VMES 2015
Science in Service to Animals™

Training the Next Generation of Veterinary Scientists

39th Annual Report
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Training the Next Generation of Veterinary Scientists
Cover Illustration by Ellen Davis

Director: Dr. Harry W. Dickerson
Managing Editors: Dr. James Moore, Dr. Scott Brown
Associate Editor: Holly Snelling
Designers: Brad Gilliland, Ellen Davis
Medical Illustrators: Ellen Davis, Tasha Obrin, Will McAbee
Photographer: Christopher Herron, unless otherwise noted
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.
Veterinary medicine is a science-based profession that requires rigorous research training of today’s graduate students to sustain the profession’s key role in the protection of animal, human, and environmental health. There is a critical and compelling need for individuals who have a holistic view of health from molecular to organismic levels; and beyond this, a grasp of how this information integrates with ecology.

With the rapid and tremendous growth in scientific data and bioinformatics over the last 20 years, it has become an increasingly daunting challenge to both teach and assimilate this knowledge in a useful and meaningful way. Needless to say, it falls on academic institutions such as the University of Georgia College of Veterinary Medicine to address this challenge, and we are up to the task.

As you will read in this year’s lead article, the education of veterinarians and veterinary scientists is a dynamic mission of the Veterinary Medical Experiment Station. As the research activities of the College have become a strong engine for the generation of scientific data, the strength of our graduate education programs has grown concomitantly. As a result, we have new graduate degree programs that are flexible, diverse, and scientifically rigorous. They are designed to meet the needs of today’s students.

This 39th VMES Annual Report lists 25 individuals who received graduate degrees in 2015 after completing a comprehensive training program that includes original, hypothesis-driven research conducted under the mentorship of a College researcher. These students are attracted to our programs by the excellent research experiences and mentoring opportunities that exist here. The training of future researchers is of utmost importance to fulfillment of the mission of the Veterinary Medical Experiment Station and to meeting the animal and public health needs of our state, nation and world.

This Annual Report provides an overview of peer-reviewed, competitive projects and new faculty start-up projects conducted during fiscal year 2015 (July 1, 2014 – June 30, 2015). Projects supported by the State of Georgia VMES funding, and projects funded with United States Department of Agriculture 1433 Formula 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 peer-reviewed publications also is provided that represent a selection of VMES-supported work and other scholarly research by College faculty.

Research in the College of Veterinary Medicine is diverse, but clearly targeted to addressing issues related to animal and human health. This diversity is both the strength and challenge of the veterinary profession. Diversity in investigations ranging from individual molecules to the whole organism to eventually to populations ensures the relevancy of the work to the rapidly changing biomedical and veterinary research environment. While our challenge lies in maintaining the focus required for establishing excellence in specific areas, we are proud to report that we are succeeding based on a number of metrics, including our continuing growth in competitive, extramural research funding.
A summary of the College’s research funding is provided above. Over the past year approximately six 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.
It is becoming increasingly clear that the health of animals is inextricably tied to the health of humans and the environment, and this has driven the growing “One Health” movement in veterinary and human medicine. Pandemic diseases can only be adequately addressed through collaborative partnerships that transcend disciplinary divisions. In particular, there is a critical need for veterinarians to lead the “One Health” drive in academia, industry, and government agencies. These leaders need a solid foundation in both basic research and clinical science to foster collaboration among these groups and facilitate progress. Training these future leaders is our mission with the Veterinary Medical Scientist Training Program (VMSTP), the Veterinary and Biomedical Sciences (VBS) Program, and the DVM-MPH Program.

Today’s veterinary students are barraged with information; in addition to the 40 hours of classes and laboratories a week that veterinary students endure during their training, there are more journals and online resources today than ever before. In 2010 there were 24,000 peer-reviewed science journals (Scientometrics, 84(3):575-603), and the explosion in online journals has vastly increased these numbers. Furthermore, with the growth of bioinformatics, the interdisciplinary field that combines computer science, engineering, mathematics,
and statistics to analyze biological systems, tremendous amounts of data are being generated. How do we make sense of all of this information?

A report by the U.S. National Academies of Science National Research Council, “Critical Needs for Research in Veterinary Science,” highlighted the changing research and education needs in veterinary medicine and their impact on animal and human health. As stated in the NRC study, “To realize the potential for translating scientific advances into animal health, veterinarians and animal scientists must bring their whole-animal understanding to every phase of research and development, from basic biological research to applied studies.” There is a societal need for veterinarians and scientists that can accelerate the application of laboratory discoveries to human and animal patient care. Increasingly, we rely on “translational researchers,” who understand the language of both basic science researchers and clinicians, to identify the key knowledge gaps in and barriers to combating disease. Veterinarian-scientists are ideally situated to play this role, as they are trained in both areas, and veterinary research is interdisciplinary in nature.

The VMSTP was created at the University of Georgia College of Veterinary Medicine just over 10 years ago through the leadership and efforts of the administration and key veterinary faculty to provide highly motivated veterinary students with a passion for research a way to simultaneously pursue both DVM and PhD degrees. Thanks to a generous donation from the Morris family, an endowment was established in 2004 to provide stipend support for up to six students per year during their DVM training. Only three other schools (Cornell University, University of Pennsylvania and University of California-Davis) similarly provide full tuition during the DVM portion of dual degree training. Since the VMSTP’s inception, the College has successfully graduated four students. Dr. Sabrina McGraw earned a PhD in wildlife genetics and population health. She then did a residency in anatomic pathology at the University of California-Davis, passed her American College of Veterinary Pathologists board examination, and is currently serving as a Captain in the United States Army. Dr. Kari Fine graduated with a PhD in tuberculosis cell biology, completed a post-doctoral fellowship at Michigan State University, and now is a Veterinary Medical Officer in the United States Department of Agriculture (USDA) Animal Plant Health Inspection Service (APHIS) in Raleigh, North Carolina. Dr. Ashley Hartley graduated with a PhD in immunology, completed a small animal medicine internship at the University of Tennessee, and recently has begun a small animal medicine residency program at North Carolina State University. Dr. Cory Gresham graduated with a PhD in Fish Genetics and is currently working in private practice.

The VMSTP currently supports 12 students at various stages in either their PhD or DVM programs. Highlights and achievements of current students include a Centers for Disease Control (CDC) Hubert Global Health Fellowship received by Dr. Julie Rushmore to spend three months of her clinical year in Africa; a travel scholarship and support for an oral presentation received by Melissa Miller from the World Association for the Advancement of Veterinary Parasitologists; an American Association of Avian Pathologists Foundation Scholarship to Valerie Marcano; and a Dean’s Award Scholarship to Jennifer Bloodgood. Julie Rushmore was also selected in 2015 to present a TEDxUGA talk regarding her research on how social networks in African chimpanzees affect disease transmission dynamics.

Each year, the VMSTP receives an increasing number of highly competitive applications from talented individuals. In the last admission cycle, seven qualified (i.e., accepted to both the DVM and PhD graduate programs) applicants were interviewed, which is the largest number interviewed thus far. Three students were accepted; two were in-state students and already enrolled in the DVM program (Matthew Jones and Ashley Rasys). The at-large student, Jacqueline Plyler, had graduated from the University of South Carolina with a degree in biomedical engineering and had received that university’s Outstanding Woman of the Year Award in 2015. She also received a Tau Beta Pi (engineering honor society) fellowship, Omicron Delta Kappa (leadership honor society) National Leader of the Year Award, and the USC Outstanding Senior Award. Jacqueline has entered her graduate training program with a UGA Presidential Fellowship.
The Veterinary and Biomedical Sciences (VBS) Program is a college-wide MS and PhD program that was founded in 2010 to consolidate graduate students, particularly in the Departments of Large Animal Medicine, Population Health, Small Animal Medicine and Surgery, and Veterinary Biosciences and Diagnostic Imaging. The 38 graduate students currently enrolled in this program either have a DVM, are interested in pursuing a DVM at a later time, and/or have a passion for research relating to the health of animals and humans. Students enrolled in this program have the flexibility to concurrently pursue residency training or participate in other clinical activities. This exposure allows the VBS students to actively engage in and explore translational research. Graduates of the VBS program have obtained positions in academia, government, industry, and private practice, both in the US and internationally.

Accolades for current VBS students include a Ford Foundation Pre-doctoral Fellowship Award to Andrea Ayala, who is studying the bi-directionality of avian pathogens at the agricultural-wildlife interface, and both Phi Zeta (veterinary honor society) chapter manuscript awards in 2015 were given to VBS students. Dr. Afonso Tiago received the award in clinical science for his manuscript, “Pharmacodynamic evaluation of 4 angiotensin-converting enzyme inhibitors in healthy adult horses,” and Dr. Qingqing Chai received the basic science award for her manuscript, “Enhancement of blood-brain barrier permeability and reduction of tight junction protein expression are modulated by chemokines/cytokines induced by rabies virus infection.”

With the explosion of information, society will depend more and more on veterinarians and researchers who understand the breadth of veterinary disease, as well as its impact on humans.
To help ease the predicted shortfall of veterinarians engaged in public practice, the CVM and the College of Public Health (CPH) entered into a partnership to train individuals with veterinary medical and public health expertise through the establishment of the DVM-MPH Dual Degree Program. This partnership began in 2006 and has since graduated 10 students with both DVM and MPH degrees. During this 5-year program, students meet all requirements of the DVM curriculum set by the CVM and complete their MPH courses through the CPH and affiliated sites. Financial support is available for up to two students per veterinary class while they are enrolled in the MPH curriculum. Currently, there are 7 students enrolled and a similar number of students in the second-year veterinary class expressing an interest in completing the program.

The majority of our DVM-MPH graduates serve the public through positions in a variety of venues, including local and state public health offices, the Department of Homeland Security, the CDC, and the USDA. For example, Dr. Shanna Siegel, one of the first graduates of the program (2008), is currently an Import/Export Veterinary Medical Officer with APHIS. Dr. Laura Adams, a 2012 graduate of the program, was a CDC Epidemic Intelligence Service Officer for two years after graduation and has since continued in the Public Health Commissioned Corps serving as a CDC Career Epidemiology Field Officer in the Arizona Department of Health Services. Dr. Adams’ classmate, Dr. Koren Custer, served as the Assistant State Veterinarian for West Virginia for two years after graduation, but missing the land of the Dawgs, returned to Georgia in the summer of 2014, to become a Field Veterinary Medical Officer with the USDA APHIS in Statesboro. She has since been deployed on several occasions to the Midwest to assist with the efforts to fight the outbreak of Highly Pathogenic Avian Influenza Virus currently plaguing that region.

The UGA College of Veterinary Medicine is proud to play a role in the training and development of these translational scientists and public health veterinarians. With the explosion of information, society will depend more and more on veterinarians and researchers who understand the breadth of veterinary disease, as well as its impact on humans. We are thankful to the Morris family and the Dean’s Office for their financial support of the VMSTP and DVM-MPH programs, and to you, our stakeholders, for your support.

For more information on the VMSTP, VBS, and DVM-MPH programs, visit [vet.uga.edu/graduate](http://vet.uga.edu/graduate)
It is estimated that 2 - 4.9 million pet dogs in the United States suffer from myxomatous mitral valve disease, a heart condition that leads to the development of congestive heart failure in approximately 15%. The pathogenic role of renin-angiotensin-aldosterone system (RAAS) stimulation in the development and maintenance of congestive heart failure, a serious clinical syndrome, is well accepted. Consequently, pharmacologic RAAS blockade, most frequently attempted through the use of angiotensin-converting enzyme (ACE) inhibitors, is considered standard-of-care for the treatment of patients with congestive heart failure; indeed, administration of these drugs is associated with improvement in both clinical signs and survival time in dogs with congestive heart failure of underlying etiologies.

While the clinical benefit of ACE inhibition is clear, it is also apparent that circulating levels of aldosterone, the end-product of RAAS stimulation, often exceed pretreatment levels in many patients receiving these agents. This unexpected and undesirable phenomenon is known as aldosterone “breakthrough”. In dogs, the incidence of aldosterone breakthrough in experimental models of RAAS activation is up to 80%, and occurs as early as 1 week after initiation of therapy with ACE inhibitors. Human patients with aldosterone breakthrough have worse functional impairment and clinical outcomes than those in which aldosterone breakthrough does not occur. Therefore, there is a critical need for information regarding the incidence of this potentially deleterious phenomenon in clinical veterinary patients.

Angiotensin II, type 1 receptor blockers (ARBs) circumvent ACE-independent pathways responsible for continued angiotensin II (and therefore, aldosterone) production during therapy with ACE inhibitors. This occurs by virtue of selectivity for the angiotensin II receptor. As these non-ACE pathways are evoked as the favored explanation for aldosterone breakthrough, it logically follows that treatment with an ARB should be associated with a lower incidence of this phenomenon. Preclinical work by our group suggests that the ARB telmisartan more completely blocks RAAS than does enalapril in healthy dogs.

The major objective of this study is to compare the incidence of aldosterone breakthrough in dogs with advanced myxomatous mitral valve disease treated with an ACE inhibitor (enalapril) or an ARB (telmisartan). We hypothesize that treatment with telmisartan will be associated with a significantly lower incidence of aldosterone breakthrough than will treatment with enalapril. To test this hypothesis, we will measure concentrations of several circulating and urinary markers of RAAS activation before and 1 month following initiation of therapy with one of these drugs.

The results of this study will provide veterinarians with objective information to guide the way in which they approach RAAS blockade in clinical patients.

Funding Agency
American Kennel Club
Principal Investigator
Dr. Amanda Coleman
Co-investigators
Drs. Amelia Sinkin (research fellow), Gregg Rapoport, Steeve Giguère
Poultry products are the most frequently implicated sources of human *Salmonella* infections in the U.S with estimated 1 million illnesses and 380 deaths per year. *Salmonella typhimurium*, *S. enteritidis* and *S. heidelberg* cause gastroenteritis and septicemia in humans and are the top serovars linked to foodborne salmonellosis worldwide. In poultry, infection and disease caused by *Salmonella* are dependent on a number of factors including age, immune status of the host, genetic susceptibility, environmental factors and stressful conditions. *Salmonella* may be transmitted vertically through contaminated eggs, horizontally by direct bird-to-bird contact or via contaminated environment, feed and water. *Salmonella* colonizes the ceca of poultry and are shed in feces for several weeks and months. Following intestinal invasion, *Salmonella* are taken up by phagocytic cells and are transported systemically via the bloodstream to various organs. Persistence in tissues is dependent on the *Salmonella* strain, age and immune status of the host.

Although numerous measures have been implemented to minimize surface contamination in poultry carcasses during processing, *Salmonella* are still frequently recovered from ground products. If systemic infection is responsible for *Salmonella* contamination in finished ground products, the identification of *Salmonella* harborage sites and the removal of these sites during processing may be the solution to prevent outbreaks of foodborne salmonellosis. While significant progress in the knowledge of *Salmonella* pathogenesis in mammalian hosts has been made in the past decade, there is still a paucity of information regarding the mechanisms of infection and systemic dissemination of different *Salmonella* serovars in avian species. Previous studies on *Salmonella* pathogenesis in poultry species were limited to in vitro assays and enumeration of recovered bacteria from tissues. In the present research we used a highly sensitive bioluminescence imaging (BLI) system to monitor specific body sites infected with bioluminescent *Salmonella* and the dynamics of bacterial colonization and clearance from these sites over time. Bacteria with chromosomal integration of the lux operon from *Photobacterium phosphoreum* (luxCDABE) encode genes to synthesize luciferase, the substrate luciferin and are able to constitute produce visible light. The analysis of emitted photons allows for quantification of bioluminescent bacteria which can be relatively correlated with colony forming units (CFUs) recovered from infected tissues.

The goal of this project was to reveal harborage sites for *Salmonella* that might contribute to contamination of ground chicken meat. One-day-old specific pathogen free (SPF) chicks were randomly divided into two challenge groups and one control group. The chicks in the challenged groups were inoculated with 108 CFU/0.1 ml of bioluminescent *S. typhimurium* or *S. heidelberg* via oral route, while the chicks in the control group were inoculated with 0.1 ml of inoculation broth. The chickens were evaluated daily for clinical signs and euthanized on different time points up to 42 days for sample collection. Blood, neck skin, drumstick with lymphatics and tibiotarsus were aseptically removed for BLI, bacteriology and immunohistochemistry. Samples of ceca, liver/spleen were also collected to confirm intestinal and systemic infections, respectively.

The results of this study showed that *S. typhimurium* and *S. heidelberg* can be detected in neck skin until 42 days post inoculation by BLI, bacteriology and immunohistochemistry, and that epidermal keratin is likely a harborage site for *Salmonella* in poultry skin. Low levels of bioluminescent *Salmonella* were detected from samples of tibiotarsus, blood and drumstick mainly in the first week post inoculation. Immunohistochemistry revealed *Salmonella* in bone marrow and in the lumen of lymphatics associated with drumstick only in the first week post inoculation.

Overall the results of this study indicate that neck skin, tibiotarsus, drumstick and blood from infected chickens are some possible sources of contamination in ground poultry meat. Systemic infection would explain the detection of *Salmonella* from blood, tibiotarsus and drumstick, while the presence of *Salmonella* in neck skin suggests surface contamination by fecal material. Neck skin with *Salmonella* attachment to epidermal keratin is likely a more significant source of contamination in ground poultry meat than bone, blood and skeletal muscle.

**Co-investigators**
Dr. Monique S. França
Dr. John J. Maurer

**Principal Investigator**
Dr. Monique França
Validation of an ELISA Panel to Assess Growth Factor and Cytokine Concentrations in Canine Platelet Rich Plasma

Platelet rich plasma (PRP) is a plasma preparation that contains a high concentration of platelets. Delivery of platelets to a site of injury is theoretically desirable because platelet alpha granules are a source of several anabolic growth factors including transforming growth factor β (TGFβ), platelet derived growth factors (PDGF), and vascular endothelial growth factor (VEGF). Accordingly, PRP has been used to treat injured tendons, muscles, ligaments, and osteoarthritic joints. Unfortunately, positive results with PRP have not been consistently reported. One potential reason for inconsistent results is that different PRP preparations are widely variable in their concentrations of platelets, white blood cells, red blood cells and also their growth factor and cytokine profiles. In addition, some investigators add calcium chloride, thrombin, gammathrombin, or batroxobin to activate the PRP before it is administered to patients. As a result, there are several variables including cellular characteristics, growth factor and cytokine profiles, and exogenous manipulation (i.e., activation) that may affect the efficacy of PRP’s use as a treatment for a specific medical condition or tissue type. Accordingly, many aspects of PRP therapy warrant further investigation including how exogenous platelet activation affects growth factor and cytokine profiles. In order to achieve this objective, a validated panel for accurately and repeatedly assessing growth factor and cytokine concentrations in canine PRP is needed.

Although many ELISAs have been developed to measure the aforementioned growth factors and cytokines, relatively few have been developed for use with canine samples. Furthermore, no ELISAs have been validated for use with canine plasma prepared using the anticoagulants ACD or sodium citrate, the two anti-coagulants most commonly used to prepare PRP. As a result, our objectives of this specific study are to evaluate the specificity and efficiency of several commercially available ELISAs for quantifying growth factor and cytokine concentrations in different samples from dogs, including PRP.

Our broader goal is to characterize different PRPs and the effects that different activation protocols have on the final PRP product in terms of both its cellular characteristics, the platelet activation and morphology, and the associated growth factor and cytokine delivery. The ultimate goal is to identify which, if any, PRP preparations are beneficial in the treatment of cartilage injury, bone regeneration, and treatment of osteoarthritis.

Thus far, we have determined that the cellular compositions of several different PRP preparations vary widely. More specifically, the platelet, white blood cell, and red blood cell contributions differ dramatically among different PRP preparations. Further, we have used different ELISAs to detect several growth factors and have begun to analyze the data. Several of these ELISAs appear to yield repeatable results when used with citrated canine PRP samples. We also have measured concentrations of the growth factors and cytokines and the effects that different activation regimes have on the final PRP product. As we note regarding the cellular characteristics, there is considerable variability in the growth factor profiles of different PRP preparations. Interestingly, PRP activation appears to have a greater effect on the concentrations of the growth factors than on cellular composition. Currently, we are completing data analysis and then will begin to transition into in vivo clinical assessments of the efficacy of PRP in canine joint disorders. It is our hope that the results of these studies will optimize the benefit of treating naturally occurring canine disease as well as have translation applicability to the use of PRP in treating common joint disorders in people.

Principal Investigator
Dr. Samuel P. Franklin

Co-investigators
Drs. David Hurley, Ben Brainard, Bridget Garner

Will Basinger (Class of 2016)
Brian Hayes (Class of 2016)
Kate Birdwhistell (Class of 2019)
Alena Strelchik (Class of 2017)
Sepsis, a life-threatening complication of bacterial infections, is a leading cause of death in people and animals worldwide. For example, sepsis affects approximately 1 in 1000 adult humans in developed countries, with mortality rates ranging from 30% to 80%. The situation is equally dire in infants and children, as sepsis is the third leading cause of neonatal death worldwide, after premature delivery and birth-related complications. Sepsis also is an important disease in animals, and commonly affects dogs, cats and horses. Bacterial sepsis is the most frequent cause of death in newborn foals within the first week of life, with mortality rates reaching 50%, and causes significant economic losses to the equine industry. Thus, a more complete understanding of how sepsis develops is critical to support the development of better ways to prevent and treat sepsis in people and animals.

Sepsis occurs when the immune response to a bacterial infection is inappropriate. Severe infection can become widespread with bacteria travelling in the bloodstream (sometimes called “blood poisoning”). The immune system fights the infection by releasing inflammatory products that recruit other immune cells and activate them to kill the bacteria. This inflammatory response is beneficial when it is controlled and confined to a small, infected area. However, when the response is widespread and exaggerated, it can cause a lot of damage. Sepsis develops when bacterial infection and the related inflammatory response spread throughout the body and directly cause damage to healthy organs and tissue.

Infection results in activation of both the immune and hormonal systems. The immune system response helps the patient eliminate the bacteria, while the hormonal system helps cope with the stresses of illness. The hormonal response to sepsis is primarily mediated by the hypothalamic-pituitary-adrenal (HPA) axis, and culminates with secretion of the hormone cortisol from the adrenal glands. Cortisol is vital for the stress response to severe illness, and plays a key role in regulating the inflammatory response. This anti-inflammatory effect of cortisol is critical in sepsis, as an unregulated inflammatory response can be as dangerous as the initial infection and result in multi-organ failure or death. Up to 50% of septic people and foals have critical illness-related cortisol insufficiency. In this condition, the adrenal glands fail to produce enough cortisol, or cortisol is made but lacks anti-inflammatory effects.

Recent studies in septic people and mice suggest that lack of the protein that carries cortisol through the bloodstream, cortisol binding globulin (CBG), may play a role in the development of critical illness-related cortisol insufficiency. Previously, it was believed that free, unbound cortisol was more active. New evidence suggests that cortisol exerts its most potent anti-inflammatory effects on some immune cells when it is bound to CBG. There is evidence that CBG exists in lower concentrations in newborns than in adults, and that septic people and animals have much less CBG than healthy individuals. We have recently documented a 25-50% decrease in CBG in healthy and septic foals as compared to healthy horses. This CBG-deficiency in the septic newborn foal may lead to the development of critical illness-related cortisol insufficiency, which then results in an unregulated and exaggerated inflammatory response that ultimately leads to organ failure and death. However, the effect of CBG on immune cell function in foals has not been evaluated to date.

Thus, the objective of this study was to characterize the effects of free and CBG-bound cortisol on immune cell (neutrophil) function in neonatal foals and adult horses using a laboratory model of bacterial sepsis. Immune cells were isolated from blood samples collected from healthy newborn foals and healthy horses, and cells were exposed to bacteria in the laboratory to simulate sepsis. Cells were treated with cortisol by itself and in the presence of CBG, and inflammatory responses were measured. Cortisol alone slightly suppressed inflammatory responses, but cortisol and CBG together had potent anti-inflammatory effects in cells from both horses and foals. These results strongly suggest that CBG-bound cortisol is an important regulator of inflammation in equine immune cells, and that age- and illness-related CBG-deficiency could be a critical factor in the development of sepsis in newborn foals.

These findings have directly supported our laboratory’s overall research goals by helping to expand our understanding of how cortisol regulates immune and inflammatory responses in septic foals. Further, our results provide a foundation for future studies to investigate new treatment approaches for critical illness-related cortisol insufficiency and sepsis in foals. This work also provided a valuable biomedical research training opportunity for a future veterinary researcher, Ms. Melanie Fratto, who is currently a 3rd year veterinary student here at UGA. Ms. Fratto was awarded a Morris Animal Foundation Veterinary Student Summer Research Scholarship to participate in this project during the summer of 2015.
Bovine respiratory disease (BRD) is the most common health problem in feedlot cattle in North America, with the reported economic impact on the US beef industry exceeding $4 billion annually. The infectious agents responsible for BRD include bovine viral diarrhea virus (BVDV), bovine herpes virus 1 (BHV1), bovine respiratory syncytial virus (BRSV), parainfluenza 3 virus (PI3V), Pasteurella multocida, Mannheimia haemolytica, Histophilus somni, and Mycoplasma bovis. Co-infection by these agents combined with environmental stressors (e.g., weaning, shipping, crowding, and weather extremes) and host factors (e.g., naïve or suppressed immune response) determine the severity of clinical disease. Modified-live virus (MLV) vaccines are commonly administered to calves in an attempt to prevent BRD. However, subcutaneous or intramuscular vaccination of calves, in the face of maternal antibodies, may result in limited immune response due to inhibition of the vaccine antigens by maternally derived neutralizing antibodies. Intranasal vaccination is a promising alternative for immune priming in young calves with maternal antibodies, because vaccine antigens delivered intranasally appear to circumvent the suppressive effects of the antibodies. Additionally, intranasal vaccination may result in superior stimulation of the mucosal immune response, which is particularly important for protection against infectious agents that enter the body by the respiratory route.

It has become common practice in some cow-calf operations to prime newborn calves with an intranasal vaccine during the first week of life and administer a booster vaccine around 2-3 months of age. However, it is not known if the booster vaccine should be given intranasally or subcutaneously. To address this question, in this study we primed 24 Angus-cross calves (1-3 weeks of age) by administering a MLV vaccine containing BHV1, BRSV and PI3 (Inforce-3®) intranasally. Sixty days later, 12 of the calves were administered the same vaccine intranasally, and 12 received the same vaccine subcutaneously. Serum neutralizing antibody (SNA) titers to BHV1 and BRSV and nasal mucosal BHV1-specific IgA levels were measured to compare the effectiveness of the two routes of administration of the booster vaccine.

Calves had high SNA titers to BRSV and BHV1 at 1-3 weeks of age; most likely these antibodies were of maternal origin. A significant decrease in SNA titers to BRSV and BHV1 was observed 2 and 8 weeks after the intranasal priming vaccination. Booster vaccination 60 days after priming did not lead to an increase in SNA titers against BHV1, regardless of the route of administration. Only intranasal booster vaccination induced a significant increase in SNA titer to BSRV 2-4 weeks after the booster vaccine was administered. These results suggest that the intranasal route of booster administration may be a more effective way to enhance immunity against BSRV in young calves previously primed with an MLV vaccine.

A sustained increase in BHV1-specific IgA titers in nasal secretions was observed in both vaccine groups after either the priming or booster vaccinations. By comparing the fold change in IgA in nasal secretions on day 21 relative to the day of booster vaccination, two patterns of response were observed in the calves that received the booster intranasally. The calves with high concentrations of nasal BHV1-specific IgA at the time of booster did not show clear recall response to the booster vaccination, whereas those with lower concentrations of nasal BHV1-specific IgA at the time of booster vaccination showed a strong (>8 fold increase) recall titer at 3 or 4 weeks after the booster vaccination. This suggests that the concentration and duration of nasal IgA antibody developed after intranasal priming vaccination may impact the efficacy of the BHV1-specific IgA response to booster vaccination by the same route. In contrast, a significant BHV1 nasal IgA response (>8 fold increase) was observed in calves that received the booster vaccination subcutaneously, regardless of the concentration of BHV1-specific IgA in nasal secretions at the time of the booster vaccination.

In summary, in this study booster vaccination 60 days after intranasal priming did not cause an increase in SNA titers against BHV1. Intranasal booster produced significantly enhanced SNA titers to BSRV in calves that were primed intranasally with the MLV vaccine. Administration of the booster vaccine either intranasally or subcutaneously induced an increase in BHV1-specific IgA titers in nasal secretions. The amount of IgA present at the time of the intranasal booster affected the specific BHV1 recall nasal antibody response. These results will help veterinarians and cattle producers decide how to most effectively vaccinate young beef calves to prevent BRD. Further studies are needed to compare the effect of the route of booster vaccination on protection against infection and clinical disease after exposure to pathogens involved in BRD.

**Immune Response to Subcutaneous and Intranasal Vaccination in Young Beef Calves**

**VACCINATING BEEF CALVES**

Dr. Joao Bittar and Dr. Roberto Palomares working with a calf at Rose Creek Farms.

Dr. Joao H.J. Bittar  
Dr. Roberto A. Palomares  
Principal Investigator  
Co-investigators  
João H.J. Bittar, David J. Hurley, Amelia R. Woolums, Toi A. Collins
Swine influenza is one of the three most important respiratory diseases of pigs. Swine influenza infection in production animals causes significant economic losses, with cost estimates ranging from $3.23 - $10.31 per hog. With commercial hog slaughter exceeding 100 million head annually, influenza may cost producers in excess of $1 billion annually. Swine influenza also poses a potential public health risk and economic losses can occur due to perceived risks associated with pork and pork production by consumers and trade partners. United States pork exports were valued at $4.9 billion in 2008 and the emergence of the 2009 swine-origin pandemic influenza virus was estimated to cost the industry >$5 million per day. For these reasons, improved control measures for swine influenza are needed.

Our work using a widely accepted murine model of influenza vaccination and infection has shown efficacy of a recombinant adenovirus (Ad5) vector system expressing influenza NP or M2. The work supported by VMES builds upon this foundation. Recombinant Ad5 vector systems are efficacious in swine, poultry and other species. The goal of this work is to utilize recombinant Ad5 vaccines expressing novel influenza vaccine antigens in combination with traditional (HA) antigens to induce more potent and broad immunity to swine influenza virus infection. The work will focus on development and testing in a murine model, and will facilitate pursuit of funding from the USDA, The Pork Board, or other stakeholders. Long-term, these novel vaccines could reduce the economic burden and public health concerns associated with swine influenza in the pork industry. Moreover, better understanding of the vaccine antigens tested here could lead to improvements in other vaccine platforms. This project also addresses USDA priorities and gaps identified at the USDA-ARS workshop, Animal Influenza Viruses Gap Analysis, where it was noted, “There is a recognized need for improved vaccines over our current commercially approved vaccines to better serve the need of the swine industry.” The Summary of Vaccine Gaps specifically noted the need for “Development of novel vaccine technologies to produce a broader or universal clinical protection,” and “Development of vaccine platforms that can be used in multiple species.”

The long-term goal of our work is to develop vaccines that can readily be implemented in production systems to prevent and control swine influenza virus despite evolution and emergence of new strains. The main focus of the work supported by VMES was to develop and test novel vaccine antigens expressed by the recombinant Ad5 vector system for the potential to induce immune responses in the mouse animal model. Positive results would support proceeding vaccine efficacy studies in swine. We engineered recombinant DNAs to express a panel of influenza antigens from swine influenza and human influenza (as an established comparator and control). The classical HA antigen was expressed in addition to the NA, as it is present in inactivated vaccines. We also engineered a HAstalk antigen, a HA protein designed without the dominant globular head. Vaccination with intact HA results in the majority of antibody responses to the head and little response to the stalk. The HA stalk is of considerable interest as the immunodominant HA head is highly mutable, resulting in vaccine evasion, whereas the HA stalk is highly conserved and antibodies directed against the stalk are broadly cross-reactive and protect against multiple influenza virus subtypes. Vaccination with a headless HA or HAstalk should preferentially elicit broadly reactive antibody responses. Each of the antigen expression constructs has been cloned and expression demonstrated. Recombinant Ad5 vaccines are being produced and testing of immunogenicity is ongoing. Upon completion of immunogenicity studies, vaccine antigen combinations will be further tested for breadth of immunity. Upon completion of these studies, we will be positioned to advance vaccine testing in swine with the goal of developing an improved vaccine to prevent economic losses due to swine influenza as well as reducing public health concerns about swine influenza.

**Principal Investigator**  Dr. Mark Tompkins
Extramural Contracts & Grants

Baxter, Gary. Hill’s Veterinary Nutrition Technician. Hill’s Pet Nutrition, Inc. $40,000.00

Brindley, Melinda. Characterization of the Arenavirus Glycoprotein Complex and Mechanism of Fusion. NIH. $161,200.00

Brown, Corrie. Acquisition of Goods and Services. USDA. $97,387.00

Brown, Corrie. African Swine Fever Sample Collection from Uganda. USDA APHIS. $49,755.00

Brown, Corrie. Animal Health Technical Assistance. USDA. $55,000.00

Brown, Corrie. Animal Health Technical Training. Veterinarians without Borders. $49,140.00

Brown, Scott. Engaging Students in Diabetic Kidney Disease: An Interactive Inquiry Approach. NIH. $107,994.00

Budsberg, Steven. Efficacy of S-006-8 in Providing Analgesia for Dogs with Chemically Induced Synovitis. Industry Sponsored. $190,478.00

Budsberg, Steven. The Effects of Tamadol on Pain and Dysfunction of Chronic Osteoarthritic Joints in Dogs. Morris Animal Foundation. $167,048

Chen, Shiyou. Response to Gene to Complement 32 in Atherosclerosis. American Heart Association. $50,092.00

Chen, Shiyou. Dedicator of Cytokinesis 2 in Smooth Muscle Phenotypic Modulation. NIH. $440,757.00

Chen, Shiyou. Novel Mechanism of Smooth Muscle Phenotype Modulation and Vascular Remodeling. NIH. $368,349.00

Coleman, Amanda. Aldosterone Breakthrough during Angiotensin-Converting Enzyme Inhibitor or Angiotensin II Receptor Blocker Therapy in Dogs with Advanced Myxomatous Mitral Valve Disease. American Kennel Club Foundation. $12,000.00


Corn, Joseph. Feral Swine Diseases Information and Training. USDA APHIS. $100,000.00

Czaja, Krzysztof. Vaginal Influence on Brainstem Plasticity and Neural Coding of Taste. NIH. $633,725.00

Dickerson, Harry. Emerging and Reemerging Infectious Disease Residency/PhD Program. Merial Limited. $129,022.00

Dickerson, Harry. The University of Georgia Veterinary Scholars Program: A Research Training Experience for Veterinary Medical Students. Merial Limited. $10,000.00

Ferrer, Maria. Effect of Sperm-bound Anti-sperm antibodies on function of bovine Spermatozoa: Sperm-oocyte Interactions. Select Sires, Inc. $3,918.00

Fischer, John. Comprehensive Evaluation of Health Status of Resident White-Tailed Deer within Parks of the National Capital Region. CESU-Piedmont. $18,672.00

Fischer, John. Relationships Involving Wildlife, Livestock, & Poultry; Exotic Arthropod Surveillance; Feral Swine Mapping System. USDA. $585,813.00

Fischer, John. Southeastern Cooperative Wildlife Disease Study. Various Other States. $588,145.00


Franca, Monique. Using Bioluminescent Salmonella to Identify Infection Sites Contributing to Contamination of Ground Turkey Meat. Industry Sponsored. $90,604.00

Franklin, Samuel. Utility of MRI for Characterizing Articular Cartilage and Subchondral Bone Pathology in Dogs with Elbow Dysplasia. American Kennel Club Foundation. $12,398.00

Franklin, Samuel. Comparison of Platelet Rich Plasma Therapy and Mesenchymal Stem Cell Therapy Supplemented with a Pglycolic Acide Nanofiber Polymer for the Treatment of Cartilage Pathology in Dogs. Industry Sponsored. $105,482.00

Fu, Zhen. Virus Clearance from the Central Nervous System. NIH via sub-award under Thomas Jefferson University. $254,260.00

Garcia, Maricarmen. Acquisition of Goods and Services. USDA ARS. $44,753.00

Gogal, Robert. Effects of Lactobacillus Rhamnosus (LGG) or a Soluble Fraction of LGG on Immunomodulatory Effect of Chronobacter Sakazakii Exposure in Neonatal Mice. Industry Sponsor. $161,904

Gogal, Robert. Influence of Maternal Lead on F1 Pigeon Hatchlings. U.S. DOD. $44,932.00

Guo, Tai. Exacerbation of Type 1 Diabetes in Mice by Bisphenol A and Genistein. NIH. $186,355

Guo, Tai. Modulation of Cytokine and Chemokine Production by LifeDrop in Human Macrophages. LiveLeaf Biosciences. $31,250.00


Hart, Kelsey. 2015 Morris Animal Foundation Veterinary Scholars Program Award. Morris Animal Foundation. $5,000.00

Hart, Kelsey. Dendritic Cell Function in Equine Neonatal Sepsis. American Kennel Club Foundation. $86,433.00

He, Biao. A Candidate Swine Influenza Virus Vaccine: In Vivo Evaluation of Novel Chimeric HemagglutininsExpressed by Parainfluenza by Parainfluenza Virus 5. NIH via sub-award under University of South Dakota. $40,590.00

He, Biao. Developing a Novel RSV Vaccine Based on Mumps Virus. NIH. $371,250.00

He, Biao. Developing a Novel Viral Vector for a Human Malaria Vaccine. NIH. $187,188

Hines, Murray E. TVDIL Infrastructure for CVM VET-LRN Veterinary Diagnostic Laboratory Program. Food and Drug Administration. $16,500.00

Hines, Murray E. GA 2015 NAHLN Member Laboratory Cooperative Agreement. USDA. $55,000.00


Hondalus, Mary K. An Academic Veterinary Career is Sustainable through Smart Financial Decisions; Spring 2015. American Veterinary Medical Association. $600.00


Jackwood, Mark. Acquisition of Goods and Services. USDA. $37,065.00

Jackwood, Mark. Improved Methods for the Control of Variant Strains of IBV. U.S. Poultry and Egg Assoc. $66,355.00

Jordan, Brian. Evaluation of Protection against GA08 IBV Challenged Leghorn Chickens Vaccinated with MA5 and 4/91. Merck Company Foundation. $165,739.00

Jordan, Brian. Evaluating the Efficiency of Infectious Bronchitis Virus Vaccine in Combination with Advent Coccidia Vaccine Application. Industry Sponsored. $38,148.00

www.vet.uga.edu/research/vmes/
Selected Publications

**DIAGNOSTIC LABORATORIES**


Fogelson, S., Yau, W. and D. Rissi. Disseminated Yersinia Pseudotuberculosis Infection In A PACA (CUNICULUS PACA)', Journal of Zoo And Wildlife Medicine, 1, p. 130, BioOne Online Journals, EBSCOhost, viewed 20 August 2015.


PATHOLOGY


Bergren, A. L., Credille, B. C., Epstein, K. and S. Giguère. Retrospective Comparison of Gastrosplenic Entrapment of the Small Intestine to Other Strangulating Small


Zhao, F., Li, R., Xiao, S., Diao, H., Dudley, A. E. and X. Ye. Multigenerational Exposure to Dietary Zearalenone (ZEA), an Estrogenic Mycotoxin, Affects Puberty and


Li, R., El Zowalaty, A. E., Chen, W., Dudley, E. A. and X. Ye. Segregated Responses of Mammary Gland Development and Vaginal Opening to Prepubertal Genistein

Li, R., Diao, H., Xiao, S., Zhao, F., Dudley, E. A. and X. Ye. Deletion of Lysophosphatidic Acid Receptor 3 (Lpar3) Disrupts Fine Local Balance of Progesterone and

De La Fuente, R., Baumann, C. and M.M. Viveiros. ATRX Contributes to Epigenetic Asymmetry and Silencing of Major Satellite Transcripts in the Maternal Genome of the


Diao, H., Li, R., Xiao, S., Zhao, F., Dudley, E. A. and X. Ye. Loss of Lysosphosphatic Acid Receptor 3 (Lpar3) Disrupts Fine Local Balance of Progesterone and Estrogen


El Zowalaty, A. E., Bauman, C. Li, R., Chen, W., De La Fuente, R. and X. Ye. Seipin Deficiency Increases Chromocenter Fragmentation and Spermatied Apoptosis and


Gyimesi, Z., Forrester, J., Doering, D., Burns, R. and R. McManamon. Ovariectomy Due to a Dermoid Cyst in an Orangutan (Pongo Pygmaeus). Journal Of Zoo And

Wildlife Medicine, 1, p. 167, BioOne Online Journals, EBSCOhost, viewed 20., 2015.


Li, R., Zhao, F., Diao, H., Xiao, S. and X. Ye. Post Weaning Dietary Genistein Exposure Advances Puberty Without Significantly Affecting Early Pregnancy in C57BL/6J


Li, R., Diao, H., Zhao, F., Xiao, S., El Zowalaty, A. E., Dudley, E. A., Mattson, M. P. and X. Ye. Olfactomedin 1 Deficiency Leads to Defective Olfaction and Impaired

Female Fertility. Endocrin., 2015.

Li, R., El Zowalaty, A. E., Chen, W., Dudley, E. A. and X. Ye. Segregated Responses of Mammary Gland Development and Vaginal Opening to Prepubertal Genistein


Biotechnology, 32(10), 1045-52., 2014.

Lin, Z., Dodd, C. A., Xiao, S., Krishna, S., Ye, X. and N. M. Filipov. Gestational and Lactational Exposure to Atrazine via the Drinking Water Causes Specific Behavioral


Bergren, A. L., Credille, B. C., Epstein, K. and S. Giguère. Retrospective Comparison of Gastrosplenic Entrapment of the Small Intestine to Other Strangulating Small


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