX (bone resorption marker). However, in UAMS1 mice, excess aberrant bone formation and bone destruction did not track with serum bone turnover markers. Clinical histopathology inflammation was significantly elevated in UAMS1 bones at 7d and 14d. The number of OCL and neutrophils in the injury site were determined by histochemical staining for Tartrate resistant acid phosphatase (TRAP) activity and immunopositive Myeloperoxidase (MPO+) cells, respectively. MPO+ cells were first detected in bones of both groups at d3 and markedly increased by d14. Similar neutrophil invasion in both groups is consistent with an inflammatory response, and suggests that these cells are not mediating the aberrant bone formation response in infected animals. TRAP+ OCL recruitment to the injury site progressively increased in both groups, with significantly more OCL in Con than UAMS1 on d14. Localization of OCL suggests that OCL are recruited early and progressively during normal bone healing to facilitate remodeling, whereas OCL recruitment during infection mediates bone destruction during aberrant bone healing.

**Research Grant**: None

**Student Support**: National Institutes of Health #5T35OD010991
Effects of maternal *S. mansoni* infection on immune response of offspring to tetanus/diphtheria immunization

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Schistosomiasis is a helminth infection that affects 200 million people worldwide, with 20 million life-threatening cases existing predominantly in Africa. Chronic infection results in eosinophilic activation, portal hypertension, and fibrosis, which can result in organ failure. As such, schistosomiasis presents a critical public health concern in the developing world where there is little to no control of disease transmission and limited access to healthcare. Importantly, previous studies have reported that maternal *S. mansoni* infection leads to fetal acquisition of *S. mansoni* antigens in utero, which may be linked to reductions in childhood vaccine efficacy often seen in helminth endemic regions. The immune effects of in utero exposure to *S. mansoni* antigens, however, are not yet understood. Here, we investigate the immunomodulatory pathways through which maternal *S. mansoni* infection impacted neonatal immunization in mice using the vaccine tetanus/diphtheria. We found that at day 14 post immunization, pups born to infected mothers had significantly decreased germinal centers in popliteal lymph nodes as compared to pups from uninfected mothers. Future studies should examine the memory and recall response and identify aberrant stimulatory/survival signals that might underlie the immunomodulation.

**Research Grant**: American Heart Association, Showalter Trust  
**Student Support**: Purdue University College of Veterinary Medicine

Consumption of cheerios as a pain assessment tool in rats

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Laboratory Animal Resources - Colorado State University

Analgesia is an important component of animal use protocols in lab animal medicine, to mitigate experimental pain and to minimize the effects of pain on research. There are few reliable, objective pain assessment tools (grimace scoring, locomotor activity) to assess pain in rats. A possible new tool for assessing pain in rats is cheerio consumption. Rats are highly motivated to consume cheerios and the time it takes for a rat to consume cheerios may serve as a proxy indicator of pain, with rats in pain taking longer to consume cheerios. Female SD rats were ovariectomized (n=27) or received anesthesia only (n=9) and split into one of three groups: treated with meloxicam, SR-meloxicam, or saline solution. Four cheerios were then dropped into the cage and time to consumption was recorded at 3 and 24 hrs post-op. Additional behaviors (activity, grooming, wound licking, orbital tightening) were recorded at 1, 3, 6, 12, 24, and 48 hrs post-op. Results showed no significant differences in cheerio consumption between groups within each of the time points. Behaviors such as orbital tightening and arched posture showed significant differences between analgesic treated groups and saline group, but other behaviors such as activity, grooming, and inactive behaviors had no significant differences. The variability in cheerio consumption behavior within individuals at different time points suggests that although cheerio consumption may be a motivating behavior, it lacks consistency in making a valid and useful rat pain assessment method on its own. However, in conjunction with other pain assessment indicators, cheerio consumption may still be a useful tool to assess pain in rats.

**Research Grant**: Office of the Vice President of Research, Colorado State University  
**Student Support**: Laboratory Animal Resources and the Office of the Vice President of Research, CSU
Mucosal bacteria in the duodenum of dogs with chronic enteropathy

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Canine chronic enteropathy (CE) or inflammatory bowel disease (IBD) is characterized by gastrointestinal signs for greater than three weeks without an underlying cause. It can be classified according to responsiveness to treatment such as diet modification, antibiotics and/or corticosteroids. Intestinal microbiota might be involved in the pathogenesis of canine CE. The objective of this study is to investigate the spatial distribution of bacteria in the duodenal mucosa of dogs without gastrointestinal signs (control) and dogs with CE. Formalin fixed paraffin embedded duodenal biopsies from 7 control and 12 dogs with CE were hybridized with universal bacterial probe (EUB338) for fluorescence in situ hybridization (FISH). For each case, ten 60x fields with labeled bacteria on the mucosal surface and within the crypts were photographed using Olympus cellSens Standard software. The images were analyzed using ImageJ software. Dogs with CE had increased numbers of bacteria on the mucosal surface (p=0.016) than control dogs. The number of bacteria within the crypts did not differ between CE and control dogs (p=0.220). Characterization of bacterial populations involved in intestinal dysbiosis (e.g. Escherichia) will potentially add information to the clinical disease activity and histological mucosal changes in CE dogs.

Research Grant: Comparative Gastroenterology Society and Veterinary Student Summer Research Scholar Program
Student Support: Comparative Gastroenterology Society and Veterinary Student Summer Research Scholar Program

Targeting specific dopaminergic pathways with cre-dependent DREADDs

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Schizophrenia remains to be a poorly understood and complicated disease that alters the CNS by affecting the mesocortical, mesolimbic and nigrostriatal dopaminergic pathways. This lack of an understanding of the disease leads to a challenge in treating the extrapyramidal symptoms caused by the conventional antipsychotic drugs. There is a need to develop an antipsychotic treatment that can target the excess dopamine neurotransmission in the mesoaccumbens pathway, enhance the mesocortical pathway and neglect to affect the nigrostriatal pathway. In order to develop this type of beneficial treatment, we need to understand how gene expression is impacted in dopamine neurons from the use of antipsychotics. Therefore, our goal was to investigate the feasibility of using a combination of a Cre-dependent adeno-associated viral vectors expressing DREADDS (Designer Receptors Exclusively Activated by Designer Drugs) in combination with the retrogradely transported herpes simplex viral vector expressing Cre into either the prefrontal cortex, nucleus accumbens, or substantia nigra to target these distinct pathways to inhibit or stimulate them. Our data indicates that AAV can infected dopamine neurons and that HSV is retrogradely transported in neurons. Additionally, we found that DREADDs can be expressed in specific dopamine neurons, based on efferent innervation, can be achieved by using AAV and HSV. One caveat to this approach is that only a small subset of dopamine neurons were labeled by this method. Future studies will investigate molecular changes that result from altering activation of these dopamine neuron populations in ways that mimic what occurs in patients with schizophrenia.

Research Grant: National Institutes of Health 2T35OD010432-16 and Mississippi State University College of Veterinary Medicine
Student Support: National Institutes of Health 2T35OD010432-16
Meta-analysis of gene expression and disease process in human and murine samples after traumatic brain injury

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Acquired brain injuries, such as those resulting from trauma, are among the most common causes of death and long-term disability in all age groups. Traumatic brain injury (TBI) initiates a complex cascade of pathophysiological responses set into motion by alterations in gene expression. Peripheral-derived immune cells play a key role in this process. The aim of this study is to evaluate human peripheral blood gene expression profiles after TBI of varying severity and type and compare this data to gene expression profiles obtained from mouse peripheral blood after the controlled cortical impact (CCI) model of TBI. Previously published studies of genome-wide gene expression were obtained using the FITBIR database and PubMed. Lists of genes were compared using the Galaxy bioinformatics system for identification of similar genes across studies. GeneCodis gene ontology analysis was also utilized to identify similar processes of pathology across studies. Comparison of differential gene expression across human studies yielded two genes appearing in more than one study: IL18R1 (Interleukin 18 receptor 1) and EZR (ezrin). Several processes overlapped between studies including neurogenesis, immune response, inflammatory response, negative regulation of cell proliferation and chemotaxis. These data indicate several pathways of interest conserved across TBI as well as genes of interest that with further study may be useful biomarkers of TBI or targets for gene therapy to speed the recovery process.

Research Grant: Virginia-Maryland College of Veterinary Medicine
Student Support: NIH T35 Training Grant T35OD011887

A practical approach to social pairing in adult female cynomolgus macaques

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As in humans, complex social relationships exist between nonhuman primates (NHPs) and form the basis for regulations addressing their needs in captivity. At the same time, understanding of the influence of sociality on health and immunity has expanded, resulting in increased awareness of its direct impact on research outcomes and translation. Strategies to effectively social house are available, however there is no agreed upon objective method for the formation of social pairs. Instead, pairs are often selected based on individual temperament and handler intuition. While this can be successful, some handlers lack sufficient experience to accurately judge temperament. A strategic approach to identify compatible cage-mates may benefit mature NHPs by limiting risk of undue stress and injury. We conducted a pilot study using an 8 year-old female macaque with previous displays of aggressive mounting and biting, with an aim to develop a practical, systematic strategy for complicated pairing. Potential same-sex cage-mates were selected based on apparent confidence, measured by social status in their current pair and behavior in the presence of a human. Potential mates were placed in adjacent cages, separated by a clear panel, where affiliative and aggressive behaviors were scored. Compatibility was further assessed by observing reaction to a high value resource (novel food) offered to each pair member. Potential mates, except those with fearful behavior, were allowed to interact under observation and then independently. Correlation between scores and compatible pairs will be evaluated with the intent to design an effective pairing schema for use in smaller colonies with limited pair options to improve NHP well-being.

Student Support: The National Institutes of Health, Award Number T35OD011118
Characterization of the IFNAR+/- mouse placental histostructure at days 14.5 and 18.5 of pregnancy

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The maternal-fetal unit is a dynamic and critical element of pregnancy. Mice and humans share a similar hemochorial placental structure. Thus, mouse models are routinely used to investigate questions about the human placenta, including the impact maternal infections have on the developing embryo. Zika virus crosses the placental structure causing grave outcomes to babies born to mothers infected with this flavivirus. This study was undertaken to characterize the placental structure of IFNAR+/- mice to investigate mechanisms associated with zika viral transfer from mother to baby. Here we employed naive pregnant IFNAR+/- mice and immunohistochemistry to characterize the placental histostructure of mid and late pregnancy. Fixed and paraffin-embedded placental tissues from IFNAR+/- mice at gestational days (gd) 14.5 and 18.5 were probed for the presence of uterine natural killer cells, epithelial and fetal-derived trophoblast cells, endothelial cells and leukocytes using monoclonal antibodies DBA lectin (Sigma L6533), cytokeratin (DAKO Z0622), vimentin (Abcam ab92547), and CD45 (Abcam ab25386), respectively. We have identified epithelial, endothelial, uterine natural killer and fetal-derived trophoblast cells in gd 18.5 placetas, and are currently assessing placental tissues from gd 14.5. Preliminary data generated by this study will be a crucial foundational step to assess the impact that the normal pregnancy cellular immune response and reproductive microbiome present at the maternal-fetal interface have on the transfer of zika virus across the placental structure.

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Student Support: USDA Fellowship

Protocol for creating in vitro thrombi for bench testing of cardiovascular medical devices

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One significant cause of cardiovascular device failure is thrombosis and thromboembolism. A major incentive for development of new ventricular assist devices (VADs) is to reduce the risk of thromboembolism. The goal of this project was to create in vitro thrombi that mimic the gross and histological characteristics of natural thrombi, for use in bench-testing embolic sensitivity of VADs. This experiment utilized the previously established Chandler Loop method [1] to mimic blood flow across a thrombogenic surface in vitro. Bovine blood was collected in a sodium citrate solution for storage. Aliquots of stored blood were then treated with calcium chloride to reverse the anticoagulant effect of the citrate. The blood was placed in a rotating loop of plastic tubing containing glass inserts to promote clotting. This thrombogenic loop was used to test variables including: type and size of tubing/connector components, the tilt angle of the rotating apparatus, rotational speed, and blood aliquot volume. All in vitro clots created were examined histologically and compared to a natural bovine thrombus. The most significant positive effects on in vitro thrombus creation were related to incorporation of glass tubing with 3D-printed glass-to-tubing connectors. These modifications of the Chandler Loop resulted in artificial thrombi exhibiting a fibrillar matrix with enmeshed erythrocytes as seen in a naturally occurring bovine thrombus. Our findings suggest that a modified Chandler Loop will produce in vitro clots that are grossly and histologically similar to naturally occurring thrombi. [1] Chandler AB: In vitro thrombotic coagulation of the blood. Lab Invest 7:110-4, 1958.

Research Grant: None.
Student Support: National Institutes of Health #5T35OD010991
**Susceptibility and transmission of Tacaribe Virus in Lone Star Ticks and Deer Mice**

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Arenaviruses are a group of segmented RNA viruses that infect mammals and snakes, with mammalian strains causing potentially fatal hemorrhagic disease in humans. Rodents serve as the reservoir for most known arenaviruses and transmit the virus through both feces and urine. Tacaribe virus is an unusual arenavirus that was isolated from bats and mosquitoes in Trinidad in the 1950s. Since then, the virus had not been isolated from any wild hosts until 2014, when Sayler et al. isolated Tacaribe virus from a pool of wild-caught Lone Star Ticks (*Amblyomma americanum*) in Florida. The isolation of Tacaribe virus from ticks is particularly intriguing because it is not believed to be vector-borne. The virulence of Tacaribe in humans is largely unknown, with only a few anecdotal cases of flu-like infection. This study seeks to discern the susceptibility of *A. americanum* ticks and Deer Mice (*Peromyscus maniculatus*) to Tacaribe virus by experimentally infecting each and performing qRT-PCR assays to determine infection. Upon successful infection of both ticks and mice, cyclic transmission will be tested. Uninfected ticks will be fed on infected mice and vice versa. RT-PCR will then be used to establish if ticks can contract and/or transmit the virus during a blood meal. Elucidating the details of viral transmission and maintenance is essential to provide a more robust understanding as to what degree Tacaribe virus may impact humans and wildlife. Improved knowledge of basic disease dynamics is imperative for scientist and health officials to successfully understand the environmental and health impacts of this under-studied virus.

**Research Grant:** Stenglein Laboratory Start-up Funds  
**Student Support:** NIH T35OD015130

**Upregulation of BMF and ETS1 promote apoptosis and alter cell adhesion in breast cancer-resistant equine MaSC**

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In the United States, 1 in 8 women are afflicted by breast cancer (BC). BC incidence rates are not universal among mammals. Horses and pigs rarely acquire BC, whereas dogs and cats are diagnosed at a frequency comparable to humans. Tumorogenesis is a result of both inherent susceptibility and carcinogenic exposure; variation in either affects BC frequency at both inter- and intra-species levels. Studies of both resistant and susceptible mammals are crucial for identifying which facets of the mammary gland confer BC resistance. Mammary stem and progenitor cells (MaSC) are associated with malignant transformation (MT). A comparative study of canine (susceptible) and equine (resistant) MaSC exposed to the carcinogen 7,12-Dimethylbenz[a]anthracene (DMBA) resulted in horse cell death within 24 hrs of treatment, while dog cell growth was unaffected. RNA sequencing found 221 differentially expressed genes (DEG) between equine treated and untreated cells, and no DEG in the dog. We hypothesize that horses have reduced susceptibility to BC via apoptosis in response to DNA damage, whereas dog cells undergo DNA repair. Genes upregulated in horse MaSC were categorized by PANTHER GO pathway analysis. Altered pathways included apoptosis and regulation of cell adhesion. BMF was targeted as a pro-apoptotic gene, and its effects included an observed increase in caspase-3 in treated horse cells. The role of ETS1 in cell adhesion was examined by staining for E-cadherin. Comet assays performed on dog MaSC revealed DNA repair within 48 hrs after DMBA treatment. As the repair process is fallible, the risk for MT is higher in dog MaSC. Future studies may target other genes upregulated in equine MaSC with potential implications in BC resistance.

**Research Grant:** National Science Foundation.  
**Student Support:** Boehringer Ingelheim Veterinary Scholars Program.
The effect of sub-inhibitory levels of ciprofloxacin on *Danio rerio* intestinal microbiota

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Agricultural runoff and effluent from sewage and hospitals can introduce antibiotics into freshwater systems. Although most levels of antibiotics found in bodies of water are below the minimum inhibitory concentration (MIC) for bacteria, they can still influence mutagenesis, horizontal gene transfer and other metabolic processes. We hypothesize that chronic exposure to sub-inhibitory levels of antibiotics promotes the emergence of resistant bacteria in the intestinal microbiota of exposed fish. In preliminary experiments, the MIC of the antibiotic ciprofloxacin for two bacterial isolates from the fish intestine was determined to be 0.500 µg/ml and the maximum concentration at which no effect was seen on growth was determined to be 0.023 µg/ml. To test our hypothesis, zebrafish (*Danio rerio*) were maintained in water containing ciprofloxacin for 8 weeks at the following concentrations: 0 µg/ml (control), 0.050 µg/ml, and 0.005 µg/ml. At specific time points, we harvested and homogenized the intestine and determined colony forming units (CFU) on plates with and without ciprofloxacin (5 µg/ml). Ratios of resistant CFU over total number of CFU were calculated to assess the emergence of resistant clones. The results indicate that resistant clones emerge within one and two weeks of exposure to 0.050 µg/ml and 0.005 µg/ml of ciprofloxacin, respectively. Next, we will assess the effect of these concentrations of ciprofloxacin on total intestinal bacterial load by real-time PCR. This study indicates that fish bathing in antibiotic contaminated water may promote the emergence of resistant bacteria.

Research Grant: Aquatic Animal Medicine Program Funds
Student Support: Cornell University, College of Veterinary Medicine, Office of Graduate Education

Pathogenesis of influenza D virus and *Mannheimia haemolytica* in cattle

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Bovine respiratory disease (BRD) is one of the most economically significant diseases of cattle and is caused by stress and a primary infection allowing for a severe secondary bacterial infection. Influenza D virus (IDV) is a common microbe identified in cattle diagnosed with BRD and has been significantly associated with some known BRD pathogens. However, IDV’s potential role in BRD has not yet been studied. The objective of this study is to evaluate the synergetic pathogenesis in cattle by co-infection of IDV and *Mannheimia haemolytica*, a common bacterium identified in BRD. Sixteen dairy calves were randomly assigned to 4 groups. Groups A and C received IDV (D/Bovine/C00046N/Mississippi/2014) intranasally at 0 days post inoculation (DPI). Groups A and B received *Mannheimia haemolytica* D153 intratracheally at 5 DPI. Group D received neither pathogen. Clinical signs were evaluated and used to calculate clinical scores for each calf. At 10 DPI, calves from groups A and C seroconverted by 10 DPI, and viral titration suggested these calves shed virus up to 7 DPI. IDV was detected in sera of 3 calves in these groups. Clinical scores rose in both groups after IDV inoculation and returned to normal after 4 and 6 DPI, respectively. After 5 DPI, group B clinical scores rose and remained high for the remainder of the study. There was no significant difference in gross pathology between groups. This data shows no increase in severity of clinical disease caused by *Mannheimia* with prior IDV infection, which suggests that IDV alone does not adequately compromise the host to lead to development of BRD.

Research Grant: None
Student Support: NIH 2T35OD010432-16, Mississippi State University College of Veterinary Medicine
Detection of *Cytauxzoon felis* in the gut and salivary glands of *Amblyomma americanum*

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*Cytauxzoon felis* is a pathogenic protozoan parasite of domestic cats transmitted by *Amblyomma americanum* (lone star tick) and *Dermacentor variabilis* (American dog tick). Historically, the mortality of cats acutely infected with *C. felis* was high (>90%). Implementation of current treatment regimens has increased survival of cytauxzoonosis to approximately 60% but cats remain subclinically infected and reservoirs of *C. felis* for life. Several surveys have been conducted across the US to determine the occurrence and prevalence of *C. felis* in cats and tick vectors. The aim of our study was to determine tissue predilection of *C. felis* within *A. americanum*. We collected ticks from multiple sources and dissected them separating gut and salivary gland tissues. DNA was extracted from each of the tissues and subjected to PCR amplification using primers specific to *C. felis*. The prevalence of *C. felis* in gut tissue of flat (non-fed) ticks was 3.6% (4 of 110) and salivary glands 0.0% (0 of 110). In engorged (partially fed, removed from host) the prevalence in gut tissue was 50% (5 of 10) and in salivary glands 30% (3 of 10). In the flat ticks, the prevalence of *C. felis* in males was 5.4% (3 of 56) and in females was 1.9% (1 of 54). In the engorged ticks, 33% (2 of 6) females and 75% (3 of 4) males were positive. We are currently determining the number of *A. americanum* nymphs infected with *C. felis* after acquisition feeding on cytauxzoonosis survivor cats that is chronically infected.

**Research Grant:** Center for Veterinary Health Sciences, Oklahoma State University  
**Student Support:** Boehringer Ingelheim and NIH R13 Grant Sponsored Students

Impact of Adeno-Associated Virus (AAV) on neuroinflammation in the retina

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Inflammation in the nervous system (neuroinflammation) is important for providing protection against invading pathogens and both intrinsic and extrinsic harmful substances. The increasing use of viral gene therapy for retinal degenerative diseases raises questions about the impact of viral therapies on the state of neuroinflammation in the retina. This study aims to investigate the impact of a commonly used viral vector, Adeno-Associated Virus (AAV), on neuroinflammation in the mouse retina. Following intravitreal delivery of AAV or vehicle controls, Micron IV fundus imaging and immunohistochemistry will be used to assess the consequences of viral-mediated gene expression on the resident macrophage (termed microglia) numbers and morphologies. We predict that high titer viral vectors trigger microglial activation and proliferation.

**Research Grant:** National Institute of Health (NIH) T-35  
**Student Support:** Students Training in Advanced Research (STAR) Fellowship
An agent-based model examining antimicrobial use and resistance prevalence in a Western Canadian feedlot

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Antimicrobial resistance (AMR) threatens the effective prevention and treatment of an ever-increasing range of infections in human and animals. Antimicrobial use (AMU) in livestock production is often scrutinized because of its perception by the public as a major driver of AMR. The current approaches to quantifying associations between AMU and AMR in livestock production include observational studies and clinical trials. Field research on AMR is limited due to challenges including the costs of identifying and tracking the AMR and treatment status of large numbers of animals over time. A better understanding of AMR epidemiology is critical to limit the spread of existing resistance genes and reduce emergence of new resistance types. Agent-based models (ABMs) provide an option to explore hypothetical system-wide consequences of policy and management changes without extensive field intervention studies. The present study’s objective is to develop a model that simulates Western Canadian feedlot management and examines the impact of restricting AMU (for metaphylactic purposes) on AMR. The model was developed through consultation with industry experts and includes parameters such as disease incidence, rate of AMR selection, rate of waning AMR, and probability of resistance spread. Parameters that are not currently monitored directly were calibrated using data collected from research reports. The model predicts the occurrence and transmission of AMR within a feedlot under typical management conditions. It is anticipated that results obtained from this model will improve our understanding of AMR in livestock production and provide insight on the impact of future policy changes regarding AMU.

Research Grant: Alberta Livestock and Meat Agency (ALMA).
Student Support: Merial Veterinary Research Scholars Program.

Functional characterization of EHV-1 specific mucosal antibodies after infection

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Equine herpes virus-1 (EHV-1) causes upper respiratory tract infection, neurologic disease, and abortion in horses. The primary site of EHV-1 infection is the nasal mucosa and respiratory epithelium. Previous studies have suggested that EHV-1 infection induces specific antibodies in the respiratory mucosa that are protective against future reinfection. However, the immunoglobulin (Ig) isotype composition and immune functions of mucosal EHV-1 specific antibodies have yet to be investigated. The objective of this study was to determine which isotypes are found in the nasal secretions of experimentally EHV-1 infected Icelandic horses. IgG and IgA were purified from nasal washes of previously infected horses and were then analyzed using bead-based multiplex assay. Different IgG isotypes, IgG1, IgG4/7, and IgG3/5, in the NW samples were EHV-1 specific. Although there was high amount of IgA present in the nasal secretion, the levels of EHV-1 specific IgA were low. The purified nasal IgGs and IgA were then tested as detection tools for EHV-1 using intracellular staining of Chinese Hamster Ovary transfected with EHV-1 glycoprotein C (gC) and flow cytometric analysis. Nasal IgGs specifically detected cells expressing recombinant gC envelope, whereas purified IgA did not. Rabbit Kidney 13 cells were infected with EHV-1, stained, and analyzed using flow cytometry. Nasal IgG detected infected cells, further confirming IgG as the main isotype responsible for EHV-1 specific mucosal immune response. Therefore, this study presents new insight into the first line of defense against EHV-1 infection. Future studies will investigate if the purified nasal IgG will neutralize EHV-1.

Research Grant: Cornell College of Veterinary Medicine, Office of Graduate Education
Student Support: Cornell College of Veterinary Medicine, Office of Graduate Education
Changes in Digit Abduction Scoring of mice over time: implications for assessment of neuromuscular activity

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Injection of botulinum neurotoxin creates temporary paralysis by inhibiting acetylcholine release at the neuromuscular junction. Currently botulinum toxin is used for various treatments including, pain relief, paralysis of joints, spasticity in patients with cerebral palsy, treatment of strabismus, hemifacial spasm, and cervical dystonia. However, due to its short acting capability, frequent injections must be utilized to maintain its effect. The efficacy of the toxin after injection is measured in a mouse model using the Digit Scoring Assay (DAS), an assay based on the degree of digit abduction due to the startle response. Based on an on-going study of a slow release vehicle for the delivery of a long-term therapeutic neuromuscular blockade, there was a growing concern about changes in scoring over time. In this mouse study, we hypothesized that changes in the DAS scoring occur over time. We evaluated 16 mice once a day for 4 weeks using a previously published grading scale. Observations were made directly by 2 observers and indirectly using the Slo-mo feature of an iPhone 7. Several factors that may affect DAS scoring were identified. An important factor causing variation in the degree of digit abduction may be due to differences in support while handling mice. The more support the mouse had while being held by the base of the tail, the smaller degree of digit abduction compared to a mouse with less support held by the tip of the tail. There was no evidence for change in toe response and recommendations to further standardize the DAS were made.

Research Grant: Akina Inc
Student Support: Boehringer Ingelheim Veterinary Scholars Program and Purdue College of Veterinary Medicine.

Tracking PEG-Fibrinogen microsphere encapsulated ECFCs after injection into equine distal limb wounds

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Endothelial colony forming cells (ECFCs) are a subdivision of endothelial progenitor cells (EPCs) aiding in angiogenesis. They are thought to be important for repair of ischemic wounds such as equine distal limb wounds that are predisposed to excessive granulation tissue. When injected into this type of wound, the ECFCs were hypothesized to localize and incorporate into blood vessels with enhanced localization and retention when protected by polyethylene glycol-fibrinogen (PEG-f) microspheres. Two full thickness dermal wounds were created on distal limbs of 3 horses, each measuring 6.25 cm2 (8 per horse). Wounds then received one of 4 randomized treatments by subcutaneous injection: serum, PEG-f microspheres (MS), naked ECFCs (EPC), or ECFCs encapsulated in PEG-f microspheres (EPC/MS). Wounds were biopsied at baseline and weekly for 4 weeks. Immunofluorescent staining for von Willebrand Factor (vWF) and quantum nanodot (Qtracker 655) labelled ECFCs were performed on EPC and EPC/MS biopsies. Tissues were then analyzed for fluorescent signal using confocal microscopy. Labeled cells were found in 2/3 EPC treated wounds and 3/3 EPC/MS treated wounds at week 1, 1/3 EPC and 1/3 EPC/MS treated wounds at week 2, and 1/3 EPC and 1/3 EPC/MS treated wounds at week 3. No labeled cells have been found at week 4. Week 3 and week 4 analysis is ongoing. Visible signals indicate the ECMCs remained viable after injection. Labelled ECFCs were found in clusters in earlier weeks. Later in the study they were found near newly formed capillaries, but had not been incorporated into the vessel walls. Preliminary data show ECFCs remain viable through the injection process, and remain present in the tissue during angiogenesis for up to 21 days.

Research Grant: Grayson Jockey Club Research Foundation
Student Support: Boehringer Ingelheim Summer Scholars
Snake mites (*Ophionyssus natricis*) as a potential vector for reptarenavirus infection in snake populations

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Inclusion Body Disease (IBD) is a fatal infectious disease of snakes characterized primarily by neurological signs. A recently identified lineage of reptile-infecting arenaviruses (reptarenaviruses) has been established as the etiologic agent of IBD. Highly variable presentation of disease among different snake species, often resulting in subclinical infection, has made the mode of transmission difficult to elucidate. Anecdotal evidence suggests snake mites (*Ophionyssus natricis*) may play a role in transmission. The goal of this study is to determine the role of *O. natricis* in reptarenavirus transmission among captive snake populations. Ten snakes of several species were sampled for blood and mites (if present). The mite samples were grouped into three subsets. The first subset of mites, along with the corresponding snake blood samples, were initially tested for reptarenavirus via RT-qPCR. The next subset of mites were kept alive and tested several weeks after collection to check for persistence of viral RNA in the absence of a blood meal. The last subset of mites were formalin-fixed, paraffin-embedded and sectioned for analysis by immunofluorescent staining (IFA) of the viral nucleoprotein. Results, to date, have confirmed reptarenavirus infection in 2 snakes and detected viral RNA in all mites collected from these infected snakes. These results are consistent with, but not diagnostic of, vector-borne transmission of reptarenavirus. Incoming results from IFA and RT-qPCR of unfed mites will further clarify the role of *O. natricis* as a potential vector. However additional studies, including mock infection trials, will be necessary to definitively establish the capability of *O. natricis* to transmit reptarenavirus.

Research Grant: Department of Microbiology, Immunology, and Pathology

Student Support: Boehringer Ingelheim Fellowship

Static posturography as a novel diagnostic tool in dogs with suspected thoracolumbar spinal cord disease

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Dogs with spinal cord disease (SCD) are evaluated through the application of subjective scoring systems during serial neurologic examinations. Post-treatment outcome is measured subjectively through the direct observation of an animal’s gait, and may overestimate or underestimates a patient’s recovery. Static posturography provides an objective, quantitative alternative to subjective gait analysis through measurement of characteristics of an animal’s balance in quiet stance. The purpose of this study was to evaluate the utility of static posturography as an objective diagnostic adjunct and prognostic indicator in dogs with suspected thoracolumbar SCD. Control dogs demonstrated a normal neurologic examination and had no known history of neurologic or musculoskeletal disease. Affected dogs presented with clinical signs of thoracolumbar SCD, including pain, weakness and incoordination. All dogs were placed in quiet stance on a Tekscan Walkway™ force and pressure measurement system. Measurements related to each dog’s balance were taken during five trials, including aggregate distance traveled by the dog’s center of force (COF), maximal cranial/caudal and medial/lateral movement of COF, and weight distribution by limb. The authors hypothesize that these values will be significantly larger in dogs with thoracolumbar SCD. This study has important implications for the development of static posturography as a novel method of evaluating recovery and efficacy of treatment in dogs with SCD.

Research Grant: None

Student Support: Boehringer Ingelheim Veterinary Scholars Program
Investigating the interaction between PGRN and NAGA as a pathological mechanism of FTLD and NCL

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Frontotemporal lobar degeneration (FTLD) is an incurable, terminal disease resulting in the progressive atrophy of the frontal and temporal lobes of the brain. One of the leading causes of FTLD is mutation in the GRN gene, encoding progranulin (PGRN), a secreted glycoprotein implicated in a wide array of processes, including inflammation and tumorigenesis. Despite decades of research, the exact function of PGRN and its mechanistic relationship to FTLD remain unclear. However, increasing evidence suggests a role for PGRN in the lysosome - most striking is that homozygous GRN mutation leads to neuronal ceroid lipofuscinosis (NCL), a lysosomal storage disease (LSD). To better understand the lysosomal function of PGRN, we completed a mass spectrometry-based screen to identify its protein binding partners. One promising candidate was the lysosomal enzyme, α-N-acetylgalactosaminidase (NAGA), whose binding has been verified by co-IP. NAGA assists in the degradation of lysosomal cargo by specifically hydrolyzing α-N-acetylgalactosaminyl moieties from glycoconjugates, and its deficiency results in Kanzaki disease, an LSD with neurological sequelae. Based on the PGRN-NAGA interaction and the association of both with neurodegenerative LSDs, we hypothesize that PGRN modulates NAGA activity in the lysosome, and that PGRN loss results in reduced NAGA activity and lysosomal dysfunction. Initial assays of NAGA enzymatic activity in WT and Grn -/- mouse liver lysates show a significant reduction in NAGA activity when PGRN is lost, with no change in total NAGA protein levels. Additionally, staining of mouse brain sections shows accumulation of undegraded NAGA substrates in the neurons of Grn -/- mice, further supporting our hypothesis.

Research Grant: NIH R01 NS088448
Student Support: Cornell Combined DVM-PhD Degree Program

Immunohistochemical characterization of dorsal root and nodose ganglia sensory neurons of the rat pancreas

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Diabetes mellitus is a prevalent disease in both veterinary and human medicine. Current treatments are not fully effective and can lead to decreased quality of life and potentially lifelong complications. Neuromodulation therapies might decrease pancreatic inflammatory responses and increase revascularization of islets to stimulate beta-cell function. To provide a neuroanatomical map, the present study characterized dorsal root ganglion (DRG) and nodose ganglion (NG) neurons innervating the rat pancreas through retrograde tracing with DiI to determine their immunohistochemical phenotype. Our hypothesis was that pancreatic sensory neurons would have a vascular sensory neuronal phenotype, and accordingly, were labeled for CGRP, Substance P, TRPV-1, and Neurofilament-M. The presence or absence of co-labeling with these markers was determined bilaterally for each DiI positive neuron in T9/T10 DRGs and NG. DRG results showed that CGRP and TRPV-1 were most frequently found in DiI positive cells, with TRPV-1 and CGRP positively co-labeling in cells 93.0% of the time whereas only 45.1% of the CGRP positive cells co-localized Substance P. Cells positively co-labeled with CGRP and NFM 44.2% of the time and exhibited a significantly larger diameter (40.61 +/- 0.94μm) compared to CGRP positive/NFM negative neurons (36.33 +/- 1.2μm). The NG pancreatic neurons were generally negative for all markers. These results indicate that pancreatic DRG neurons, but not NG neurons, have, in part, a nociceptive role most likely related to inflammation. Only about half of these neurons are myelinated, so different stimulation techniques will be needed to target the separate populations in further neuromodulation studies.

Research Grant: NIH SPARC 1OT2OD023861-01
Student Support: Merial, Florida Veterinary Scholars Program
Effect of acute exposure to green tea extract and citrus fruit juice on antioxidant defenses in healthy pigs

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Catechins, the functional polyphenols from green tea, mitigate oxidative stress and inflammatory responses. Low oral bioavailability of catechins limit its utilization in therapeutics and lemon juice has been suggested to enhance the bioavailability. We hypothesize that lemon juice (LJ) increases catechin bioavailability and shows a synergistic effect on antioxidant activity with green tea extract (GT). Pigs (n=26, 45.5±3.4kg) were provided two doses of GT (190mg/kg/day) or GT plus LJ (0.75ml/kg/day) (GL) and blood samples were collected for 48 hrs using catheters placed in jugular veins. The dose of GT was selected based on literature reporting beneficial effects in humans and adjusted to pigs. A subset of blood samples were used for the current study (n=3/group, 0 and 3 hr post treatment where Vmax of blood catechins level expected). Activities of antioxidant enzymes (catalase (CAT) and superoxide dismutase (SOD)) and level of lipid peroxidation (malondialdehyde, MDA) were measured. Two pigs in GT tended to decrease in CAT activity and MDA level, whereas all pigs in GL tended to increase in activities of CAT and SOD (p > 0.05). CAT, SOD and MDA were not correlated (p > 0.05). Neither GT nor GL cause hepatotoxicity. In summary, acute administration of GT or GL did not alter antioxidant defenses or oxidative stress. The inconsistent trends observed may be due to the small subset analysis from the large scale experiment. Ongoing blood catechins analysis will provide further insight on whether LJ affects bioavailability and physiological function of GT. This study acts as a platform for larger studies evaluating beneficial activity of phytochemicals on oxidative stress and inflammation in animal disease models such as stroke.

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Student Support: Boehringer Ingelheim, Veterinary Medical Experiment Station, UGA College of Vet Medicine

Correlates of mucosal immune control of feline enteric coronavirus replication

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Feline infectious peritonitis (FIP) is a deadly disease that results from a mutation from the relatively harmless and ubiquitous feline enteric coronavirus (FECV). Most cats are exposed to FECV but the virological outcome varies among individual cats. Some cats are resistant to infection or may clear infection while other may become episodic or persistent virus shedders. Another common outcome is reinfection presumably due to waning immunity. The variability of outcomes helps to perpetuate the virus within cat populations such as breeding colonies and in shelter environments. The present study aims to determine the mucosal immune correlates with the different virological outcomes. To achieve this cats from a FECV infected colony were longitudinally evaluated for fecal FECV by PCR and seropositivity. To assess the mucosal immune response, colonic biopsies were collected and mucosal lymphocytes were phenotyped by flow cytometry. FECV-specific cell-mediated responses were measured using IFN-g ELISPOT and the expression of T regulatory cell and Th17 genes were assessed by q-PCR. In addition to serology, the humoral response was determined using FECV-specific IgA ELISPOT and ELISA for fecal IgA. The goal is to identify specific immune correlates associated with control of viral replication. With this information, a rational vaccine strategy might be devised that will reduce or eliminate replication of FECV and effectively reduce the likelihood of spontaneous mutations that could lead to the emergence of FIPV and the associated devastating clinical diseases.

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Student Support: Ms. Morgan was supported by Boehringer Ingelheim Fellowship
Feasibility of a biodegradable intraluminal guide to aid intestinal anastomosis in an \textit{in vivo} swine model

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Intestinal anastomosis is a common procedure performed in veterinary and human medicine. It allows for continuity to be restored to bowel following resection of a pathologic segment. Various conditions are implicated in this such as intussusception, volvulus, neoplasia, impaction, and perforation. Stenosis and leakage at the anastomotic site are common complications. We proposed to develop a biodegradable intraluminal anastomotic guide with the goal of improving the accuracy of anastomosis and reducing post-surgical complications. Preliminary studies \textit{ex vivo} showed proof of concept that the use of a guide improved the accuracy and ease of an anastomosis. We hypothesized that similar results would occur \textit{in vivo} with reduction of post-surgical complications when compared to a traditional hand-sewn method. The guide, composed of layers of polyurethane and polyvinylpyrrolidone in a hollow cylinder, was fabricated to the size of bowel anticipated in a 70 kg pig and designed to degrade in 30 minutes to 3 hours. Young pigs (n=6) had 2 enterotomies performed, one repaired solely with a hand-sewn end-to-end anastomosis, and one repaired with the use of the anastomotic guide. The pigs were monitored 14 days post-operatively at which time they were sacrificed and a necropsy examination performed. Results demonstrated that anastomoses performed with the use of a guide withstood a 10% (166 vs. 151 mmHg) greater luminal burst pressure and maintained a 17% (27 vs. 22 mm) larger luminal diameter. Subjective data suggests the addition of a guide eased the performance of the anastomosis. These findings support the hypothesis that the use of an anastomotic guide may be beneficial to the performance of intestinal anastomosis.

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\textbf{Student Support}: Center of Excellence Summer Research Program, University of TN College of Veterinary Medicine

Treatment effects of probiotic Bifidobacteria on anti-CTLA-4 immunotherapy in a mouse model of prostate cancer

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Anti-CTLA-4 and anti-PD-1/PDL-1 antibodies are promising cancer immunotherapy agents whose therapeutic efficacies have been shown to be influenced by gastrointestinal (GI) microbiota composition in animal models. Previous studies have demonstrated that intestinal microbiota are essential for therapeutic efficacy of anti-CTLA-4 immunotherapy in a mouse model of sarcoma and that feeding probiotic \textit{Bifidobacterium} spp. to mice in a melanoma model prior to treatment can bolster effects of anti-PDL-1 immunotherapy. Inspired by the underwhelming results of anti-CTLA-4 in human prostate cancer clinical trials, we investigated whether feeding probiotic \textit{Bifidobacterium} spp. to mice would improve therapeutic efficacy of anti-CTLA-4 immunotherapy in an allograft mouse model of prostate cancer. All mice (11 week, male, FVB) were inoculated subcutaneously with 1x10^6 cells of a murine prostate cancer cell line driven by the Myc oncogene (Myc-CaP) and were divided into five treatment groups: no treatment (control), \textit{Bifidobacterium} spp. gavage, low dose anti-CTLA-4 (1mg/kg), low dose anti-CTLA-4 with \textit{Bifidobacterium} spp. gavage, and high dose anti-CTLA-4 (10mg/kg). Tumor volumes were measured every other day by digital calipers and treatment efficacy was determined by comparing tumor volume over time, tumor fold growth over time, and time to endpoint (tumor measures 2 cm in any direction). Data were normally distributed. Rate-based T/C was calculated for all groups and values were compared via two-tailed, heteroscedastic t-tests. Analysis revealed there were no statistically significant differences between treatment and control groups.

\textbf{Research Grant}: Prostate Cancer Foundation Challenge Award
\textbf{Student Support}: NIH T32 Training Grant OD11089-39
Transcriptomics of IgE-mediated cutaneous reactions in a canine model of atopic dermatitis

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Atopic dermatitis (AD) is a common, chronic, recurrent, inflammatory, and pruritic allergic skin disease that develops spontaneously with nearly identical clinical phenotypes in humans and dogs. The cutaneous reactions induced by intradermal injection of anti-immunoglobulin E (IgE) antibodies in both humans and dogs grossly and histologically mimic changes seen in naturally occurring allergic dermatitis in these species. The main objective of this study was to evaluate the molecular signature of IgE-mediated cutaneous reactions using next-generation RNA sequencing (RNA-seq). Intradermal injection of saline, histamine and anticanine-IgE antibodies was performed on the left and right thorax of eight healthy male castrated Beagles. Clinical scoring was conducted at 20 min and 6 h for global wheal scores and late phase reactions, respectively. Skin biopsies were obtained for histological evaluation and RNA isolation at 6 h and 24 h from anti-IgE-associated skin reactions, and at 6 h from the saline injection site, which served as the control. For the purpose of this study we also optimized the methodology for the extraction of RNA from small skin biopsies of suitable quality for sequencing by comparing the collection and storage of skin tissues in RNAlater to immediate snap freezing. Extracted RNA was subjected to both RNA-seq and real-time PCR for genes of interest. Comparative transcriptome analysis of canine IgE-mediated skin reactions will reveal differences in gene expression related to epidermal keratinocyte differentiation, innate and adaptive immune responses, and pruritogenic pathways. Our observations will allow for molecular comparison of the IgE-mediated model to natural human and canine AD.

Research Grant: Merial-Boehringer Ingelheim
Student Support: Boehringer Ingelheim, Veterinary Medical Experiment Station, UGA College of Vet Medicine

Adaptation of PS and TF positive microparticle procoagulant activity assays for use in cat blood samples

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Assays that detect the procoagulant activity (PCA) of tissue factor positive (TF+) and phosphatidylycerine positive (PS+) microvesicles (MVs) have been used in studies of pathological thrombosis. Platelets can form MVs and interfere with assay results, and need to be removed. The objectives of this study are to 1) Determine if a centrifugation protocol that effectively clears platelets from canine/human blood clears platelets from cat blood, 2) Determine if PS+MV PCA assay used in dogs/people can be adapted for use in cats, 3) Determine if a TF+MV PCA assay can be adapted for use in cats. Blood was collected from 3 healthy cats into 3.2% sodium citrate vacutainer tubes. MV rich platelet free plasma was obtained using a previously described protocol. Platelet contamination was determined using a semiquantitative platelet contamination score (PCS). MVs were created by incubating whole blood with 10μg/mL LPS for 5 hrs at 37C, or by forcing blood through a 22g needle 15x. PS+MV PCA was detected by using PS capture and prothrombinase complex chromogenic thrombin generation assay (Zymuphen MP-Activity; Aniara). PCA associated with TF+MVs will be detected as described by L. Kidd et all, 2015. The mean +/- PCS was higher than in dogs (n=3; mean PCS 13.4+/−18.8, dogs: n=9; mean PCS 0.2557 +/-0.27024; p=0.3496). PS+MV PCA was detectable in cat plasma, in PS Eq nM: (Cat 1 LPS: 39.06+/−3.67 CV=9.41%, NH: 8.13+/−3.62 CV=44.49%); Cat 2 LPS: 13.39+/0.09 CV 0.74%, NH: 4.43+/−0.33 CV=7.4%, Cat 3 LPS: 59.28+/−3.73 CV=6.30%, NH: -3.06+/−1.33 CV=43.30%). Hemolyzed samples were out of range and are not included. Overall intraassay coefficient of variation (CV) was 30.34%, overall inter-assay CV 18.6%. TF results are pending.

Research Grant: Seed Grant, Western University of Health Sciences Office of Research.
Student Support: Petsmart Charities Scholarship.
Addressing a role for pathologic estrogen metabolism in female-specific pulmonary arterial hypertension

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Pulmonary arterial hypertension (PAH) is a cardiovascular disorder typically resulting in right heart failure and death, 3-4 times more likely in women. PAH is characterized by elevated pulmonary arterial pressure due to vascular smooth muscle cell (VSMC) proliferation and vessel wall thickening. Estrogen provides cardiovascular protection in pre-menopausal women by inhibiting VSMC proliferation. 4,4’-Methylenedianiline (DAPM) is an environmental aromatic amine. Rats treated with DAPM exhibited a female-specific increase in pulmonary arterial pressure and pulmonary arteriolar medial hyperplasia. The DAPM females showed an increase in serotonin (5-HT) and a decrease in the serum ratio of estrogen metabolites 2-hydroxyestrogen (2-OHE1)/16α-hydroxyestrogen (16α-OHE1), both positive biomarkers for PAH. Human cells treated with non-selective estrogen receptor (ER) antagonist ICI 182,780 or the selective serotonin reuptake inhibitor, fluoxetine, inhibited DAPM-induced pulmonary VSMC proliferation and 5-HT uptake. Our hypothesis was that DAPM and/or estrogen metabolites induce VSMC proliferation through an ER-dependent dysregulation of 5-HT transport. Human premenopausal VSMCs from healthy females compared to female patients with PAH were cultured and assayed for proliferation. The PAH cells showed a 3-fold increased proliferation rate compared to the normal VSMC. Ongoing studies are examining whether DAPM, estradiol, 2-OHE1 or 16α-OHE1, or DAPM plus each of these increases VSMC proliferation in PAH compared to normal cells. We are also utilizing western blot analysis and selective inhibitors to test whether ER-α, ER-β, or G-protein coupled estrogen receptor (GPER) expressed in these cells may mediate its mitogenesis.

Research Grant: AHA 14GRNT20490300
Student Support: NIH T35 Training Grant T35OD011151

Expression of immune checkpoint molecules in canine histiocytic diseases

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Elevated levels of immune checkpoint molecules have been associated with spontaneous malignant cancers in several species. This study aimed to compare the expression of programmed death ligand-1 (PD-L1) and programmed death ligand-2 (PD-L2) in canine histiocytoma and histiocytic sarcoma tissues. Samples were identified via a search of Virginia Tech Animal Laboratory Services (ViTALS) records and review of histologic specimens for presence of appropriate diagnostic criteria. Scrolls of formalin-fixed paraffin-embedded tissues (50 μm from each of 11 histiocytic sarcomas and 10 histiocytomas selected) were cut, and RNA was extracted then converted to cDNA in preparation for quantitative PCR analysis. To characterize the canine mRNAs encoding immune checkpoint molecules relevant to this analysis, endpoint PCR was performed using cDNA templates derived from normal canine spleen. To date, sequencing of PCR products confirms expression of mRNAs for full-length PD-L1 and PD-L2 identical to predicted sequences recorded in the NCBI GenBank database. Furthermore, other products, likely arising from alternative pre-RNA processing, were detected for PD-L2. Characterization of these additional isoforms, predicted to lack one or more putative functional domains responsible for delivering checkpoint signals cell to cell, is ongoing. Primers and TaqMan probes designed to detect full-length PD-L1 and PD-L2 will be used to compare normalized expression of the checkpoint molecules in the two tumor types. We predict that PD-L1 and PD-L2 will have higher expression in histiocytic sarcoma than in histiocytoma, based on the more malignant nature of histiocytic sarcoma and the tendency of histiocytoma to undergo immune-mediated regression.

Research Grant: Virginia-Maryland College of Veterinary Medicine
Student Support: Virginia-Maryland College of Veterinary Medicine
Associations between administration of direct fed microbials with *E. coli* O157 shedding in feedlot cattle

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*Escherichia coli* O157 has been associated with food-borne outbreaks of disease in humans, most often involving contaminated ground beef products. Cattle act as asymptomatic reservoirs, contaminating pen-mates and the environment through shedding of *E. coli* in their feces. Several control measures have been proposed, however only few have been proved effective for reducing fecal shedding of this bacterium. Direct-fed microbials (DFM) are probiotics that act by excluding harmful bacteria like *E. coli* and preventing its colonization in the digestive tract. The objective of this study was to determine whether the administration of a high-dose DFM (*Lactobacillus acidophilus* NP51 and *Propionibacterium freudenreichii* NP24) was associated with *E. coli* O157 shedding in feces of cattle in feedlot operations. Twenty commercial feedlots in Nebraska, 10 that administer DFM and 10 that do not, were sampled three times in summer 2017. Twenty-two pen-floor fecal samples were collected from three pens in each feedlot, per visit. Samples were subjected to cultural and molecular procedures for detection (immunomagnetic separation, plating on selective media, followed by PCR confirmation) and spiral plating for quantification. This is an ongoing study; up to week 5, a total of 528 samples have been processed and tested. If the results show that Bovamine Defend is effective at reducing *E. coli* shedding in feedlot cattle, it may be used as an effective control measure to reduce the pathogen load entering the slaughter plant and subsequently reduce the burden of *E. coli* O157 illnesses in humans.

**Research Grant**: Chr. Hansen Inc. Award # 35429 and the College of Veterinary Medicine, Kansas State University

**Student Support**: NIH T35OD010979

Anesthesia enhances subthreshold critical slowing-down in a stochastic Hodgkin-Huxley neuron model

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Critical slowing-down (CSD) emerges spontaneously in subthreshold voltage tracings from stochastic neuron models on approach to spiking threshold and is predicted to occur in populations of neurons influenced by general anesthetics. Numerical simulation was used to investigate the subthreshold behavior of a type-I integrator Hodgkin-Huxley model endowed with stochastic descriptions of ion channel kinetics and subject to the influence of phasic GABAA inhibition. The model was driven by multiple Poisson distributed trains of inhibitory GABA impulses and investigated for various model parameterizations as a function of proximity to spiking threshold via application of a constant excitatory input current. Reduction of the GABAA conductance decay rate was used to model the influence of propofol anesthesia. Transmembrane potential tracings were numerically simulated and power spectral densities, autocorrelation functions, and membrane potential histograms of the zero-mean fluctuations were computed to characterize subthreshold behavior. For a given reduction in GABAA conductance decay rate, nonlinear growth in amplitude simultaneous with decay in frequency and increasing temporal persistence of transmembrane voltage fluctuations were observed as distance to spiking threshold was reduced. The magnitude of these statistical signatures of CSD increased in conjunction with increased anesthetic effect. In a Hodgkin-Huxley model equipped with stochastic ion channel kinetics and phasic GABAA inhibition, anesthesia enhances the magnitude of critical slowing-down on approach to spiking threshold.

**Research Grant**: None

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The effect of housing environment on teat skin staphylococcal populations

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Teat skin colonization has been found to be a risk factor for staphylococcal mastitis in dairy cattle. The purpose of this study was to determine whether dairy cattle housing types affect the staphylococcal populations in teat skin swabs. The hypothesis was that the prevalence and distribution of staphylococcal species would differ between teat skin samples collected from farms utilizing sand bedded free-stall housing and farms utilizing compost bedded pack housing. Twenty farms (n = 10 new sand bedded free-stall; n = 10 compost bedded pack) were studied. Samples were collected from teat skin surfaces before and after pre-milking teat disinfection (1 composite sample containing skin swabs from one teat of 10 randomly selected animals in each herd before and one teat after teat disinfection [n = 40 samples]). Swabs were placed in peptone water, diluted 1:10, plated on mannitol salt agar and incubated at 37°C for 24 hours. After 24 hours, 10 staphylococcal colonies, including at least one of each morphologically distinct colony types, from each of the plates were sub-cultured on Columbia Blood Agar (CBA). The plates were reread at 48 hours and any new colonies (up to 10) were sub-cultured on CBA. Thus far, bacterial speciation has been done using matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry. The proportion of samples positive for a given result were compared between groups using the Fisher’s Exact test (P< 0.05). Overall, no clear relationship between bedding type and the prevalence of different staphylococcal species has been found. Research is underway to determine whether housing environment effects the prevalence of staphylococcal species in bedding and milk on these farms.

Research Grant: None
Student Support: Mastitis and Milk Quality Research Lab at the University of Missouri

Development of a SNP genotyping test to detect Sod-1 mutations responsible for canine degenerative myelopathy

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Degenerative Myelopathy (DM) is an adult-onset, progressive neurodegenerative disease that occurs in several breeds, particularly Rhodesian Ridgebacks (RR) and Pembroke Welsh Corgis (PWC). Affected dogs demonstrate progressive hind leg ataxia leading to paresis and eventual end-stage paraplegia. Treatment for DM is limited and prognosis is poor. Consequently, most owners decide to euthanize within one year of diagnosis. Homozygous G to A missense mutations in exon 2 of the Superoxide Dismutase 1 (Sod-1) gene are associated with the development of DM in affected breeds. The goal of my project is to help develop a high performance, cost-effective canine Sod-1 Single Nucleotide Polymorphism (SNP) -Restriction Fragment Length Polymorphism (RFLP) test through the Atlantic Veterinary College. Collaborations with RR and PWC breeders from across Canada were established to obtain buccal swabs from their previously tested dogs for the Sod-1 SNP, including G/G unaffected, G/A carrier and A/A affected dogs (N=20 per group). DNA from cheek cells will be extracted using DNA Genotek kits and then PCR-RFLP will be performed. PCR-RFLP includes (1) amplification of the SNP-containing region, (2) restriction enzyme digestion (Eco57) followed by gel electrophoresis to distinguish unaffected (wild-type), carrier (heterozygous) and affected (homozygous) dogs. Results will be compared with those previously obtained and confirmed by sequencing. Following completion of this pilot study, our results will be validated by a larger cohort study (N=100 per group), with the ultimate aim of offering this test as part of a canine genetic testing repertoire at AVC.

Research Grant: KRESCENT grant
Student Support: Veterinary Student Research Award (VetSRA)
In vitro susceptibility of ruminant Corynebacterium pseudotuberculosis isolates against 18 antibiotics

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Corynebacterium pseudotuberculosis is a gram-positive bacterium that causes a chronic and recurring disease called caseous lymphadenitis (CL) in sheep and goats. In cases of CL, bacteria infiltrate lymph nodes and cause purulent, cottage cheese-like filled abscesses that respond poorly to antimicrobial therapy. CL is currently considered an untreatable disease that results in major economic loss for producers. Highly lipid soluble antibiotics might be effective against the bacteria; however, there are no CLSI-approved breakpoints for antibiotics for CL. One of the first steps in establishing breakpoints is to identify the Minimum Inhibitory Concentrations (MICs) of known antibiotics against the bacteria in vitro. In this study, we used a commercially available panel of antibiotics used for food-animals to determine the in vitro MICs for 53 caprine and ovine C. pseudotuberculosis isolates. Our results showed that the antibiotics were able to inhibit the growth of C. pseudotuberculosis in vitro. We also compared our results with the results of a previous study that determined the MICs of equine derived C. pseudotuberculosis isolates. Of the 6 drugs used for both equine and small ruminant isolates, there were significant differences between equine and small ruminant MICs for ceftiofur, penicillin, and gentamicin. These results may be useful in empirical drug selection for treatment of CL in the future. Some of the drugs tested would not be used clinically because of the potential for violative drug residues and caution should be exercised in selecting drugs for use in food animals.

Research Grant: None
Student Support: College of Veterinary Medicine & Biomedical Sciences, Texas A&M University

Application of irreversible electroporation to treat pancreatic and breast cancer

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Pancreatic and triple negative breast cancer (TNBC) are among the deadliest forms of cancer. Pancreatic cancer in particular has the lowest five-year survival rate at approximately 7 percent. As the need for an effective treatment rises annually, research in this area is increasingly necessary. A novel form of ablation therapy has recently been developed, termed irreversible electroporation (IRE). This therapy is a non-thermal and focal technique, that is thought to destabilize the cell membrane and nucleus of cancer cells, inducing a unique form of cell death. The goal of the current study was to better understand the underlying cellular mediators and influences on the tumor microenvironment following application of IRE to 4T1 (breast) and Pan02 (pancreas) cells. The effects of IRE in vitro were evaluated by cytotoxicity assays, live/dead stains, cytokine ELISA assays, and gene expression. The effects of IRE in vivo were assessed by daily tumor size, end of study tumor burden, histopathology, and tumor gene expression. In vitro, IRE application results in cellular death and changes in cellular mediators of the tumor microenvironment, while in vivo, IRE has been shown to ablate the primary tumor and lead to a reduction in metastases. Here, we report that IRE has the capacity to reduce the ability of the tumor to escape immune recognition in both TNBC and pancreatic cancer. IRE is an effective method of cancer treatment, and future studies will validate clinical application.

Research Grant: Virginia Tech Institute for Critical Technology and Applied Science Center for Engineered Health and Virginia-Maryland College of Veterinary Medicine
Student Support: NIH T35 Training Grant T35OD011887
A forward genetic screen for drivers of mammary tumorigenesis and progression in context of PI3K hyperactivity

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The most common carcinoma in women, and one of the leading causes of cancer-related death, are invasive mammary tumors. Creating \textit{in vivo} models that accurately recapitulate mammary tumorigenesis and progression is difficult due to high genetic heterogeneity within and between breast carcinomas. Common genetic alterations in human breast carcinomas are activating mutations in the catalytic subunit of PI3K. We conducted a forward genetic screen using a Cre-inducible Sleeping Beauty (SB) transposon system in the context of PI3K hyperactivation, aiming to discover genetic events that cooperate with an oncogenic PI3K mutation. The T2/Onc3 transposon activates endogenous proto-oncogenes or inactivates tumor suppressor genes by insertional mutagenesis. In conjunction with a R26-LSL-SB11 transposase and tissue-specific Cre, the transposon mobilizes and integrates into the genome. Mice with the PI3K mutation and SB had accelerated tumorigenesis compared to controls. RNA sequencing showed molecular subtypes with correlating T2/Onc3-induced insertion mutations, including estrogen receptor (+/-) subtypes. RNA and DNA sequencing defined common insertion sites of the SB transposon, allowing for detection of the most frequently mutated genes. We identified 20 tumor suppressor genes and 35 oncogenes as common insertion sites, including known candidates like PTEN and HRAS.

\textit{In vitro} work to knock out tumor suppressor genes in MCF-10A cells using a CRISPR/Cas9 system and overexpress oncogenes using cDNA clones and lentiviral vectors is ongoing. This model provides a source of genetically heterogenous mammary tumors with the same initiating mutation (PI3K) useful for identifying cooperating pathways and drivers of specific tumor phenotypes.

\textbf{Research Grant}: American Cancer Society Research Professor Award (to D.A.L.), Genentech/Roche Inc.  
\textbf{Student Support}: NIH T35 Training Grant #T35OD011118

Can \textit{in utero} electroporation of microRNA-CSMN1 enhance corticospinal motor neuron development \textit{in vivo}?

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Unlike peripheral motor neurons, corticospinal motor neurons (CSMN) do not regenerate after axonal damage. Lesions to the spinal cord frequently result in irreversible motor paralysis. Consequently, understanding CSMN development may be important for developing spinal cord injury therapies. Many transcription factors have been identified to control projection neuron development, however, it is still unclear how they are regulated. MicroRNAs (miRNAs) are post-transcriptional regulators that target messengerRNA (mRNA) to repress translation, including mRNA that encodes transcription factors that may specify CSMN or callosal projection neuron (CPN) fate. CSMN and CPN have partially shared embryonic birthdates and laminar location within the cortex, however, they have very different targets and functions. Twenty miRNAs were identified to have higher expression in purified populations of CSMN vs. CPN in a differential miRNA expression analysis at postnatal day 1 (P1) in the mouse. Of these miRNAs, miR-CSMN1 was found to be more highly enriched in CSMNs on P1 but not on P4. Interestingly, miR-CSMN1 is predicted to target two transcription factors important for CPN fate. Succeeding functional experiments have demonstrated that miR-CSMN1 controls projection neuron fate in embryonic cortical cultures. We hypothesize that miR-CSMN1 will increase CSMN cell fate specification \textit{in vivo}. miR-CSMN1 expressing plasmids were used for \textit{in utero} electroporation gain-or-function experiments. Established markers, including Ctip2, Fezf2, and Satb2, will be used to evaluate projection neuron identity. Ultimately, understanding miR-CSMN1 control over projection neuron fate determination could impact novel stem cell therapies.

\textbf{Research Grant}: NIH K08, AO Spine North America  
\textbf{Student Support}: NIH T35 Training Grant
**Antimicrobial resistance and virulence of fecal *Escherichia coli* in grey seals in the Gulf of St-Lawrence**

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Grey seals (*Halichoeres grypus*) are a highly migratory group of animals that may reside in waters adjacent to densely populated areas. There is potential for the acquisition of antimicrobial resistance (AMR) genes by gastrointestinal *Escherichia coli* in seals from agricultural or waste water effluent. Exposure to pathogenic or AMR *E. coli* in seal feces could be a health risk to communities that rely on seal hunts. AMR in Canadian seal populations has not been reported. The objective of this study is to investigate the presence of AMR and pathotypes of fecal *E. coli* in Atlantic Canadian seal populations. Fecal samples were collected from grey seals around the Magdalen Islands, diluted in buffered peptone water, and then plated to MacConkey agar. Five lactose-fermenting colonies from each sample were identified using MALDI-TOF mass spectrometry. Virulence factors were detected using multiplex PCR, allowing pathotype assignment. Three *E. coli* isolates per seal were tested for AMR using disk diffusion assay and resistant isolates were further characterized with broth microdilution testing. *E. coli* was detected in 20 of 23 seals. Extra-intestinal pathogenic *E. coli* (ExPEC) and enteropathogenic *E. coli* (EPEC) pathotypes were identified in 23% and 10% of isolates, respectively (n=70). Resistance was detected to ampicillin (n=1), amoxicillin/clavulanic acid (n=1), cefoxitin (n=1), cephalixin (n=2), and tetracycline (n=3). Prevalence of AMR and known *E. coli* pathotypes were relatively low compared to other food animal products. Therefore, risk of human exposure from fecal contamination in raw seal meat processing is low. Comparison of these findings to Baffin Island, Nunavut, ringed seal (*Pusa hispida*) populations is underway.

**Research Grant**: Association des Chasseurs de Phoques intra-Québec and Canadian Wildlife Health Cooperative (CWHC)

**Student Support**: Veterinary Summer Research Award (VetSRA), Atlantic Veterinary College

**Evaluating the effect of HZE ions on metastasis in MMTV-PyMT-induced mammary tumors**

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High atomic number and energy (HZE) nuclei are components of galactic cosmic rays that pose significant and uncertain health risks for manned missions to interplanetary space. Preliminary carcinogenesis studies in C3H mice have indicated that whole-body exposure to HZE ions increases the risk of hepatocellular carcinoma metastasis. To further investigate this observation, a genetically engineered mouse model (GEMM) of metastasis is utilized. FVB/N-Tg (MMTV-PyMT) mice carry a transgene consisting of a mouse mammary tumor virus promoter controlling the expression of the mouse polyomavirus middle-T antigen, leading to early mammary tumor development and metastasis. Male MMTV-PyMT mice are crossed with female DBA/2J and FVB/N and individuals from each background are exposed to 0.2 Gray of 300 MeV/n Si28 ions (HZE ions), or sham irradiated. Metastases are quantified using area-based measurements to determine metastatic density using digital analysis of whole slide images. Results will be presented at the National Veterinary Scholars Symposium.

**Research Grant**: None

**Student Support**: NIH SIP
Nickel homeostasis and bacterial pathogenesis: examining the NikR regulatory system in *Brucella abortus*

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*Brucella* spp. are Gram-negative bacteria that infect a range of domesticated and wild animals causing abortions, infertility and a debilitating febrile illness in humans. Some *Brucella* strains are considered zoonotic; therefore, posing significant threat to public health. As an intracellular pathogen, the bacterium invades phagocytes (i.e., macrophages, dendritic cells, placental trophoblast), and compromise the regular activity of the infected cells. The goal of this study is to decipher the molecular function and role of a putative metal responsive transcriptional regulatory protein NikR in the pathogenesis of *Brucella abortus*. Metals are essential micronutrients for the support of metabolism and physiology in all cells, and in particular, nickel is a co-factor required for the urease enzyme of *Brucella* and this urease is essential during oral infections. Nickel import and export homeostasis may be a good target for potential novel therapeutics to combat brucellosis. A recombinant *Brucella* NikR protein (rNikR) was expressed in E. coli BL21 and purified by affinity chromatography. Electrophoretic mobility shift assays demonstrated positive binding in the promoter region of the *nikABCDE* operon on an excess nickel environment. A DNA Footprint assay will be performed to identify the exact sequence of binding and quantitative reverse transcription will provide information on the mRNA expression. These findings serve to characterize the genetic regulatory events mediating nickel homeostasis in *Brucella*.

**Research Grant**: Virginia-Maryland College of Veterinary Medicine  
**Student Support**: NIH T35 Training Grant T35OD011887

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Developing a novel porcine model of laryngopharyngeal reflux disease

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Laryngopharyngeal reflux (LPR) disease is believed to involve chronic backflow of gastric refluxate, resulting in damage to the laryngopharyngeal epithelium. Gastric refluxate has been shown to contribute to many laryngological conditions, including laryngitis, sore throat, ulcers, and globus pharyngeus. Approximately 10% of laryngologic patients and over 50% of patients with voice disorders have symptoms of LPR. Despite the prevalence of LPR, there is no suitable animal model. The pig provides a unique opportunity to study laryngeal disease as porcine and human vocal folds are very similar in terms of architectural, biochemical, neuromuscular, and cellular properties. In this pilot study, a novel in vivo pig model was developed to simulate the clinical condition of human LPR more closely by challenging healthy, uninjured laryngeal epithelia with acidified pepsin. An indwelling esophagostomy catheter was placed surgically and positioned near the aryepiglottic folds. The pigs were randomly assigned to a reflux group (n=3) and a sham (n=1). The reflux group received a continuous rate infusion of acidified pepsin solution, and the sham received saline. Autopsies were completed on days 8 and 12. Laryngeal tissues were examined grossly and histologically for differences between treatment groups. Immunohistochemistry for CD3+ T-cells was quantified via digital pathology. Grossly, cloudy fluid was observed in the larynges of the reflux group. Differences between treatment groups in histopathology and CD3+ T-cell quantification and localization were not statistically significant. This pilot study paves the way for future LPR studies, in which an improved surgical approach should allow for increased study duration.

**Research Grant**: None  
**Student Support**: Merial Veterinary Scholars Program
Anti-Mullerian hormone association with time to pregnancy and failure to maintain pregnancy in beef cattle

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Anti-Müllerian Hormone (AMH) is a dimeric glycoprotein that is present in plasma and serum, and is highly repeatable within a mature animal. Moreover, AMH is positively correlated to antral follicle count, which has been positively associated with various fertility factors in beef and dairy cattle. However, significant correlation between serum AMH concentrations and beef heifer fertility has not been established. The objective of this study was to investigate the relationships between baseline serum AMH concentrations and reproductive success, or failure, in beef heifers. The study population (n = 96) consisted of beef heifers from 10 multi-breed single-sire breed groups. All heifers were approximately 2 years of age at breeding with expectations of calving at 3 years of age. Prior to breeding, each heifer’s identification number, birthdate, breed type, weight and body condition score were recorded. Baseline blood samples were collected for serum AMH concentration analysis. Each animal participated in a synchronized estrus protocol followed by timed artificial insemination and breeding by natural service exposure. Pregnancy evaluations were conducted at 42, 69 and 158 days post-initial artificial insemination. Where pregnancy was confirmed, fetal crown-rump length and gestational age were determined via transrectal ultrasonography. Preliminary findings based on crude data suggests that heifers that achieved pregnancy after the first artificial insemination had a higher average serum AMH concentration than heifers that achieved pregnancy after the second artificial insemination. However, the data will undergo further statistical analysis to determine advanced correlations.

Research Grant: None
Student Support: Boehringer Ingelheim Veterinary Scholars Program

Testing natural killer (NK) cell gene expression in pigs to better understand NK cell memory

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Having a better understanding of the role of natural killer (NK) cells in memory of the pig immune system can aid in many areas including vaccine development. Previous experiments have shown that the mouse immune system has NK cell memory using contact hypersensitivity (CHS) testing. We are interested in determining if the pig immune system also has NK cell memory. CHS is an acute type of hypersensitivity that causes skin inflammation induced by repeated exposure to hapten (small molecules that elicit an immune response). To determine if the pig immune system has NK cell memory using CHS, hapten trials were designed. These trials consisted of painting either the hapten or vehicle on the pig’s back, waiting either 7 or 21 days, then challenging the pigs with different hapten or vehicle on each ear, and then measuring the change in ear thickness 24-72 hours post challenge to evaluate the inflammatory response. After 72 hours, the pigs were euthanized and blood, liver cells, and ears were collected. These trials have shown hapten-specific memory at days 7 and 21. To expand our mechanistic understanding of NK cell memory, we tested NK cell gene expression in the liver and blood derived mononuclear cells from the hapten trials. To do this we purified RNA from peripheral blood mononuclear cells (PBMCs) and liver cells collected from hapten-sensitized pigs and control pigs. We have also developed 4 new assays to specifically quantify RNA expressed from Nkp46, perforin, interferon gamma, and Thy 1.1 genes, and used these tests on the liver and blood derived mononuclear cells. These assays are currently being used with RT-qPCR to see the effect of hapten sensitization on gene expression in liver and blood.

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Student Support: NIH T35 Training Grant 5T35OD012199-15
Effect of cranberry, blueberry and blackberry extracts on feline oral squamous cell carcinoma viability

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Feline oral squamous cell carcinoma (FOSCC) is the most common oral cancer in domestic cats. These tumors are extremely invasive and frequently invade into bone. Euthanasia is often selected shortly after diagnosis due to progressive disease and treatment failure. There is a need for more treatment options for cats with FOSCC. Berries contain numerous phytochemicals which have demonstrated anticancer activities against human oral squamous cell carcinoma. These anticancer activities include reduction of the growth rate of pre-malignant cells, stimulation of apoptosis and cellular differentiation, and reduction of inflammation and angiogenesis. The aim of this study is to determine if crude extracts from cranberries, blueberries and blackberries have anti-neoplastic activity against FOSCC cells in vitro, and to determine which berry extract has the most effect on tumor cell viability. An MTT assay was used to determine viability of a FOSCC cell line (SCCF2) after 72 hours of culture in serial dilutions of berry extracts, with carboplatin serving as a positive control. The results showed that at a concentration of 63 μg/ml, carboplatin reduced FOSCC viability by 68%, followed by cranberry and blueberry extracts reducing viability by 48.4% and 44.4%, respectively. The same concentration of blackberry extract only reduced viability by 20.9%. Overall the findings demonstrate that crude cranberry and blueberry extracts negatively affect SCCF2 viability to a similar degree, with blackberry extract having the least effect. Future studies will evaluate fractionated cranberry and blueberry extracts for anti-neoplastic properties, and the bioactive factors will be identified via UPLC-MS/MS and NMR techniques.

Research Grant: None
Student Support: AVC Veterinary Student Research Award

Prevalence and genetic strain types of Trypanosoma cruzi infection in working dogs and vectors across the U.S.

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Trypanosoma cruzi is a zoonotic protozoal parasite spread by Triatomine bugs that is endemic to the Americas where it causes Chagas disease in humans, dogs, and other mammals. Infection can be asymptomatic or cause a variety of symptoms ranging from fatigue to cardiac disease and death. Human and veterinary medicine suffer from the inability to determine the likely outcome in infected hosts. To begin to address the hypothesis that genetic strain variation of T. cruzi contributes to variation in disease outcome, we measured the parasite discrete typing units (DTUs) circulating between vectors and naturally-infected dogs. Department of Homeland Security working dogs are highly trained in scent detection and protection duties, and are at high risk for vector exposure. In 2017, we sampled blood from 269 working dogs along the US-Mexico border and received 511 samples from vet clinics across 32 states. Triatomines were opportunistically collected from canine environments. Serum was tested for anti-T. cruzi antibodies using up to three serological assays, and two qPCR assays were used to detect and type T. cruzi DNA in canine buffy coat and vector hindgut samples. Overall seroprevalence was 6.5% (95% CI: 4.9-8.5). Four canines (0.5%, n=776) had detectable parasite DNA, of which one was determined to be strain type TcIV but analysis is ongoing. Among 49 Triatoma gerstaeckeri and T. rubida, 42.8% were infected comprised of TcI (43.7%), TcIV (37.5%), and TcI/IV mix (18.7%). Determining the prevalence of T. cruzi in these working dogs is critical for quantifying the economic impact of infection, and data on the genetic diversity of the parasite is a first step to developing more specific diagnostic tests for U.S. strains.

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Metabolic stress biomarkers in dairy cattle during the dry-off period

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The dry period is the critical time between lactations in which a cow’s mammary gland remodels and regenerates in preparation for the ensuing lactation. Similar to cows entering early lactation, high-producing animals can experience many stressors during the dry off period, including dietary changes, abrupt milking cessation, and physiological imbalances. Metabolic stress occurs when an animal’s physiologic homeostasis is disrupted from an inability to meet nutrient requirements and results from a combination of aberrant nutrient metabolism, chronic inflammation, and oxidative stress. Early lactation cows that suffer from metabolic stress are susceptible to health disorders that cause production losses. There is little information, however, regarding the occurrence and impact of metabolic stress in dry cows. Therefore, the purpose of this study was to investigate well-known metabolic stress biomarkers in dairy cows throughout the early dry period. A descriptive study was performed by collecting blood samples from 32 cows at a commercial dairy herd at -6d, 0d, +1d, +2d, +6d, and +12d. Serum samples were utilized to quantify albumin, calcium, cholesterol, nonesterified fatty acids, and beta-hydroxybutyrate concentrations. Nonesterified fatty acid concentrations reached the highest levels 1 day after dry-off. Beta-hydroxybutyrate concentrations initially decreased at dry-off, but then increased at +1d and +2d after dry-off. Concentrations of albumin, calcium, and cholesterol remained consistent. Some biomarkers associated with altered nutrient metabolism changed at dry-off. Future studies should be directed towards assessment of other metabolic stress biomarkers and their impact on dry dairy cattle health and well-being.

Research Grant: Meadow Brook Laboratory
Student Support: Boehringer-Ingelheim, MSU College of Veterinary Medicine and Graduate School

Identification/characterization of double/single strand RNA binding sites of the N-protein of CCHF virus

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Crimean-Congo hemorrhagic fever (CCHF) is a zoonotic tick-borne virus (Nairovirus) from the family Bunyaviridae. It is of great scientific significance because of the lack of treatment options available for human disease and its potential use as a bioterrorist weapon. The goal of the project is the expression and purification of the “stalk domain” of the nucleocapsid protein. This region specifically binds to the panhandle region of viral genomic RNA. Thus, this interaction is likely a target for therapeutic intervention of this viral disease. The gene sequence encoding the stalk domain has been incorporated in the bacterial plasmid. The plasmid will be transformed in the bacteria and grown on an agar plate having kanamycin. The bacteria receiving the plasmid will survive. The colonies will be picked and tested for the expression of the stalk domain, using SDS-PAGE. The colony showing the best expression will be grown in one liter cultures for more expression. The protein will be purified by Ni-NTA technology and used in screening chemical compounds in future.

Research Grant: NIH
Student Support: Merial Veterinary Research Scholars Program
In vitro effects of the chemotherapy agent Paccal Vet (Paclitaxel) on canine hemangiosarcoma cell lines

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Hemangiosarcoma is a malignant neoplasm seen in dogs that originates from the vascular endothelium. Canine hemangiosarcoma has a high metastatic rate and carries a poor prognosis. Due to poor prognosis associated with the disease, investigation of new treatment options to improve long-term prognosis for patients is needed. Paccal Vet (Osamia Pharmaceuticals) is a water soluble nanoparticle formulation of the drug paclitaxel and this study tested the drugs effect on three canine hemangiosarcoma cell lines in vitro. The aim was to characterize Paccal Vet’s efficacy and its mechanism of action in hemangiosarcoma cell lines including cell viability, cell cycle arrest, cell death mechanism, anti-angiogenic effect, and impact on Vascular Endothelial Growth Factor and basic Fibroblast Growth Factor production. The effects of cell viability and anti-angiogenesis were evaluated using different clinically relevant concentrations of Paccal Vet at 24, 48, and 72 hours. MTT assay showed dose and time dependent cytotoxic effects in treated cells. Inhibitory Concentration 50% of three hemangiosarcoma cell lines ranged from 360ng/ul to 610ng/ul which are clinically achievable doses. Cell cycle showed cell cycle arrest at G2/M phase for treated cells. Annexin V and Caspase Glo 3/7 assays showed significant increases in apoptosis for treated cells. Reverse Transcription-PCR was performed on the three cell lines to validate the gene expression of Vascular Endothelial Growth Factor and basic Fibroblast Growth Factor. Results obtained from this study provided insight into potential use of Paccal Vet in vivo to treat canine hemangiosarcoma.

Research Grant: None
Student Support: Boehringer Ingelheim Veterinary Scholars Program

Seizure inhibition and onset site localization by focal TTX infusion in a rat model of temporal lobe epilepsy

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Temporal lobe epilepsy is common in humans. Seizures usually start in the hippocampus. To test mechanisms of ictogenesis and develop more precise treatments, it would help to localize seizure onset sites in animal models. We hypothesized that inhibiting a focal region of the hippocampus in epileptic pilocarpine-treated rats would prevent seizures. Rats were surgically implanted with cannulae directed to the ventral hippocampus attached to subcutaneous mini-osmotic pumps to continuously infuse tetrodotoxin (TTX) to block action potentials or saline. Local field potential (LFP) recording electrodes (32/rat) were implanted in brain regions where seizures might start: septum, amygdala, olfactory cortex, dorsal and ventral hippocampus, and entorhinal cortex. Rats (n=4) were monitored for spontaneous seizures at least 9 h/day for weeks. Results were analyzed while blinded to electrode locations and periods of TTX infusion. 288-515 spontaneous seizures were recorded/rat. In one rat, during saline infusion, seizure frequency was 0.96 ± 0.15 per hour, earliest electrographic seizure activity was recorded first in the left ventral hippocampus in 80% of seizures, and average peak LFP amplitude in the left ventral hippocampus during slow wave sleep was 5.2 ± 0.2 mV (mean ± sem). Focal infusion of TTX into the left ventral hippocampus reduced average peak LFP amplitude to 35% of baseline (p < 0.001, t test) indicating focal inhibition. While LFP amplitude was focally suppressed, seizure frequency was reduced to 13% of baseline (p < 0.001). LFP amplitude and seizure frequency returned to baseline levels after TTX infusion stopped. These findings reveal that onset sites can be identified and seizures can be blocked by focal inhibition.

Research Grant: NIH
Student Support: NIH
Machine learning reveals leptin acts to influence the expression of rate-limiting TCA cycle enzymes in tilapia

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The “Omics” revolution continues to transform biology. Studies utilizing transcriptomics, genomics, proteomics, metabolomics, and the like produce large amounts of robust data. However, classical statistical methods can oftentimes miss significant and unique findings in such enormous datasets. By identifying unique patterns within the data, machine learning algorithms can solve some of these problems. This, in turn, has the broader effect of changing the traditional paradigm of the scientific method. The present study employs transcriptomic (RNAseq) analysis coupled with novel machine learning approaches to identify the actions of the catabolic stress hormone, leptin, on the rostral pars distalis (RPD) transcriptome in tilapia (Oreochromis mossambicus). These analyses revealed that rate-limiting enzymes of the TCA cycle were under the control of leptin. Quantitative reverse transcription-PCR (qRT-PCR) was then used to confirm and expand on these findings. In summary, our study has used a cutting-edge machine learning approach to reveal a novel cellular metabolic pathway under the influence of leptin.

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Student Support: None

In vitro maturation of caprine oocytes held at room temperature

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Developing a protocol to recover and transport oocytes, from live or deceased caprine species of interest, is crucial to maximizing embryo production and species conservation. It would be especially useful if recovered oocytes could be kept viable in a media at room temperature during overnight transport to laboratories equipped to process them. We hypothesized that maturation rates of oocytes held at room temperature for a holding time of 18 hours will not be different from that of oocytes placed into in vitro maturation immediately after retrieval. The objective of this study was to determine whether oocytes held prior to in vitro maturation display similar rates of nuclear maturation as determined by the extrusion of the first polar body. Oocytes were retrieved from goat ovaries collected from a local abattoir. Only morphologically normal oocytes were selected for this study and allotted into two experimental groups. Oocytes in the control group were placed immediately in maturation media and incubated for 24 hours at 38.5°C; whereas, oocytes in the holding group were kept in Emcare holding media for 18 hours at room temperature before being placed in maturation media. The data was analyzed using Chi-square with Yates correction. Overall, the maturation rate of caprine oocytes was 24% (21/88). The maturation rates between control oocytes (23%; 10/44) and oocytes in the 18-hour holding group (25%; 11/44) did not differ (P ≥ 0.05). We concluded that holding caprine oocytes for 18 hours before being placed in maturation media could be an attractive strategy for transporting oocytes to laboratories working with assisted reproduction.

Research Grant: None

Student Support: Boehringer Ingelheim
Comparing the prevalence of *Babesia* spp. infections in wild carnivores on Cape Cod, Massachusetts and mainland

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*Babesia* is a tick transmitted protozoan parasite that can infect multiple vertebrate hosts. Human babesiosis is recognized worldwide, and this infection frequently presents as coinfection with or is mistaken for Lyme disease. Cape Cod, Massachusetts is a region known to be hyperendemic for Lyme disease in people. Previous studies detected a prevalence of 95-97% of raccoons being infected with at least one *Babesia* species, but to our knowledge *Babesia* infections in raccoons on Cape Cod have not yet been studied. We predict the prevalence of *Babesia* spp. in wild carnivores, including raccoons, on Cape Cod is higher than that of mainland. This study aims to determine and compare the prevalence of *Babesia* infection of wild carnivores on Cape Cod to that on mainland. The USDA Animal and Plant Health Inspection Service’s Wildlife Service provided blood clots from their annual rabies surveillance from 2014 to 2016. Samples were tested by two independent PCR assays. The first assay used primers to amplify across the V4 region of the 18S rRNA gene from *B. sensu stricto* clade. The second assay used primers to amplify a fragment of the V4 region of the 18S rRNA gene from the *B. microti-like* clade. To date, DNA has been extracted from 460/499 samples and 19/499 samples have been tested with both PCR assays. Out of the 19 samples, 15 were from raccoons and 4 were from striped skunks. 40% (6/15) raccoons and 0% (0/4) skunks tested positive for *B. sensu stricto* while 13% (2/15) raccoons and 75% (3/4) skunks tested positive for *B. microti-like* DNA. The apparent prevalence of infection in this population is lower than previous studies. Unfortunately, the number of samples processed to date does not yet allow us to address our hypothesis.

Research Grant: Research Grant: None
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Crossing disease boundaries: evaluating Parkinson’s disease-associated genes in Duchenne muscular dystrophy

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Both Duchenne (DMD) and golden retriever muscular dystrophy (GRMD) are X-linked recessive disorders caused by dystrophin deficiency, which leads to muscle wasting. Parkinson’s disease (PD) is a progressive neurological disorder caused by mutations in various genes. While the pathology of these conditions differ, several overlapping molecular pathways exist. In the hopes of expanding current knowledge, we compared genes of interest between the two conditions. Whole genome microarray mRNA profiling, quantitative (Q)-RT-PCR, western blotting, H&E staining, and immunofluorescence microscopy were performed in dystrophin-deficient GRMD muscles to evaluate genes involved in the pathogenesis of PD. Microarray profiling revealed increased α-Synuclein (SNCA) and γ-Synuclein (SNCG) and decreased Parkinsonism associated deglycase (PARK7 also known as DJ-1) in dystrophin-deficient GRMD muscles compared to normal. PARK7 expression was confirmed with QRT-PCR and had a fold change of -1.694 in GRMD vastus lateralis muscle. Interestingly, SNCG protein was up regulated and localized to the peri-nuclear area of regenerating fibers in GRMD muscle. SNCA protein was expressed in PD rat brain tissue but not in PD rat or GRMD skeletal muscle. Genes associated with PD may modify the pathogenesis in dystrophin deficiency. The information gathered from this study could potentially be used to discover biomarkers and one day lead to novel therapies for both PD and DMD.

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Integrating prediction of parturition and calcium supplementation for prevention of subclinical hypocalcemia

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Accurately predicting parturition has the potential to allow for strategic prevention of metabolic disorders such as subclinical hypocalcemia, which affects between 25% and 54% of lactating dairy cows in the U.S. Adequate cytosolic ionized calcium concentration (ICC) is vital for the regulation of neurotransmission and muscle contraction. Cows diagnosed with hypocalcemia can develop problems such as displaced abomasum, uterine prolapse, and retained placenta due to the low ICC suppressing smooth muscle contraction. Moocall is a tail-mounted sensor that uses an algorithm to predict when cows are likely to calve by measuring tail movement patterns triggered by labor contractions. This device sends 2 text messages for prediction of parturition when tail movements reach a certain level of intensity that generally suggests that parturition will occur within 1-2 hours. We hypothesize that the first message Moocall sends predicting parturition can be used as a time point for strategic prevention of hypocalcemia in dairy cows. Devices will be placed on multiparous Holstein dairy cows. Excel random function will be used to assign cows to treatments (calcium supplemented and control). Calcium-supplemented cows will receive an oral bolus containing 43 g of calcium (Bovikalc) at the time of the first message predicting parturition followed by two boluses at 0 and 24 h after calving. Control cows will not receive calcium supplementation, but will receive a sham bolus administration. By evaluating the accuracy of Moocall and the effects that administering an oral calcium bolus prior to calving has on cows, the welfare of the cow can be improved by regulation of calcium homeostasis at calving and associated health disorders.

Research Grant: University of Illinois College of Veterinary Medicine
Student Support: University of Illinois College of Veterinary Medicine

Functional maturation of the cotton rat immune system through sequential viral infections

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Laboratory animals are raised in specific pathogen free environments. Recent research has demonstrated that the immune system of laboratory mice is phenotypically as immature as that of a human infant. Exposing lab mice to mouse pathogens leads to a phenotypical maturation of their immune system. Cotton rats (Sigmodon hispidus) are an ideal model to study the pathogenesis of human respiratory viruses and are used for the development of vaccines and anti-virals. We hypothesized that the immune system of cotton rats are similarly immature as that of mice, and that infecting cotton rats with different viruses would lead to maturation as measured by differences in resistance to virus infection, generation of antibody, and T-cell responses. Cotton rats were infected with three human viruses (i.e. influenza, parainfluenza, and measles viruses) or inoculated with keyhole limpet hemocyanin dinitrophenyl in different combinations in weekly intervals and then challenged with respiratory syncytial virus (RSV). Viral titers in the lung post RSV challenge indicated significant reduction in viral titers of infected versus untreated cotton rats. The same trend was visible in nasal titers. T-cell proliferation assays four weeks post infection indicated significant reductions in T-cell responses. Neutralization assays showed a trend in infected cotton rats having a higher antibody response against RSV compared to untreated cotton rats. It appears that prior infection changes the resistance of cotton rats against infection with RSV. Subsequent studies will evaluate whether cotton rats with an artificially matured immune system will be better models for vaccination studies, and what the mechanisms behind the maturation process are.

Research Grant: None
Student Support: NIH T35 Training Grant T335OD012199
Phylogenomic approach to design an optimized $\mu$Utrophin for the treatment of Duchenne Muscular Dystrophy

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Computational analysis of Dystrophin orthologs and paralogs from a broad sampling of animal species was performed to identify amino acids involved in intramolecular interactions. The goal of this effort is to design and produce $\mu$Utrophin transgenes and test them in animal models of Duchenne Muscular Dystrophy (DMD) to identify the single best candidate for clinical translation. DMD is an x-linked recessive disease afflicting approximately 1 in every 3,500 males. It is caused by mutations in the dystrophin-encoding DMD gene that abrogate protein expression resulting in a degenerative muscle disease that causes respiratory and cardiovascular failure ultimately leading to early death. Dystrophin is known to protect muscle cell membranes from the mechanical stresses developed during forceful contraction. In order to develop both an effective and durable therapy for this devastating disease, a focus has been put on the optimization of transgenes to be inserted into vectors with the capacities for both systemic delivery and scalable production (adeno-associated virus (AAV)). By utilizing the EVCouplings computational program developed by the Marks lab we have discovered intriguing evolutionarily conserved amino acid interactions within the dystrophin protein between adjacent spectrin repeats which we believe are critical for the structural stability of the dystrophin/utrophin rod under mechanical load. We also believe that the therapeutic efficacy of $\mu$Utrophin transgenes depends on the structural stability of the rod domain. This information has empowered us to redesign novel constructs to be tested in vivo, using standardized assays as well as some assays recently optimized in our own lab (Song & Rosenblum et al 2016).

Research Grant: NIH-National Institute of Neurological Disorders and Stroke Project #: 5R01NS094705-02
Student Support: NIH T35 OD010919

Causes of acute paralysis in dogs and cats

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Acute paralysis in cats and dogs is a common presentation in small animal emergency clinics; however, the etiologic prevalence is not well recorded. A retrospective review from January 2012 to July 2017 captured 545 dogs and 23 cats who presented to the North Carolina State University Small Animal Emergency Service (NCSU SAES) for an acute (less than 3 weeks) onset of paralysis (neurologic grade of 3 or higher). Intervertebral disc disease (IVDD) was diagnosed by advanced imaging or surgical intervention in 423 (77.5%) dogs. Distribution of IVD herniation was as follows: 395 (65.9%) type I discs, 30 (5.5%) non-traumatic missile discs, 18 (3.5%) type II discs, 11 (2.0%) acute on chronic discs. Presumptive IVDD was diagnosed in 30 (5.5%) dogs. Vascular disease was diagnosed in 24 (4.4%) dogs with 14 (2.6%) being fibrocartilaginous embolism (FCE). Other diagnostic categories (unknown, neoplastic, infectious/inflammatory, etc.) were diagnosed in 69 (12.6%) dogs. Dachshunds were the most common breed at 169 reports. 88.2% (149) of dachshunds were diagnosed with a type I disc. Secondary to acute paralysis, progressive myelomalacia was recorded in 18 (3.2%) dogs and syringohydromyelia was recorded in 7 (1.3%) dogs. Vascular disease was diagnosed in 15 (65.2%) cats. 14 (60.9%) cats were diagnosed with aortic thromboembolism (ATE). IVDD was diagnosed in 4 (17.4%) cats. Presumptive IVDD was diagnosed in 2 (8.7%) cats. Infectious/inflammatory diagnoses were recorded in 2 (8.7%) cats.

*percentages in parentheses are reported with respect to total number of cats or dogs included in the study

Research Grant: CVM Veterinary Scholars Program
Student Support: Merial
Pilot study using nanoparticle structure to treat cartilage defects in a sheep model

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Osteoarthritis (OA) is a debilitating disease affecting the articular cartilage (AC) of joints decreasing the quality of life for millions of people annually and creating a large economic impact through its associated medical treatments. Healing of AC poses a challenge because it lacks adequate blood, nervous, and lymph supply and it is under constant mechanical load; thus, intervention is necessary. No current methods have successfully regenerated AC in a critical defect. The purpose of this study is to test if the use of a novel nanofiber gel (NanoSlurry) will positively impact chondrogenesis by recruiting cytokines and growth factors, and mimicking native AC geometry, thus delaying the onset of OA. The NanoSlurry was developed at Northwestern University (Chicago, IL) and shipped to the University of Wisconsin-Madison School of Veterinary Medicine (Madison, WI) where it was bilaterally implanted into a full thickness cartilage defect or microdrilled defect on the femoral condyle of 3 sheep. After 7 days post-operation the femoral condyles were harvested and evaluated radiographically, histologically, and via MRI. Pilot animals showed significant integration of the NanoSlurry into surrounding, healthy AC; however, refinement in surgical technique is necessary to ensure proper placement and security of the gel within the defect. Based on preliminary histology and MRI results, we anticipate that the NanoSlurry will continue to integrate well into native cartilage and will lead to successful chondrogenesis or generation of cartilage-like tissue. The full study is on-going at the time of this submission.

Research Grant: Michael S and Mary Sue Shannon Gift Donation for Musculoskeletal Regeneration Research.
Student Support: University of Wisconsin- Madison, School of Veterinary Medicine, Office of Academic Affairs.

Investigation of sensory thresholds in Cavalier King Charles spaniels with and without Syringomyelia

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Ninety-two percent of all Cavalier King Charles Spaniels (CKCS) suffer from Chiari-like malformations (CM), a skull malformation that causes crowding of the foramen magnum and turbulent cerebrospinal fluid (CSF) flow. In many cases CM is accompanied by the formation of a fluid-filled pocket within the spinal cord called Syringomyelia (SM) that together with the skull malformation can result in severe neuropathic pain mainly localized to the head and neck region. Owners of affected CKCS frequently complain that their pet is suffering from significant pain; however, routine examination including head and neck palpation does not always correlate with the reported clinical signs. The purpose of this study was to obtain quantitative data on sensory thresholds in these dogs through the use of thermal and mechanical stimuli using a temperature probe and specialized calibrated hemostatic forceps. Fifty-four dogs underwent routine neurological examinations, sensory thresholds testing, and magnetic resonance imaging (MRI) was performed to diagnose CMSM. No significant difference in sensory threshold latencies were found between dogs with and without SM or between dogs with owner-reported clinical signs versus those reported asymptomatic. There was a trend toward decreased thermal thresholds associated with dogs that were painful on neurological examination compared to those that were not. Mechanical thresholds were significantly lower on the side of the neck that corresponded to lateralization of SM in dogs with asymmetrical syrinxes (P = 0.016, 0.028). This information can be leveraged to optimize treatment protocols and objectively study efficacy of future therapeutics in CKCS.

Research Grant: This work was funded by the American Cavalier King Charles Spaniel Club Charitable Trust through the American Kennel Club Canine Health Foundation
Student Support: AVMA/AVMF 2nd Opportunity Summer Scholarship; George H. Hitchings New Investigator Award
Regulation of canine Neutrophil Extracellular Trap formation by immune-mediated hemolytic anemia therapeutics

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Canine immune-mediated hemolytic anemia (IMHA) has a mortality rate of up to 80%, primarily due to thromboembolism. Hypercoagulability in IMHA may be due to formation of Neutrophil Extracellular Traps (NETs). NETs are webs of DNA and protein released by neutrophils in response to infectious and inflammatory stimuli. NETs are pro-thrombotic and markers of NETs are increased in dogs with IMHA. Multiple immunosuppressive and antithrombotic agents are employed to treat dogs with IMHA, but the ideal IMHA therapies remain unknown. Based on their mechanisms of action, some IMHA therapies may inhibit NETosis, and, given the role of NETs in thrombosis, such therapies might be superior to those that do not. We hypothesized that some established IMHA therapies (heparin, aspirin, cyclosporine, mycophenolate), but not others (dexamethasone, clopidogrel, azathioprine), would inhibit NETosis. We tested this hypothesis through an ex-vivo model of NETosis. Neutrophils were isolated from the peripheral blood of healthy dogs and incubated with various concentrations of different test drugs, followed by a NET stimulator (platelet activating factor, PAF or phorbol-12-myristate-13-acetate, PMA). After 3 hours, extracellular DNA, representing NETosis, was measured using the cell impermeable dye SytoxGreen. Aspirin (1.2-1200 μg/ml) significantly decreased PMA and PAF-induced NETosis (p<0.006). Cyclosporine (28.8-2880 ng/ml) reduced 7 μM but not 7 nM PMA- or PAF-induced NETosis (p=0.0014). Dexamethasone and azathioprine did not significantly effect NETosis. Testing is in progress for heparin, mycophenolate, and clopidogrel. Identifying drugs that reduce NETosis in dogs could guide IMHA therapy, improving disease outcomes.

Research Grant: Iowa State College of Veterinary Medicine College Seed Grant and Iowa State College of Veterinary Medicine laboratory start-up funding to Dr. LeVine
Student Support: Boehringer Ingelheim Veterinary Research Scholars Program

A novel histological atlas of the octopus

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Octopuses are charismatic inhabitants of many public aquariums and are a popular attraction for visitors. Aspects of octopus physiology, gross anatomy and clinical care have been well documented. However, current literature on the detailed histological microanatomy of the octopus is incomplete and limited to the digestive tract and the reproductive tract. This project seeks to create a complete histological atlas of the tissues and organs of the octopus through gross examination and extensive sampling of multiple species including the East Pacific red octopus (Octopus rubescens) and the Giant Pacific Octopus (Enteroctopus dofleini). These data will be compiled to create an online histological atlas of the octopus, providing users with a publicly available learning tool and educational service with an interactive self-assessment feature. These data will serve as a baseline for veterinarians, biologists, and pathologists, allowing for a better appreciation of normal tissues, and, in comparison, lesions and disease processes. In turn, a better understanding of normal tissue parameters will translate to improved veterinary care for octopuses and a better perception of octopuses by aquarium visitors.

Research Grant: Biomedical Sciences Summer Research Program
Student Support: Boehringer Ingelheim Scholar Program
Effects of environmental enrichment on stress and the microbiota in young mice

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Reproducibility of an experiment is one of the principles of the scientific method, and the ability to improve this would have profound effects on research techniques. Enrichment is shown to decrease stress levels in mice, having the potential to affect study reproducibility. The gut microbiota (GM), bacteria that inhabit the intestinal tract, varies with environmental factors, including those associated with stress. These variations have the potential to alter model phenotypes. We investigated two mouse strains with differences in anxiety-related behavioral phenotypes, BALB/cJ (anxiogenic) and C57BL/6J (anxiolytic). Mice were divided into five treatment groups (n=8 per strain), receiving either daily handling, sunflower seeds, igloos, crinkle paper bedding (Enviro-Dri), or no additional enrichment. Fecal samples were collected on day 0, 7, and 42 and evaluated using 16S rRNA gene sequencing for characterization of GM composition and richness. Behavioral tests (open field, elevated plus, light/dark) were performed to evaluate differing stress-related behaviors among groups correlating with GM changes. We predict that enrichment variation will affect GM composition, with the most drastic changes occurring between day 0 and 7 of treatment. Furthermore, we predict dramatic changes in mice receiving sunflower seeds, with the handled groups also showing stark differences. We expect handled mice to show lower anxiety-like behavior (increased light/open space exploration) correlating with increased GM diversity and richness. Discovering enrichments that affect the GM will increase reproducibility by decreasing variations amongst subjects, allowing for increased experimental accuracy and better treatment options.

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Effect of dietary virgin coconut oil on GALT immune cell production of IL-17 in weanling piglets

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Dietary antibiotic supplementation of weanling piglets has been the gold standard to ensure piglet growth performance. However, use of sub-therapeutic antibiotic dosages in production animal feed selects for antibiotic resistant bacteria. Recent research has focused on development of animal feed supplements to maintain immune function and growth without antibiotic supplementation. This project investigated the ability of dietary virgin coconut oil to modulate immune cells in gut-associated lymphoid tissue (GALT) to favor an anti-inflammatory environment. Coconut oil, which is comprised of 91% saturated fatty acids, affects gut microbial dynamics and spleen lymphocyte proliferation. We hypothesized that piglets fed a diet with virgin coconut oil but without antibiotics would: 1) produce less pro-inflammatory cytokines, like Interleukin-17 (IL-17), in GALT, as opposed to piglets fed a diet lacking both virgin coconut oil and antibiotics (control); 2) produce similar amounts of IL-17 in GALT to piglets fed an antibiotic-enhanced diet. We used immunohistochemistry (IHC) to evaluate IL-17 (Abcam, Cambridge, MA) quantity in villi and Peyer’s patches of the ileum of piglets in the following dietary treatment groups (n=4 pigs/treatment): antibiotic only, virgin coconut oil only, control. IL-17 was quantified in three fields (40x) of villi and three fields of Peyer’s patches for the sample and control tissue on each slide using ImageJ (US NIH, Bethesda, MD). At the time of abstract submission, IHC quantification was underway. This project, in combination with future evaluation of other immune cell markers, will determine if dietary virgin coconut oil supplementation affects the GALT immune environment of weanling piglets.

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Student Support: National Institutes of Health #5T35OD010991
Prevalence of early lactation hoof lesions and its association with reproductive performance of dairy cows

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Lameness is of growing concern among dairy herds in the US. It negatively affects cow welfare and is reported to be associated with decreased milk production and poor fertility. This study was designed to evaluate the prevalence of early lactation hoof lesions as well as its association with reproductive performance in dairy cows. We hypothesized that cows with hoof lesions at early lactation would have decreased cyclicity, lower pregnancy risk after first AI, and greater pregnancy loss (PL) compared to healthy herd-mates. Jersey cows (n=700) in a free stall barn with concrete floors were enrolled at 20 ± 3 DIM for 12 weeks. Cows were assessed for hoof lesions in a chute and body condition scored (BCS). After enrollment cows were scanned twice (27 and 41 DIM) and if a corpus luteum was identified in either scans, they were recorded as showing cyclic. Cows were followed until the first AI and all pregnancy events were recorded. The herd showed a 26.7% prevalence of hoof lesions distributed as 64.0% sole hemorrhage, 12.2% sole ulcer, 11.2% digital dermatitis, 8.1% white line disease, and less than 4% other lesions.

The proportion of cows that were cycling for healthy and lame cows was 48.3% and 39.4%. Healthy and lame cows also showed a 39.8% and 31.3% proportion of pregnancy, respectively, after first AI. Pregnancy loss rates were similar for healthy and lame cows at 1.5% and 1.9% respectively. This data shows that cows who are lame in early lactation are more likely to have decreased cyclicity and lower pregnancy risk after first AI. This study confirms the importance of hoof health in maintaining efficient reproduction as well as proper animal welfare in a dairy herd.

Research Grant: Agricultural Relief Fund (RARF) -Minnesota Agricultural Experiment Station
Student Support: Department of Veterinary Population Medicine, University of Minnesota

Quantifying the use and mechanism of defective viral genome oligonucleotides as a preventative antiviral

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Broad spectrum antivirals can be an important tool in the prevention of an emergency epidemic. If vaccines are not available, a broad spectrum can reduce the likelihood of the disease from spreading to other areas. However, most broad spectrum antivirals produce side effects, are impractical, or are toxic. The aim of this study is to better understand the use of defective viral genome derived oligonucleotides (DDOs) as an alternative to current antivirals for emergency epidemic prevention. DDOs are derived from DVGs (defective viral genome), which is a truncated RNA genome that forms during viral replication and elicits a Type-I interferon response both in vitro and in vivo. In repeated preliminary studies, mice pre-treated intranasally with DDO were better protected against Influenza A Virus (IAV), than the control. In this study, the antiviral effect was measured by reduced weight loss, viral titer, and qPCR. Part I sought to determine the appropriate amount of DDO to administer, in addition to its lasting effect. Results showed that DDOs have a more effective response 12 hours post administration of DDO, compared to 6 hours and 24 hours. In addition, 5μg of DDO was determined to be the appropriate dose to administer. Part II of the study will further explore the mechanism behind this antiviral effect by looking at RIG-I and TLR pathways in knock out mice. By better understanding the mechanism in which the DDO creates an antiviral response, the sooner DDOs can be used to prevent the spread of disease. Although they may not directly treat disease, they can be used as a preventative to control the pathogen from spreading to other farms that might have been exposed to the emerging pathogen.

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Student Support: Merial Veterinary Research Scholars Program (NIH T35OD010919)
Assessment of Zika Virus neurotropism

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Zika Virus (ZIKV) is an emerging infectious disease that typically presents with mild illness, fever, conjunctivitis, arthralgia, headache, and maculopapular rash. However, it can also cause various neurological disorders, including meningoencephalitis, Guillain-Barre Syndrome, and microcephaly in infants. The mechanisms by which ZIKV causes these neurological disorders are not well understood, warranting further investigation. Recently, our lab discovered that two African ZIKV strains, MR766 and IbH30656, persistently infect, without damaging, sensory neurons of the trigeminal and dorsal root ganglia, which could lead to persistent shedding in various bodily secretions. To determine whether ZIKV strains from South America act similarly, PRVABC59 from Puerto Rico and FLR from Columbia were used to infect sensory trigeminal and dorsal root ganglia along with autonomic ciliary ganglia and superior cervical ganglia cultured from six-week-old Swiss Webster mice. MR766 was used as a positive control. A five-day time course was performed for all strains where each day neurons were fixed, immunostained for ZIKV, counted, and the percent of all cultured neurons that were infected was calculated. Additionally, titrations were performed to quantify virus released from infected neurons. Due to an increase of neurological disorders associated with South American ZIKV outbreaks, we expect these strains to behave differently than the African strains.

Research Grant: Virginia-Maryland College of Veterinary Medicine
Student Support: Virginia-Maryland College of Veterinary Medicine

Telomeres and varying lifespans in a range of rodent species

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The order Rodentia contains species with a great range of lifespans, offering a promising chance to study longevity and aging. Telomeres, repetitive DNA sequences that protect the ends of chromosomes, are an important aspect of aging. Shortening of telomeres can lead to cellular senescence, yet active lengthening of telomeres by the enzyme telomerase can contribute to cell immortality and cancer. The aim of this project is to establish telomere length and telomerase activity in rodent species of varying lifespans. Cultured primary fibroblasts from the African grass rat (Arvicanthis niloticus - mean life span 6.7 years), guinea pig (Cavia porcellus - 12 years), and fox squirrel (Sciurus niger - 16 years) have been selected for the study; this being the first time that telomere length and telomerase activity have been evaluated in the African grass rat and fox squirrel. Furthermore, the use of quantitative real-time PCR (qPCR) to measure telomere length and telomerase activity in these wild species is a novel approach. Adaptation of qPCR assays to these species represents a notable technological improvement, as it allows for more accurate quantitation, requires less sample, and is easier to use than previously employed techniques. It is important that we specifically investigate rodent fibroblasts, as they are currently being used as a model of mammalian aging. Understanding their telomere biology will help us compare these rodent models to other species and expand our understanding of longevity in mammals.

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Student Support: NIH Veterinary Summer Scholars Program (T35-OD015130)
Prevalence, species distribution, and mechanism of methicillin resistant *Staphylococcus* in companion animals

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Methicillin-resistant *Staphylococcus* (MRS) are leading causes of skin, ear, and wound infections in companion animals. Methicillin resistance in *Staphylococcus* is typically due to PBP2a, a protein with low affinity for most β-lactams. MRS often have concurrent resistance to other antibiotics, resulting in limited treatment options. The goal of this study was to determine prevalence, species distribution, and mechanism of resistance of MRS from clinical cases in dogs, cats, and other companion animals submitted to the Veterinary Diagnostic Laboratory at ISU from 2012-17. The phenotypic methicillin resistance rate of *Staphylococcus* was 24.5% (605/2470) overall, 19.4% (316/1626) in *S. pseudintermedius*, 39.2% (252/643) in coagulase negative *Staphylococcus* (CoNS), and 18.4% (37/201) in coagulase positive *Staphylococcus* (CoPS, including *S. aureus*). Cross resistance to other β-lactams was quite common among MRS isolates, especially when oxacillin MIC was >4 µg/mL as opposed to >0.5 - <4 µg/mL. PBP2a was detected by agglutination in MRS at 78.4% (442/564) overall, 92.2% (271/294) in *S. pseudintermedius*, 58.7% (138/235) in CoNS, and 94.3% (33/35) in CoPS. A subset of MRS isolates (n=107) were tested for susceptibility to antibiotics of high importance in humans. Non-susceptibility was found in one isolate to tigecycline, and two isolates to daptomycin. All isolates were susceptible to linezolid and vancomycin. These results indicate a relatively high prevalence of MRS in companion animals, which may result in difficulty treating clinical cases associated with these pathogens. Thus, routine susceptibility testing of *Staphylococcus* isolates from companion animal clinical infections is highly warranted.

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Mitigation of snake venom induced coagulopathy using CORM-2 infused cryoprecipitate in canine whole blood

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Snake envenomation affects thousands of dogs annually in the United States; many will develop coagulopathy that reduces coagulation and accelerates fibrinolysis. Unfortunately, the current gold standard of antivenom therapy is expensive, non-specific, and variably successful. Therefore, investigation into alternative therapies for venom induced coagulopathy is essential to improving the efficacy of medical treatment. Recent in vitro research on human and canine plasma shows that carbon-monoxide-releasing-molecule-2 (CORM-2) effectively reduces the pathologic effects of snake venom by making fibrinogen more resistant to cleavage. However, pilot studies have shown that CORM-2 inhibits platelet function and reduces clot strength in whole blood. In order to safely deliver CORM-2 in whole blood, we used commercially available canine cryoprecipitate consisting of concentrated blood factors. Thromboelastography (TEG) was used to measure various dynamics of clot formation of canine whole blood exposed to prairie rattlesnake (*C. viridis*) venom in vitro. We hypothesize that cryoprecipitate will provide a safe and effective vehicle for CORM-2 delivery in whole blood. We expect that cryoprecipitate infused with CORM-2 will prevent fibrinolysis and enhance coagulation of canine whole blood exposed to *C. viridis* venom in vitro. If successful, this treatment could greatly impact the effectiveness of treatment for snake envenomation by making therapy more affordable and accessible.

**Research Grant:** Unknown

**Student Support:** Morris Animal Foundation
Evaluation of leak pressure and closure time of interrupted vs. continuous double layer esophagotomy closure

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The retrieval of foreign bodies and resection of recurrent esophageal strictures are the most frequent indications for esophageal surgery in cats and dogs. Few intra-operative complications occur. Most complications occur postoperatively as incisional dehiscence and stricture formation. The incidence of complications may be lowered by optimizing incisional closure; however, previous study of closure techniques has been primarily directed at the number of layers closed with less focus on the suture pattern used. In our study, 3 cm esophagotomy incisions made in cadaveric swine esophagi were closed using two different double layer closure techniques. Group one incisions (n = 15) were closed with a simple interrupted pattern and group two incisions (n = 13) were closed with a simple continuous pattern. Data were compared using a t-test or Mann-Whitney Rank Sum test as applicable with significance at P < 0.05. Median (range) leak pressures for groups one and two were 16.0 (5.4-54.9) mmHg and 38.7 (11.3-81.9) mmHg, respectively (P = 0.03). Mean closure times (± standard deviation) for groups one and two were 19 min ± 2 min and 14 min ± 1 min, respectively (P < 0.01). The double layer simple continuous closure maintained a higher median immediate leak pressure and was faster than the double layer simple interrupted closure.

Research Grant: None
Student Support: Boehringer Ingelheim

Effect of selective dry cow therapy on udder health and milk microbiome in dairy cattle

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Selective dry cow therapy (SDCT), as compared to blanket DCT, is one strategy to help ensure judicious use of antimicrobials in dairy production. Potential deleterious effects of intramammary (IMM) antibiotics on the milk microbiome have yet to be explored. The purpose of this study was to determine the effects of a SDCT protocol on udder health and milk microbiome in post-partum dairy cattle. In a randomized clinical trial, the udder health of 100 animals from a commercial dairy was assessed before the dry period. Animals with somatic cell count (SCC) <200,000 cells/mL were considered to be free of IMM infection and were enrolled. Eligible cows were randomly allocated into either the treatment group which received an IMM infusion of long-acting ceftiofur hydrochloride (Spectramast DC, Zoetis), or control group (no IMM antibiotic infusion). After calving, milk samples will be aseptically collected from all cows at days 3, 7, 21, and SCC will be measured. Differences in SCC will be analyzed using repeated measures adjusted for multiple comparison. Milk microbiome samples will be rarefied to equalize sequence depth, and low-quality sequence data and chimeric reads will be removed. The Qime pipeline will be used for clustering, taxonomic classification and descriptive and statistical analyses, primarily with default settings. No difference in udder health between treated and untreated cows is expected post-calving. Milk microbiome differences between the two groups are unknown, as no previous studies have investigated this area. SDCT in low SCC cows has the potential to reduce antimicrobial use on commercial dairy farms while neither compromising udder health nor disrupting milk microbiota post-partum.

Research Grant: Colorado State University Integrated Livestock Management
Student Support: USDA-NIFA Animal Health & Disease Research Program Funding 2017-36100-06008
Stress induced transcription factors synergistically stimulate the herpes simplex virus 1 ICP0 promoter

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Herpes simplex virus 1 (HSV-1) has a primary site of latency in sensory neurons of the trigeminal ganglia when infection is initiated in the ocular, nasal, or oral cavity. Reactivation from latency is crucial for virus transmission and recurrent disease. Increased stress correlates with reactivation in humans. The synthetic corticosteroid dexamethasone (DEX) stimulates reactivation from latency in small animal models confirming stress is important for reactivation. DEX inducible cellular transcription factors were previously identified and several were Kruppel-like transcription factors (KLF). KLF15 was previously shown to stimulate the HSV-1 infected cell protein 0 (ICP0) promoter, which is an important viral transcriptional regulatory protein. We hypothesized that the HSV-1 ICP0 promoter is activated by two stress-induced transcription factors, the glucocorticoid receptor (GR) and KLF15. To test this hypothesis, we transfected mouse neuroblastoma 2A (Neuro-2A) cells with the ICP0 promoter, KLF15, GR, and treated cells with DEX to activate the GR. We found that the GR and KLF15, strongly activated the ICP0 promoter compared to the GR or KLF15. We also tested a deletion construct promoter -95 ICP0 and found activation by the GR + KLF15 + DEX was not as efficient. We are examining two other viral promoters (ICP6 and VP16) because VP16 is required for activating the ICP0 promoter and ICP6 is necessary for DNA replication in quiescent cells. We conclude that the GR and KLF15 cooperate to stimulate ICP0 promoter activity and ICP0 promoter sequences between -97 to -800 are important for KLF15 and GR mediated promoter activation.

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Stress behavior in feedlot cattle and the impact of acclimation and low stress cattle handling techniques

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Beef calves entering a feedlot are influenced by the stresses of weaning, transporting, and interacting with new individuals. Acclimation and low stress cattle handling (ALSCH) may decrease stress experienced by calves during this transition period. The objective of this study was to identify distressed and relaxed behaviors in feedlot calves to determine if ALSCH practices reduce the level of stress experienced by cattle. In this study, newly weaned comingled calves were transported to a feedlot and randomly enrolled into pens. Half of the pens received ALSCH practices and half served as the control group receiving traditional handling practices. Calves in ALSCH pens were acclimated by having trained professionals enter the pen and facilitate calf movement about the pen as a herd. Calves were then moved through a tub and curved chute system in the processing barn without being restrained. Calf stress was determined by analyzing behavior patterns in the pens during and after acclimation. Still photos taken at 6am, 8am, 12pm, 4pm, and 7pm were selected to assess various times of activity and rest while avoiding human interaction. The percentage of calves standing, lying, eating, and drinking was recorded and analyzed for an indication of relaxed versus stressed behavior. When comparing the ALSCH and control pens, the first cohort reported more control calves standing and lying in the pen (39% and 31% respectively) compared to ALSCH calves (30% and 24% respectively). However, less calves were able to be counted in the ALSCH pens (66%) than control pens (82%). This result may be due to lack of visibility of ALSCH calves because of tighter herding behavior. More cohorts will be analyzed to produce more significant results.

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Student Support: Boehringer Ingelheim Veterinary Research Scholars Program
The effect of anal fin color on male mating depth preference in Bluefin Killifish (*Lucania goodei*)

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Bluefin killifish (*Lucania goodei*) populations provide the opportunity to study the population biology of color polymorphism. In most natural systems, one color morph in a species with color polymorphism will go to fixation due to natural selection or genetic drift. However, in *L. goodei* populations found in springs, males display both red and yellow anal fin colors. This polymorphism is controlled by a single locus, and each naturally occurring population has both color morphs. One hypothesis for the maintenance of polymorphisms within populations is that there are different microenvironments where each color morph has a higher level of fitness. The aim of this study was to determine the effect that male *L. goodei* anal fin color has on preferential mating depth in order to determine if mating depth could be a driving factor in the presence of color polymorphism in this species. Red is more vibrant in clear water at shallower depths, so males with red anal fins should display higher preference for mating in shallow water when compared with yellow-finned males. One male and five female *L. goodei* were placed in a tank set up with spawning mops at three different depths. The mops were removed twice daily for five days and the eggs were removed from the mops and counted. The eggs were placed in a solution of methylene blue to determine whether they had been fertilized. Preliminary data showed that the eggs were most often laid and fertilized at the top of the tank regardless of the coloration of the male. These results indicate that depth is unlikely a major factor in maintaining polymorphism within *L. goodei* populations. Alternative hypotheses to explain maintenance of color polymorphism are being tested.

Research Grant: None
Student Support: Office of the Director, NIH, T35 OD011145

Comparison of survival among different categories of chronic kidney disease in dogs

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Chronic kidney disease (CKD) is a common cause of morbidity and mortality in dogs that can be due to many different underlying disease processes. While several studies have investigated prognosis in dogs with CKD, survival studies in which the category of disease is based on a renal biopsy evaluation are lacking. The objective of this study was to determine if disease category influenced survival time of dogs with CKD. Retrospective evaluation of the database from the International Veterinary Renal Pathology Service was performed. This database contains a diagnosis based on comprehensive renal biopsy evaluation as well as follow-up information for a subset of cases. Median survival times post-biopsy were calculated using Kaplan-Meir survival curves generated using Microsoft Excel. Of 1,186 canine renal biopsies since 2008, follow-up information was available for 19% of cases (231/1,186). Nine disease categories contained at least 10 cases with follow-up. While survival times in each category displayed substantial overlap, dogs with membranoproliferative glomerulonephritis (MPGN), amyloidosis, and nephrosclerosis had the shortest median survival (~100-200 days) while dogs with membranous glomerulonephropathy and mixed MPGN had the longest median survival (~1100 days). Dogs with mesangio proliferative glomerulonephritis, focal segmental glomerulosclerosis, juvenile nephropathy, and tubulointerstitial disease had intermediate survival (~550-750 days). Regardless of disease category, dogs biopsied when serum creatinine was ≥ 5 mg/dL had a median survival of only 6 days. Results from this study provide prognostic information for clinicians and owners that can lead to more informed decisions and improve animal welfare.

Research Grant: None
Student Support: Boehringer Ingelheim Veterinary Scholars Program & College of Veterinary Medicine, Texas A&M U
Can the MAPK pathway circumvent normal mechanisms of DNA replication initiation in melanoma?

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Melanoma is responsible for the vast majority of skin cancer mortality. Around 50% of human cases of melanoma are the result of a mutation constitutively activating BRaf, a protein kinase member of the MAPK pathway. MAPKs are highly conserved signal transducers that play a role in cell growth and proliferation. Vicinal protein labeling identifies treslin, a master regulator of origin of replication opening and DNA replication, as a target of the MAPK pathway. Treslin is classically regulated by processes that control the cell cycle, while MAPK is activated in response to growth factors. Here we investigate the possibility that overactive MAPK signaling circumvents normal regulation of treslin to stimulate cell division in tumorigenesis. To test this hypothesis, we utilized an assay capable of separating phosphorylated and non-phosphorylated protein via the addition of a phosphate-group tag allowing a visual mobility shift on western blot. We shut off the MAPK pathway by treating melanoma cells with a small molecule inhibitor of BRaf (Plx4032). Results of our phos-tag western blot assay demonstrated that the phosphorylation of the MAPK pathway member Erk is downstream of and dependent on active BRaf, however data on the phosphorylation status of treslin in these cells was inconclusive due to the lack of fidelity of available treslin antibody. To overcome the challenges from lack of antibody, ongoing studies focus on the creation of a plasmid construct containing exogenous Flag-HA-His-tagged treslin. Future studies are directed at identifying specific phosphorylation sites of the treslin molecule using mass spectrometry that may serve as potential therapeutic targets.

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Student Support: NIH, Office of the Director.

Mitochondrial defects are associated with aggressive canine osteosarcoma

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Osteosarcoma (OSA) is an aggressive mesenchymal carcinoma of the bone. The pathologies of human and canine OSA are similar, which makes canine OSA an excellent model for investigating the etiology and pathogenesis of OSA. Our preliminary data suggests heterogeneity in mitochondrial (mt) DNA content among canine OSA cell lines and tumors, with lower mtDNA associated with higher invasiveness. We therefore hypothesized that aggressive OSA have unique mt defects. Our goal in this study is to identify the nature of mitochondrial defects in OSA that are associated with the aggressive phenotype. We used canine OSA cell lines as our model and compared their inherent mitochondrial genome and functional differences. We investigated the causal role of mtDNA depletion towards mitochondrial dysfunction and OSA aggressiveness in Ethidium Bromide (EtBR)-induced mtDNA depleted OSA cell lines. We observed heterogeneity in mitochondrial parameters among OSA cell lines and the most invasive OSA cell line contained the lowest mtDNA content, markedly reduced respiratory capacity, reduced expression of electron transport chain proteins ATP5B and CcOIVi1 and increased expression of OSA metastasis genes Ezrin and β4 Integrin. Interestingly mitochondrial morphology in OSA cells were mostly “doughnut shaped”, typical of “stressed” mitochondria, compared to the filamentous network observed in healthy mitochondria. Moreover, these defects in mitochondrial morphology and functions were more prevalent in EtB induced-mtDNA depleted OSA cells. Our data suggests that mitochondrial genome and functional defects are prevalent in canine OSA which might be targeted for therapeutic treatment of OSA.

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Student Support: Boehringer Ingelheim Veterinary Scholars Program
Evaluation of an herbal compound used for management of lower urinary tract disease in healthy dogs

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Lower urinary tract disease occurs commonly in dogs. While conventional therapy typically involves modified diet and pharmacological intervention, traditional Chinese and Western herbs have been recommended as alternative and complementary treatments. There are little published data on such treatments. The purpose of this pilot study was to evaluate the efficacy of Tripsy, an herbal treatment recommended for dogs with lower urinary tract disease. We hypothesized that Tripsy would be associated with increased urine volume, decreased urine saturation for calcium oxalate and struvite, and differences in urine metabolomics when compared with placebo. Eleven healthy dogs were evaluated using a randomized placebo cross-over study in a pairwise fashion, each dog receiving treatment every 12 hours for a two-week period. After a one-week washout period, each dog received the alternate treatment for two weeks. An approximate 12-hour voided urine was collected at the end of each treatment period. Samples were analyzed for electrolytes, minerals, and creatinine using an automated chemistry analyzer; citrate and oxalate by ion chromatography; pH by electrode; and ammonia by ion-select electrode. Upper limit of metastability (calcium oxalate relative index) was evaluated by monitoring for precipitation after adding ammonium oxalate to whole urine. Relative supersaturation for calcium oxalate and struvite (an estimate of urolith formation potential) was estimated using an iterative program. Results are pending.

Research Grant: Companion Animal Nutrition and Wellness Institute
Student Support: Companion Animal Nutrition and Wellness Institute

Demographics of the spring (April-June) nuisance beaver (Castor canadensis) population on PEI

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On PEI, beavers causing or threatening infrastructure damage outside the regular trapping season are often trapped under nuisance permit. Besides annual totals, little information has been collected on the beavers. This study examined 97 nuisance beavers trapped across PEI between 12-April-8-June. Age, sexual maturity and breeding status were determined by evaluating root surface openings and annual cementum layers of teeth and gross/histological evidence of corpora lutea (CL), corpora albicantia, spermatogenesis, placental scars and mammary tissue. Ages ranged from 1.5-14.5 years (y) with 72% of the beavers 1.5-3y. Of sexed beavers (77), 45% were male. The proportion of sexually mature males and females gradually increased with age between 1.5-2, 2.5-3, and 3.5+y. In females there was also a significant positive correlation in number of CLs and age class (p < 0.01). Five females were pregnant with estimated dates of parturition between mid-May to late-July; however, cycling females were trapped as late as June 8, extending possible parturition dates into fall. The high prevalence of 1.5-3y beavers could be due to current dispersal from natal colonies, or tendency to dominate spring family damming. Sexual maturity in both sexes appeared to be reached most commonly at 2.5-3y, but as early as 1.5-2y, and sexual productivity in females increased up to 3.5-4y. A lack of placental scars and mammary tissue in non-gravid females suggests that spring nuisance trapping does not directly affect females that have recently given birth, or orphan nursing kits, thus reducing the animal welfare concerns of spring nuisance trapping. These results will better inform management decisions on the beaver population going forward.

Research Grant: AVC Veterinary Student Research Award
Student Support: Unknown
Blood response patterns in juvenile Kemp’s ridley sea turtles with granulomas following fishing hook removal

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Anglers in the Mississippi Sound often unintentionally catch Kemp’s ridley sea turtles. Following hook removal, some of these animals develop granulomas where the hook was embedded and removed. To refine diagnostic protocols and examine the turtle’s progression of pathophysiologic response to granuloma formation, CBC and serum chemistry results were compared between and among our control group (blood results from patients at the initial day of capture by hook) with granulomas (blood results from patients who developed granulomas after hook removal) and animals deemed releasable after treatment. Cell counts and serum chemistry values among groups were compared using the Kruskal-Wallis and Dunn’s tests for multiple comparisons, with p < .05 were considered significant. The granuloma group had higher WBC, heterophils, and urea values than granuloma and control groups. Turtles cleared for release also had lower phosphorus and potassium concentration, and higher Na/K ratio than the control group. Chloride was highest in the healthy group. Physiological responses and healing processes in Kemp’s ridley sea turtles are not fully understood; this work is a first step towards improving diagnostic and treatment protocols for a common ailment in sea turtles. Our goal is to use CBCs and serum chemistry to guide treatments for efficient rehabilitation and enhance survival for preservation of this critically endangered species that form granulomas.

Research Grant: Unknown
Student Support: Boehringer Ingelheim Veterinary Scholars Program and Mississippi State University CVM

Establishment of normal morphometrical parameters for equine small and large intestinal segments

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Biopsies obtained from the equine small and large intestine are routinely submitted to diagnostic pathology services in order to identify architectural and inflammatory lesions that can 1) be correlated to clinical signs of gastrointestinal disease (GID), and 2) determine an etiopathogenesis in order to provide prognostic information or guide treatment. However, unlike in canine and feline gastroenterology, normal ranges of histochemical and immunohistochemical parameters have not yet been established for equine segments of intestine. In this study, intestinal samples including mucosal and submucosal layers excised from three intestinal segments commonly biopsied during clinical evaluations of GID (proximal jejunum, distal jejunum, and pelvic flexure of the large colon) were collected and routinely processed for histochemical and immunohistochemical evaluation from seven horses euthanized for reasons unrelated to colic or GID. Architectural and inflammatory parameters were measured to establish normal morphometrical ranges for each intestinal segment. Architectural parameters included: mucosal area per total area, villus height, crypt death, number of goblet cells per unit area, number of Mucosal Associated Lymphoid Tissue (MALT) foci per unit area, and the number of S100-positive enteric ganglia and nerve fibers per unit area. Inflammatory parameters included: the number of lymphocytes, eosinophils, plasma cells, mast cells, macrophages and neutrophils per high power field found in an average of two counts per three consecutive villi and adjacent mucosal and submucosal layers identified by histochemical (H&E, PASH) or immunohistochemical (CD3, CD20, CD117, S100, Mac387) stains.

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Student Support: University of Pennsylvania School of Veterinary Medicine, NIH T35 Grant OD010919
Effect of the marijuana compound cannabidiol (CBD) in mild and moderate autoimmune disease

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Autoimmune diseases in veterinary medicine can be difficult to treat. With increased use of marijuana compounds in humans, there is interest to understand the mechanisms of these compounds to treat either human or animal autoimmune diseases. We established the experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis to examine the effects of CBD as a possible treatment. We induced mild and moderate EAE disease in mice then treated them for five days with 75 mg/kg CBD by oral gavage. We hypothesized CBD will attenuate EAE by preferentially suppressing neuroinflammation with little effect on the peripheral immune response. We examined immune function and neuroinflammation at days 3, 10, and 18 after disease initiation. CBD attenuated clinical disease as shown by clinical score and onset of disease. Assessment of pro-inflammatory cytokine production in the spleen showed that cytokine production was maximal in moderate and mild disease at day 10. CBD significantly inhibited IFN-γ in both CD4+ and CD8+ T cells in moderate disease but not mild disease. IL-17A production was not significantly altered by disease or CBD. The mechanism for immune suppression was not dependent on regulatory cells. Neuroinflammation as assessed by T cell infiltration into the brain demonstrated robust T cell staining in moderate disease which was decreased by CBD at day 18. The results suggest that the mechanism by which CBD decreases disease involves early suppression of IFN-γ production in the periphery and later suppression of neuroinflammation. The significance of this work is that CBD could be beneficial for veterinary autoimmune diseases.

Research Grant: NIH P20 GM103646
Student Support: NIH 2T35OD010432

Characterization of viral entry mechanisms of Cache Valley Virus using lysosomotropic agents

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Cache Valley Virus (CVV) is an orthobunyavirus in the family Bunyaviridae and an important mosquito-borne agricultural pathogen in North America. Infection of CVV can lead to embryonic death, congenital defects and abortion among pregnant ruminants. Its importance in public health has significantly increased in the last two decades due to its potential to cause neurotropic disease in humans. Despite its importance as a zoonotic pathogen, our understanding of its replication cycle in arthropod vectors and mammalian hosts remains limited. Similar to other arthropod-borne viruses, it has previously been hypothesized that the entry of CVV is a pH-dependent process and therefore requires the acidification of various endosomes in the endocytosis pathway. However, mechanistic evidence supporting such a hypothesis has not yet been available. In this study, the effects of three lysosomotropic agents, ammonium chloride, chloroquine and monensin, were evaluated for the inhibition of viral entry of CVV in mosquito C6/36 cells. The differential outcomes of different chemical treatments indicate the functional importance of various endosomes in the process of viral entry.

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Student Support: NIH T35OD010979
Do organ-specific endothelial cells determine tissue tropism of metastasizing cancer cells?

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The majority of cancer-related mortality is due to metastases and not the primary tumor burden. Although it has been well established that the metastasis of cancers to various tissues is not arbitrary, the mechanisms that determine metastasis sites is poorly understood. The endothelial lining of the vascular lumen is the primary barrier in metastatic events. The endothelium has been proposed to have organ-specific functions and phenotypes influenced by the unique microenvironment of each organ and it has been hypothesized that these organ-specific functions are relevant in health and disease states including cancer. Here, we evaluate the role of organ-specific endothelial cells (O-S ECs) in determining the metastatic behavior of various cancer cell lines. We isolated O-S ECs from Tie2GFP mice and seeded them in microfluidic PDMS channels to create organ-specific vasculature in a microfluidic device with control over the microvascular architecture. We tested a variety of microvascular architectural designs to determine if cellular attachment was more likely to occur at specific architectural landmarks. We also tested a variety of vessel diameters. Fluorescent cancer cell lines with known tissue tropisms will be passed through each of the organ-specific microfluidic devices to determine if the tropism was retained in the absence of parenchymal tissue. We quantified the O-S ECs isolated from different tissues and developed a protocol for seeding these into microfluidic devices. Overall, cancer cells adhere more consistently at branching points within the architecture than in linear sections. We optimized the system for HUVECs and are currently optimizing it for organ-specific microfluidic vasculatures.

Research Grant: Novo Nordisk Foundation Bio-X Scholarship
Student Support: NIH T35 Training Grant

Designing a Marek’s disease virus vaccine strain utilizing di-codon deoptimization of the UL54 gene

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Marek’s disease virus (MDV) is an alphaherpes-virus of poultry, which can cause visceral tumors and nerve enlargement. Although several highly effective vaccines are currently available, more virulent strains continue to surface. Previous work, exchanging the di-codons of one gene for other synonymous di-codons less preferential to the host, demonstrated that deoptimizing the UL54 gene could markedly attenuate MDV. In this experiment, we combined the deoptimized gene with a deleted Meq oncogene vaccine candidate. The goal was to produce a superior vaccine without any undesired lymphoid atrophy. Groups of 20 maternal antibody negative birds received experimental (B40ΔMeq, B40ΔMeq-UL54deop1, or B40ΔMeq-UL54deop2) vaccine strains at hatch. Half of the birds were bled twice and buffy coats isolated for quantitative PCR to measure virus load. Lymphoid organ weights were measured from 5 birds per group at day 15. The remaining birds were monitored for signs of pathogenicity until 8 weeks of age. Groups of 17 birds were inoculated with one of the vaccine strains, including commercial strains Rispens or HVT+SB1, followed by challenge with vv+ MDV strain 648A. The virus load of 648A was measured by qPCR from 10 birds on day 9 or 10. Each experiment was replicated twice. The deop1 vaccine provided the best protection, but caused lymphoid atrophy in at least 80% of birds. Deop2 caused no lymphoid atrophy, but protection was reduced. Data from qPCR showed a decrease in the viral genome copy number of the majority of birds vaccinated with the deoptimized strains. This data supported the conclusion that while deoptimization of UL54 eliminated lymphoid atrophy of the ΔMeq vaccine candidate, it also led to decreased protection.

Research Grant: USDA-ARS
Student Support: Joan E. and Richard Witter Fellowship
Impact of feeding method on overall activity of indoor, client owned cats

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Pet cats have obesity rates estimated between 35-67%. Easy access to calorie-dense dry foods contribute to overeating, reduced exercise, and weight gain. The goal of this randomized cross-over study is to determine if feeding cats with food-dispensing toys instead of a food bowl will increase their overall activity as measured by an activity monitor*. Twenty-eight indoor, client-owned cats fed at least 90% of their daily calories from dry commercial cat food will be recruited for the 5-week study. The study size was determined based on a paired T-test analysis with 0.8 power and 0.6 correlation. The cats will be randomly assigned to eat their normal food from toys followed by a bowl (TB) or a bowl followed by a toy (BT). Owners will be provided with 5 types of food-dispensing toy systems for their cats to choose from and instructed to place their cat’s entire daily ration in toys hidden around the home to mimic hunting behavior. Each cat spends week one acclimatizing to the activity collar and transitioning from bowls to food-dispensing toys. During the second week, TB cats continue transitioning to toys while BT cats return to their regular food bowls. Activity levels of all cats are recorded during week 3. During week 4, BT and TB cats transition to using food-dispensing toys and their regular food bowls, respectively. Activity for both groups is recorded during week 5. We hypothesize that activity will increase during weeks cats use the toys for eating as compared to weeks when bowls are used.

*Actical, Philips Respironics, Bend, Oregon

Research Grant: College of Veterinary Medicine intramural funds
Student Support: Center of Excellence (COE) Summer Research Program

Using the T-Screen bioassay to assess thyroid function in felines

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Thyroid hormones (TH) are essential for brain development, function, cellular metabolism, and maintaining homeostasis. The synthesis and release of thyroid hormones are regulated by the hypothalamus-pituitary axis, a negative feedback loop. Given the essential nature of TH, significant changes in thyroid function may be associated with severe deficiencies and developmental disorders. Feline hyperthyroidism (FH), for example, was first described in 1979 and it has become one of the most common endocrine disorders among senior felines. While the underlying cause of FH remains unknown, one of the suspected contributors to the disease are polybrominated diphenyl ethers (PBDEs). We plan to use the T-screen, a bioassay that detects interference at the molecular level, to examine the effects of PBDEs on cell proliferation. The T-screen will be used to assess the growth of a cell line derived from a rat pituitary tumor (GH3), which undergoes increased proliferation in the presence of triiodothyronine (T3). We will then use clinical samples of euthyroid felines exhibiting hyperthyroid symptoms to determine if something in the serum may be acting as a T3 analog. These samples have been tested for T3, and we will use the T-screen to measure any difference in cell growth from what is expected based on the previous concentration of measured T3 and what is seen from the bioassay. If the assay of the serum results in a statistically significant increase from the previous assay, further steps should be taken towards research in hidden endocrine disruptors. Pending the results of the assay, we plan to use mass spectroscopy to determine whether specific PBDEs are in serum and acting as biologically active hormones in future research.

Research Grant: Start-Up funds through the Petroff Laboratory, Michigan State University College of Veterinary Medicine, Veterinary Diagnostic Laboratory.
Student Support: NIH T35OD016477 to Michigan State University
Two-dimensional echocardiography-derived tricuspid annular plane systolic excursion in conscious, healthy dogs

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The clinical importance of quantitative indices of right ventricular (RV) systolic function is becoming increasingly apparent in dogs with cardiac disease. One RV function index, tricuspid annular plane systolic excursion (TAPSE), has been shown to provide valuable prognostic information for human and canine patients with cardiac disease. TAPSE has previously been evaluated in dogs using M-mode (MM) echocardiography, a one-dimensional technique that may be limited by its acquisition angle dependence. Measuring TAPSE by 2D echocardiography (2D TAPSE) may overcome this limitation. The objective of this study is to determine the feasibility and repeatability of 2D TAPSE, generate reference intervals for 2D TAPSE, and to determine if 2D TAPSE can reliably track anticipated changes in RV function secondary to atenolol administration (proof-of-concept). Seventy-five healthy dogs of varying age, sex, breed, and weights were enrolled in this prospective study. All dogs underwent a single echocardiogram, and a subset of twenty dogs were administered a single oral dose of atenolol and underwent a second echocardiogram 3-hours post-pill. Pre- and post-atenolol TAPSE measurements will be made by a single blinded investigator, and measurement variability and repeatability studies will also be conducted. TAPSE measurements are currently underway and data analysis will be performed shortly thereafter. The implications of this research are to help guide clinical assessment of RV function and provide a basis for further research that could yield prognostic information for dogs with cardiovascular disease.

Research Grant: None
Student Support: Merial Veterinary Scholars Program

Suppression of LPS-induced TNFα in equine macrophages utilizing a pharmacological inhibitor of NF-kappaB

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Endotoxemia is an important cause of morbidity and mortality in horses. The clinical symptoms are secondary to the release of proinflammatory cytokines (such as TNFα) generated through intracellular signaling mechanisms. The clinical conundrum is the cytokines are critically important for immune protection; however, in excess, they are the major player in life-threatening clinical signs, such as hypovolemia. An important signaling pathway for generation of these proinflammatory cytokines involves the transcription factor NF-kappaB. This preliminary study sought to evaluate the effectiveness of a pharmacological inhibitor of NF-kappaB (caffeic acid phenethyl ester or CAPE) to abrogate LPS-induced TNFα production. Monocytes were harvested from whole blood equine samples collected in EDTA by centrifugation in Percoll gradients. The monocytes were plated, allowed to adhere to plastic for 24hrs. The cells were then co-cultured in the presence of CAPE (50μg/mL) for 2h before stimulation with LPS (10μg/mL, E coli O55:B5). Cell supernatants were collected 24h later and assayed for TNFα by ELISA. CAPE inhibited LPS-induced TNFα production (LPS alone 4.9pg/mL ± 2.8 vs. LPS/CAPE 1.1pg/mL ± 0.7; p = 0.06). These in vitro findings pave the way for future studies to optimize CAPE dose and in vivo challenges.

Research Grant: Department of Pathobiology, Oklahoma State University CVHS
Student Support: Boehringer Ingelheim and NIH R13 Grant Sponsored Students
Epidemiology of *Trypanosoma cruzi* in urban dwelling opossums and feral cats of the Rio Grande Valley, Texas

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*Trypanosoma cruzi* is a zoonotic protozoan parasite known to infect a wide range of mammals, but minimal information is known about the infection of urban dwelling animals in the United States. In the Rio Grande Valley (RGV) of TX, our ongoing epidemiological investigations have documented anti *T. cruzi*-antibodies in people and their pet dogs. We hypothesized that urban wild and feral animals from the region serve as infectious reservoirs which could bridge between sylvatic and domestic transmission cycles. In early 2017 samples were collected from urban dwelling opossums and feral cats in the RGV. After euthanasia (performed by animal control for reasons unrelated to our study), whole blood and tissue samples were collected from feral cats and wild opossums. The tissues collected included intercostal muscle, heart, esophagus, biceps femoris muscle, sciatic nerve, mesentery and colon; from opossums only, anal gland tissue and anal gland secretions were also collected. Through serological testing of 167 cats using immunochromatographic and indirect fluorescent antibody testing, 13.2% of cats were antibody-positive on at least two tests. All tissue and blood samples were subjected to qPCR for parasite detection. Histopathology and discrete typing unit (DTU) determination are planned for these tissues as well. Of 100 opossums 12% tested positive for parasite DNA with 9% having multiple positive samples including heart, intercostal muscle and anal gland secretion; of 167 cats 1.8% tested positive with 1.2% having multiple positive samples. Given the high abundance of feral cats and opossums in urban foci, it is likely these species serve as wild reservoirs around urban dwellings.

**Research Grant:** State of Texas Insect Vector Research Grant  
**Student Support:** Boehringer Ingelheim Veterinary Scholars Program & College of Veterinary Medicine, Texas A&M U.

Immunostimulant and antibiotic use improves treatment outcomes in a sheep model of *P. aeruginosa* CAUTI

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Catheter associated urinary tract infections (CAUTI) are among the most common types of nosocomial infections in human hospitals, with *Pseudomonas aeruginosa* being one of the common pathogens isolated. *P. aeruginosa* is of particular interest due to its frequent association with antimicrobial resistance. We hypothesized that concurrent use of a non-specific immunostimulant along with antibiotic treatment would improve clearance of *P. aeruginosa* in a sheep model of CAUTI. Furthermore, we hypothesized that the use of Ertapenem, for which *P. aeruginosa* exhibits intrinsic resistance, would select for emergence of isolates that are resistant to broader spectrum carbapenem antibiotics. A two-week study was performed using an ovine model of *P. aeruginosa* induced CAUTI. Sheep were organized into groups that allowed for the evaluation of the efficacy of Zelnate and Ertapenem. Subjects were treated with Zelnate the day of inoculation and 3 days after were treated with once-daily administration of Ertapenem for 5 days. Antimicrobial resistance was evaluated using broth dilution MIC assays as well as a Diatab test for carbapenemases. The treatment group receiving the immunostimulant and antibiotic showed a statistically significant decrease in bacterial colonization, however they failed to clear the infection and additional work to define the biological significance of this finding is warranted. Analysis of resistance patterns of isolates obtained at the conclusion of the study failed to detect the presence of carbapenemase genes in *P. aeruginosa*, however additional research is underway to determine if there is increased resistance of these isolates to carbapenems mediated through intrinsic mechanisms.

**Research Grant:** Iowa State University College of Veterinary Medicine Seed Funds and USDA Formula Funds  
**Student Support:** USDA-NIFA Project
Rapid identification of *Mannheimia haemolytica* tetracycline resistance in Illinois cattle

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Bovine Respiratory Disease (BRD) is a major health concern in North American feedlot cattle contributing to major economic losses. *Mannheimia haemolytica* is a bacterium considered to be the predominant pathogen associated with BRD. Antibiotics, specifically tetracyclines, have often been used as a feed additive for prevention and treatment of bacterial infections common in feedlot cattle. Because the increased use of antibiotic treatment can select for antibiotic resistance, a method for rapidly identifying resistance can aid in drug selection and treatment success. This study aims to evaluate MALDI-TOF mass spectrometry as a method for rapid identification of *M. haemolytica* tetracycline resistance in Illinois cattle. *M. haemolytica* isolates were collected from tissues taken from cattle with respiratory disease submitted for necropsy to the University of Illinois Veterinary Diagnostic Laboratory. Isolates were subjected to MALDI-TOF, an evolving diagnostic methodology that can provide rapid identification of microbial isolates, as well as information about antimicrobial resistance profiles. Traditional PCR methods were used to detect the *tetH* genotype commonly associated with tetracycline resistance in *M. haemolytica*. Mass spectrometry peaks from tetracycline-resistant and susceptible isolates will be analyzed to detect the presence of unique protein peaks that might identify resistant isolates. Data from these analyses will be combined with information from the PCR assays, as well as clinical and demographic information. A method for rapid detection of tetracycline-resistant *M. haemolytica* isolates would improve treatment outcomes for cattle with respiratory disease.

**Research Grant**: Donor Funds  
**Student Support**: Office of the Director, NIH, T35 OD011145

Panfungal next-generation sequencing of fixed animal tissues enhances identification of fungi on histology

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Molecular methods have proven valuable for identification of fungi observed on histopathology due to subtle nuances in some fungal morphologies and the fastidious nature of fungal cultivation. A recent panfungal PCR assay on formalin-fixed, paraffin-embedded (FFPE) animal tissues using dye terminator sequencing was unable to identify 30% of fungi for which PCR amplification was successful. We hypothesized that the inability to sequence PCR product could have been due to heterogeneity of fungal sequences. The objective of this study was to employ panfungal next-generation sequencing (PNGS) on DNA previously extracted from 50 blocks for which conventional sequencing was unsuccessful. The 50 blocks contained a variety of tissue types, host animals, and fungi. PNGS was performed on an Illumina MiSeq instrument using ITS2 primers. Resultant sequences were processed using open-source bioinformatics software, QIIME, and an ITS sequence database. Heterogeneous populations of fungal DNA were identified in 46/50 blocks. The number of fungal taxa sequenced from each block ranged from 1 to 12, with a median of three. The histologically suspected fungus represented the two most abundant fungal sequences in 30 blocks. Contaminating fungal DNA was found in 16 blocks reconfirming the need to interpret sequencing results in the context of histopathology. Panfungal NGS improved the sensitivity of the conventional panfungal PCR assay by 24%. This study is the first known example of successfully using PNGS on FFPE tissues to identify mixed populations of fungi. PNGS will aid in identification of emerging fungal pathogens as well as prompting future investigations into the mechanism and implications of mixed fungal infections.

**Research Grant**: None.  
**Student Support**: AVMA/AVMF 2nd Opportunity Summer Research Scholarship
Restoration of the dystrophin glycoprotein complex in GRMD dogs Treated with an AAV-microdystrophin construct

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Background: Duchenne muscular dystrophy is a fatal X-linked muscle disease caused by the absence of dystrophin and an associated glycoprotein complex (DGC) at the muscle cell membrane. Genetic treatments for DMD should restore not just dystrophin but also other members of the DGC. These treatments must first be tested in genetically homologous animal models such as golden retriever muscular dystrophy (GRMD). In a recent study, GRMD dogs treated with an adeno-associated virus (AAV)-microdystrophin construct had dose-related dystrophin expression and functional improvement. We hypothesized that other DGC proteins would be restored in these dogs. Methods: Expression of three DGC proteins (β-dystroglycan, sarcoglycan, and sarcospan) and the dystrophin homologue, utrophin, was analyzed in cranial sartorius (CS) and vastus lateralis (VL) muscle samples from three GRMD AAV-microdystrophin dosage groups and a placebo (n = 12 total; 3 in each group) using quantitative PCR (qPCR), Western blot, and immunohistochemistry (IHC). Results: qPCR showed overall downregulation of mRNA, particularly of β-dystroglycan in the CS muscle. Reduction of mRNA could reflect a negative feedback response triggered by increased protein. Western blot and IHC studies are ongoing to define the location and relative amounts of the four proteins. Discussion: To be fully effective, microdystrophin must restore the DGC. Our finding of DGC mRNA downregulation likely reflects negative feedback. Follow up protein studies should more clearly define whether the DGC has been restored. These results will shed light on the dynamics of DGC proteins, potentially informing variables such as the most efficacious dose of the AAV-microdystrophin construct.

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Student Support: National Institutes of Health #5T35OD010991

Common origin of celiac and cranial mesenteric arteries in dogs-prevalence and clinical significance

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A common trunk of the celiac and cranial mesenteric arteries (celiacomesenteric trunk; CMT) has been reported as a rare anatomic variant in domestic animals and humans. A possible association with other vascular anomalies such as portosystemic shunts (PSS) has been proposed in dogs. In this retrospective study a cohort of dogs presented to the University of Tennessee Veterinary Medical Center for various neurologic conditions and undergoing magnetic resonance imaging (MRI) of the thoracolumbar or lumbosacral spine from January 2013 to May 2017, and a cohort of dogs diagnosed with a PSS based on computed tomography (CT) during the same time period were evaluated retrospectively for presence of a CMT. Cases that presented with a common trunk were evaluated for predisposition based on breed, size, sex, age, vertebral anomaly, and presence of a portosystemic shunt. In addition, medical records of dogs with a CMT found on spinal MRI were evaluated for possible indicators of a concurrent PSS. A CMT was found in 7/606 dogs undergoing MRI (1.2%). In 3 of these dogs, clinical and laboratory abnormalities were present that have also been seen in patients with PSS. However, a definitive (imaging or surgical) diagnosis was not established. None of the 47 dogs diagnosed with a PSS based on CT had a concurrent CMT. Based on this study, a CMT is an anatomic variant in dogs which may or may not be associated with concurrent PSS. Prospective studies are needed to definitively confirm or rule out a PSS in dogs in which a CMT is found incidentally on spinal or abdominal imaging and elucidate significance of this anatomic variant, if any.

Research Grant: None
Student Support: Merial Veterinary Research Scholars Program, Centers of Excellence Summer Research Program
Cotton rats as a model for airway induced allergens using house dust mite

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Cotton rats are an excellent model for the study of pathogenesis in viral human respiratory infections including respiratory syncytial virus (RSV), adenovirus, measles, and influenza. In contrast to the mouse, these viruses replicate and are cleared similar in the cotton rat to what is documented in humans. Often, allergies and asthma complicate the severity of respiratory viral infections in humans. In this study, we aimed to establish a reproducible protocol for allergy studies in cotton rats to investigate its role in respiratory infection. Cotton rats were sensitized to house dust mite antigen (HDM) and subsequently challenged with HDM. The adjuvant used to induce an allergic reaction was aluminum phosphate (APhos) or monophosphoryl lipid A (MPLA) which caused either a Th1 or Th2 based immune response. The allergic response was assessed using bronchoalveolar lavage (BAL), histology, ELISA, and lung wet to dry ratios. Evidence of an allergic response included increased numbers of eosinophils and increased mucous in the lungs and nasal passages. We showed that T-cells from HDM sensitized animals were stimulated to secrete IL-4 and INFγ when exposed to HDM. Because eosinophils were a major component of the allergic response, we attempted to define the level of the eosinophil recruitment factors CCL11 and IL5 and the eosinophil survival factors GM-CSF and IL33. Based on contigs derived from an RNA sequencing project we designed primers for PCR to demonstrate the presence of these factors in HDM challenged versus naive lungs. Results are ongoing. In summary, we have established a lung allergy model in the cotton rat as model system to study the interaction of allergy with viral respiratory infection.

Research Grant: none
Student Support: Hartke Research Fellow

Role of angiotensin II on ROS production in Parkinson’s disease

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Calcium channel signaling and the subsequent production of reactive oxygen species (ROS) has been shown to play an integral role in the pathophysiology of the mammalian neurodegenerative disorder commonly known as Parkinson’s disease. Progressive dopaminergic (DA) neuronal loss in the substantia nigra of the midbrain is responsible for many of the debilitating effects observed in Parkinson’s, including the patients’ progressive loss of motor function. It is widely accepted that calcium influx into DA neurons results in the production of ROS and the development of oxidative stress within the cell, ultimately leading to premature cell death. One major mechanism of calcium-induced ROS production in DA neurons is under the influence of interactions between NADPH oxidases (NOX) and the binding of angiotensin II, the active enzyme in the Renin-angiotensin-aldosterone-system (RAS), to AT1 receptors. What is not as well understood is whether AT1 receptor binding has the ability to influence calcium channels directly, or only through mediation by NOX. This lab attempts to elucidate the role of AT1 receptors by downregulating the expression of NOX1, a ubiquitous isoform of NOX in DA neurons, and monitoring calcium channel activity in response to treatment with angiotensin II. The information derived from these experiments will expose critical steps in the degenerative cell signaling pathway, and also has the potential to help identify targets for therapeutic intervention in the treatment of Parkinson’s disease as well as other mammalian neurodegenerative illnesses.

Research Grant: Unknown
Student Support: NIH Grant T35OD015130
Evaluation of dasatinib in an intrasplenic xenograft mouse model for treatment of canine histiocytic sarcoma

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Histiocytic Sarcoma (HS) is an aggressive cancer in dogs and is commonly seen in Bernese mountain dogs (BMDs). The current treatments for histiocytic sarcoma, including the conventional chemotherapeutic doxorubicin, result in a short biological response. Preliminary data from our laboratory has demonstrated that dasatinib significantly reduced the viability of HS cells \textit{in vitro}. We hypothesized that dasatinib would inhibit tumor growth, decrease metastatic load and increase survival in comparison to the vehicle control group in an \textit{in vivo} model of HS. The HS cell line (BD-L), previously established in our laboratory from a BMD and transfected with a luciferase vector to generate bioluminescent imaging of tumors, was used. One and half million cells were injected into the spleens of NOD/SCID immunodeficient mice under sterile conditions and monitored using the In Vivo Imaging System. At day 14 post splenic injection, treatment was started with five mice receiving 30 mg/kg dasatinib intraperitoneally once a day, and five control mice receiving vehicle. The mice treated with dasatinib had significantly decreased tumor burden and increased survival time in comparison to the control group. All mice in the vehicle control group reached humane endpoints for euthanasia by day 30 post injection, while all mice in the treatment group were clinically stable at day 57, the day of this submission. Investigation of downstream signaling pathways are ongoing. The results of our \textit{in vivo} studies point to a novel approach for treatment of HS and provide the rational for the initiation of clinical trials with dasatinib in this challenging malignancy.

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\textbf{Student Support}: Boehringer Ingelheim, and MSU Graduate School Fellowship Funds

Canine osteosarcoma as a model for investigating the therapeutic potential of microRNA-34a prodrug in humans

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Osteosarcoma (OS) is the most common primary malignant bone tumor seen in both children and dogs. Currently, standard of care treatment for both humans and dogs is a combination of surgery and chemotherapy; however, survival times have not improved within the last fifteen years and the majority of patients will succumb to metastatic disease. MicroRNAs are small, noncoding RNA molecules that function to post-transcriptionally regulate multiple cell processes by suppressing and inhibiting translation of target mRNA into protein. Various microRNA subtypes, including miR-34a, act as tumor suppressors and are downregulated in some cancers such as OS. Treatment of human OS cells with an exogenous miR-34a prodrug leads to reductions in proliferation, induction of apoptosis, and suppresses the invasive ability of the cells. Because of the highly conserved nature of microRNA, it is hypothesized that miR-34a exposure will have a similar effect on canine OS cells. We investigated the intracellular processing of a miR-34a prodrug in canine OS through quantitative RT-PCR and examined the \textit{in vitro} anti-tumor effects with clonogenic and proliferation assays. We utilized western blot to identify alterations in target proteins following treatment. We have demonstrated through clonogenic assay that transfection of canine OS cells leads to a reduced colony forming ability and western blot results show reductions in target proteins, suggesting the presence of functional miR-34a following treatment. Our results indicate that canine OS can serve as an informative model in the preclinical development of miR-34a therapy in humans.

\textbf{Research Grant}: UCDMC Collaborative/Interdepartmental Seed Grant
\textbf{Student Support}: SVM Center for Companion Animal Health Endowment Funds
Enhancing human NK cell function by engineering the CD16a IgG Fc receptor to improve tumor cell killing

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As a crucial player in innate immunity, natural killer (NK) cells function as cytotoxic lymphocytes to rapidly kill virally infected cells and tumor cells via the release of perforins and granzymes. Additionally, NK cells produce anti-tumor cytokines, including IFNγ. A key anti-tumor function of NK cells is their ability to kill tumor cells via antibody-dependent cell-mediated cytotoxicity (ADCC). Anti-tumor therapeutic monoclonal antibodies (mAbs) are a rapidly growing class of cancer therapeutics. Many clinically successful therapeutic mAbs utilize ADCC as a mechanism of action, which is exclusively mediated by the IgG Fc receptor CD16a (FcγRIIIa). We hypothesize that increasing the IgG binding affinity of CD16a will enhance the tumor cell killing ability of therapeutic mAbs. We have engineered several versions of CD16a constructs, which were subsequently expressed in NK-92 cells, a human NK cell line lacking endogenous CD16a. We are currently examining the IgG binding affinity of these engineered CD16a constructs using low affinity CD16a as a control. Additionally, ADCC assays using the therapeutic mAbs rituximab and trastuzumab were performed to determine the tumor killing ability of the engineered CD16a constructs. Higher affinity versions of CD16a expressed in NK-92 cells or NK cells derived from induced pluripotent stem cells could potentially be used as an effective off-the-shelf cellular therapy in combination with therapeutic mAbs for the treatment of diverse types of cancer.

Research Grant: National Institutes of Health Award Number R01CA203348
Student Support: National Institutes of Health T35 Training Grant T35OD011118

Use of an adenovirus expressing EHV-1 IR2P or administration of interferon-gamma (INF-γ) for control of EHV-1

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Equine Herpes Virus 1 (EHV-1) is a common DNA virus in horses causing respiratory disease, viremia, neurological disorders, and spontaneous abortion. Current vaccinations do not protect against transmission of the virus or its symptoms. This is likely because of immunomodulatory properties of the virus. Countering immunemodulation by stimulating the innate immune system may improve protection from EHV-1. Our hypothesis is that treatment with a recombinant adenovirus expressing IR2 (rAD-IR2), a regulatory protein, or interferon-gamma (INF-γ) will protect horses from EHV-1 infection. EHV-1 seronegative horses (n=11) were randomly distributed into three groups. Each group was given a treatment of either rAD-IR2, INF-γ, or control adenovirus. Horses were then challenged infected with EHV-1 strain Ab4, 24 (INF-γ,) or 48 hours (rAD-IR2, controls) after treatment. Disease progression was monitored with physical exams daily. Blood and nasal swabs were taken daily for 14 days and every other day until day 21 post-infection. Viral nasal shedding was quantified by real-time PCR. All three groups showed mild respiratory disease and 2/4 horses in the rAD-IR2 group showed neurological signs. rAD-IR2 treatment did reduce viral nasal shedding on day 2 but not quite statistically significant (p=0.18). INF-γ treatment significantly increased viral nasal shedding. Viremia and induction of immunity is currently being investigated.

Research Grant: USDA-NIFA
Student Support: NIH T35 Grant T35OD016477
Immunomodulatory role of CTL4/CTLMA2 in antibacterial defense in the malaria vector, *Anopheles gambiae*

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The C-type lectin heterodimer, CTL4/CTLMA2, is important for gram-negative bacterial defense in the malaria vector, *Anopheles gambiae* (*A. gambiae*). CTL4/CTLMA2 negatively regulates plasmodium parasite melanization, however no connection to bacterial melanization has been established. Melanization is an arthropod-specific immune response that eliminates microbes by restricting nutrient access and by exposure to toxic melanin biosynthetic intermediates. Melanization is not necessary for *A. gambiae* defense against *E. coli*, and evidence from other mosquitoes suggests that *E. coli* is preferentially cleared by phagocytosis rather than melanization. This project seeks to determine if CTL4/CTLMA2 negatively regulates gram-negative bacterial melanization and to identify if its silencing compromises antibacterial defense by facilitating melanization-induced host damage or by biasing immune effector functions toward melanization and away from phagocytosis. Using *in vivo* RNA interference and an enzyme activity assay, we preliminarily report that the activity of the rate limiting melanization enzyme is enhanced in CTL4/CTLMA2 knockdown mosquitoes (CTL KDs) following *E. coli* challenge. Furthermore, we have preliminary evidence that inhibiting melanization in CTL KDs significantly improves mosquito survival following bacterial challenge. This suggests that CTL4/CTLMA2 modulates gram-negative bacterial melanization and that this regulation either prevents incidental host damage or facilitates effective bacterial clearance. Efforts are on-going to understand this mechanism. These studies will afford a deeper understanding of the processes driving effective immune responses against gram-negative bacteria in a major malaria vector.

**Research Grant:** University of Pennsylvania MSTP grant T32 GM007170-43. University of Pennsylvania School of Veterinary Medicine intramural funds.

**Student Support:** None

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**GLP-1 activates the enteric nervous system of the GI tract & the dorsal vagal complex of the hindbrain**

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Glucagon-like peptide-1 is a gut-brain peptide produced and secreted by L-cells of the gastrointestinal tract (GI tract) upon food consumption, and play an important role in the physiological regulation of appetite and food intake. The goal of this work is to assess GLP-1 and its role in regulating food intake in rats by activation of the enteric nervous system (the myenteric and submucosal plexus) of the GI tract and the areas of the dorsal vagal complex of the hindbrain. After a group of 9 male Sprague Dawley rats were food deprived overnight, the natural peptide GLP-1 or saline was perfused into the abdominal aorta of via Intra-arterial catheterization. The rats were humanely euthanized 90 min following the perfusion, and the myenteric and submucosal plexuses of the small intestines (duodenum, jejunum, ileum) and dorsal vagal complex of the hindbrain were processed for detection of Fos-like immunoreactivity using c-Fos, a proto-oncogene used as a marker for neuronal activity. The results one can expect to see is a detection of c-Fos activation of GLP-1 receptor by GLP-1 in the sites of action that regulate appetite and food intake, which are the myenteric and submucosal neurons of the duodenum, jejunum, and ileum, and areas of the dorsal vagal complex (area postrema, nucleus tractus solitaries and dorsal motor nucleus of the vagus).

**Research Grant:** None

**Student Support:** None
Electronic cigarette vapor exposure modulates lung responses in a mouse model of asthma

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Electronic cigarettes (E-cig) are modern tobacco-free nicotine delivery devices and a popular alternative to conventional cigarettes, yet little is known regarding their effects on lung function. We investigated the effects of E-cig vapor exposure on lung responses in mice and whether these effects may differ in susceptible populations (e.g., asthmatics). To reproduce asthmatic mouse models, male BALB/c mice (n=11/group) were exposed to saline or house dust mites (HDM) via intranasal instillation 1X/week for 3 weeks, followed by exposure to filtered air or E-cig vapor 2 hours/day for 28 days. After the final exposure, lung function was assessed prior to sacrifice. Blood and broncho-alveolar lavage fluid (BALF) were collected for cytology analysis, and lung histopathology and gene expression were determined.

Results: E-cig-exposed mice had high cotinine levels (91-113 ng/mL), the major nicotine metabolite. Saline+E-cig significantly decreased tidal and minute volumes at 3 and 6 mg/mL of methacholine compared to respective controls, while HDM+E-cig was also significantly decreased for those volumes and at 12.5 mg/mL of methacholine. HDM+E-cig mice also showed a 1.7X up-regulation of Muc5ac (mucin) gene expression. Although BALF inflammation was unremarkable in all groups, lung gene expression showed significant increase in the eosinophil-associated genes Ccl8 and Ear11 in HDM+Air and HDM+E-cig groups (fold change=3.1 and 6.4; 4.5 and 6.6, respectively). Il13, INF-γ, and Epx genes were significantly down-regulated in both E-cig groups. Overall, these data suggest that 28 days post HDM treatment, inflammatory genes remain dysregulated; whereas E-cig exposure decreased lung function and may promote immunosuppressive effects.

Research Grant: Louisiana’s Governors Biotechnology Initiative (GBI-BOR#013)
Student Support: NIH T35-OD011151

Detection and molecular characterization of *Trichomonas gallinae* in two avian populations in PEI

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Avian trichomoniasis is an emerging disease in Atlantic Canada that affects pigeons, doves, songbirds and birds of prey. The causative agent, *Trichomonas gallinae*, is a protozoan parasite that infects the upper digestive tract mucosa. It forms caseous lesions that can occlude the oral cavity, esophagus and crop, leading to death by dehydration or starvation. Commensal relationships with reservoir species, such as rock pigeons (*Columbia livia*) in Atlantic Canada, perpetuate the parasite in the environment. The prevalence of *T. gallinae* in Prince Edward Island is known to range from 10%-54% and 27-38% in finch and rock pigeon populations respectively. The purpose of this project is to collect recent data on avian trichomoniasis by sampling two populations for the parasite: birds admitted to the Atlantic Veterinary College Wildlife Service during the summer months and humanely live-trapped wild rock pigeons. Specific goals are to describe the current prevalence of the parasite, the avian species infected with it, and to conduct molecular characterization of Island *T. gallinae* isolates to understand its genetic diversity. Oral swabs were cultured using BioMed Diagnostics InPouch TF test kits. Positive samples will be characterized with PCR amplification and sequencing of the rDNA internal transcribed spacer region and the Fe-hydrogenase gene. Preliminary results found three positive infections in pigeons presented to the AVC Wildlife Service. Additionally, care recommendations will be made to reduce the possibility of transmission to other avian patients. Avoidance of transmission within the Wildlife Service will reduce the impact the care and release of birds back into the environment will have on wild bird populations.

Research Grant: Term Research- SJG
Student Support: NSERC USRA, Merial Veterinary Research Scholars Program
Parasite burdens and other objective health measures of wild horses in Arizona

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Wild horses have been the focus of public debates for many years, yet there is little quantitative data to draw from to support 
or contradict specific management interventions. Published scientific research is, in large part, limited to studies of repro 
ductive behavior and methods of contraception, with rare papers addressing environmental impact and only a single North American study evaluating parasite burdens on a herd of wild horses in Nova Scotia. Virtually no comprehensive health 
studies have been done on a single population. In this study, we investigate the parasite burdens on two populations of wild 
horses residing in differing environments in Arizona. One resides in the heart of the Sonoran Desert, and the other along a 
riverbank within the Tonto National Forest. We also utilize noninvasive, manure-based methods to build a more comprehen 
sive health profile on the Sonoran herd. In addition to parasites, the Sonoran herd samples were analyzed for other indicators 
of health and metabolism, including volatile fatty acids, pH, cortisol, sand content, microbiome DNA, and genomic DNA. 
Body condition scores were evaluated on a 1 to 9 scale. Arizona’s wild horses are a unique natural resource and provide an 
as of yet untapped opportunity to improve our understanding of equine parasite dynamics and the ability of horses to adapt 
to conditions such as the extreme heat of the desert. In turn, this data will benefit the horses themselves and the environment 
they inhabit by helping researchers, biologists, environmental scientists, agriculturalists, veterinarians and policy makers to 
improve monitoring and management strategies.

Research Grant: Midwestern University intramural funds 
Student Support: Merial Veterinary Scholars Program

Utilization of environmental DNA for monitoring elusive herpetofauna and viral disease of conservation concern

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Collection and characterization of DNA shed by organisms into bodies of water has shown to be an effective method of 
assessing aquatic biodiversity, detecting cryptic species, or surveying for pathogens in systems where traditional surveil 
lance measures are lacking. However, applications of this environmental DNA (eDNA) as a non-invasive tool for species 
conservation in context of disease outbreaks have not been previously assessed. The aim of this study is to examine the 
effectiveness of using eDNA methods to simultaneously survey for elusive species and gauge disease pressures within their 
environment. We explored the presence of ranavirus, an emerging infectious disease linked to die-offs of populations of 
amphibians, fish, and reptiles, in likely habitats of the four-toed salamander (*Hemidactylium scutatum*), a species of conser 
vation concern in New York state. In order to determine if eDNA could be used to identify locations that presented a higher 
risk of disease contraction within the species, we sampled a network of vernal pools in triplicate biweekly for 8 weeks 
during the breeding season of *H. scutatum*. Water was collected from each pool and eDNA was concentrated from the water 
by passage through a filter. DNA extractions were performed on collected filters and a quantitative PCR assay for detection 
of *H. scutatum* and ranaviral DNA was performed on the DNA extracts. This allowed for assessment of the co-occurrence of 
host and pathogen in vernal pools and quantification of changes in *H. scutatum* and ranavirus DNA copy number over time. 
These findings will help inform future *H. scutatum* and ranavirus surveillance efforts and establish the utility of eDNA as a 
tool for concurrent host and pathogen monitoring.

Research Grant: NYS Department of Environmental Conservation Herpetofaunal Health Team 
Student Support: NIH T35 Training Grant OD010941
Effect of using corn syrup with fructose on insulin and glucose responses to an oral sugar test in horses

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Equine metabolic syndrome (EMS) is characterized by obesity, insulin dysregulation (ID), and predisposition to laminitis. Early identification of affected horses allows veterinarians to recommend preventative measures to reduce the risk of laminitis. An oral sugar test (OST) using Karo Light corn syrup (KLCS) has been validated as a screening test for EMS (positive if insulin is $\geq 45$ mIU/mL at 60 or 90 minutes after giving corn syrup), but veterinarians and owners often use whatever type of corn syrup is convenient, despite brand differences in sugar content. In dogs and humans, fructose increases hepatic glucose metabolism, lowering insulin and glucose responses to OSTs. A similar effect in horses would increase the number of false negatives from OST screening. OSTs using KLCS (with glucose and maltose) and OSTs using Fox’s corn syrup (FCS, with high fructose corn syrup) were performed twice each on Arabian horses previously diagnosed with EMS/ID. Repeatability was assessed for both types of corn syrup. Differences in area under the curve (AUC) and peak concentrations for insulin and glucose were assessed using a one-way ANOVA (significant at < 0.05). Repeatability was assessed using Bland-Altman Plots. Significant differences were not noted between KLCS and FCS for either AUC or peak concentrations. However, when insulin results were compared to the EMS positive insulin cut off ($\geq 45$ mIU/mL), tests with fructose correctly identified horses with EMS only 8 of 14 times; OSTs without fructose identified EMS in 12 of the 14 tests. Based on this, fructose does not have a substantial impact on glucose metabolism in horses, but may interfere with the results of an OST.

Research Grant: None
Student Support: Boehringer-Ingelheim and MSU College of Veterinary Medicine and Graduate School

Creation of lubricin deletion mutants and quantification of recombinant human lubricin production

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Lubricin, or proteoglycan 4 (PRG4), is a mucinous glycoprotein secreted into the joint by synovial fibroblasts and superficial zone chondrocytes. Lubricin is the primary boundary lubricant in synovial fluid and protects articular cartilage through its anti-adhesive properties. Lubricin is composed of three protein domains; an N-terminus somatomedin B domain, a central mucin-like domain, and a C-terminus hemopexin-like domain. In order to assess the distinct functions of each of these three domains, deletion mutants were created using PCR site-directed mutagenesis of recombinant human proteoglycan 4 (rhPRG4). In order to optimize expression of both mutant and full-length rhPRG4 in a suspension-adapted human embryonic kidney cell line (293F), supernatants were collected daily over a 6-day production period. rhPRG4 expression was assessed in the presence and absence of valproic acid (VPA), a histone deacetylase inhibitor. Lubricin was quantified from day 1 to day 6 via western blotting and sandwich ELISA. rhPRG4 expression was highest at 48hrs of culture, and VPA resulted in sustained rhPRG4 expression over non-VPA treated cultures, especially from day 3-6. There is significant interest in recombinant lubricin therapy for the treatment of various medical conditions including osteoarthritis, dry eye, and prevention of postoperative intra-abdominal adhesions. Future plans include assessing the lubricating and anti-adhesive properties of full-length rhPRG4 in addition to each of the rhPRG4 deletion mutants.

Research Grant: None
Student Support: NIH T35 Training Grant- OD010941
Investigating the relative abundance of *Staphylococcus* and *Corynebacterium* on healthy and allergic cat skin

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Atopic dermatitis in humans and dogs is associated with an increased abundance of *Staphylococcus* and *Corynebacterium* spp. Although atopic dermatitis is not widely recognized as a disease affecting cats, cats do suffer from allergic skin diseases. A study based on next generation sequencing demonstrated higher abundances of *Staphylococcus* spp. in the interdigital area and ear canal of allergic cats. We hypothesize that *S. aureus*, *S. pseudintermedius* and *Corynebacterium* spp. predominate in the microbiota of cats, and are more abundant in the skin of allergic cats. Superficial skin swabs were collected from the axilla and interdigital space from 17 healthy cats and 10 cats with allergic skin disease. DNA was extracted and real-time quantitative PCR (qPCR) was used to quantify *Staphylococcus* spp., *S. aureus*, *S. pseudintermedius*, and *Corynebacterium* spp. Statistical significance (p < 0.05) of comparisons were tested with Kruskal-Wallis tests. Allergic cats had significantly more *Staphylococcus* spp. in the interdigital space relative to their axilla (p=0.0206). *Staphylococcus* spp. was more abundant in the axilla of healthy cats compared to allergic cats (p=0.0305), however no significant differences were observed between the two groups. Only four samples had detectable *S. pseudintermedius*; and *S. aureus* was not detected in any of the samples. *Corynebacterium* spp. qPCR results are still pending. These results suggest that although the genus *Staphylococcus* was identified in significant abundances in the skin of cats, *S. aureus* and *S. pseudintermedius* are not predominant in the feline microbiota. Further studies are needed to evaluate the abundance of other *Staphylococcus* species on healthy and allergic feline skin.

**Research Grant**: None

**Student Support**: Boehringer Ingelheim Veterinary Scholars Program & College of Veterinary Medicine, Texas A&M University

Possible role of biofilm production in *E. coli* urinary tract infections

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Studies suggest that between 14% and 26% of all dogs will develop at least one urinary tract infection (UTI) during their life. While *E. coli* is the most common cause of canine UTIs, *Staphylococcus* spp., *Klebsiella* spp., *Enterococcus* spp., *Pseudomonas* spp., *Proteus* spp., and *Streptococcus* spp. are also routinely cultured from patients. The majority of these urinary tract infections are easily treated; however, some patients develop resistant infections. In people, the ability of certain uropathogenic bacteria to form biofilm structures resulting in difficult to clear infections has been documented; however, this is not well studied in canines. The purpose of this study is to identify uropathogenic bacteria that are capable of producing biofilms from isolates collected from canine patients with naturally occurring UTIs. To assess potential biofilm production, isolates obtained from patients with naturally occurring UTIs which were identified at a veterinary diagnostic laboratory will be analyzed using the previously described crystal violet assay. Results will be presented at the meeting.

**Research Grant**: Merial Veterinary Scholars Program

**Student Support**: Merial Veterinary Scholars Program
Does proximity to railroads increase arsenic-related health risks?

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Arsenic-contaminated soil and water pose serious health concerns for both humans and animals. Exposure to arsenic can occur through ingestion of contaminated water or through food grown in arsenic-containing soil, through aerosolized particles or through dermal contact. Railroads have historically transported arsenical-based pesticides and housed arsenic-containing cattle-dipping vats. Moreover, railroad rails are coated in arsenic. We hypothesize that the risk of arsenic exposure increases with proximity to railroads. Escambia and Santa Rosa counties in Florida provided test cases for the characterization of arsenic contamination. These counties were chosen because of past arsenic use on cotton production, the transportation of cattle, and the presence of arsenic-containing superfund sites. A previous study of 89 soil samples from these counties provided data for a spatial statistical analysis of arsenic levels. An additional 25 soil samples and 10 water samples were collected in summer 2017. Samples were collected near railroads and elsewhere in the counties for comparison. Data from this work will help confirm the locally variable presence of arsenic and better equip scientists and public health officials to raise public awareness and prioritize remediation of arsenic-contaminated soil and water.

Research Grant: Donor Funds
Student Support: Office of the Director, NIH, T35 OD011145

Pharmacokinetics and efficacy study of mirtazapine in guinea pigs (Cavia porcellus)

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Guinea pigs are cecal fermenters requiring high levels of feed intake to ensure normal gut motility. Transport, age-related disease, diet change, and other sources of chronic stress can reduce appetite leading to gastrointestinal stasis which can be life threatening in this species. Mirtazapine, a tetracyclic antidepressant, is used in dogs and cats to treat nausea and inappetance, and has been shown to increase feed intake in cats. It has anecdotally been used as an appetite stimulant in guinea pigs, but a therapeutic dose of mirtazapine has not yet been established for this species. Six healthy male guinea pigs were given one of three doses of mirtazapine (1.88, 3.75, or 7.5 mg) for four days with a 7-10 day washout period. Each guinea pig received all doses over three different sessions in a randomized crossover design. Blood for serum pharmacokinetic analysis was collected prior to the first dose of each session and at time points 0.5, 1, 2, 8, 12 and 24 h after the first dose was administered. Body weight, feed intake, and fecal output were recorded every 24 hours for each guinea pig during the dosing session and washout period. Significant differences in weight gains, feed intake, and fecal output were not seen when the experimental doses were compared to three male control guinea pigs of similar age, suggesting that mirtazapine does not have a significant effect in young, healthy guinea pigs. However, the 3.75 and 7.5 mg doses of mirtazapine did demonstrate a trend of increasing weight gains when compared to the controls. Further studies in older guinea pigs that are already inappetant or anorexic could yield more significant data in support of mirtazapine as an appetite stimulant in this species.

Research Grant: Office of Vice President for Research at Colorado State University
Student Support: Pfizer (through ASLAP Foundation)
Evaluation of a light abatement strategy for feline friendly housing

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Cats housed in veterinary hospitals are consistently exposed to stress-inducing environments filled with unfamiliar visual and auditory stimuli. A decrease in stress has been documented when cats are offered a hiding place within their cage. Unfortunately, these masking devices are not always a practical option in a medical setting because patients are not visible to the technical staff. Hiding structures may also result in tangling of intravenous lines and monitoring devices. The aim of this study was to investigate the efficacy of a stimulus abatement strategy that could be easily adapted to any cage design utilizing an opaque sheet of plexiglass for light and noise reduction. Thirty healthy cats entered into this cage selection study were allowed to choose between adjoining cages with randomly assigned open, clear plexiglass shielded or opaque shielded cage fronts. The testing room mimicked light and sound levels found in our teaching hospital’s intermediate care area. Cage selection and behavioral stress levels were monitored for one hour on six consecutive days. Univariate and multivariate analysis of variance will be performed. Correlation coefficients will be generated. Variables assessed will include age, stress scores, chronological test # (1-6), time of day (morning, mid-day, afternoon), side (L/R), and cage front. Significance was set at p< 0.05.

Research Grant: None
Student Support: CVM Veterinary Scholars Program, Merial Grant, Fund for Discovery, Herbert Benjamin Endowment

Effects of in utero exposure to DEHP and high-fat diet on uterine development in mice

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Di(2-ethylhexyl) phthalate (DEHP) is an endocrine-disrupting chemical found in many consumer products. DEHP exposure is related to endocrine and metabolic diseases in humans, and food ingestion is the main source of DEHP exposure. Studies have suggested that DEHP and adipose signaling may act through similar metabolic pathways, specifically PPARg. It is well-documented that obesity increases the risk of developing endometrial carcinomas, but no link has yet been found to suggest DEHP involvement. In this study, we investigated the effects of prenatal exposure to DEHP and high-fat diet on the development of the uterus. Pregnant dams were orally dosed with either a corn oil control or 20 mg/kg/BW DEHP, and fed either a control diet of a balanced maintenance chow or a “western” high-fat diet with 45% of calories derived from fat. Diets were fed from day 0.5 of pregnancy, and continued until parturition. Uterine tissues from post-natal day (PND) 8 and PND 21 pups were collected from all treatment groups. Preliminary results indicated in utero exposure to a high-fat diet resulted in accelerated adenogenesis, uterine gland development, at PND 8. By PND 21 the pups exposed to high-fat diets or DEHP in utero showed increased proliferation of the uterine luminal epithelium. These results suggest that in utero exposure to DEHP or a high-fat diet may lead to uterine epithelial hyperplasia later in life. Uterine epithelial hyperplasia is associated with implantation failure in women, as well as being a premalignant lesion of endometrial carcinoma.

Research Grant: EPA RD-83543401
Student Support: Office of the Director, NIH, T35 OD011145
Evaluation of the risk factors for reverse corkscrew claw deformity in dairy heifers

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An emerging hoof deformity of the medial hind claw, known as, reverse corkscrew (RC) was the focus of this study. RC is observed in young dairy heifers and adult cattle, and the condition refers to the abaxial rotation of the axial wall of the medial hind claw in contrast to the traditional corkscrew deformity commonly observed in the lateral claws of hind feet. The medial claw rotation causes abnormal wear, abnormal growth, and an increased risk for lameness in herds that generally have other causes of lameness under control. There are no peer reviewed studies documenting the prevalence and associated risk factors for RC, and this is the first such study exploring RC using Midwest dairy farms. Herds (n=xx) were selected based upon being ‘high’ or ‘low’ risk for RC using hoof-trimming observations from a network of hoof trimmers trained by the Dairyland Hoofcare Institute. For each herd, the prevalence of RC was determined using direct observation and a 3-point scoring system (1=normal, 2=mild, 3=severe) for each heifer rearing group and for the mature high producing cows. Assessment of the management, housing and feeding practices for each management group was made for each farm and the data were collected in a purpose-built tablet database, and subsequently analyzed in SAS (SAS, version xx). We hypothesize that heifers raised in facilities that have sand bedded freestalls, headlocks at the feed bunk, high stocking densities, and where feed is not accessible throughout the entire day, will be at greater risk for RC and our data will be used to test this hypothesis. Prevention of RC will improve heifer and cow foot health and reduce the amount of associated lameness.

Research Grant: Dairyland Initiative
Student Support: University of Wisconsin-Madison School of Veterinary Medicine, Office of Academic Affairs.

Analysis of seminiferous tubule epithelium & surface area in unilateral abdominal cryptorchid testes in rats


Pathobiological Sciences (Stout), Equine Clinical Sciences (McCauley, Riggs, Mitchell), Comparative Biomedical Sciences (Al-Bagdadi), College of Veterinary Medicine, Louisiana State University, Baton Rouge, Louisiana.

Cryptorchidism, the failure of the testes to descend into the scrotum at birth, affects 1% of newborn boys in the United States. The frequency of undescended testes has doubled in humans during the last forty years. We believe that over time, progressive damage resulting from the cryptorchid testes needs to be statistically documented. It could guide the decision for the treatment, prognosis, and the fate of the testes. Five male rats were randomly selected. Unilateral abdominal cryptorchidism of the right testes was induced surgically. Rats were sacrificed at 12 weeks, 7 weeks, and one rat’s testes were surgically descended after 7 weeks postsurgery and sacrificed after 7 weeks post correction. A 5 mm. thick slice was obtained from the cranial half of each testes, and these were immersed in Bouin’s fixative for 24 hours, dehydrated in graded series of alcohol, cleared in xylene and embedded in paraffin. Five micron thick sections were stained with Hematoxylin and Eosin, and subjected to light microscopic morphometric data collection for analysis. The cell count and surface area were obtained from each testes and their seminiferous tubules. The average number of cells per seminiferous tubules per testes decreased progressively in correspondence with the length of time, and reached a lower cell average at 12 weeks of cryptorchidism. This indicates that the increase of cellular degeneration by apoptosis and necrosis is progressive over time. The seminiferous epithelium of the surgically descended testes show complete recovery except the surface area of the descended testes was a quarter of the surface area of the scrotal testes. Further investigation is needed to better understand cryptorchidism.

Research Grant: None
Student Support: Boehringer-Ingelheim Veterinary Research Scholars Program
A geospatial approach to “The Link” and its local implications

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The link between animal abuse and domestic violence is well recognized phenomenon, which has led to a call for adoption of mandatory reporting of animal abuse by veterinarians. The purpose of this study was to explore the application of visual analytics in assessing this overlap between human and animal violence and its proximity to local veterinary clinics in an urban environment. Forty-five reports of animal cruelty and 11,508 reports of family violence occurring in Lafayette, IN were extracted from police records from January 1st, 2011 through June 20th, 2017. These cases were imported and analyzed via geospatial mapping software developed by VACCINE, Purdue University’s Department of Homeland Security Center of Excellence. This software, Visual Analytics Law Enforcement Toolkit (VALET), was used to create and compare heat maps of animal cruelty, child abuse, and domestic violence. Spatial analysis revealed a high degree of correlation in certain census tracts. Sixty percent of the animal cases occurred at the same street address as reported family violence. Six addresses contained at least one involved person present in both a human and animal case, though this may be an underestimate as not every report had associated involved persons information available. Geospatial mapping methods may help encourage reporting of abuse by veterinarians and focus interventions in areas of strategic need. Although data analysis would benefit from increased reporting of animal cruelty cases, visual analytics allows for identification of areas at high risk for household violence, which would enable animal welfare personnel to more effectively reach underserved areas of the community.

Research Grant: None
Student Support: Merial Veterinary Research Scholars Program

Lying time as an early indicator of disease in veal calves

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Veal calves face unique challenges that can negatively affect their health and welfare. Many veal calves arrive at growing facilities with poor immunity, leaving them susceptible to diseases such as diarrhea, respiratory disease, and navel infections. Observing calf behavior can be used as a tool to study and understand animal health, as current research in dairy cows shows that changes in behavior can be an early indicator of disease. For example, cows with illness spend more time lying to help conserve energy for mounting an immune response. The objective of this study is to investigate the relationship between veal calf lying behavior and diarrhea, respiratory disease, and navel inflammation. One cohort of 40 calves from a veal farm in Ohio were included in the study. Calves were housed individually in one room of a mechanically-ventilated barn. Health exams were conducted twice weekly for 6 weeks starting on the day after arrival to the facility to diagnose diarrhea, navel inflammation and respiratory disease. Lying behavior was recorded using electronic data loggers (HOBO Pendant G Acceleration Data Loggers) secured to the hind legs of the calves. The loggers measured lying time, the number of lying bouts, and lying bout duration daily. It is predicted that calves diagnosed with diarrhea and respiratory disease will spend more time lying than healthy calves before and after diagnosis, but calves with higher navel scores will spend the least amount of time lying down because this posture may cause pain. By assessing the relationship between calf health and lying behavior, veal growers can diagnose disease earlier and adjust management strategies to improve calf comfort, health, and welfare.

Research Grant: The Ohio State University College of Veterinary Medicine
Student Support: Epperson Research Fellow
**Superoxide dismutase 2 is upregulated in astrocytes in a macaque model of HIV**

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Human immunodeficiency virus (HIV)-associated neurocognitive disorder (HAND) is prevalent among HIV patients and has been linked to mitochondrial dysfunction and overproduction of reactive oxygen species (ROS) in the central nervous system. Superoxide dismutase (SOD) 2 is a mitochondrial antioxidant enzyme essential for quenching ROS and maintaining cellular viability. In this study, we hypothesized that SOD2 expression is enhanced in the brain to compensate for increased ROS generation during HIV infection. Using a simian immunodeficiency virus (SIV)-infected macaque model of HIV, we measured SOD2 mRNA and protein levels in cortical gray matter (GM) and white matter (WM). Quantitative PCR (qPCR) indicated that SOD2 mRNA was increased in GM (relative mRNA $36.1 \pm 19.6$ for SIV vs. $1.9 \pm 0.7$ for uninfected, n=6/group) and WM (relative mRNA $97.0 \pm 43.1$ for SIV vs. $1.5 \pm 0.4$ for uninfected, n=6/group) during SIV infection. In addition, SOD2 immunohistochemical staining was measured by digital image analysis (Nikon Elements) and showed enhanced expression in both GM (area fraction $0.19 \pm 0.04$ for SIV vs. $0.06 \pm 0.04$ for uninfected, n=6/group) and WM (area fraction $0.12 \pm 0.02$ for SIV vs. $0.01 \pm 0.004$ for uninfected, n=6/group) in SIV-infected animals. Double immunofluorescence labeling was imaged using confocal microscopy and demonstrated that SOD2 primarily co-localizes with the astrocytic marker glial fibrillary protein (GFAP) in the frontal cortex of SIV-infected animals. Together, our data indicate that neuroprotective SOD2 expression by astrocytes is enhanced in the brain during SIV infection, revealing SOD2 as a novel potential target for HAND therapy.

**Research Grant:** NIH R01NS089482  
**Student Support:** Boehringer Ingelheim and the Johns Hopkins University School of Medicine

**Identification of plant-derived compounds to treat allergic disorders**

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Mast cells, a particular type of immune cell, are critical mediators of allergic response in humans. Allergens bind to the IgE antibody occupied receptors (FcεRI) on mast cells resulting in their activation and rapid release of inflammatory mediators via a process termed as “degranulation”. Thus, development of inhibitors that target the antigen-FcεRI pathway in mast cells is clinically significant because these pharmacologic agents can then be used to treat patients with allergic disorders. Previous reports have demonstrated that crude extracts from several plants inhibit mast cell degranulation response to antigen. However, the lead plant-derived compounds that are responsible for this effect have not been identified yet. The objective of the current study is to test the role of 6 different plant based lead compounds (Osthole, Rutin, Forskolin, Quercetin, Betulinic acid, and Oleanolic Acid) in regulating FcεRI-mediated degranulation in mast cells. We used a rat mast cell line (RBL-2H3) that expresses FcεRI to assess degranulation to IgE/antigen in the presence/absence of varying concentrations of the lead compounds. Quercetin, Osthole, and Oleanolic Acid demonstrated a dose-dependent inhibition of degranulation; however Rutin, Forskolin and Betulinic acid had no effect on this response. Thus our study has identified 3 lead compounds that targets the antigen-FcεRI pathway in mast cells. In addition, this in vitro system will form the foundation for future studies that will test the role of these 3 compounds in rodent allergy models.

**Research Grant:** R00HL121073 from NHLBI (NIH).  
**Student Support:** NIH Training Grant 5R25HL103156-07
Combined effects of zoledronic acid and radiation therapy on canine osteosarcoma cells

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Canine osteosarcoma (OS) is a suitable comparative oncology model, as it accounts for the majority of bone cancers in dogs as well as human children and young adults. In non-surgical candidates, localized radiation therapy (RT) is utilized. To increase RT’s effectiveness, bisphosphonates have been added to OS treatment protocols. Synergy in primary and metastatic models has been exhibited in studies on human and murine cancer cells, but has yet to be displayed in canine cells. The purpose of our study was to examine if the same would be true in canine OS. We hypothesized that adding Zoledronate (ZA), a third-generation bisphosphonate, to RT would increase apoptosis of canine OS cells compared to either individual treatment. Abrams and D-17 canine OS cell lines were cultivated in 96 well plates; 3,000 cells per well were incubated for 24 hours. Four groups were evaluated: group 1 treated with 10 μM ZA, group 2 irradiated at 400 cGy, group 3 treated with ZA and RT, and group 4 control. Viability, cytotoxicity, and apoptosis were determined by the Triplex ApoTox assay (Promega). In Abrams cells, no difference in cell viability with combined therapy (p=0.254) was found, but significant increases in cytotoxicity (p < 0.0001) and apoptosis (p=0.0003) were seen compared to controls. D-17 cells had no difference in viability (p=0.289) or apoptosis (p=0.188), but did have a significant increase in cytotoxicity (p<.0015) compared to controls. Our results show the combination of ZA and RT has significant effects on canine OS cells, especially the Abrams line. We plan to continue investigating varying concentrations and doses of ZA and RT to find optimal synergy with the two therapies in canine OS cells.

Research Grant: None
Student Support: The Mizzou Advantage initiative in One Health / One Medicine

Evaluation of novel drug targets in canine histiocytic sarcoma

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Disseminated histiocytic sarcoma (HS), a hematologic malignancy, is a rapidly progressive cancer with short survival times in both human and canine patients. Because HS is rare in humans but common in dogs, the canine cancer is a good model for investigating new treatments. Canine HS has modest but short-lived susceptibility in vitro and in vivo to anthracycline drugs such as doxorubicin, which act partly by poisoning topoisomerase 2 (TOP2A). The addition of other agents with different mechanisms of action to doxorubicin regimens could improve outcomes without worsening toxicities. The model HS cell line, DH82, expresses enzymes related to cell proliferation for which specific inhibitory drugs, with modest toxicities, are available. Our hypothesis is that pharmacologic inhibition of these drug targets, inosine-5’-monophosphate dehydrogenase 2 (IMPDH2) and/or ribonucleotide reductase (RRM2), could act additively or synergistically with TOP2A poisoning by doxorubicin to potentiate HS killing in vitro. We first sought to verify that all three targets (TOP2A; IMPDH2; RRM2) are typically expressed in HS by RT-PCR of archived HS biopsy specimens (n=10). We found 10/10 specimens expressed IMPDH2, 9/10 expressed RRM2, and 10/10 expressed TOP2A. Doxorubicin treatment of DH82 decreased viability in a dose-dependent (0.01-5.0 μg/mL) manner consistent with reported IC_{50} values. We are now testing the susceptibility of DH82 to IMPDH2 and RRM2 inhibitors alone, and in combination with doxorubicin to hunt for combinatorial effects. Our results confirm that doxorubicin is potent inhibitor of HS growth, and that other two other important drug targets are frequently expressed in this tumor.

Research Grant: Hercules Oncology Research Fund
Student Support: NIH T-35 Biomedical Research Training Grant T35OD011070; NCSU Veterinary Scholars Program
**Feline and human immunodeficiency virus (FIV and HIV) induce synaptic excitotoxicity in the brain**

Keira Sztukowski, Jiayi Shou, Craig Miller, Sue VandeWoude, and Seonil Kim

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Feline immunodeficiency virus (FIV) is a lentivirus that naturally infects wild and domestic cats. FIV shares its structure, cell tropism, and pathology with human immunodeficiency virus (HIV), including wide-ranging neurological deficits in the chronic stages of infection. Over 50% of HIV-infected individuals suffer from HIV-associated neurocognitive disorders (HAND), yet the molecular mechanisms leading to neuronal dysfunction and death are poorly understood. This study aims to use FIV as a model to elucidate the molecular pathways underlying HIV-induced neuronal dysfunction. Among HIV-induced neuron-damaging products, the HIV envelope glycoprotein gp120 triggers elevation of intracellular Ca\(^{2+}\) in neurons, resulting in apoptosis. By quantifying neuronal activity using intracellular Ca\(^{2+}\) imaging in mouse cultured hippocampal cells, this study confirmed that the FIV envelope glycoprotein gp95 also elevates intracellular Ca\(^{2+}\) activity, which could lead to excitotoxicity and neuronal dysfunction. This suggests that gp120 and gp95 could share the same pathological process in neurons. In addition, by using pharmaceutical inhibitors, we revealed that gp95 interacts with the chemokine receptor, CXCR4, and activates the release of intracellular Ca\(^{2+}\) mediated by the glutamate NMDA and AMPA receptors (NMDAR and AMPAR), neuronal nitric oxide synthase (nNOS), cGMP-regulated protein kinase II (cGKII), and the endoplasmic reticulum-associated Ca\(^{2+}\) channels, inositol triphosphate receptors (IP3Rs). These results provide understanding of the molecular pathway involved in HAND and possibly give rise to novel therapeutic targets to treat chronic lentivirus infection in both felines and humans.

**Research Grant:** Colorado State University Department of Biomedical Sciences

**Student Support:** NIH T35 Training Grant T35OD015130

**PDK4 and mitochondrial metabolism in canine model of idiopathic familial dilated cardiomyopathy**

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The Doberman pinscher (DP) is a canine breed with a high incidence of developing idiopathic, non-ischemic dilated cardiomyopathy with an elevated mortality rate. A common mutation causing a deletion of the pyruvate dehydrogenase kinase 4 (PDK4) gene, shows a positive correlation with developing the disease. PDK4, a vital mitochondrial protein, controls the switch between the metabolic pathways of glycolysis and oxidative phosphorylation based on nutrient availability. DPs lacking the PDK4 gene are unable to utilize the more energy efficient pathway, oxidative phosphorylation, and thus are more susceptible to apoptosis. This study investigated the effect of the mutation on mitochondrial function and characterized the apoptosis pathway in skin fibroblasts from DPs that were healthy/wild type (PDK4+/+), heterozygous (PDK4+/-), and homozygous (PDK4-/-) for the PDK4 mutation. The hypothesis of this study was that PDK4+/− and PDK4−/- cells would undergo mitochondrial mediated cell apoptosis when deprived of glucose while the PDK4+/+ cells would be more viable under these metabolic stress conditions. Preliminary data shows that deprivation of glucose causes mutated cells to show higher levels of ROS production and caspase 9 generation than normal cells which is indicative of a mitochondrial induced apoptosis pathway. AAV-CBA-PDK4-mediated gene replacement experiments were performed in vitro using fibroblasts to confirm cause-effect relationships and generate pre-clinical data to support the development of a gene therapy program for PDK4-affected Dobermans.

**Research Grant:** Florida Veterinary Scholars Program, Doberman Pinscher Club of America, Cooper’s Fund

**Student Support:** Florida Veterinary Scholars Program, Boehringer Ingelheim Veterinary Research Scholars Program
**Plasma copeptin as a measure of surgical stress in the canine patient**

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Stress directly affects the physiological and psychological well-being of pet animals and may alter disease outcomes and prognosis. Traditionally, cortisol has been used in veterinary research as a measure of stress, but with limited clinical use due to several factors affecting its release and levels. Arginine vasopressin (AVP), along with corticotrophin releasing hormone, synergistically activates the hypothalamic-pituitary-adrenal axis in response to stressful stimuli. AVP is difficult to measure clinically due to its unstable nature and analytical problems. Copeptin, a glycopeptide released from the same parent hormone as AVP, is stable, easily analyzed, and has documented use as a measure of stress in human medicine. However, no studies in veterinary research have explored the use of copeptin as an indicator of stress. We measured the effect of surgical stress on copeptin release in dogs. Plasma copeptin was measured in seven dogs before and after elective surgery of ovariohysterectomy using enzyme immunoassay. This is the first study measuring copeptin in canine plasma. In contrast to human studies, our results did not show a statistical difference in pre-surgery (0.50 ng/mL) and post-surgery (0.57 ng/mL) copeptin levels in plasma. This could be due to species differences, interference from the premedication or pain management, or analytical procedures followed, and should be pursued further. More studies need to be done to clarify the role of copeptin as a measure of stress in dogs in a clinical setting to understand its value in canine health and welfare.

**Research Grant:** Western University of Health Sciences  
**Student Support:** PetSmart Charities® Summer Scholar Program

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**Assessment of GI injury in Alaskan sled dogs using intestinal fatty acid binding protein and diamine oxidase**

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**Background:** Changes in gastrointestinal (GI) permeability and injury are caused by a breakdown of the protective gastrointestinal epithelial barrier and commonly occurs in humans, horses, and dogs following strenuous exercise. Gastrointestinal injury and increased permeability raise the risk of ulceration and translocation of intestinal bacteria causing sepsis or systemic inflammatory response syndrome (SIRS). Current methods to assess intestinal injury and permeability in dogs are either invasive, difficult to perform, or have high variability. Intestinal fatty acid binding protein (I-FABP) and diamine oxidase (DAO) are two enterocyte proteins absorbed from the epithelium with intestinal injury. Hypothesis/Objectives: We hypothesize I-FABP and DAO concentrations will be correlated with previously obtained assessments of intestinal permeability and injury. **Animals:** Serum was collected after various distances of a racing trial in conditioned Alaskan sled dogs. **Methods:** I-FABP and DAO levels will be quantified using commercially available canine-specific ELISA assays. Protein concentrations will be correlated with 5-sugar gastrointestinal permeability and severity of gastroduodenal ulceration, previously obtained by one of the authors (Davis). **Results:** Pending. **Conclusions and Clinical Importance:** This study establishes the utility of serum I-FABP and DAO in the assessment of gastrointestinal permeability and injury in dogs. Future research will continue to validate these easily quantified biomarkers and investigate their potential both as a prognostic marker as well as an assessment of therapies in diseases of gastrointestinal injury in dogs, including sepsis/SIRS, exercise, obesity, and heart disease.

**Research Grant:** None  
**Student Support:** Boehringer Ingelheim, Veterinary Medical Experiment Station, UGA College of Vet Medicine
Developing a PIV5-based ETEC vaccine

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Enterotoxigenic *Escherichia coli* (ETEC) is one of the leading bacterial agents of diarrhea, which is the number one cause of death in children’s diarrhea under five years old. This type of infection kills thousands of people every year in developing countries and affects millions of people from developed countries as Traveler’s diarrhea. ETEC also causes outbreaks in animal populations that are devastating to these countries’ economies. Yet, there is no licensed vaccine available currently. Experimental vaccines have some limitations. Parainfluenza virus 5 (PIV5), a paramyxovirus, is not known to cause any illness in humans. Previous work has demonstrated that PIV5 is an excellent vaccine vector. In this study, two multiepitope fused antigens of ETEC WZ1 and WZ2 were inserted in PIV5 genome between the SH and HN genes. These two recombinant viruses (rPIV5-WZ1 and rPIV5-WZ2) were successfully rescued and confirmed by whole genome sequencing. One plaque-purified clone of rPIV5-WZ1 or rPIV5-WZ2 containing the exact input sequences was selected for future study. In future studies, we expect to determine WZ1 and WZ2 proteins expression in viruses-infected cells and test the immunogenicity and efficacy of rPIV5-WZ1 and rPIV5-WZ2 in animal models.

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**Student Support:** NIH Office of Research Infrastructure Programs, Grant Number 2T35OD010433-11

Development of new ELISA assays targeting anti-HSV-2 and anti-ZIKV antibodies

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To better understand the role of sexual transmission in Zika virus (ZIKV) pathogenesis, a nonhuman primate (NHP) model of vaginal transmission was developed at the CNPRC. After vaginal inoculation of female rhesus macaques (RM), a commercial ELISA kit was used to test for the presence of ZIKV-specific-antibodies. They were detected in plasma but not in cervicovaginal lavage (CVL). Also, a NHP model of the interactions between Herpes simplex virus-2 (HSV-2) and Human Immunodeficiency Virus is being developed. For that purpose, RM were inoculated intravaginally HSV-2. HSV-2 DNA was consistently detected in CVL after inoculation. However, plasma HSV-2-specific IgG was not detected using several assays. Our hypothesis is that our inability to detect strong antibody responses in RM infected with ZIKV and HSV-2 is due to technical issues with the commercial ELISA Kits we used. Our aim is to develop new ELISA assays to measure anti-ZIKV and anti-HSV-2 IgG subclass and IgA antibody responses in RM. In this study, a new indirect ELISA protocol is tested. We titrate each reagent to determine its optimal concentration, and we vary the time and temperature of each incubation step. These assays will clarify whether anti ZIKV antibody responses are present in the CVL and the nature of the humoral response to HSV-2 infection. Finally, the new assays will enable us to determine whether the IgG humoral response triggered by HSV-2 infection is limited to IgG1 anti-HSV-2 antibodies or if IgG2 and IgG3 anti-HSV-2 antibodies are also elicited.

**Research Grant:** Unknown

**Student Support:** Merial (Merial Veterinary Scholars Program)
Progression and persistence of eosinophilic rhinitis in ozone-exposed rats

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Epidemiological studies suggest that elevated ambient concentrations of ozone, the most common gaseous air pollutant in photochemical smog, are associated with activation of eosinophils in the nasal airways of children, a pathologic feature of both atopic and non-atopic rhinitis. Our laboratory has recently reported that rodents repeatedly exposed to ozone develop nasal eosinophilic inflammation, mucous cell metaplasia, and type 2 immunity that are all dependent on group 2 innate lymphoid cells. Progression and persistence of ozone-induced eosinophilic rhinitis after repeated inhalation exposures has not been previously investigated. The present study was designed to determine the severity of ozone-induced rhinitis in rats after episodic inhalation exposures to ozone over the course of 10 weeks. Male rats were exposed to 0 or 0.8ppm ozone (4 h/day) for 9 consecutive weekdays (2-week inhalation exposure). Other rats received three 2-week inhalation exposures separated by 2 weeks of no exposure. All rats were sacrificed 1 day or 2 weeks after the last exposure day. Nasal tissues were processed for light microscopy, immunohistochemistry, and morphometry. Density of eosinophils in the nasal mucosa was significantly greater in rats that were exposed for three 2-week ozone exposures, as compared to those exposed for a single 2-week exposure. Ozone-induced eosinophilic rhinitis persisted for 2 weeks post-exposure with no significant change in severity. The results of this animal toxicology study suggest that eosinophilic rhinitis may progress with repeated episodic exposures to elevated levels of ambient ozone and that this may be a long-lasting adverse effect in humans.

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Student Support: NIH Grant R25HL103156

Combination cellular immunotherapy and radiation therapy for the treatment of cancer

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Eight million people die from cancer each year. Many suffer from the negative consequences associated with current aggressive treatments. Ideal cancer therapies are those that provide the greatest response with minimal side effects. Both radiotherapy and cellular immunotherapy provide the benefit of local treatment without significant systemic effects. NK92 immunotherapy is activated by a variety of tumor associated ligands. These ligands can be upregulated on tumor cells following irradiation. Due to this, we sought to test the hypothesis that the combination of radiotherapy and NK92 immunotherapy will result in a greater reduction of tumor burden relative to either stand alone treatment. Flow cytometry confirmed the presence of the NKG2D and 2B4 receptors on NK92 cells and the upregulation of their respective ligands on irradiated MDA breast cancer cells in a dose dependent manner. NK92 cells were shown to be activated to kill MDA cells via cytotoxicity assays following irradiation at multiple doses with a serial dilution of NK92:MDA cells. Finally, the effects of radiation on NKG2D ligands and CD48 expression levels were measured in vivo. Flow cytometry results from the collected tumors substantiated what was seen in vitro. NKG2D and 2B4 receptor ligands were upregulated in tumors irradiated with 4 Gy compared to the controls. The unirradiated contralateral tumors expressed higher levels of these ligands suggesting combination regional radiotherapy and cellular immunotherapy may target unirradiated minimal residual disease sites. These findings support the hypothesis that combination NK92 cellular immunotherapy and radiotherapy will significantly reduce tumor cell burden relative to either treatment alone.

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Student Support: NIH T35 Training Grant 5T35OD010989-16
Flow cytometric identification and quantification of circulating tumor cells in dogs with osteosarcoma

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Osteosarcoma (OSA) is a malignant primary bone cancer that destroys bone, results in lameness, causes pathogenic fractures, and has a high rate of metastasis. The current standard of care for appendicular OSA consists of limb amputating or sparing surgery followed by chemotherapy that aims to delay or prevent metastasis. Fewer than 15% of dogs with OSA have radiographic evidence of pulmonary metastasis at time of diagnosis, yet more than 85% will develop metastatic disease within a year of diagnosis. This suggests metastatic cells exist prior to diagnosis but are not detectable with current radiographic approaches. Metastasis is usually associated with circulating tumor cells (CTCs). Such cells are extremely rare in peripheral blood and not detectable with routine hematologic analysis. In humans with carcinoma, quantification of CTCs correlates with likelihood of metastasis. Studies regarding CTCs in canine cancers with high metastatic potential are lacking. The objective of this study was to devise a method for detecting OSA CTCs in dogs, and to apply this assay longitudinally to blood samples from dogs undergoing amputation and chemotherapy. A method for intracellular flow cytometric detection of collagen I and osteocalcin was optimized using OSA cell lines, mixing experiments, and control antibodies directed to epithelial and endothelial cell epitopes. Then, approximately 1000000 nucleated cells in bi-weekly blood samples were analyzed for antigen expression. Results to date suggest that collagen I positive cells are detectable in the majority of pre-amputation samples and again immediately prior to radiographic recognition of pulmonary metastases. Analysis of CTC number in relation to outcome remains to be completed.

Research Grant: Ontario Veterinary College Pet Trust Fund
Student Support: Merial Veterinary Research Scholars Program

The effect of a short, leashed walk on heart rate and temperature in hospitalized canines

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Exercise can influence heart rate and temperature in normal, healthy dogs. However, stress and anxiety have been shown to reduce heart rate variability in hospitalized canines. The aim of this study was to examine the effects of a short, leashed walk that is typical of hospitalized patients at the Atlantic Veterinary College’s Veterinary Teaching Hospital on heart rate and rectal temperature. A linear mixed model with an autoregressive structure of order one was applied to the data. The results showed there is no effect of a short, leashed walk on heart rate and rectal temperature. In addition, there were no variables associated with rectal temperature. However, there were significant associations between heart rate and age (p=0.047), weight (p=0.000), and reason for presentation to the hospital (p=0.036).

Research Grant: None
Student Support: Atlantic Veterinary College Veterinary Summer Research Award (VetSRA)
Comparison of dogs with and without pulmonary valve stenosis using ECG-gated computed tomography angiography

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Pulmonary valve stenosis (PS) is a common congenital heart defect of dogs. Currently, transthoracic echocardiography (TTE) is the standard modality used to evaluate for PS. The use of electrocardiographic-gated computed tomography angiography (ECG-gated CTA) in veterinary medicine is limited. The aim was to investigate ECG-gated CTA for characterization of PS. The ECG-gated CTA studies were achieved without anesthesia. Cardiac landmarks were measured in 12 dogs (12 English bulldogs) without PS and 14 dogs (12 English bulldogs, 1 French bulldog, and 1 Boxer) with PS. The pulmonary trunk (PT) and aortic root (Ao) were included in the cardiac measurements. Measurements (mean +/- standard deviation) were made in systole and diastole for both modalities. Parametric analysis was used to compare means. We hypothesized the PT:Ao ratio using ECG-gated CTA will be larger in dogs with PS compared to dogs without PS, and there will not be a significant difference of the PT:Ao ratio during systole or diastole. The PT:Ao ratio was significantly larger in dogs with PS for both modalities (p < 0.05). The PT:Ao ratio for dogs with PS on ECG-gated CTA was 1.58 +/- 0.24 during systole and 1.52 +/- 0.27 during diastole. The PT:Ao ratio on ECG-gated CTA without PS was 1.09 +/- 0.22 during systole and 1.03 +/- 0.23. The PT:Ao did not differ between modalities for dogs without PS during systole or diastole (p = 0.093 and p = 0.576, respectively). The PT:Ao did significantly differ for dogs with PS between modalities during systole and diastole (p < 0.05). There was no significant difference between the systolic and diastolic PT:Ao values within each modality (p < 0.05). The use of a PT:Ao ratio on ECG-gated CTA can be used to evaluate for PS.

Research Grant: Internal Funds of The Ohio State University, College of Veterinary Medicine
Student Support: Wolfe Research Fellow

Effect of anti-glaucoma medications on subconjunctival scarring in vitro

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Glaucoma is a progressive disease leading to vision loss in dogs due to an elevated intraocular pressure (IOP). Surgical techniques aimed at lowering IOP by shunting intraocular fluid out of the eye using implants are limited by scarring. Prior research in humans suggests that latanoprost promotes scarring, potentially resulting in poorer outcomes following glaucoma shunt surgery. However, this has not been shown in dogs, a species in which latanoprost has a different mechanism of action. The purpose is to compare the effect of three topical medications on Tenon’s fibroblasts in vitro. We aim to demonstrate that treatment with latanoprost increases fibroblast migration, proliferation, and profibrotic cytokine secretion compared to control and dorzolamide or timolol treated cells. A pure culture of Tenon’s capsule fibroblasts was established by harvesting Tenon’s capsule explants from normal dogs and placed with DMEM with 10% FBS. Cells were then exposed to 100uM latanoprost, dorzolamide, or timolol. A multiplex assay was used to determine the concentration of 13 cytokines in the cell culture media after 24 hours of treatment. A scratch assay was used to measure cell migration over 48 hours. A colorimetric assay was used to measure cell proliferation over 72 hours. Tenon’s fibroblast cell culture lines were successfully isolated. Cell viability was not affected by drug treatment for 24 hours. Supernatant from treated samples was collected and is awaiting assay availability. Proliferation and scratch assays are in progress. Changes in proliferation, migration, or cytokine expression may be attributed to profibrotic effects of latanoprost, suggesting that treatment with antiglaucoma medications may affect shunt survival.

Research Grant: None
Student Support: NIH grant T35OD011070- T-35 Interdisciplinary Biomedical Research Training Program (IBRTP)
Susceptibility of crude oil exposed Fundulus grandis to Streptococcus agalactiae infection

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Toxic disasters, such as the hypoxic dead zone in Louisiana and the Deepwater Horizon BP oil spill that occurred in 2010, have had a devastating effect on marine species’ health, but specifically the host-pathogen interactions of native organisms are not yet understood. In addition to potential developmental, behavioral, and reproductive issues, the immunological effects of this event have not yet been fully evaluated. Disruptions of the developmental environment are of particular concern in considering later immunocompetence and pathogen susceptibility to exposed organisms, including fish. Streptococcus agalactiae has a broad host range but is a well-documented pathogen of the gulf killifish (Fundulus grandis) in the Gulf Coast region. Pathology is characterized by exophthalmia, sepsis and meningitis with histologically identifiable intravascular bacteria. Exposure to polycyclic aromatic hydrocarbons may yield differing responses to pathogens present in the environment. In this study we evaluated the effects of exposure of embryos of F. grandis to 0, 10 and 32% of the water accommodated fraction (WAF) of polycyclic aromatic hydrocarbons (PAH) respectively, on the gulf killifish’s response to S. agalactiae challenge (Gulf coast strain LADL 97-151). Evaluation of responses included morbidity, mortality, and histopathology. Statistical comparisons were made between oil exposed gulf killifish (F. grandis) and control groups regarding their survival following a subsequent pathogen challenge at 9 days post challenge.

Research Grant: None
Student Support: Louisiana State University, Dr. Kenneth F. Burns Lectureship and Clinical Clerkship Foundation

Case study of diet digestibility and gut microbiome changes in a dog undergoing CHOP chemotherapy for lymphoma

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Nutritional strategies in the management of patients undergoing chemotherapy are still in its infancy. Chemotherapy has been shown to cause shifts in gut microbiota in humans. Given the parallels between human and canine neoplastic disease further evaluation of shifts in the gut microbiome during treatment with chemotherapy in dogs is warranted. Cooked navy beans and rice bran have demonstrated cancer chemoprevention properties and a strong potential to support a healthy gut microbiome. The first aim of this study is to document shifts in commensal and opportunistic gut microbiota following CHOP therapy for canine lymphoma and to evaluate the digestibility of a novel diet containing navy beans and rice bran during chemotherapy. This project will also describe healthy canine gut microbiome of retrievers that are at high risk for cancer. A 96hr total fecal collection was performed to assess apparent total tract digestibility(ATTD) after diet change and chemotherapy. This study will integrate digestibility with gut microbiome as a novel approach to provide nutritional support during treatment. Stool samples were collected at five time-points from an adult 12-year-old male castrated Labrador diagnosed with multicentric B-cell lymphoma with ocular involvement. The first and second stool collection were performed prior to and after one week of chemotherapy. On week four of chemotherapy the dog was transitioned to a diet containing 25% cooked navy bean powder and heat stabilized rice bran and additional collection points were performed at weeks 7, 9, and 11. The microbiome was analysed via 16S amplicon sequencing using the Illumina platform and QIIME. The 96hr total fecal collection was performed on week nine for ATTD analysis.

Research Grant: None
Student Support: This research supported by the Boehringer Ingelheim Veterinary Scholars Program and CSU
Localization of respiratory circuit candidate neurons using light-sheet microscopy in larval zebrafish

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High-speed light-sheet microscopy combined with genetically-encoded calcium indicators allows visualization of neuronal activity at single-cell resolution across the whole brain of transparent zebrafish larvae. This type of population recording facilitates investigation of the interactions between neurons embedded in circuits that span multiple brain regions. Here, we use this method to search for neuronal populations that may be pre-synaptic partners of facial branchiomotor neurons (FBMNs). These neurons are involved in respiratory behavior, giving us the opportunity to look for other components of the zebrafish respiratory circuit. Importantly, their segmental organization can be modified with genetic mutations to observe the effect of a positional shift on network architecture. Preliminary results show the spatial distribution of neurons with activity patterns that are temporally associated with those of FBMNs in both wild-type and mutant larvae where FBMNs are located in the wrong hindbrain segment. Overall, our study narrows down the candidate neurons whose identity and connectivity should be further assessed to understand the importance of cranial motor circuit organization in the formation of synaptic connections during development.

Research Grant: NIH (NINDS F32-NS083099 and R01-NS026539)
Student Support: Boehringer Ingelheim Veterinary Scholars Program

Evaluating the risk of avian malaria for penguins at the Potter Park Zoo in Lansing, Michigan

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Penguins in captivity are highly susceptible to avian malaria, a vector-borne disease caused by Plasmodium species, so they are commonly given prophylactic treatment. This is true for the penguins at the Potter Park Zoo in Lansing, Michigan, where the avian malaria vector, the Culex mosquito, is present. We will investigate the prevalence of malaria and the risk of penguins contracting the disease by catching mosquitoes and examining the DNA extracted from the abdomens. The mosquitoes were captured at Potter Park Zoo several times between May and June, 2017. Each mosquito was bisected using sterile technique and the DNA was extracted from the abdomen following Qiagen DNeasy protocols. Polymerase Chain Reaction (PCR) was used to amplify the targeted DNA fragments for blood meal analysis and Plasmodium detection, and was followed by gel electrophoresis and visualization of results. Any positive samples from the blood meal analysis were sent to the Michigan State University Genomics facility for sequencing; these results are still pending. The sequences will be analyzed by comparison to known sequences in GenBank. With this information, we will determine the hosts of the mosquitoes as well as detect the malaria parasites if they are present. Among the mosquitoes screened, I expect that there will be a very low feeding preference for penguins. Plasmodium is present in the mosquitoes. Despite the mosquitoes’ preference for other hosts, however, the presence of avian malaria parasites in the local mosquito population indicates that the prophylactic treatment for the penguins is prudent.

Research Grant: Graduate Office Fellowship
Student Support: Merial
Proteinuria in dogs with atopic dermatitis: a retrospective analysis

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Atopic dermatitis is an inflammatory skin condition in dogs, resulting in intense pruritus, self-trauma, and papules, amongst a variety of other cutaneous lesions. These animals are most commonly treated with immunomodulators, such as cyclosporine or oclacitinib, or systemic anti-inflammatories such as glucocorticoids. Given the inflammatory nature of atopic dermatitis, proteinuria is expected to occur in some atopic dogs. In this retrospective study, the records of 77 client-owned dogs with atopic dermatitis were analyzed for evidence of proteinuria. Animals with proteinuria before or at the time of diagnosis of atopy were further studied to determine whether the proteinuria persisted after treatment with oclacitinib, cyclosporine, or glucocorticoids. It was hypothesized that systemic treatment of atopic dermatitis would decrease or eliminate proteinuria in these dogs. Preliminary results of this on-going analysis indicated that most dogs exhibiting proteinuria prior to, or at the time of diagnosis with atopic dermatitis, did not experience lessening or resolution of proteinuria following treatment of atopy. This study revealed that proteinuria is present in a small number of dogs and can be attributed to atopic dermatitis. In addition, proteinuria is unlikely to resolve, even after the atopic dermatitis becomes well-controlled with treatment.

Research Grant: Gift Funds
Student Support: Boehringer Ingelheim Veterinary Scholars Program

Cord blood antibodies and the risk of early parasitemia in Malian infants

Tiffani Turinski, Andrew Teo, Alassane Dicko, Michal Fried, Patrick Duffy

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Plasmodium falciparum infection is a risk to both pregnant women and their fetuses. Malaria exposure results in the development of protective antibodies. However, intermittent preventive treatment during pregnancy with sulfadoxine-pyrimethamine (IPTp-SP) can reduce exposure, and therefore potentially reduce the titers of malarial antibody transferred to the infant. The current study analyzes the impact of cord blood antibodies to three parasite antigens (MSP1, MSP3, AMA1) and one pregnancy-specific antigen (VAR2CSA-DBL5) on early childhood risk of parasitemia. Maternal gravidity and IPTp-SP doses are investigated for their impact on antibody levels. Antibody levels to DBL5 increased in a gravidity-dependent manner, while in contrast antibody levels to AMA1 decreased in higher gravida. In univariate analyses, increasing SP doses did not have an impact on time to parasitemia in early childhood, however, high levels of MSP3, AMA1, and DBL5 antibodies each corresponded to decreased time to first parasitemic episode compared to low antibody titers. When stratified by gravidities, children delivered by first time and >2 times mothers tended to experience earlier parasitemia episodes as antibodies to MSP3, AMA1 and DBL5 increased. The results suggest that antibodies to malaria antigens are highly dynamic. Higher cord blood antibody titers, possibly due to exposure during pregnancy, may correspond to decreased time to first parasitemic episode in the offspring. Efforts to protect pregnant women against exposure during pregnancy are important.

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Student Support: National Cancer Institute
Comparison of novel needle and technique in collection and proliferation of equine mesenchymal stem cells

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Mesenchymal stem cells (MSCs) are non-hematopoietic multipotent stem cells commonly harvested from bone marrow. Grafting of autologous bone marrow-derived cells as raw bone marrow, concentrated bone marrow, and bone marrow-derived culture expanded MSCs has greatly increased for treatment of musculoskeletal diseases and trauma in equine athletes, leading to a need for more efficient harvesting of bone marrow and MSCs. We previously demonstrated that bone marrow aspiration with multiple advancements of a conventional aspiration needle resulted in a greater number of stem cell progenitors compared to single site collection. In this study, we sought to compare this currently used technique against a novel closed-end aspiration needle. The closed-ended tip with reverse advancement decreases peripheral blood contamination and increases the concentration of cells harvested. This study will allow evaluation of initial collection and proliferation of cells between techniques and needles. Bone marrow was aspirated from the sternum of 12 horses using both needles with a randomized location. Total nucleated cell count (TNCC), culture expansion with passage counts, and colony forming unit (CFU) assay was performed and compared. Maximizing the concentration at first collection could increase MSCs for point-of-care kits, but has not been seen to have a large effect if culture expanded. With the increasing prevalence of MSC therapy, the information from this study can be used to determine the technique and needle design for the highest quantity and quality of bone marrow for MSC derivation. This can be applied for continuing innovation and advancement of more efficient and effective MSC collection and therapies for the equine athlete.

Research Grant: The Link Endowment Fund; College of Veterinary Medicine & Biomedical Sciences at Texas A&M University One Health Initiative
Student Support: One Health Initiative, College of Veterinary Medicine & Biomedical Sciences, Texas A&M U.

Validation of a real-time quaking-induced conversion assay for antemortem diagnosis of chronic wasting disease

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Chronic wasting disease (CWD) is a fatal neurodegenerative disease affecting cervids, such as white-tailed deer, mule deer, and elk. This prion disease results from the abnormal folding of normal prion protein into an aggregated, protease-resistant, diseased isoform that propagates throughout the lymphoid tissues and the brain. Due to a prolonged incubation period, only during the late stage of disease do animals display clinical signs such as abnormal behavior and poor body condition score. The brief window between clinical manifestation and death makes it imperative to develop early, antemortem-based detection methods to aid in managing the disease’s spread through cervid populations. Currently, the gold standard of diagnosing CWD is by examination of lymph node and postmortem brain tissues by IHC. Thus, the purpose of this study was to validate a newly developed RT-QuIC prion protein seeding assay, which allows rapid antemortem detection of CWD prion at minute quantities with high sensitivity. This is a well-designed multi-institutional study utilizing a large set of 702 recto-anal mucosa-associated lymphoid tissue samples collected antemortem from white-tailed deer. First, we optimized the assay using a highly purified recombinant monomeric prion substrate for higher reproducibility. Blinded analysis of 648 samples showed approximately 15% to be CWD-positive. The data will be unblinded at the end of the study to be analyzed against other partnering laboratory’s results and currently approved IHC methods. We anticipate that our RT-QuIC results will be as sensitive as those from postmortem obex IHC. Overall, validation of RT-QuIC will offer a robust high-throughput diagnostic platform for antemortem CWD detection.

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Development of portable diagnostics for onsite detection of significant poultry diseases

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Early detection of disease outbreaks is of particular importance in the food animal industry where outbreaks have the potential to spread rapidly to large numbers of animals, imperiling food security and human health. Disease surveillance efforts would benefit greatly from a detection platform that decreases the time between sample collection and assay result, eliminates the hassle of sample transport, and reduces the need for specialized laboratory equipment. The goal of this research project is to explore the utility of Biomeme’s portable quantitative PCR (qPCR) system as a detection platform for major infectious diseases of poultry. Once optimized, this approach would employ field-stable reagents and pathogen-specific test strips to perform rapid, onsite qPCR assays powered by a smartphone paired to a handheld qPCR device. Known positive infectious bronchitis (IBV) tracheal swab samples were used to compare the efficacy of Biomeme’s protocol against the National Veterinary Services Laboratories (NVSL)-approved protocol, which uses MagMAX-96 DNA extraction followed by AgPath-ID One-Step RT-PCR. While the Biomeme platform did correctly identify negative cases and nearly all positive cases, it did so at higher cycle thresholds than the NVSL protocol, suggesting that a more rapid, field-based diagnostic may come at the cost of decreased sensitivity. Future work will involve production of field-ready, IBV-specific test strips for complete portability of the assay, as well as expanding to other relevant poultry diseases.

Research Grant: None
Student Support: NIH/Merial Summer Research Program

Investigating mouth rot in farmed Atlantic salmon

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Tenacibaculum maritimum is a Gram-negative filamentous bacteria that has been identified as the causative agent for “mouth rot” in farmed Atlantic salmon raised in British Columbia. Lesions associated with this disease present as yellow bacterial plaques on the teeth, gingiva, tongue, vomer and/or gill arches of smolts: fish recently transferred to salt water. Typically no other clinical signs are observed with this disease; mortality is acute. The objective of this study was to determine if size was associated with mouth rot in Atlantic Salmon in British Columbia. Atlantic salmon were sampled prior to and during the course of a mouth rot outbreak on two farms. Dead fish from various pens were collected daily over a period of five weeks and classified based on their disease status. Approximately 3,000 fish were sampled. A large proportion of fish (86.6%) with mouth rot were off feed; 20.9% of dead fish without mouth rot had no food in GI tract. Nearly half (48.2%) of fish with mouth rot had poor condition factor (<1.0). The mean weight of fish with and without mouth rot varied by site. Statistical analysis suggests average weight of fish affected by mouth rot was lower than fish without mouth rot, after controlling for time of sample, pen, and farm. At the site level, fish with clinical signs of mouth rot were approximately 30 grams lighter than unaffected fish. Smaller fish may be at higher risk for infectious diseases due to poor smoltification and impaired immune function. Future studies to improve our understanding of this disease could evaluate the pathology and immune status among various fish sizes within pens.

Research Grant: UPEI AVC (VetSRA), Canadian Excellence Research Chair in Aquaculture
Student Support: UPEI AVC (VetSRA), Marine Harvest Canada
Assessment of the skeleton’s mechanosensitive anabolic pathways using endogenous fluorescence in mouse models

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The skeleton is sensitive to mechanical loading and understanding the cellular mechanisms by which bone forms in response to load could be important in developing anabolic therapies for bone-wasting diseases. This in vivo loading study was conducted on mice that endogenously express GFP in association with the activation of the DMP1 or TCF/LEF promoters to assess the anabolic response of the tibia to mechanical load. Both DMP1 and TCF/LEF are highly expressed in osteocytes and are known to be responsive to mechanical stimuli. Osteocytes are the most abundant cells in the bone and are regarded as the mechanosensory cells responsible for communication with other bone cells to initiate bone formation and remodeling. Following loading, the tibiae were sectioned by means of cryosectioning and analyzed under a fluorescence-ready microscope. The number of fluorescent osteocytes will be indicative of the anabolic response of the tibia to applied mechanical load.

Research Grant: None
Student Support: Merial Veterinary Research Scholars Program

The iBunny project: electrocardiography of pet rabbits using a smartphone-based ECG device

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Rabbits are the third most relinquished companion animal behind cats and dog. Consequently, the frequency of routine surgical procedures has also increased. However, rabbits have a much higher risk of death related to perioperative sedation and anesthesia compared to other species. Electrocardiography (ECG) is the gold-standard tool for the detection of cardiac arrhythmias, which can be indicators of underlying cardiac and extra-cardiac pathology. The use of electrocardiography as a pre-anesthetic tool could ultimately reduce the risk of death in rabbits. The objective of this study is to compare the performance of a smartphone-based ECG device (Alivecor, “AC”) with the conventional computer-based ECG device (“PC”) in domestic rabbits. We aimed to compare QRS-complex amplitude, T-wave amplitude and polarity between both devices. Currently, ECG traces for 56 rabbits were recorded, with 22 of those analyzed. Preliminary results indicate significant differences in R, S, T waves and total amplitude of QRS complex between the AC and PC devices. Subjectively, ECG traces recorded with the AC device were easier to read than the PC device. Once traces of all enrolled rabbits are analyzed, we will also analyze the effect of body weight, chest conformation, and hair length on the ECG traces obtained with the AC device. Our results may support the use of the smartphone ECG in rabbit health.

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Research Grant: None
Student Support: Morris Animal Foundation
Assessment of renal angiotensin II immunoreactivity in an ischemic model of feline chronic kidney disease

Autumn Vetter, Amanda Coleman, Bianca Lourenco, Cathy Brown, Dan Rissi, James Stanton, Chad Schmiedt, Elizabeth Howerth, Jaime Tarigo

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Over one third of all domestic cats will be affected by chronic kidney disease (CKD) in their lifetimes. Unfortunately, a full understanding of the pathways involved in feline CKD is limited, hindering our ability to prevent its occurrence and progression. Hallmark histologic lesions of feline CKD include chronic tubulointerstitial nephritis and fibrosis. In human CKD and in rodent models of CKD, the renin-angiotensin system (RAS) appears to be a major mediator of renal fibrosis, with angiotensin II (Ang II) acting as the major effector protein of this pathway. Predictably, clinical outcomes in human CKD have been improved by use of medications that block the RAS, and it is reasonable to suspect that these drugs may provide a viable therapeutic option in feline CKD as well. To date, little work has been done to characterize the intra-renal RAS in cats. Our group has recently described an ischemic model of feline renal fibrosis which induces chronic histological and biochemical changes that mimic those observed in naturally occurring CKD. Using archived renal tissue from healthy cats (n=8) and cats having previously undergone ischemic injury as a model of CKD (n=6), immunohistochemistry was performed in order to localize and semi-quantitate intra-renal Ang II. Compared to normal control tissues, those from cats having undergone ischemic injury displayed increased Ang II immunoreactivity. These results suggest that the RAS may be activated in cats with naturally occurring CKD and will provide the basis for future studies of cats with spontaneous disease. Understanding the role of RAS in feline CKD will help us better evaluate our current approach to medical management of this disease.

Research Grant: Grants on the Edge, University of Georgia, College of Veterinary Medicine and the Office of Research, FY 2017
Student Support: Morris Animal Foundation, Veterinary Medical Experiment Station, UGA College of Vet Med

Histological, parasitic and bacterial assessment of White Sea Urchins (*Tripneustes ventricosus*) in Saint Kitts

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*Tripneustes ventricosus* commonly known as the White Sea urchin, inhabit shallow coastal areas in the Caribbean. They are important herbivores as they keep algae and sea grass growth at bay. The White Sea urchins’ gonads (roe) are a delicacy especially in Japan and Barbados. Yet, there is very minimal information on diseases of *T. ventricosus*. The aim of this survey was to describe pathology of *T. ventricosus* and identify their parasitic and bacterial populations. We opportunistically sampled *T. ventricosus* from the southern part of the island and performed comprehensive postmortem examination, including collection of samples for histopathology, assessment of wet mounts for parasites, and culturing bacterial swabs of the gonads. Urchins affected with spine loss had less gut contents relative to unaffected urchins. Few correlations were seen in regard to size, circumference and sex of the urchins. Microscopic lesions identified included degeneration of interpyramidal muscle of the Aristotle’s lantern, ectoparasitism and bacterial aggregates in the test and gill. Seven types of ciliates and two types of flagellates were observed in the wet mounts. From the bacterial identification sequencing it was revealed that *Vibrio sp.* were present in the gonads. This baseline assessment of *T. ventricosus* infection and disease status is essential for predicting disease impact on St. Kitts’ populations and for informing human health risks where roe is eaten raw. Moreover, since they occupy a crucial niche, survey results can be used as health indicators of the aquatic ecosystem.

Research Grant: None.
Student Support: Merial Veterinary Scholars Program.
Role of calcium-induced phosphorylation of NF-κB in T cell development and function

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The fidelity of adaptive immunity to pathogens depends on the capacity of lymphocytes to recognize the pathogen and mount an appropriate effector response. A crucial second messenger implicated in this activation and differentiation is antigen-induced changes in intracellular calcium levels. We have shown that the antigen-induced differentiation program reflects quantitative features of these signals. However, a critical gap in our understanding is the precise mechanisms by which intracellular Ca2+ signals drive fate specific patterns of gene expression in lymphocytes. Our initial efforts have established that Ca2+ signals critically regulate the activation of members of the NF-κB family of pro-inflammatory transcription factors in T cells. However, virtually nothing is known about the mechanisms by which Ca2+ controls NF-κB function and specificity. Transcriptional analyses of activated T cells demonstrate that Ca2+ drives the expression of at least twelve NF-κB-dependent genes. We identified a novel mechanism of Ca2+-dependent phosphorylation of the NF-κB subunits c-Rel (on serine 34) and p65 (on serines 316 and 536). The goal of this work is to determine how Ca2+-dependent control of c-Rel and p65 phosphorylation regulates gene expression and T cell differentiation. We hypothesize that Ca2+-dependent phosphorylation of these serine residues regulates NF-κB nuclear localization, DNA binding, and transcriptional activity at specific promoters. To test this hypothesis, we generated 3 mouse lines each with a non-phosphorylatable alanine substitution at one of these p65 and c-Rel phospho-acceptors. These mice will be used to define the role of each residue in antigen-induced gene expression and T cell differentiation.

Research Grant: NIH grants RO1AI060921 and RO1HL096642
Student Support: NIH T35 OD010919

Evaluating the role of single viral capsid mutations on the infectivity of carnivore protoparvovirus-1

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Carnivore protoparvovirus-1 is a 26nm-sized non-enveloped single-stranded DNA virus known to cause feline panleukopenia in cats and canine parvoviral disease in dogs. The virus was previously thought to have jumped directly from domestic cats to dogs resulting in the pandemic spread of canine parvovirus, but recent evidence suggests that wild carnivores served as important unrecognized reservoir hosts in the evolution of these viruses. Among parvovirus isolates collected from wild and domestic carnivores, the genome is most variable at capsid (VP2) amino acid residue 300, suggesting this position is critical in allowing the cross-species transfer of the virus between different carnivore species through its interaction with the host receptor (transferrin receptor). The focus of this study was to explore the importance of this specific residue in regards to infectivity and viability of the virus by altering VP2 position 300 in an FPV infectious clone through site-directed mutagenesis. Wild-type FPV, which in domestic cats always contains an Ala (GCT) at VP2 position 300, was mutated to an Asp (GAT), a residue commonly observed in alternate wildlife hosts, to determine its effect on fitness in cat cells. The results demonstrated that the FPV mutant containing an Asp at VP2 position 300 was markedly reduced in viral titers versus the wild-type Ala, suggesting that altering this position can have profound effects on infectivity in a species-dependent manner and that VP2 position 300 is a key site in controlling host range.

Research Grant: Virginia-Maryland College of Veterinary Medicine
Student Support: Virginia-Maryland College of Veterinary Medicine
Acute effects of Keyhole Limpet Hemocyanin in Zebra Finches (Taeniopygia guttate)

Michael Wallis, Jennifer Grindstaff

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Corticosterone (CORT) is a common glucocorticoid of avian species and a key messenger within the Hypothalamic-Pituitary Axis modulating a variety of physiological responses, including activation of the immune response. It is known that increased circulating glucocorticoids, in response to a stressor, cause a change in circulating leukocytes in vertebrate species. In avian species, acute stressors have been shown to increase circulating CORT and increase the Heterophil: Lymphocyte ratio (H/L). Keyhole Limpet Hemocyanin (KLH) is a common vaccine adjuvant which, due to its large size and high number of Pathogen-Associated Molecular Patterns, triggers a humoral immune response in vertebrate species. While KLHs’ humoral effects have been described in avian species, there is no current information on the acute effects of exposure in avian models. To investigate these effects, we sampled male Zebra Finches (Taeniopygia guttate) one hour prior to and either one or six hours after injections with KLH or a control. These samples were used in a CORT assay and for H/L ratio calculation. We hypothesize that individuals treated with KLH will have higher H/L ratios and CORT Levels than control groups. Data analysis is currently underway. If our hypothesis is correct we might expect to find that there is an initial increase in CORT in response to the KLH injections at the one hour mark but no significant change in H:L ratio. At the 6 hour interval there might be a decrease in CORT levels and an increase in the H:L ratio. These results would indicate that within the six-hour post injection window KLH exposure results in activation of the innate immune system prior to the eventual activation of humoral immunity.

Research Grant: None
Student Support: Unknown

Behavioral indicators of pain after lingual irradiation in CD1 mice

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Oral mucositis is a common consequence of the radiation and chemotherapy used to treat head and neck malignancies. It can result in decreased nutritional intake and can cause severe pain, both of which decrease quality of life. Oral mucositis often limits treatment dosages, and the associated pain signaling can possibly lead to cancer progression. These factors can result in decreased treatment effectiveness and poor long-term prognosis for the patient. While there are ongoing clinical studies aimed at finding methods to reduce pain directly associated with oral mucositis, there is a need to understand the affects of radiation-induced pain on the nervous system and pain pathways as a whole in order to develop better pain control methods. The purpose of this study is to quantify orofacial and peripheral pain and hypersensitivity over time in mice that have undergone lingual irradiation. A panel of behavioral assays was developed to measure changes in sensitivity and response to mechanical, thermal and chemical stimuli, after lingual irradiation. Responses in the irradiated branch of the trigeminal nerve (mandibular), and an unirradiated branch of the same nerve (ophthalmic) were evaluated; tests were also performed to evaluate for evidence of widespread sensitization. Results are pending and will be correlated with various molecular endpoints. We anticipate that the results will indicate which pain pathways and parts of the nervous system are affected by lingual irradiation and which assay is best at detecting discomfort so that methods for pain control in cancer patients can be improved in the future.

Research Grant: American College of Veterinary Radiology
Student Support: NIH T35 Training Grant T35OD011070
Knowledge, attitudes, and behaviors regarding antibiotic use in dairy cattle among New York dairy farmers

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There has been a global initiative for more judicious use of antibiotics in agriculture, including in dairy farming, due to concerns that overuse may contribute to antibiotic resistance. However, there is only a limited understanding of the attitudes of U.S. dairy farmers towards antibiotic use, which hinders development of effective farm-level interventions to promote judicious antibiotic use. The objective of this ongoing study is to investigate the knowledge, attitudes, and behaviors of NYS dairy farmers concerning antibiotic use in cattle. Semi-structured in-person interviews are being conducted with a convenience sample of farmers. Interview data are analyzed using thematic analysis. Interviews have been conducted with 11 farmers, and a preliminary analysis of a subsample of five interviews was performed. Major topics addressed included basic knowledge of antibiotic use and antibiotic resistance, adherence to judicious antibiotic use practices, and veterinarians as a source of information on antibiotic use. Most participants were able to accurately define the term antibiotic and describe antibiotic resistance, suggesting at least a baseline level of scientific knowledge. Interestingly, all participants characterized their antibiotic use as judicious, and many emphasized they prefer to focus on disease prevention rather than treatment. However, some participants expressed the belief that not all dairy farmers use antibiotics judiciously. Most reported consulting their veterinarian when they had questions about antibiotic use. Preliminary results suggest that NYS dairy farmers perceive their use of antibiotics as prudent and thus may lack motivation to change their practices.

Research Grant: None
Student Support: Merial Veterinary Research Scholars Program, NIH T35 Training Grant – OD010941

Validation of fluorescently-labeled Listeria monocytogenes’ infection in human endometrial epithelial cells

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University of Wisconsin-Madison, School of Veterinary Medicine (Wenzel); University of Wisconsin-Madison, Cellular and Molecular Pathology (Wolfe), Wisconsin National Primate Research Center (Wiepz), University of Wisconsin-Madison, Comparative Biosciences

Listeriosis is a food borne illness known to cause adverse pregnancy outcomes. Previously, the third trimester of pregnancy was considered to be the most at-risk for infection, however, listeriosis is known to occur throughout gestation. The bacteria responsible is Listeria monocytogenes. We are attempting to authenticate the use of a fluorescently-labeled strain of Listeria to use in research. We chose to work with strain 2203 as it originated from a North Carolina outbreak of miscarriages in women. 2203 mCherry is a bioluminescent version of the 2203 wild type (WT) strain. It allows for the capability of easier in vivo imaging for further studies on the timeline and pathology of Listeria infection. We hypothesized that the addition of mCherry did not change infectiousness. We incubated Ishikawa cells (human endometrial adenocarcinoma) with both WT and mCherry 2203. After 1 hour of inoculation, gentamicin was added and cells were incubated for another 5 hours. Then they were processed for colony plating, flow cytometry, and immunocytochemistry microscopy. Our results indicate that WT and mCherry 2203 infect with similar patterns. If 2203 mCherry can be authenticated, we will have a new tool to study the timeline of infection in vivo in nonhuman primates.

Research Grant: NIH Project Number 5R01AI107157-03, The maternal-fetal interface in listeria-induced pregnancy loss (PI: TG Golos)
Student Support: NIH T35 Short-term Research Training for Veterinary Students in Wisconsin (PI: D. Bjorling)
Prevalence of Papillomavirus in a unique feral horse herd

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Papillomaviruses (PV) can affect a wide variety of species and commonly cause skin lesions. While well researched in humans, how PV affects the equine population remains an active area of interest. This study aimed to characterize the prevalence of PV in the wild horse herd on Sable Island, Nova Scotia. There are approximately 500 feral horses on this island and they have been isolated from other horses for more than 200 years. Skin samples were collected from 25 horses that had died over the winter months, DNA was extracted and PCR performed using degenerate PV primers. Amplified DNA was interpreted using gel electrophoresis. No PV DNA was detected in any of the 25 samples, giving a result of 0/25. Using the “rule of three” statistical analysis, a maximum possible prevalence was calculated. If PV is present on Sable Island, this study suggests that it is occurring at a rate of 12% or lower in this wild herd. This is much lower than the 30% prevalence that we have found in Western Canadian domestic horse herds.

Research Grant: Townsend Equine Health Research Fund and the Experiential Discovery and Learning Program in Large Animal Veterinary Medicine From The Agriculture Development Fund of Saskatchewan
Student Support: Merial Veterinary Scholars Program and Townsend Equine Health Research Fund

Pneumonia in juvenile bighorn sheep (Ovis canadensis): the role of Mycoplasma ovipneumoniae carriers

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Pneumonia threatens the viability of North American bighorn sheep (Ovis canadensis) populations. Fatal epizootics affecting all ages result when the bacterium Mycoplasma ovipneumoniae is introduced into naive, healthy bighorn sheep populations. High rates of lamb pneumonia-induced mortality associated with the same genetic strain type of M. ovipneumoniae may recur for years following an all-age epizootic. We are testing the hypothesis that M. ovipneumoniae carrier ewes are the source of M. ovipneumoniae infection and subsequent disease in lambs, using an experimental study in captive animals. Post-epizootic bighorn sheep ewes (n=5) were commingled and longitudinally sampled over a 2-year period. We identified one persistent carrier and 4 non-carriers. After commingled breeding, the ewes were separated into 2 pens: pen 1 with 1 carrier and 1 non-carrier, and pen 2 with 3 non-carriers. We predicted that lambs raised in the carrier pen would develop pneumonia but lambs raised in the non-carrier pen would remain healthy. To date, only lambs in the carrier pen have developed pneumonia. If this pattern holds, the experiment will be repeated next year with different non-carriers commingled with the carrier. These experiments represent one replication of a larger multi-center study using broadly consistent methods involving post-epizootic bighorn sheep carrying different M. ovipneumoniae strains. This larger study is expected to demonstrate the essential role of M. ovipneumoniae carriers in the epidemiology of pneumonia in bighorn lambs, providing critical insights into our understanding the biology and epidemiology of the disease necessary for development of successful management strategies.

Research Grant: Wild Sheep Foundation, US Forest Service, Boehringer-Ingelheim Veterinary Scholars Program, WSU-CVM Office of the Dean, WSU-CVM Darden Memorial Research Endowment
Student Support: Besser Lab Mentor Grant Fund
Role of CX3CR1 in pathogenesis of murine lupus

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Lupus nephritis (LN) is a manifestation of the autoimmune disease Systemic Lupus Erythematosus (SLE) which occurs in more than 50% of SLE patients. It is a major cause of morbidity and mortality for those with SLE. Current immunosuppressive treatments lead to increased risk of infection as a major side effect, thus treatment options with decreased risk are desired. Recent studies have shown that increased levels of monocyte-derived conventional dendritic cells with the unique CX3CR1 receptor expression are present in the kidney of patients with LN, making CX3CR1 a potential therapeutic target. The purpose of this study was to understand the effects that deletion of the CX3CR1 gene has on lupus-prone MRL/lpr mice. We hypothesized that the deletion of the CX3CR1 gene in lupus-prone MRL/lpr mice will attenuate lupus-like disease. Tissue samples were collected from three groups of 4-month-old female MRL/lpr mice (CX3CR1−/−, CX3CR1+/−, and CX3CR1+/+), and then either stained with hemolysin and eosin (H&E) and stained for immunohistochemistry (IHC) analysis. The samples were then analyzed to quantify the degree of leukocyte infiltration. Overall, the results demonstrated that there was no significant difference in infiltration among the three genotypes. These findings do not support the hypothesis that deletion of the CX3CR1 gene results in amelioration of lupus-like disease.

Research Grant: Virginia-Maryland College of Veterinary Medicine
Student Support: NIH T35 Training Grant T35OD011887

Psychosocial effects of service dogs on individuals with physical disabilities within two age groups

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Service dogs are well-known for the functional tasks they perform to help individuals with physical disabilities. However, these dogs’ impact on functioning, quality of life, and other psychosocial areas of health has not been examined quantitatively. The objective of this research was to empirically evaluate the effects of service dogs on overall psychosocial functioning including social, emotional, and work/school functioning within age categories. Analyses included 157 individuals enlisted through a national service dog provider, Canine Assistants, including those paired with a service dog (n=98) and those on the waitlist to receive one (n=59). Primary outcomes were measured with the Pediatric Quality of Life Inventory between those with and without a service dog within two age groups. For individuals 25 and younger (n=96) those with a service dog had significantly improved overall and work/school functioning compared to those on the waitlist (t=2.196, p=0.031; t=2.389, p=0.019). Improvement in social functioning approached significance (t=1.910, p=0.059), while there was no difference in emotional functioning in this younger age group (p=0.434). For individuals older than 25 (n=61) those with a service dog had significantly higher overall, work/school, social, and emotional functioning than those on the waitlist (t=3.573, p=0.002; t=2.647, p=0.011; t=2.076, p=0.043; t=4.404, p < 0.001). The findings suggest that service dogs have significant psychosocial effects on recipients with physical disabilities, and that age may play a role in perceived social and emotional functioning. This is important for further research on the psychosocial benefits of service animals and the individuals they assist.

Research Grant: Elanco Partnership: Canine Assistants
Student Support: Boehringer Ingelheim Veterinary Scholars Program
Characterization of heart failure risk and type in hypertensive geriatric vervet monkeys

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Heart failure (HF) is a clinical syndrome of two recognized types: heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). The prevalence of HFpEF is increasing at a rate of 1%/year in the U.S. and accounts for over 50% of cases. The majority of HFpEF patients are female, over the age of 65, and frequently also have hypertension, diabetes, pulmonary congestion, and exercise intolerance. Currently no successful HFpEF treatments are available, and lack of good animal models is an obstacle to understanding etiologies and potential therapeutic strategies. The aim of this study was to evaluate spontaneously hypertensive vervet monkeys to determine if they may be an applicable animal model of HFpEF. Sixteen healthy geriatric females were matched based on age, weight, waist, plasma lipids, glycemic status, and environment. Half had chronic hypertension. Monkeys were evaluated by echocardiography; thoracic radiography; circulatory cyclic guanosine monophosphate (cGMP) and brain natriuretic peptide (BNP); pulse wave velocity; blood pressure; respiratory rates and walking speed as a proxy for exercise tolerance. Hypertensive monkeys had 24% higher plasma triglycerides (p = 0.02) and 58% higher BNP levels (p = 0.09). cGMP levels were associated with BNP levels (R=0.50, p = 0.05) and metabolic health indicators waist circumference and plasma cholesterol (R=-0.58 and -0.61, p < 0.05 for both respectively). Interim data analysis suggests that hypertensive monkeys do not show physical function or respiratory rate differences. Radiographic and echocardiographic assessments for heart morphology, systolic and diastolic function, and pulmonary congestion are ongoing and will be presented.

Research Grant: P40 OD010965 and UL1 TR004120 
Student Support: NIH T35 Training Grant T35OD010946

Bioinformatics analysis of flea microbiome identifies distributions of microbial taxa and biochemical pathways

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Fleas are commonly referred to as ectoparasites because they live on the outside of the host and serve as vectors for numerous pathogens that cause important human and animal disease. As more information about the flea microbiome becomes available, we can learn more about why fleas select their hosts on a molecular level. In this study, 16s sequencing data were obtained from 24 fleas. Of these, 8 were from Northern California and 16 from Southern California. Identified microbial taxa associated with Southern versus Northern fleas, such as Rickettsia and Wolbachia (p-value < 0.0001). The microbial taxa identified from the flea samples were further analyzed with the online galaxy platform. Predicted metagenome data from the initial 16s data was generated with PICRUSt toolkit. These bioinformatics resources allowed us to identify over 6000 orthologous KEGG gene groups associated with more than 325 metabolic and biochemical pathways. Our preliminary results include southern fleas being enriched in transporters, oxidative phosphorylation, and DNA repair compared to northern fleas. We are continuing to analyze and interpret the data through large scale literature mining efforts aimed at identifying possible functional connections between biochemistry, the microbiome and parasite disease relationships. These efforts have identified an interesting connection between geographical distribution of ectoparasites and differences in fatty acid degradation, which may provide clues about how Northern and Southern fleas differ in disease transmission. Our work is valuable and may offer novel drug targets that can be used to reduce parasite associated disease in dogs, cats and humans.

Research Grant: Unknown
Student Support: Henriksen Summer Research Fellowship
Clinical signs and response to diet and exercise regimes in horses with Type 2 polysaccharide storage myopathy

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Exertional rhabdomyolysis (ER) occurs with Type 1 Polysaccharide Storage Myopathy (PSSM1) caused by a glycogen synthase \( (GYS1) \) mutation. ER also occurs with PSSM2 which is characterized by abnormal skeletal muscle glycogen aggregates, but lacks the \( GYS1 \) mutation. Currently low-starch/high-fat diets and exercise regimes are recommended for both PSSM1 and PSSM2. We recently found that, unlike PSSM1, muscle glycogen concentrations in PSSM2 are not elevated. Our objectives were to define clinical signs of PSSM2 in two breeds and determine if clinical signs improved with the standard PSSM diet/exercise regime. PSSM2 horses were identified from the Neuromuscular Diagnostic Lab database (2008-2016). Owners of Warmbloods (WB) and Quarter Horses (QH) with PSSM2 and regional control horses without PSSM answered a questionnaire. Results were analyzed using logistic regression \[JMP Statistical Software, p<0.05\]. Compared to control WB (n=22), significantly more PSSM2 WB (n=42) had signs of ER, reluctance to go forward, reluctance to collect, performance decline, atrophy, altered behavior and muscle fasciculations. Significantly more PSSM2 QH (n=17) had ER, altered behavior, and sensitivity to grooming than control QH (n=14). With recommended diet and exercise, 80% of WB and 65% of QH improved, but none became asymptomatic. Thus, although not a glycogen storage disease, clinical signs of PSSM2 in both breeds significantly improve with a low-starch/high fat diet and regular exercise. Further research is necessary to determine the basis for PSSM2 and whether histopathologic findings of amylase-sensitive glycogen aggregates in muscle represent a single disease process. This study was limited by the design and number of respondents.

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Student Support: Boehringer-Ingelheim and MSU College of Veterinary Medicine and Graduate School

Effects of Vitamin A deficiency on immune response to bovine respiratory syncytial virus infection

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Human respiratory syncytial virus (HRSV) is an RNA virus and leading cause of severe lower respiratory tract infections in infants and young children. Bovine RSV (BRSV) is a closely related virus that causes lower respiratory tract infections in young calves and contributes to the development of bovine respiratory disease, the leading cause of morbidity and mortality to both the beef and dairy industries worldwide. Experimental evidence reveals that Vitamin A (VA) contributes to the proper function of the immune response to infection and vaccination. Currently, there is a lack of research showing the specific role of VA in regulating the immune response to RSV infection. Therefore, the goal of this study was to evaluate the effects of VA deficiency (VAD) on the immune response to BRSV infection. Neonatal calves were fed a VA sufficient (VAS) or VAD diet, and then animals were challenged via aerosol inoculation with BRSV. Animals were monitored daily for clinical signs and virus shedding, and were euthanized on day 7 after infection. We observed no significant differences in clinical illness or gross pathology in the lungs. Interestingly, however, we observed significant changes in the inflammatory milieu in the infected lungs, including reduced expression of IL-17 and IL-6 in VAD animals compared to VAS calves. We also observed differences in the virus burden in the lungs of VAD compared to VAS animals, as measured by qRT-PCR. Together, our results suggest that nutrition plays an important role in regulating the immune response to RSV infection in the neonate. Therefore, future studies will be focused on determining the mechanisms by which VA influences disease outcome during respiratory infection.

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Student Support: Boehringer Ingelheim Veterinary Scholars Program
Impact of enrofloxacin dosing on gastrointestinal pharmacokinetics and selection for resistant *E. coli*

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Antimicrobial resistant (AMR) bacteria in cattle has been identified as a potential food safety concern, however it is uncertain how treatment protocols influence selection for AMR foodborne pathogens. Developing effective dosing regimens that decrease selection for AMR bacteria may mitigate the threat to human health while still effectively treating disease. The objective of this study was to determine the impact of 2 FDA approved dosing schedules for enrofloxacin. We hypothesized that a single high dose will achieve a greater concentration of drug within the gastrointestinal tract resulting in a lower concentration of AMR *E. coli* in the feces. We tested our hypothesis by treating 12 steers either at a high dose once or a low dose repeated daily for 3 days. Results through one-way ANOVA showed that *E. coli* concentration at time points 12, 24, and 36 hours were significantly different in the high dose study in conjunction with an increased median MIC at 24 hours. The low dose study showed significantly different *E. coli* values at 24, 36, 48, 60, and 72 hours with increased MIC at 12, 24, and 48 hours as well as overall higher median MIC starting at 12 hours and persisting throughout the study. Overall, both treatment regimens cause a significant, but short-lived reduction in the concentration of fecal *E. coli* and there was a small, brief increase in median MIC with the low dose regimen. The findings of this study demonstrate the differential impact of dosing regimens of enrofloxacin on the gastrointestinal *E. coli* populations as well as their corresponding MICs, suggesting that the high dose regimen should be used preferentially to minimize selection for AMR *E. coli*.

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Student Support: NIH- Grant T35OD011070 and CVM Veterinary Scholars Program

In vivo gene knockdown approach for validation of gene function in *Cryptosporidium parvum*

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*Cryptosporidium parvum* is a parasitic protozoan of medical and veterinary significance worldwide. Infections with *C. parvum* occur through ingestion of contaminated water or food, and cause a diarrheal syndrome called Cryptosporidiosis, that may be life-threatening in immunosuppressed individuals. Currently, there is only one approved drug, nitazoxanide, used for the treatment of *Cryptosporidium* infections but it is ineffective in malnourished children and immunosuppressed individuals. In this study, we endeavored to develop an in vivo assay for interrogating gene function throughout the life cycle of *C. parvum* using phosphorodiamidate morpholino oligomers. By targeting the *C. parvum* lactate dehydrogenase (LDH) gene, we achieved over 90% knockdown of its expression during *C. parvum* growth and development in IFN-γ knockout mice. To analyze the effect of LDH knockdown, we performed real-time PCR to quantify the amount of *C. parvum* oocysts shed by infected mice treated with LDH-target morpholino compared to those treated with control (off-target) morpholino. We then used the oocysts shed by the two groups of mice to infect HCT-8 cells to assess the effect of LDH knockdown on viability. We found that LDH knockdown significantly decreased the growth and development of *C. parvum*, and that the oocysts shed contained daughter parasites with significantly reduced infectivity. These studies have developed an antisense gene knockdown approach for studying gene function in *Cryptosporidium*, and validated LDH as an essential gene for growth, development and viability of *C. parvum*. This technology will be useful in functionally characterizing and validating potential molecular drug targets in *Cryptosporidium*.

Research Grant: Bill & Melinda Gates Foundation

Student Support: Boehringer Ingelheim Veterinary Scholars Program
Ultrasonic vocalization and physiological responses in rats

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Vocal communication is one of the most complex behaviors in both humans and animals. It requires muscle control to drive breathing, adjust laryngeal configuration and move tongue and jaw. The goal of this project was to investigate the effect of changes to the autonomic nervous system (ANS) on the vocal sound output. If changes to the ANS are reflected in the vocal output, an animal’s vocalization could serve as a non-invasive tool to better understand well-being. The ANS could affect vocalization either directly by acting on all three motor systems involved, or by affecting the emotional state of the animal and modulatory effects on the hindbrain. Work in nonhuman primates and rodents suggests a strong relationship between ANS activation and call rates. However, those studies have been performed in juveniles. The role of the ANS in adult animals has remained unclear. We used heart rate (HR) to estimate ANS activation and tested the hypothesis that vocal characteristics are associated with sympathetic activation in rats (Rattus norvegicus). If changes in the ANS activation are reflected in the vocal output, we expected that acoustic features, such as fundamental frequency, call duration and sound intensity, would co-vary with HR. Preliminary data suggest that average HR is elevated at call onset but often decreases quickly back to baseline, although the rat continues to call. Fundamental frequency does not co-vary in a consistent pattern. Interestingly, in all animals tested, HR variation was significantly higher during vocalization than during baseline recording. If HR variation is related to the emotional responding of an animal, as suggested by other researchers, vocalization could serve as a noninvasive proxy.

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Student Support: Merial Veterinary Research Scholars Program

Antiviral properties of equine mesenchymal stem cells against equine herpesvirus type 1 (EHV-1) in vitro

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Equine herpesvirus type 1 (EHV-1), a global problem in horses, causes upper respiratory illness, myeloencephalopathy, abortions, and newborn death. It currently lacks effective treatments and vaccines. Mesenchymal stem cells (MSCs) are adult multipotent progenitor cells isolated from various tissues, including peripheral blood. MSCs have regenerative properties and are routinely used by equine practitioners as a biologic treatment for orthopedic diseases. Our group has previously shown that equine MSC exhibit antibacterial properties, in part mediated through secreted antimicrobial peptides (AMPs). As some AMPs exert broad-spectrum effects on bacteria and viruses, we began to explore antiviral properties of MSC secreted factors, with the long-term goal of using MSC as a therapy to control EHV-1. This in vitro study aims to determine if equine MSC secreted factors inhibit EHV-1 replication, and if so, how. We found that MSC secreted factors inhibit the replication of 2 pathotypes of EHV-1 (neuropathogenic NY03 and non-neuropathogenic Ab4) in three host cells lines. We also generated preliminary evidence that MSC secreted factors act to inhibit the viral replication cycle after EHV-1 entry. Moreover, gene expression analysis of infected host cells in the presence or absence of MSC secreted factors suggests that these factors increase the antiviral response of host cells. These data thus far support the fact that MSC secreted factors possess antiviral properties, as documented by the inhibition of EHV-1-replication and increased cellular anti-EHV-1 response. Continued study on how MSC secreted factors inhibit EHV-1 replication will help us to determine if these cells can be used as a therapy to control the spread of EHV-1.

Research Grant: None
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Geographic distribution and genetic diversity of porcine circovirus type 3 from pigs in U.S. swine farms

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Porcine circovirus 3 (PCV3) from pigs was first reported in United States in 2016, and later described in China, Korea and Poland in 2017. The role of PCV3 as a cause of disease is still unclear, however, it has been associated with cases of wasting, porcine dermatitis and nephropathy syndrome, myocarditis, systemic vasculitis and abortion. Previous pilot studies indicate that PCV3 may be endemic in swine herds. In this study, we want to investigate the geographic distribution of PCV3 in cases submitted to University of Minnesota Veterinary Diagnostic Lab (UMN VDL) and explore the genetic diversity of whole genome of PCV3 in the U.S. The study population is the swine cases submitted to the UMN VDL from February 2016 to March 2017 and tested PCV3 using an in-house qPCR assay. We obtained 533 clinical samples from 124 swine cases from 12 different states. Thirty-seven percent of total samples were PCV3 qPCR positive while thirty-seven percent of cases were positive. Positive cases were found in 8 of 12 states. Seventeen PCV3-positive samples obtained from pig farms in eight states with different age group and health conditions will be sequenced and analyzed. The whole genome of PCV3 is generated by assembling two PCR amplicons of 1kb in length. Genetic differences of PCV3 whole genome and ORFs in different isolates would be analyzed by making multiple sequence alignment and phylogenetic analysis. The sequences obtained in this study will be compared to the 17 PCV3 sequences currently available in GenBank. The sequencing and genome analysis of PCV3 are still on going. The findings in geographic distribution of PCV3 indicate PCV3 is widely distributed in U.S swine farms.

Research Grant: Veterinary Population Medicine funds, University of Minnesota
Student Support: The University of Minnesota College of Veterinary Medicine

Gram negative enteric bacterial antibiotic resistance in the normal flora of snakes

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The growing popularity of owning and interacting with exotic animals has increased the chances of humans and animals encountering infectious bacterial agents which can be present in the normal flora. Handling commonly owned reptiles such as snakes and turtles increases the risk of zoonotic disease, especially with antibiotic resistant bacteria. Since the diversity of enteric gram negative bacteria in reptiles was not well known, this study aimed to determine bacterial prevalence, antibiotic resistant bacteria, and specific genes leading to resistance in snake flora. Cloacal swabs were used to acquire samples of enteric bacteria from eleven different snakes. Seven snakes were captive bred and owned, while four were caught in the wild. Enteric bacteria were isolated on specific broth and agar plates and identified using a Sensititre (ThermoScientific) system and analytical profile index. Minimal inhibitory concentration results were also collected. Salmonella and Klebsiella were isolated from eight individual snakes, Citrobacter from seven snakes, and Morganella from five snakes. Of the 37 bacterial isolates, 26 (70.3%) were resistant to cefazolin, 24 (64.9%) to cephalothin, and 21 (56.8%) to ticarcillin. Resistance was confirmed by PCR tests that resulted in four isolates presenting a DHA gene, one presenting a CTX2 gene, and one Providencia rettgeri isolate that presented with both genes. These genes represent an innate mutation allowing for broad spectrum and AMPc beta-lactamase drug resistance and furthering the infectious potential of these bacteria. Our data confirms the existence of resistance in the normal flora and potential hazards involved with handling these exotic reptiles.

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Student Support: Boehringer Ingelheim Veterinary Scholars Program and MSU CVM
Radiographic evaluation of cardiac silhouette in clinically healthy Humboldt penguins (*Spheniscus humboldti*)

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Wild populations of Humboldt penguins (*Spheniscus humboldti*) on the coasts of Chile and Peru have been declining due to food scarcity caused by the El Niño Southern Oscillation, and human interference. Part of conserving this vulnerable and threatened species is maintaining the health of penguins within zoo collections. A variety of cardiovascular diseases have been reported in individuals from the *Spheniscidae* family including ventricular septal defects, *Dirofilaria immitis* infection, pulmonary hypertension, congestive heart failure, and valvular dysplasia. The aim of this study was to establish a routine methodology for evaluating the cardiac silhouette of clinically healthy Humboldt penguins using vertebral heart score (VHS), cardiocoelomic width ratio (CCWR), and a novel cardiac silhouette to keel ratio (CKR). Ventrodorsal and right lateral radiographs were taken of two mature Humboldt penguins during routine health evaluations. An echocardiographic exam of each penguin was performed to confirm that there was no evidence of cardiac structural remodeling due to disease. Right lateral radiographs were used to determine VHS (8.4v, 8.9v) and CKR (4.04, 3.66). Ventrodorsal radiographs were used for calculating CCWR (0.58, 0.55). Initial work shows that a standard radiographic study provides objective measures for cardiac silhouette evaluation. Nine more individuals will be enrolled. An accurate clinical picture of cardiovascular disease in Humboldt penguins requires diagnostics tailored to this specific species. Additional research looking at these radiographic measurement techniques in diseased Humboldt penguins as well as validating reference ranges with larger sample sizes in all penguin species is needed.

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**Student Support:** Merial Veterinary Research Scholars Program

*Bordetella bronchiseptica* vs *Bordetella pertussis* and their interaction with *Dictyostelium discoideum*

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*Bordetella* species are gram negative bacteria that cause respiratory infections. *B. bronchiseptica* causes Kennel Cough in canines and infects a wide host of other mammals, while *B. pertussis* only infects humans causing the disease Whooping Cough. While much is known about the ability of these bacteria to colonize and cause disease in the respiratory tracts, little is known about their environmental reservoirs or if these reservoirs are important for spread and transmission of the bacteria. We hypothesize that the ability of bordetellae to interact with the amoeba *Dictyostelium discoideum* as an environmental reservoir is important for these interactions. We preformed assays to assess the ability of both *B. bronchiseptica* and *B. pertussis* to survive inside *Dictyostelium discoideum* and their ability to localize to the fruiting body(sori) of the amoeba. The results showed that *B. bronchiseptica* survives intracellularly in the amoeba and is also present in the fruiting body(sori) while *B. pertussis* does not survive intracellularly and therefore does not make it to the fruiting body(sori). These data indicate that *B. bronchiseptica* can utilize amoeba spores to travel to new locations and infect hosts such as canines. *B. pertussis* fails to survive amoebic predation and therefore cannot localize to the amoeba sori and utilize the amoeba as a transmission vector. Altogether, these data indicate that the ability of *Bordetella* species to interact with the amoeba correlates with their host range and has potential implications for transmission between hosts.

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**Student Support:** Boehringer Ingelheim, Veterinary Medical Experiment Station, UGA College of Vet Medicine
Population pharmacokinetics of new oral itraconazole solution in captive lesser flamingos

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Captive flamingos are highly susceptible to aspergillosis. Compounded itraconazole has poor systemic absorption and existing formulations can be cost prohibitive. Itrafungol, a recently FDA approved novel oral itraconazole suspension, may be an affordable alternative for treating this disease. This new product could decrease treatment costs by 1/4. The objective of this study is to investigate the pharmacokinetics of itraconazole oral formulation (Itrafungol, Elanco lab) in lesser flamingo (Phoeniconaias minor) in order to determine bioavailability, absorption rate, distribution and half-life of the Itrafungol product. 17 lesser flamingos (Phoeniconaias minor) were administered itraconazole (10 mg/kg) orally via gavage. To minimize stress and handling, a population pharmacokinetic (PK) approach was utilized. Following drug administration, serial blood samples were collected and analyzed by HPLC. Pharmacokinetic software was used to calculate pharmacokinetic parameters. Preliminary results indicate sample collection intervals demonstrated adequate absorption and elimination phases of itraconazole. Itraconazole was detected in plasma at all sample times in every bird with a peak concentration at 3 hours and a second peak at 16 hours post dosing. Itraconazole concentrations remained above therapeutic levels (1.0 μg/mL) consistently throughout the 24 hour sampling period. Sporanox (Janssen) has traditionally been used to treat avian fungal infections. However, a 30 day treatment with Sporanox costs $113 versus $28 for a 30 day treatment with Itrafungol. Based on preliminary results, 10 mg/kg Itrafungol orally once a day results in adequate therapeutic concentrations of itraconazole to treat fungal infections in flamingos.

Research Grant: None
Student Support: College of Veterinary Medicine & Biomedical Sciences, Texas A&M University

Effects of a humanized gut microbiota on lung histopathology in a murine model of allergen mediated asthma

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Asthma is one of many chronic inflammatory-mediated disorders increasing in prevalence in industrialized nations over the last several decades. Recent evidence supports an underlying effect of the microbiota, suggesting that shifts in the dominance of different taxa of gut microbes alters immune function and susceptibility to various atopic diseases. In this experiment, we are investigating whether mice which have been transplanted and bred to carry an increased-allergy associated humanized gut microbiota will show exacerbated lung histopathology following exposure to an enteric pathogen and repeated challenge with an allergen. 88 C57BL/6 mice, half harboring humanized microbiota and half with a conventional mouse microbiota, were divided into 8 groups (n=11/group). Half were inoculated with Campylobacter jejuni 260.94, bacteria shown to induce a Th2-shifted immune response commonly seen in asthma, and half were sham inoculated. Later, mice in each group were repeatedly sensitized with either house dust mite allergen (HDM) or sham. Prior to sacrifice, mice were anesthetized and tested for lung function. Left lung lobes were fixed in formalin, sectioned transversely, embedded in paraffin, and stained for assessment of inflammation, mucus cell metaplasia, and number of eosinophils. Slides will be digitized, quantified stereologically, and assessed using ANOVA. We expect varying degrees of pathology between groups, with the most severe change in mice with a humanized microbiota challenged with C. jejuni and HDM. Preliminary results showed a significant difference in mucus cell metaplasia between HDM+ and HDM- conditions, but no significant difference due to other variables.

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Glucocorticoid receptor expression is decreased with nuclear localization in airways of pasture asthma horses


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Severe human asthma is defined as poorly responsive to inhaled glucocorticoids. We investigate a spontaneous animal asthma model, equine pasture asthma (EPA), affecting grazing horses during summers in the southeastern US. EPA recapitulates characteristics of severe human asthma including neutrophilic airway inflammation, and hyper-responsiveness to methacholine bronchoprovocation diagnostic of severe asthma (<1mg/ml). Our analysis of the EPA lung transcriptome identified decreased glucocorticoid receptor (GCR) expression. We hypothesize that GCR protein expression is decreased in bronchioles of horses with pasture asthma. Based upon predicted conservation of epitopes between equine and human GCR (100% nucleotide and amino acid homology), antibodies to human GCR were employed to characterize GCR protein expression in lung tissue from horses during clinical EPA exacerbation. Compared to non-diseased control horses, distinct decreases in GCR expression were identified in bronchiolar epithelium from EPA horses. Moreover, nuclear staining predominated in bronchiolar epithelium of EPA horses. In contrast, both cytoplasmic and nuclear staining were evident in bronchiolar epithelium from control horses. We conclude that GCR protein expression is decreased and its intracellular localization is shifted primarily to the nucleus in airways of EPA horses. These findings are congruent with descriptions of nuclear GCR localization and decreased GCR binding affinity in Type I steroid resistant human asthmatics, and align to anecdotal descriptions of EPA as poorly responsive to glucocorticoid administration without removal from inciting environmental factors.

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Student Support: NIH T35 Training Grant 2T35OD010432-16; Mississippi State Univ. College of Veterinary Medicine.

Protein kinase C isoforms in combinational treatment of paclitaxel and substituted quinolines

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Paclitaxel is an antineoplastic agent used to treat breast cancer. However, paclitaxel also mediates the upregulation of Protein Kinase C family, an off-target effect. Recently, combinational approach of paclitaxel and substituted quinolines, PQ1 - gap junction enhancers, has been shown to attenuate breast tumor growth. Thus, the purpose of this project is to assess the PKC expression in the vital organ of mice bearing mammary tumors with the treatment of paclitaxel and PQ1. Mice were implanted with estradiol-17 (1.7 mg/pellet) before the injection of 1 x 10^7 T47D breast cancer cells subcutaneously into the inguinal region of mammary fat pad. Animals were treated intraperitoneally with DMSO (control), paclitaxel (10 mg/kg), PQ1 (25 mg/kg), or a combining treatment of paclitaxel and PQ1. Isolated brains and tumors were evaluated for differential pattern of PKC α, βII, γ, δ and ε using western blot analysis. The results showed that paclitaxel and PQ1-treated brains have a 4-fold increase in PKC βII compared to control without paclitaxel or PQ1. There were no significant changes in PKC α, δ, and γ in paclitaxel or PQ1-treated alone; however, the combinational treatment has a 20% increase in PKC δ expression. Interestingly, PKC ε has a 24%, 19%, and 42% decrease in Paclitaxel, PQ1, and combination, respectively, compared to control. Overall, these findings suggest that there are differential changes in PKC isoforms in paclitaxel and PQ1-treated animals and subsequently the treatment of paclitaxel and PQ1 can activate PKC-mediated signal pathway.

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Student Support: Boehringer Ingelheim Veterinary Scholars Program
Custom 3D-printed drill guides for surgical stabilization of the canine thoracic spine

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Dogs presenting with fractures of the thoracic spine can often benefit from surgery to stabilize the affected vertebrae using metal implants and polymethylmethacrylate. However, the narrow implantation corridor through which the surgical implants must pass without compromising the spinal cord or breaching the thoracic cavity means that free-handed implant placement is technically challenging and can have potentially devastating consequences. Therefore, we hypothesized that custom 3D-printed drill guides based off of pre-planned trajectories can provide a safe and accurate way to make drill tracts for surgical implants in the canine thoracic spine. Our goals were to design a replicable protocol for making guides for thoracic vertebrae T8-T13, and to test the safety and accuracy of drill tracts made using the guides. High resolution CT images of 12 canine cadaver spines were used to create 3D representations of the thoracic spine and to plan ideal implant trajectories with Mimics software. Customized drill guides that conform to desired vertebrae were then created with the software 3-Matics and printed using a Projet MJP 2500 printer with the photopolymer Visijet M2 RW. In simulated surgeries, the guides were used to drill tracts in five of the cadavers, and these tracts were visualized with post-procedure CT scans. Preliminary results suggest that the guides are effective in constraining the drill tracts to safe implantation corridors, and analysis of accuracy is ongoing. This study will demonstrate the efficacy of custom 3D-printed surgical drill guide use for canine thoracic spine surgery.

Research Grant: None
Student Support: NC State VSP, Merial Grant, Fund for Discovery, Herbert Benjamin Endowment

Effects of metformin on the equine gut microbiome

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Equine metabolic syndrome (EMS) and pituitary pars intermedia dysfunction (PPID) are clinical syndromes associated with obesity, hyperinsulinemia, and insulin resistance (IR). Although both exhibit insulin resistance, EMS and PPID can be distinguished by the IR mechanism and other symptoms. Metformin is a commonly used pre-diabetic drug in humans and horses that is thought to increase insulin sensitivity through a mechanism involving the gut microbiome. Metformin-induced changes in the gut microbiota of mice and humans include increased abundance of Akkermansia, bacteria associated with increased metabolic rate, decreased obesity, and insulin sensitivity. The objective of this study is to determine whether the same changes occur in the equine gut microbiome and can be correlated to the beneficial effects of the drug. We hypothesize that giving metformin to horses will enhance Akkermansia in the gut microbiome and decrease the effects of IR in horses at risk for EMS and PPID. For this study, 4 horses were treated with metformin over a week period, with 2 horses serving as controls. To assess insulin sensitivity, blood samples were collected during an oral sugar test (OST) at the beginning and end of the study. To characterize the gut microbiome over the administration of metformin, fecal samples were collected daily and sequenced using 16S rRNA analysis. We anticipate detecting heightened insulin sensitivity and pronounced Akkermansia in the gut microbiome associated with the effects of metformin.

Research Grant: University of Missouri Metagenomics Center
Student Support: Grant from Boehringer Ingelheim
Assessment of an immunomodulator on the duration and severity of signs of URI in shelter dogs and cats

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Upper respiratory infections (URI) in cats and dogs can be caused by multiple bacterial and viral agents and are very common in animals housed in shelters due to high risk of exposure. Clinical signs of URI delays adoption and drains shelter resources. While antibiotics treat many bacterial infections, effective anti-viral medications for dog and cat agents are not as available. Stimulation of the non-specific (innate) immune system has been shown in several studies to aid in the management of bacterial and viral pathogens. A potent stimulator of innate immunity that is comprised of cationic liposome complexes containing two toll-like receptor agonists (MucosImmune) has been used in several dog and cat studies either parenterally (systemic immune stimulation) or by mucosal (local immune stimulation) application and shown to be safe and effective in some scenarios. The randomized, masked, placebo controlled study described here aims to evaluate the combination of oral and subcutaneous administration of MucosImmune as a treatment for URIs. The study hypothesis is that cats and dogs with clinical signs of URI that are administered MucosImmune by the combined routes will have improved clinical outcomes when compared to placebo (sterile saline) treated controls. Preliminary data was collected over a 36-day period prior to the study’s commencement and showed that a total of 52 cats and 16 dogs were moved into isolation and treated per shelter guidelines. The cats remained in isolation for an average of 6.98 days (median 7 days, range 2-15 days), while the dogs remained in isolation for an average of 4.94 days (median 6 days, range 1-9 days). The prospective trial is ongoing for the next 5 weeks.

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Student Support: PetSmart Charities Fellowship