Anticipating Zika
40th Annual Report
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Anticipating Zika
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The key to improved animal well-being is animal health.
The key to improved animal health is veterinary research.
The Veterinary Medical Experiment Station (VMES) was established as a budgetary entity by the state legislature in July 1976 following approval by the University of Georgia Board of Regents in 1973.

MISSION

The VMES mission is to coordinate research on animal disease problems of present and potential concern to Georgia’s livestock and poultry industries.

SPECIFIC VMES OBJECTIVES ARE:

• To improve the health and productivity of domestic livestock, poultry, fish, and other income-producing animals and wildlife through research;
• To assist in preventing disease epidemics by providing laboratory resources and highly skilled scientific personnel;
• To assist in protecting human health through the control of animal diseases transmissible to man;
• To improve the health of companion animals, which serve to enrich the lives of humankind;
• To train new scientists in animal health research in order to provide continuity and growth in this vital area of veterinary medicine.

The Veterinary Medical Experiment Station is committed to enhancing animal production, profitability, and well-being by improving animal health.

All programs and activities of the Veterinary Medical Experiment Station are conducted without regard to race, color, national origin, age, sex, or handicap.
The overarching goal of research conducted by investigators at the UGA College of Veterinary Medicine and the Veterinary Medical Experiment Station is to improve the quality of health of animal and human populations. This goal is spotlighted in our lead article on Zika virus by Drs. Melinda Brindley and Courtney Murdock, two researchers in the College’s Departments of Infectious Diseases and Population Health. It is a testament to the quality, breadth and relevancy of the College’s research that projects were immediately begun in 2016 to create vaccines against this rapidly emerging virus threat. Novel investigations are also underway to understand the basic biology of the Zika virus in both the mosquito and animal host. These studies will undoubtedly contribute to the development of critically needed diagnostics, therapies, and vaccines of immediate benefit to human health.

Listed in this VMES Annual Report are the names of 22 individuals who received graduate degrees in 2016 after completing comprehensive training programs that include original, hypothesis-driven research conducted under the mentorship of College researchers. These students are attracted to our programs by the excellent research experiences and mentoring that characterize our College. The training of future researchers is of utmost importance to fulfillment of the mission of the Veterinary Medical Experiment Station and to meeting the future animal and public health needs of our state, nation and world.

This 40th Annual Report is a milestone in the long and productive history of the Veterinary Medical Experiment Station. It provides an overview of peer-reviewed, competitive projects and new faculty start-up projects conducted during fiscal year 2016 (July 1, 2015 – June 30, 2016). Projects supported by the State of Georgia VMES funding, and projects funded with United States Department of Agriculture 1433 Animal Health Capacity Grant funds are reviewed by veterinary scientists for quality of science and focus on relevant animal health issues or disease problems. The research must be innovative and applicable to the improvement of animal health. Further information on these projects is available by contacting the VMES office staff by phone, e-mail or website, or directly from the investigators themselves. A list of publications is provided. These peer-reviewed papers represent a selection of VMES-supported work and other scholarly research by the faculty of the UGA College of Veterinary Medicine.

The diversity of the research in the College of Veterinary Medicine is both a strength and a challenge. Diversity in investigations ranging from the molecular level to the whole organism and to populations ensures the relevancy of the work to the rapidly changing biomedical and veterinary research environment. The challenge lies in maintaining the focus required for establishing excellence in specific areas, which includes emerging and re-emerging infectious diseases such as the research on Zika virus described by Drs. Brindley and Murdock. We are succeeding based on several metrics, including our continuing growth in highly competitive, extramural research funding. For the first time in the College’s history, more than $24 million in extramural funding was attained in a single fiscal year. This is a testament to the quality of our faculty, staff, and students in the College of Veterinary Medicine.
A summary of the College’s research funding is provided above. Over the past year approximately nine research dollars were leveraged for each VMES dollar invested. Expenditures are from all sources including State Appropriations, Extramural Research Funding, and Donations – Includes all expenditures and personnel costs.
Zika virus belongs to the family of *Flaviviridae*, and is related to several other important human pathogens including dengue virus, yellow fever virus, and West Nile virus. In healthy individuals, Zika virus infection is asymptomatic 80% of the time. Twenty percent of infections result in a mild fever, rash, and mild achiness. Although the virus was identified more than 60 years ago, it was not the focus of research because it did not adversely affect many people and was not associated with significant human disease.

**History**

Zika virus was first identified in 1947 when a sentinel monkey in the Zika Forest of Uganda was found to be feverish. At the time, scientists used sentinel animals to search for new pathogens by placing them in wilderness areas and monitoring their health for signs of illness. When a sentinel animal was found to be ill, samples from the animal were taken and analyzed. A few years later Zika virus was found again, this time in mosquitoes, and several species of monkey tested positive for Zika antibodies. Other small mammals were not associated with the virus, and it was concluded that the virus transmits primarily between *Aedes* mosquitoes and primate or human hosts. Although the virus occasionally infected humans in Africa, it was not associated with severe disease, and was seen as a benign, self-limiting febrile (fever-causing) illness. Over the next five decades, there were small periodic outbreaks of Zika in both Africa and Asia.

Zika gained international attention when it caused a large epidemic in the Yap Islands in the western Pacific Ocean in 2007, infecting nearly 75% of the island’s population in a 4-month period. The virus was subsequently detected on several neighboring islands and spread throughout Oceania. In early 2015, Zika was detected in Brazil, where there was an established population of *Aedes* mosquito species, and *Ae. aegypti*, *Ae. albopictus*, *Ae. hensilii*, and *Ae. polynesiensis* are considered competent vectors for transmission. *Ae. aegypti* is considered the primary vector for Zika and is thought to be the driver of the epidemic, primarily because it is both abundant in urban settings and preferentially uses humans as a blood source. Recent studies spread across North, Central and South America. The rapid expansion of Chikungunya, and now Zika, out of Africa has followed the global spread of two very important mosquito vectors, *Ae. aegypti* and *Ae. albopictus*. Because both dengue and chikungunya are transmitted by these two mosquito species, many aspects of the ecology of Zika virus transmission are similar to that of these previous invasive arboviruses.

**Modes-of-transmission**

**Vector-borne transmission**

Zika virus is an arbovirus, a category of viruses that cycles between an arthropod vector and a mammalian host (FIG X). Zika has been isolated from a number of *Aedes* mosquito species, and *Ae. aegypti*, *Ae. albopictus*, *Ae. hensilii*, and *Ae. polynesiensis* are considered competent vectors for transmission. *Ae. aegypti* is considered the primary vector for Zika and is thought to be the driver of the epidemic, primarily because it is both abundant in urban settings and preferentially uses humans as a blood source. Recent studies
have found Zika in monkeys in the Americas, suggesting that it may establish a sylvatic cycle (where a virus cycles between primates and mosquitoes), similar to the one seen in Africa.

Zika virus transmission has also been linked to sexual partners, suggesting the virus can also be sexually transmitted. Zika RNA has been detected at high levels in the urine and saliva, and in semen months after a febrile disease. Although it is assumed that Zika transmission can occur through sexual contact, it is not the main route of transmission or the driver of the epidemic. In any case, women who are pregnant or trying to become pregnant should be aware of the risks, and currently the CDC is recommending that pregnant women with a partner that has traveled to Zika endemic areas practice protective sex.

Mother-to-baby transmission of the virus was first hypothesized after doctors noticed a distressing increase in the number of newborn babies with microcephaly in Brazil. Microcephaly is a congenital birth defect in which the growth of the fetal brain is stunted, resulting in an abnormally smaller head and brain than normal. Microcephaly results in a wide range of developmental conditions, for which there currently are no treatments available. Many things can cause microcephaly during pregnancy including genetic mutations, environmental factors (toxins, drugs, alcohol), or viral infections (rubella virus, human cytomegalovirus, and varicella-zoster virus). Initially, several hypotheses for the increase in microcephaly cases were proposed. However, when Zika viral RNA and viral particles were identified in the brain of a microcephalic infant, along with the timing and geographical overlap between the microcephaly cases and the Zika outbreak, it was concluded that Zika can cause microcephaly.

Other forms of transmission

Because Zika virus particles replicate in the blood stream, like other blood-borne diseases it could contaminate the blood supply. For example, Zika virus has been detected in the blood supply in Brazil during the current outbreak. When local transmission is not occurring, meaning Zika is not being actively transmitted by mosquitoes in a given locale, the blood supply can be protected by screening potential donors with a travel questionnaire, and preventing donations of blood from people who have traveled to areas with ongoing Zika transmission. However, when local transmission is occurring, screening donors without a laboratory test is not effective due to the high rate of asymptomatic cases. The first cases of locally transmitted Zika in the US were identified in late-July in parts of Miami, FL. Currently, no FDA-licensed test for Zika exists, but two tests are being investigated, and the FDA recommends the blood to be screened by laboratory testing.
This conclusion has been supported in various animal models that also result in birth defects including intrauterine growth restriction and microcephaly after Zika infection.

**All aspects of Zika are being addressed through multiple interdisciplinary collaborations across UGA; from the social and economic consequences of the outbreak, to creating a vaccine in addition to experiments to understand the virus in both the mosquito and animal host.**

**Birth defects and pathogenesis**

Although several viruses, such as rubella and some herpesviruses, cross the placenta and infect the developing fetus, flaviviruses were not associated with this presentation. Worldwide, approximately 390 million cases of dengue virus infection occur each year; dengue virus is a virus closely related to Zika. With the large number of people infected each year, associations with trans-placental infection would become obvious. As the Brazilian outbreak is decreasing, several birth defects have now been attributed to Zika virus, including early pregnancy loss and severe microcephaly, as well as more subtle changes including problems with ear and eye development, less severe microcephaly, and reduced birth weight. Additionally, there are concerns that even among children who do not show physical defects despite their mother’s Zika infection during pregnancy, additional problems such as learning disabilities or cognitive defects may manifest as the surviving babies grow older. Because this virus family was not previously known to induce birth defects, the mechanism responsible for Zika virus-induced microcephaly was unknown. Several groups quickly began working on the problem by developing animal models and in vitro systems to examine how Zika virus can infect the developing brain and induce damage. They have determined that Zika virus has the ability to grow in the cells and economic consequences of the outbreak, to creating a vaccine in addition to experiments to understand the virus in both the mosquito and animal host.

In non-pregnant adults, the majority of people infected with Zika appear asymptomatic. In fact, most people are unaware they were infected. About 20% of infected individuals develop a fever, mild flu-like symptoms, joint pain and a rash. After the large Zika outbreak in French Polynesia in 2013, Zika virus infection was linked with a rare post-infection autoimmune neuropathy called Guillain-Barré syndrome, although the mechanism underlying the link is unknown. This syndrome can result in weakness and paralysis that can be temporary or permanent, and sometimes leads to death.

**Vaccines and prevention**

There are no approved vaccines for Zika, but several groups at the UGA CVM are working to produce a Zika vaccine. Biao He (Department of Infectious Diseases) has developed a vaccine candidate and is currently testing it in mice. Ted Ross and others at the new Center for Vaccines and Immunology at the CVM have also developed a vaccine candidate and are currently testing it in mice, as well as several vaccine candidates developed by the biotech company, GeoVax. While we await an effective vaccine, the best prevention strategies currently available are vector control to decrease the number of mosquitoes. Although this seems straight forward, mosquito control is very complicated and is a politically charged approach. *Aedes* mosquitoes can lay eggs in as little as a teaspoon of water, making it nearly impossible to eliminate breeding grounds especially in areas with recurring rains. Gutters, outdoor pots, and even tree holes and flowers can hold onto enough water for mosquitoes to lay eggs. Several chemical agents are available to kill both the larval and adult stages of the mosquitoes, but resistant populations can develop quickly and there are environmental considerations to account for when treating large areas.

**Zika related research at UGA**

Several groups at UGA, in addition to those previously mentioned, started Zika-related research projects in 2016. All aspects of Zika are being addressed through multiple interdisciplinary collaborations across UGA; from the social and economic consequences of the outbreak, to creating a vaccine in addition to experiments to understand the virus in both the mosquito and animal host. Courtney Murdock and Melinda Brindley at the CVM, Departments of Infectious Diseases and Population Health, are collaborating to examine how the mosquitoes’ environment affects their ability to transmit Zika virus. Murdock has also initiated a collaboration with Fiocruz, Fundação Oswaldo Cruz, the most prominent science and technology health institution in Latin America dedicated toward fighting large problems in public health, in Brazil to examine the effects of insecticide resistance on Zika transmission. Jianfu Chen (Department of Genetics, Franklin College), Julie Moore (Department of Infectious Diseases) and Melinda Brindley are examining how Zika virus induces microcephaly in a mouse model. In
addition, the Brindley lab has collaborated with Steve Stice (College of Animal and Dairy Science), Tom Hodge (Tamir Biotechnology), and Qun Zhao (Department of Physics and Astronomy, Franklin College) to develop an embryonated chicken egg model for Zika-induced microcephaly. Future work will focus on how the virus infection causes microcephaly by determining which cells get infected and the fate of those cells during the course of fetal development and virus infection. In addition to animal models, virus infection in defined neuronal cell populations are also underway.

Mosquito transmission potential

As an arbovirus, Zika virus transmission is dependent on the arthropod vector, in this case *Aedes* mosquitoes. Although not native to the US, both *Ae. aegypti* and *Ae. albopictus* mosquitoes were introduced to the US and have established populations. *Ae. albopictus* is considered a more temperate mosquito, and has spread into 26 states. *Ae. aegypti* is a more tropical mosquito and prefers the warmer south, especially along the coastal regions. Many aspects of the life history of *Ae. aegypti* make this mosquito species a very efficient vector of human disease. This mosquito feeds almost exclusively on human blood, and breeds in man-made containers, rests indoors, and is active during the day, all of which translate to high human exposure. Like *Ae. aegypti*, the life history of *Ae. albopictus* lends itself to efficient disease transmission. *Ae. albopictus* is also a day biter that often co-occurs with humans and breeds in artificial containers. However, these mosquitoes can also thrive in natural containers such as rain-filled tree-holes, and can feed on a wider diversity of hosts (e.g. domestic animals, birds, reptiles) making its role as a mosquito vector in Zika transmission less certain.

Transmission of mosquito-borne pathogens, including Zika, relies heavily on how both mosquito and pathogen traits integrate. For example, how long a mosquito lives for, how efficient the pathogen is at infecting the mosquito vector, and how fast the pathogen develops within the mosquito after infection will determine the length of time a mosquito is infectious. Additionally, how often this mosquito bites and which hosts it prefers to feed on (e.g. humans or other animals) will determine the contact rate humans experience with this vector. Finally, how many eggs females produce throughout their lifespan, as well as survival in the larval environment, will determine overall population sizes of mosquito vectors. Because mosquitoes live in environments that vary throughout the day and across seasons, variations in a variety of factors, including temperature, precipitation, relative humidity, resources in the larval and adult environments, can impact these mosquito and pathogen traits and the transmission of mosquito-borne disease.

Mitigating and preventing Zika transmission is challenging because we currently lack drugs or a vaccine that can shorten diagnosed infections and prevent infection entirely. Our only means of controlling transmission is through the control of mosquito vector populations. Mathematical models are extremely useful for predicting how quickly Zika will spread, identifying which regions of the world and across which seasons people are most vulnerable, and determining how to help direct mosquito control and public education campaigns. However, accurate predictions from these models are hard to obtain because we know very little about Zika development within both mosquito vector species, especially *Ae. albopictus*, and the environmental factors that influence this relationship.

To increase the prediction power of mathematical models, the Murdock and Brindley labs are collaborating on a National Science Foundation-funded project to determine how environmental variations affects the likelihood of *Ae. aegypti* and *Ae. albopictus* of being infected with Zika, and how long it takes after infection for the mosquito to become infectious (thus, ready to transmit the virus). Mosquitoes are cold blooded, meaning their body temperature reflects the environment in which they live. Thus, both high and low temperatures can alter mosquito metabolism, immune function, and pace of life, potentially affecting the susceptibility of mosquitoes to acquire Zika infection, changing the time to infectiousness (e.g. shortening or lengthening) of Zika, and the proportion of the mosquito’s lifespan over which she is infectious. Previous work by Dr. Murdock with the human malaria – *Anopheles* mosquito system, has suggested that malaria transmission is optimized at a given temperature, and is inhibited by both cooler and warmer temperatures. Thus, temperature change across a season, geographic regions, and as the result of climate change will likely have strong effects on malaria transmission. Determining the minimum, maximum, and optimum temperatures that permit Zika virus transmission will enable more accurate maps and models of how Zika virus will spread in the US or other locations previously not effected by Zika virus. This enhanced predictive capability will facilitate targeted proactive strategies (e.g. deployment of vector control teams, public education, vaccines / therapeutics once they come on line, and limited resources) to areas most at risk to prevent and mitigate ZIKV transmission in the US as well as other regions of the world.
Impaired bone healing after a fracture remains a challenging problem in human and veterinary orthopedics. Among treatments with the potential to improve bone union is platelet-rich plasma (PRP). PRP is prepared by processing a patient’s blood to reduce erythrocytes and leukocytes while increasing the concentration of platelets in the plasma layer. The PRP is then delivered to injured musculoskeletal tissues to provide factors, such as transforming growth factors-β (TGFβ), platelet derived growth factors (PDGF), and vascular endothelial growth factors (VEGF), that potentially can stimulate tissue healing. Accordingly, PRP has been used to treat damaged tendons, muscles, ligaments, osteoarthritic joints, and bony delayed unions in humans, horses, and dogs. While current data suggest that PRP is beneficial in some medical conditions including management of signs associated with osteoarthritis in dogs, initial results have been equivocal regarding the efficacy of PRP in improving bone healing, depending upon the animal species, and the type of fracture or bone defect that has been treated. Our goal with this study was to further evaluate whether PRP is useful in improving bone healing.

Most studies assessing treatments intended to improve bone healing are performed in research animals in which consistent, well-defined bone defects are created. Because dogs often suffer deterioration of their anterior cruciate ligament (ACL) and undergo a surgical treatment that requires bone healing, we elected to perform a clinical trial in these dogs to address the question of whether PRP can hasten bone healing. At this time, the surgical procedure that provides the most consistent results and that is performed most commonly is the tibial plateau leveling osteotomy (TPLO). In this procedure, the proximal tibia is cut with a bone saw (essentially creating a fracture), the orientation of the bone is adjusted, and the cut bone is stabilized with a bone plate and screws. This procedure helps dogs cope with being ACL-deficient and enables most to run, play, and work effectively. Importantly, the TPLO procedure creates a consistent fracture in which bone healing is subsequently needed and always assessed.

This study was a resounding success in that it provided the most extensive research study to date assessing whether PRP can augment bone healing.

We conducted a prospective, randomized, double-blinded clinical trial in dogs with naturally occurring ACL-deficiency. We enrolled 64 dogs with ACL-deficiency and randomized approximately half to have PRP delivered directly in the region of the cut bone at the time of surgery. The remaining dogs had saline placed in the osteotomy. The osteotomy
was then stabilized with commercially-unavailable titanium TPLO implants that allow the use of MRI for evaluation of bone healing. All dogs were re-evaluated 4, 7, and 10 weeks after surgery including use of MRI, ultrasonography, and radiography (X-rays) to assess bone healing. In return for enrollment and completion of the required follow-up, all owners received the care at a cost savings of over 50%.

At the end of the study, complete sets of data were available for 60 dogs, 27 of which were in the control group and 33 in the PRP group. Thus far, only the radiographic scores relating to healing of the osteotomy have been tabulated and compared. While these scores increased at all time points after surgery, there was no significant effect identified for body weight, gender or treatment group (PRP versus control). Consequently, administration of PRP in dogs undergoing the TPLO procedure is highly unlikely to have a positive effect on bone healing. It is important to note, however that TPLO involves having a well apposed osteotomy, which makes radiographic identification of a treatment effect more challenging than if a bone defect model were used.

This study was a resounding success in that it provided the most extensive research study to date assessing whether PRP can augment bone healing. Further, this clinical trial, with its financial support provided by the AO Foundation and the associated financial benefits for enrollees, enabled many owners to obtain exceptional medical care for their dogs that otherwise might not have been possible. This study also enabled our team to address a clinically relevant question that pertains to both human and veterinary patients that improves rather than compromises animal health.

Finally, this study has created educational and research opportunities for graduate, veterinary, and undergraduate students. It is our hope that the experience gained by the undergraduates will strengthen their desire to pursue a career in the medical field. Likewise, we hope that the veterinary and graduate students will be stimulated to pursue careers that involve biomedical research and discovery.

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Comparative Medical Research Donation Fund – New Faculty Startup
CD117 (KIT protein) is a transmembrane tyrosine kinase receptor that is widely expressed in a variety of canine tumors, including mast cell and gastro-intestinal stromal tumors. Although a few case reports have documented CD117 expression in canine lymphoma, no large studies have been performed to assess the prevalence of CD117 expression in this neoplasm. The rationale for determining the prevalence of CD117 expression is that it could potentially provide a novel targeted treatment approach for lymphoma. In recent years, tyrosine kinase inhibitors, such as Masitinib, have been used successfully in the treatment of canine mast cell tumors, and this drug has some efficacy in the treatment of canine epitheliotropic lymphoma.

Lymphoma is one of the most common forms of treatable malignant neoplasia in the dog. Although survival times of dogs with high grade lymphoma without treatment is about six weeks, this can be extended to 14 months with traditional chemotherapy. If CD117 expression is prevalent in lymphoma, tyrosine kinase inhibitors, such as Masitinib, may further improve the expected outcome of dogs with lymphoma. The goal of this retrospective study was to determine the prevalence of CD117 in previously diagnosed cases of canine lymphoma.

Hematoxylin and eosin (H&E) stained slides of over 100 cases of canine lymphoma from the UGA – Tifton Diagnostic and Investigational Laboratory’s archive were evaluated as candidates for inclusion in the study. After the cases were reviewed, immunohistochemistry for CD20, CD3, and CD117 was performed. CD20 and CD3 were used to categorize each lymphoma according to the World Health Organization’s Classification system for canine malignant lymphomas. For CD117, immunostaining was assessed using the following parameters: percentage of positive staining neoplastic cells in a given section, staining distribution in the cell (i.e. membranous, cytoplasmic, perinuclear), and strength of staining (i.e. weak, mild, moderate, and strong).

Ultimately, 87 cases of lymphoma were included in the final assessment. Of the lymphomas evaluated, 83 (95%) were of lymph node origin, two (2.3%) originated from the spleen, one originated from the stomach (1.2%), and one from the small intestine (1.2%). Immunohistochemistry revealed 59 (68.0%) lymphomas of B lymphocyte origin (expressing CD20).
and 28 (32.2%) T cell lymphomas (expressing CD3). For the B cell lymphomas, 37 (62.7%) were marginal zone lymphomas, 18 (30.5%) were diffuse large B cell lymphomas, 3 (5.1%) were follicular lymphomas, and one was classified as a lymphocytic-plasmacytic lymphoma. Twenty (71.4%) of the T cell lymphomas were peripheral T cell lymphomas - not otherwise specified, 6 (21.4%) were T cell zone lymphomas; with one (3.6%) intestinal T cell lymphoma and one (3.6%) lymphoblastic T cell lymphoma.

CD117 expression in neoplastic cells occurred in only two cases (2.3%) of lymphoma. In both cases, the majority of neoplastic cells (50-60%) had mild to moderate to strong staining, which was predominantly membranous to cytoplasmic. Both CD117 positive lymphomas were of T lymphocyte origin: a splenic lymphoblastic T cell lymphoma and an intestinal T cell lymphoma.

If the low number of CD117 positive lymphomas in this study is representative, this would indicate a low prevalence of CD117 expression among canine lymphomas. However, in cases in which CD117 is expressed in the majority of neoplastic cells, use of tyrosine kinase inhibitors could potentially be of benefit.

Both lymphomas expressing CD117 in this study were of T lymphocyte origin, which is consistent with findings of previous case reports documenting CD117 expression in lymphomas. Consequently, the prevalence of CD117 expression may be higher among T cell lymphomas versus B cell lymphomas. Further studies should be performed to determine if there is a higher prevalence of CD117 expression in these lymphoma types.

Tyrosine kinase inhibitors (i.e. Masitinib) also target platelet-derived growth factor receptor (PDGFR), which can be expressed in canine lymphoma. Therefore, assessment of PDGFR expression in lymphoma may warrant further exploration as well. Such studies could lead to the development of an immunohistochemistry and/or molecular diagnostic panel to test for lymphomas potentially sensitive to tyrosine kinase inhibitor therapy.

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Funding
VMES State Funding - New Faculty Startup
Pharyngeal Pumping in the Hematophagous Parasite, *Haemonchus contortus*

*Haemonchus contortus*, a blood feeding pathogen that inhabits the abomasum (true stomach) of small ruminants, causes anemia and ill health in sheep and goats. *H. contortus* organisms obtain their blood meals via coordinated and rhythmic contractions in the muscles of the pharynx (throat). This pharyngeal pumping mechanism, which is required by the parasite to feed itself, is both an attractive target for the development of new antiparasitic drugs and the probable target of some of the existing ones. To develop a platform for medium-throughput screening of compounds that impair the health or feeding capability of *H. contortus*, we have characterized the physiological and pharmacological properties of pharyngeal pumping in the fourth larval stage (L4) of this parasite’s life cycle. Although the adult worms cause disease, they cannot be easily studied in the laboratory.

The early larval stages (L1 to L3), though easy to cultivate and study, are less relevant for our purposes; the L3 stage does not feed, and the L1 and L2 stages eat bacteria rather than blood. Therefore, we collected *H. contortus* eggs from the stool of infected animals, cultured them in vitro to the L3 stage, and later developed them further to the more active, host-stage L4 form. We first confirmed that worms cultured to L4 in vitro exhibited pharyngeal pumping, as do L4 isolated from experimentally infected gerbils. Using video-microscopy at room temperature, we recorded pharyngeal pumping events in L4s isolated from gerbils, and showed that pumping was stimulated by exogenous application of 5-hydroxytryptamine (5-HT), the neuromodulator that activates feeding in other nematodes.

The optimization of conditions that promote the robust level of pumping needed to screen for compounds that inhibit pumping is an iterative, ongoing process.

However, the rate of pumping was irregular and erratic. Dr. Janis Weeks and Kristin Robinson at University of Oregon investigated pharyngeal pumping in L4s cultured from L3s in vitro, using two methods: fluorescent dye ingestion and electrophysiology. A common method for evaluating feeding in cultured larvae is to incubate them with a fluorescent substrate, such as FITC-conjugated bovine serum albumin (BSA), to visualize ingestion of dye into the gut. The

**Figure 1.** A. *H. contortus* L4 after incubation in Alexa Fluor 555-BSA conjugate, to confirm feeding. The ingested fluorescent dye accumulated in the intestine. L4 were cultured from L3 in vitro. B. Electropharyngeogram (EPG) recorded from *H. contortus* L4 in a microfluidic EPG chip, 36°C. Each voltage deflection (E, excitation; R, relaxation) represents one pharyngeal pump. Pump frequency during this segment was ~2 Hz (pumps/s).
original fluor, FITC, proved problematic due to autofluorescence of the parasites, whereas Alexa-Fluor 555-conjugated BSA worked well. Dye ingestion was most reliable in serum-augmented culture medium containing a low concentration of 5-HT.

A more quantitative and reproducible approach for assaying feeding is to record the electrical signals emitted by pharyngeal muscles and neurons, termed anelectropharyngeogram (EPG). A microfluidic device (chip) used to record EPGs from other parasitic and non-parasitic nematodes was customized for use with the *H. contortus* L4; these long, thin larvae have an annoying tendency to coil up, but with careful handling can be positioned in microfluidic recording channels. The chips and recording instrumentation were provided by NemaMetrix, Inc., a spin-off company from the University of Oregon. The optimization of conditions that promote the robust level of pumping needed to screen for compounds that inhibit pumping is an iterative, ongoing process.

We have obtained EPG recordings from L4 at 37°C, but the pumping has been erratic compared to that of other nematodes, including human hookworm, that have been recorded in microfluidic chips. In hookworm, Weeks and collaborators found that whereas dye ingestion indicates successful activation of L3 to L4 in vitro, it does not predict which worms will produce robust, sustained EPG activity. It is not yet clear whether the feeding habit of *H. contortus* differs intrinsically from other species, or whether we have yet to optimize recording conditions.

In summary, we are using three techniques to study feeding in the L4 stage of *H. contortus* to learn more about the fundamental biology of this behavior and to develop an experimental platform for studying both existing and candidate anthelmintic drugs.
Prion diseases (transmissible spongiform encephalopathies) are a group of invariably fatal, transmissible, neurodegenerative diseases, which include scrapie in sheep and goats, chronic wasting disease in cervids, bovine spongiform encephalopathy in cattle, and Creutzfeldt-Jakob disease in humans. Prion diseases can be infectious, spontaneous, or familial in origin. Most of the current prion research is focused on the human forms of disease, which are primarily either spontaneous or familial. In contrast, agriculturally important prion diseases, such as scrapie, are naturally infectious. As a result, the direct study of scrapie in a pathophysiologically relevant system is important to the improved production efficiency and health of small ruminants.

Classical scrapie is an economically important disease of sheep and goats. Costs in the U.S., which are attributed primarily to decreased production, testing, and increased trade restrictions, are estimated to be $10–$20 million annually. Scrapie has thus been targeted for eradication for more than a decade and eradication remains an important goal for the competitiveness of the U.S. small ruminant food and fiber industries. Furthermore, scrapie in sheep provides a natural, outbred model for human prion diseases, as currently there are no cell culture models for human prions.

Because of the inevitable lethality of prion and prion-like diseases, the development of successful treatments and early diagnostic tests is vital. The lack of treatments is partially due to incomplete knowledge of the prion replication cycle at the subcellular level and the absence of cell culture models for human prion diseases that propagate natural human prion isolates. My long-term goal is to address these shortcomings, which are primarily due to a fundamental knowledge gap regarding the co-factors that define whether a cell is resistant or susceptible to prions.

Using sheep microglial cells and an unbiased transcriptomic approach (RNA-Seq), we recently identified increased transcription of matrix metalloproteinase-14 (MMP14), which is a potent activator of pro-MMP2, in prion-resistant microglia as compared to prion susceptible microglia. This finding supports previous work, which identified MMP2 as inversely associated with prion susceptibility in one pair-wise comparison from a different cell line. The goal of this project was to more robustly test the association of MMP2 levels with prion resistance by measuring prion susceptibility, MMP2 levels, and MMP14 transcript levels in multiple clones of sheep microglial cells. The results obtained failed to identify a consistent correlation between prion susceptibility and MMP2 levels or MMP14 transcript levels. This work highlights the need to robustly test prion-related cell culture findings beyond one or two pair-wise comparisons, and suggests that other factors contribute to the varying prion susceptibility of these clones.
Because of the inevitable lethality of prion and prion-like diseases, the development of successful treatments and early diagnostic tests is vital.

In the future, we will investigate additional genes that have been previously associated with prion susceptibility in pair-wise comparisons, confirm their consistent association with either prion resistance or prion susceptibility, and then test for causation through either over-expression or under-expression of those genes. The results from this research will provide rational strategies for the development of much-needed cell culture systems to propagate human prions. Additionally, the identification of cofactors will provide new targets for anti-prion therapies.
Wild aquatic birds are considered the natural reservoirs of influenza A viruses, which may be transmitted to other animal species including domestic poultry (chickens, turkeys, quail and ducks). Influenza A viruses are classified numerically into multiple subtypes based on the virus surface glycoproteins hemagglutinin (HA) and neuraminidase, such as H1N1, H3N2, H5N1, and H7N9. In chickens, avian influenza viruses are classified based on pathotype as either Low Pathogenic Avian Influenza (LPAI) or Highly Pathogenic Avian Influenza (HPAI) viruses. Of the 16 HA subtypes identified so far in birds, only the H5 and H7 subtypes are associated with HPAI viruses. A common feature of HPAI viruses that results in systemic disease in poultry is the presence of multiple basic amino acids in the HA cleavage site. In contrast, LPAI virus infections are mainly restricted to the gastrointestinal and/or respiratory tract. 

The spread of the reassortant H5N2 virus caused the worst animal disease outbreak in recent history in the United States. This outbreak affected birds in both backyard and commercial poultry farms, particularly in the Midwest, and cost farmers and the United States government millions of dollars. Due the negative impact of vaccine use on international trade, the use of vaccines against HPAI virus is not approved as a control measure for eradication of HPAI outbreaks. However, this recent outbreak led to efforts to stockpile vaccines against HPAI H5 influenza virus as part of a larger influenza control strategy.

Protective efficacy following prime-boost vaccination in turkeys against avian HPAI H5N2 virus clade 2.3.4.4

Following the emergence of HPAI H5 viruses in poultry in China in 1996, viruses of the so-called H5 Goose/Guangdong lineage have continued to evolve into clades (i.e., groups with a common ancestor) and subclades. Clade 2.3.4.4 represents a newly emerged HPAI H5 virus that quickly spread through migratory birds and diversified throughout the world. Upon reaching North America in late 2014, clade 2.3.4.4 H5N8 viruses reassorted with LPAI viruses of North America lineage, giving rise to novel reassortant H5N2 viruses.

The timing between vaccination and challenge revealed important differences in the protective efficacy of the vaccination strategies tested in this study.

In collaboration with scientists at the Southeast Poultry Research Laboratory-USDA, we evaluated the efficacy of vaccine regimes in preventing infection and clinical signs of disease caused by a HPAI H5N2 avian influenza virus of the clade 2.3.4.4 in turkeys. Two-day old turkey poults were randomly divided into 4 groups. Birds in group 1 served as unvaccinated controls. Birds in group 2 (AdInac-AdInac) were vaccinated with an adjuvanted inactivated influenza vaccine and boosted at 3 weeks of age with the same vaccine. Birds in groups 3 (alpha-AdInac) and 4 (alpha-alpha), were vaccinated...
initially with an alphavirus vectored vaccine followed by either an adjuvanted inactivated influenza vaccine or an alphavirus vectored vaccine boost at 3 weeks of age, respectively. At 6 weeks or 16 weeks of age, birds were challenged with a lethal dose of a HPAI H5N2 virus (A/turkey/Minnesota/12582/2015) and vaccine efficacy was monitored.

Unvaccinated control birds displayed severe signs of disease including depression, diarrhea, and nervous signs and succumbed to infection as early as 3 days post challenge. The timing between vaccination and challenge revealed important differences in the protective efficacy of the vaccination strategies tested in this study.

Vaccinated birds challenged at 6 weeks of age showed no apparent clinical signs of disease irrespective of the vaccine regime tested. All vaccine strategies provided comparable levels of protection, though virus shedding was still detected in birds in group 4 (alpha-alpha). We observed great variability in the level of protection by different vaccine regimes in birds challenged at 16 weeks age. While levels of protection decreased in all vaccinated groups over time, a significant reduction in protective efficacy was observed in the homologous alphavirus vectored vaccine group (group 4), with protection dropping to 16%.

Overall, the prime boost strategy (group 3) provided the best protection in older birds with 89% of the birds surviving the lethal challenge. Our study highlights the importance of studying not only different vaccine platforms, but also vaccination regime and strategies to maximize protection against HPAI especially with regards to the longevity of vaccine-induced immune response.

Principal Investigator
Dr. Daniel R. Perez

Graduate Research Assistants
Dr. Adebimpe, Jefferson Da Silva Santos

Funding
USDA ARS
Investigation of the pathogens contributing to naturally occurring outbreaks of infectious bovine keratoconjunctivitis (pinkeye) using next generation sequencing

Infectious bovine keratoconjunctivitis (IBK) or pinkeye affects cattle worldwide and results in significant economic losses to the cattle industry. It is estimated that pinkeye losses can exceed $100 per incidence in beef cattle as a result of reduced weight gain, treatment costs, and discounted price per pound of body weight when the animal is sold at auction (Merck). Thus, the disease undoubtedly has a considerable economic impact in Georgia beef cattle.

Pinkeye is a clinical syndrome defined by a typical progression from a watery eye (epiphora), squinting (pain from sunlight), and redness (conjunctivitis) to an ulcerated cornea with cloudiness due to edema and inflammation. Ultimately, the characteristic pink eye appearance develops as a result of infiltration of blood vessels along the outer edge of the cornea. In the worst cases, the eye may rupture, resulting in permanent blindness.

*Moraxella bovis*, a bacterium, is recognized as a primary cause of IBK. It has also been shown that colonization of the eye with *Moraxella bovis* can occur in the absence of clinical disease. A study by O’Connor and co-investigators in 2012 suggests there is weak evidence for a causal role for *Moraxella bovis* in pinkeye; however, it is currently the only organism that has been shown to experimentally produce IBK, although not consistently when inoculated into healthy eyes. Inclusion of external factors, such UV irradiation of the eye or scratching of the cornea, followed by experimental infection, results in more consistent development of clinical IBK. Extrinsic factors leading to corneal irritation also are important for the development of the disease under natural conditions.

Infections with other bacteria or viruses also occur in association with *Moraxella bovis* in cases of IBK. *Moraxella bovoculi* and *Mycoplasma* species have also been implicated as additional causes of pinkeye, but experimental infections with these organisms alone have failed to reproduce the disease. These findings have raised new questions about the role that other organisms may play in the pathogenesis of pinkeye. Seasonal variation in detection of *Moraxella bovis* from cases of IBK has also been reported. Potentially these differences are related to differences in the organisms involved in the clinical disease during different times of the year. Diagnosis of IBK is usually based on clinical signs, environment, history, and culture of the organisms involved. Although culture will detect viable bacteria present in the sample, the results can be unrewarding if the sample is mishandled. Additionally, the organisms detected are dependent on the particular methods or media used for culture and the differential growth of the organisms present. To overcome these problems, PCR based methods have been used, but these only seek to identify selected organisms, thereby biasing the testing process.
The recent development of next generation sequencing technology has revolutionized our ability to identify infectious organisms. This technique allows sequence-independent amplification of bacterial or viral nucleic acids, avoiding the potential limitations of traditional diagnostic methods, including failure of bacteria or viruses to replicate in culture or unsuccessful PCR amplification due to genetic divergence from known viruses or bacteria. Next generation sequencing has been used to identify the microbiome (all bacterial species) of multiple body sites in humans, including the eye. While previously thought to be a sterile site, at least in humans, normal eyes actually appear to have resident bacteria and this is thought to be true for cattle as well. It is possible that changes in the normal flora of the bovine eye during periods of stress may also contribute to this multifactorial disease process.

The primary objective of this study is to use the capabilities of next generation sequencing diagnostic technology to potentially identify novel pathogens that contribute to IBK that may have not been identified by previous diagnostic methods. A secondary objective is to determine if there is variation in the organisms associated with the clinical syndrome on different farms or during different times of the year. New information gleaned from this study would be directly relevant to therapeutic or preventive measures for this disease.
<table>
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<tr>
<th>Project Title</th>
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<td>Effect of Platelet Rich Plasma on Osseous Healing in Dogs Undergoing High Tibial Osteotomy (tibial plateau leveling osteotomy; TPO)</td>
<td>AO Foundation</td>
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<td>Credible, Brenton. Antimicrobial Resistance in Bacteria Isolated From the Respiratory Tract of Stocker Cattle</td>
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<td>Impact of Uterine Inflammation on Reproductive Efficiency in Beef Cattle.</td>
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<td>Kath, Krzysztof. Vagal Influence on Brainstem Plasticity and Neural Coding of Taste</td>
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<td>Emerging and Re-emerging Infectious Disease Residency/PHD Program.</td>
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<td>The University of Georgia Veterinary Scholars Program: A Research Training Experience for Veterinary Medical Students.</td>
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<td>Ferrer, Maria. Accuracy of Circulating Cell-free Fetal DNA-based Fetal Sexing in Mares.</td>
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<td>Filipov, Nikolay. Bovine Metabolomics: A Novel Approach towards Characterizing and Ameliorating Fescue Toxicosis, Heat Stress, and Their Interaction.</td>
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<td>Mycobacterium Tuberculosis-Manganese Interactions and Neurotoxicity.</td>
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<td>Fischer, John. Diagnostic, Field and Training Assistance for Wildlife Health Assistance for Wildlife Health and Disease Monitoring.</td>
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<td>Southeastern Cooperative Wildlife Disease Study. Various Other States.</td>
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<td>Wildlife Disease Related Assistance Provided by SCWDS to Federal/State Wildlife Agencies: Southeastern US and the Conservation Community at Large.</td>
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<td>Franco, Monique. Characterization of the Predisposing Factors and Pathogenesis of Focal Duodenal Necrosis in Egg Layers.</td>
<td>Iowa State University - Egg Industry Center</td>
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<td>Franklin, Samuel. The Effect of Platelet Rich Plasma on Osseous Healing in Dogs Undergoing High Tibial Osteotomy (tibial plateau leveling osteotomy; TPO).</td>
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<td>Fu, Zhen. Rabies Seed Virus Verification. Industry Sponsor.</td>
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<td>Virus Clearance from the Central Nervous System. Thomas Jefferson University as flow through from National Institutes of Health.</td>
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<td>Giguere, Steve. Host-Directed Prevention of R. equi Pneumonia in Foals. Texas A&amp;M University as flow through from Grayson-Jockey Club Research Foundation. Inc.</td>
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<td>Fitness and Persistence of Drug-Resistant R. equi. Grayson-Jockey Club Research Foundation.</td>
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<td>Goddenker, Nicole. Host and Environmental Factors Driving Hockworm-induced Mortality in Small, Isolated Fur Seal Populations. Morris Animal Foundation.</td>
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<td>He, Hao. Developing a Novel Mumps Virus Vaccine. National Institutes of Health.</td>
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<td>Developing a Parainfluenza Virus 5 (PIV5)-based PRRSV Vaccine. US Department of Agriculture.</td>
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<td>Mechanism of Paramyxovirus Replication. Georgia State University – as flow through from National Institutes of Health.</td>
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<td>Mucosal Protection Against HIV Generated by PIV5 Priming and VLP. Emory University as flow through from Department of Health &amp; Human Services.</td>
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<td>Howeth, Elizabeth. Improved Live Attenuated Brucella Vaccines to Reduce Human Disease. Texas A&amp;M University as flow through from National Institutes of Health.</td>
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<td>Development and Testing of Avian Respiratory Disease Pathogen Specific Real Time Quantitative RT-PCR Primers and Probe Sets for Use with IDEXX’s MAX Mix. Industry Sponsor.</td>
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<td>Promoting testing and surveillance for Bovine Viral Diarrhea virus in Florida &amp; Georgia Dairy Herds using bulk tank milk samples. University of Florida as flow through from Southeast Milk, Inc.</td>
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<td>Using the Dystocia Simulator in Beef Cow Education Programs to Teach Bovine Dystocia Management (Obstetrical Assistance) to Improve Cow and Calf Health in Georgia Beef Herds. GA Commodity Commission for Beef.</td>
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The key to improved animal well-being is animal health. The key to improved animal health is veterinary research.