The Clinical Trial Service at Iowa State University College of Veterinary Medicine

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THE CLINICAL TRIAL SERVICE AT IOWA STATE UNIVERSITY COLLEGE OF VETERINARY MEDICINE

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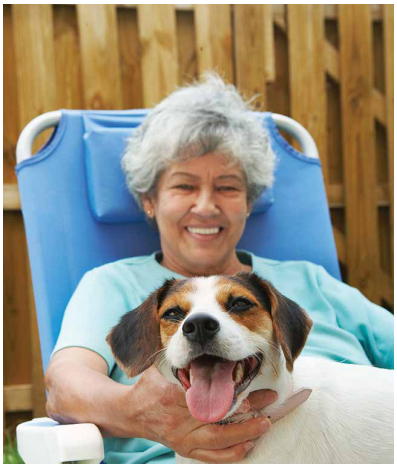

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VETERINARY CLINICAL TRIALS AT IOWA STATE UNIVERSITY: SHAPING VETERINARY MEDICINE ONE PATIENT AT A TIME

The Clinical Trial Service at Iowa State University College of Veterinary Medicine is pioneering innovations in veterinary medicine, while providing state of the art treatments to companion animals. Work completed by the Center advances both human and veterinary medicine, while offering unmatched care and expertise to animals of our community.

The Iowa State University College of Veterinary Medicine (ISU CVM) was the United States' first public veterinary school and continues to serve as a beacon for quality veterinary medical education. In addition to training world class veterinarians in a diverse range of specialties, the CVM operates a state of the art Animal Medical Center and Diagnostic Laboratory, providing medical and surgical care for both large and small animals. The CVM leverages its relationship with the university to perform critical veterinary research, improving the lives of animals while also providing advances in human medical knowledge. The Clinical Trial Service of the college partners with pet owners to evaluate innovative new treatments outside of the laboratory in clinical settings, providing new treatments to pets, while gathering scientific data that shapes the future of veterinary medicine.

World Class Medical Facilities for Faculty and Staff

The Lloyd Veterinary Medical Center ISU CVM is the largest, most comprehensive veterinary medical hospital in the state, treating many different animals – from small pets to livestock – with unmatched expertise. The Lloyd Veterinary Medical Center staff consist of numerous board-certified veterinarians and veterinary specialists, along with veterinary school residents and interns, fourth-year students, and registered veterinary technicians. Within the Veterinary Medical Center, the Hixson-Lied Small Animal Hospital focuses on treating companion animal illness, as well as performing clinical research at the Clinical Trial Service. The Small Animal Hospital is an American Animal Hospital Association accredited hospital, employing 31 boarded veterinary specialists, along with veterinary students and dedicated technical staff.

The Clinical Trial Service works within

the CVM to develop new treatments, drugs, diagnostic and surgical procedures, and medical devices, through veterinary clinical trials and translational medical studies. In addition to the highly trained staff of the Veterinary Medical Center, the CVM offers expansive veterinary facilities and research staff, along with a state of the art diagnostic laboratory. To further advance research initiatives, the Clinical Trial Service partners with the ISU Department of Bioinformatics to utilize high performance computing during studies, and the Department

of Statistics to analyze the complex data collected during clinical trials. By using these expansive biomedical resources, veterinary researchers are able to engage in high quality scientific studies that shape the face of modern veterinary medicine.

Veterinary Medicine and Human Health

Clinical trials in animals are essential for advancing veterinary medicine, and animal research in general has long been a cornerstone of medical advancement for humans. Even the most powerful modern computer cannot yet predict exactly how a given medicine will interact with the complex biology of a living organism. Comparative medicine is the study of biological similarities (and differences) across animal species. Comparative medicine is crucial in helping to determine the molecular mechanisms of health and disease in humans, as well as animals. Animal models help facilitate the journey back and forth from understanding the basic mechanism to producing an effective treatment or cure. Traditionally, this research has been carried out in laboratory animals under strict and uniform environmental conditions. These conditions are often necessary in the early stages of medication development to establish whether or not a treatment works; however, humans live in diverse environments that may cause different responses to a treatment in ways that are difficult to predict in the laboratory. Veterinary research in pets offers an attractive alternative perspective to the controlled environments of laboratory drug testing.

Laboratory animals are typically genetically identical or very similar, share a uniform environment and diet, and are kept on strict schedules. These factors are critical for many types of medical studies, but are not always representative of how treatments affect humans. Companion animals, on the other hand, share their daily environments and daily schedules with humans. For example, they are often exposed to the same pathogens, allergens and potential toxins that their human owners encounter on a regular basis in the home, and their diseases may reflect our own. They also may receive medications from their owners in similar schedules to how owners might take their own medicine, which may be different from the rigid intervals of a laboratory setting. Pets are also as genetically diverse as their owners and receive more diverse diets than laboratory animals. Further, dogs and cats metabolize many medications in a similar fashion to humans than the common laboratory rat. This variety in genetic background, diet, schedule and environment helps researchers better replicate how medicines and treatments are administered in diverse populations of humans. While laboratory animal research remains critical to medical discovery, studies performed in companion animals may better predict how new treatments will perform in human patients.

Both owners and their pets receive benefits from participating in clinical studies beyond contributing to medical science. Sick pets benefit from cutting edge treatments and more in-depth diagnostic monitoring and care, while owners typically receive these treatments at a discount, or may even be compensated fully for enrolling their pet in a clinical study. Participation in clinical trials at the ISU CVM's Clinical Trial Service offers pet owners the opportunity to receive low cost, state of the art veterinary care for their pets, while also benefiting the greater good for both humanity and our companion animals.

The investigative work performed at the Clinical Trial Service is funded by both research grants and private funding streams, giving veterinary researchers at ISU the opportunity to work on a wide variety of diseases and medical interests.

Clinical Trials for Healthier Lives

In addition to these critical studies, the Clinical Trial Service is engaged in numerous other studies aimed at improving companion animal and human health. Research is currently underway to better understand cardiac function and treatments in cats, including the effects of steroids and vitamin D on cardiac function, and evaluating lung ultrasound as a potential diagnostic tool for feline respiratory health.

In dogs, researchers and veterinarians are working together to understand how pregnancy affects heart health in female dogs and evaluate the effect of carrying large litters on maternal health. They are evaluating new platelet treatments for dogs with bleeding problems, and studying the effects of certain types of fats on feline kidney function. They are undertaking studies to improve surgical techniques for a common eye problem in cats, and are testing a new eye drop treatment for corneal ulcers in dogs. All of these studies work to not only improve the life of our pets, but to also provide a richer understanding of these processes and compounds in human health.

Pioneering Cancer Treatments in Pets

An estimated one in four dogs over the age of 10 years will die of cancer while nearly 50% of older dogs will be diagnosed with cancer during their lifetimes. One of the ISU CVM's most advanced centers is their Veterinary Oncology Service. The center provides world class treatment for pets with cancer, including surgery, chemotherapy, immunotherapy, and specialized radiation therapy, all with the primary goal of extending life while preserving and improving quality of life.

One of the most advanced treatments that the Oncology Service will offer, starting summer 2018, is stereotactic radiation therapy. This technology allows veterinarians to focus radiation beams on only the tumor, leaving the neighboring healthy tissue intact and functional. This is particularly powerful when treating brain tumors and other cancers where maintaining the integrity of the surrounding tissue is critical for getting pets back to their normal selves. ISU veterinary staff use these advanced treatments in conjunction with one another to target tumors quickly and efficiently.

In addition to treating cancer, the ISU CVM Clinical Trial Service and Oncology Service partner with one another to pioneer new cancer remedies to the benefit of both pets and their owners. Current research includes a study aimed at investigating the impact and role of cachexia (body weight/muscle mass loss) on dogs diagnosed with lymphoma, with the goal of tailoring treatments to balance the maintenance of quality of life with the effective treatment of lymphoma. Another study aims to test the effectiveness of a common human lymphoma treatment in dogs – determining the appropriate dosage and identifying possible side effects. These studies help to prolong comfortable lives for pets, and provide insight into how specific treatments can be of benefit in human cancer research.

A Healthy Future for All

For many people, life is incomplete without the company of a pet. Keeping pets happy and healthy as long as possible goes hand in hand with our own health and wellbeing. The health of our pets is closely tied to our own health, as many of our medical conditions are reflected in dogs and cats. At Iowa State University College of Veterinary Medicine's Clinical Trial Service, cutting edge advances in animal care benefit local pets, work to shape the future of veterinary medicine, and inform medical practices for human health.

BRIDGING THE GAP: TRANSLATING ANIMAL RESEARCH TO HUMAN HEALTH

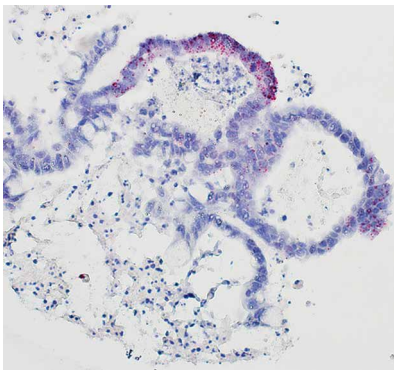
Gastrointestinal diseases are common and can be debilitating if left untreated. Recent developments in intestinal stem cell research have led to advances in researchers' ability to grown healthy intestinal tissues in the laboratory, but translating these findings from mice to humans is proving difficult. Scientists at Iowa State University College of Veterinary Medicine are pioneering this technology in dogs to bridge the gap between human and animal health.

A Worldwide Problem

Diseases of the gastrointestinal system afflict millions of people worldwide, at great costs to human comfort and public health. Inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis, are associated with severe inflammation in the intestines caused by repeated inflammatory cycles. While the specifics of each human disease vary, basic signs include chronic or intermittent vomiting, diarrhea, reduced appetite and weight loss. These diseases cause immeasurable suffering worldwide and represent a great burden on public health costs, but their causes are often poorly understood and treatment options may be limited.

Colorectal cancer is a cancer of the large intestines, often originating in the same intestinal lining (epithelial cells) and requiring early detection for effective treatment. Interventions for colorectal cancer often require surgical removal of the cancerous mass and are prone to complications when the cancer is advanced. Together, IBD and colorectal cancer are among the most prevalent gastrointestinal disorders worldwide, with IBD afflicting millions of people worldwide and colorectal cancer claiming over half a million lives a year.

Many of these gastrointestinal diseases are heavily tied to the behavior of the intestinal lining (epithelium). The intestinal lining is critical for nutrient absorption and proper hydration, and the proper functioning of the lining is essential to maintaining normal health and wellness. Both chronic IBD and colorectal cancers can lead to changes in the intestinal lining that are life threatening and require aggressive medical intervention. Further, congenital problems with the intestinal lining can be deadly to newborns if not caught early, often leading to severe malnutrition and reliance on intravenous nutrition. Large scale problems with the lining can be devastating for patients, and in severe cases, the current best treatment is



gut transplantation from an organ donor. Transplants present a number of potential complications including donor shortages, organ rejection and the need to remain on immunosuppressant medications for the duration of the patient's life.

Recently, researchers discovered intestinal stem cells in the epithelium of the gut. These cells are capable of forming new intestinal linings, complete with the appropriate epithelial cell types, that adequately replicate the intestinal tissue. Scientists have also discovered that from these cells, a

fully functional intestinal lining can be grown in Petri dishes in the laboratory. These functional intestinal structures, called enteroids, have revolutionized the study of epithelial cells and the intestine, and represents a tremendous opportunity for scientists to better understand disease mechanisms of IBD and colorectal cancer. In addition to replicating diseases and testing potential treatments for their remission in the lab. These enteroids also present the possibility of using a patient's own intestinal stem cells to grow healthy intestinal lining that could later be transplanted back into the patient to repair tissue damaged by IBD or cancer.

While much of this research has been pioneered in laboratory mice, the physiological differences between mice and humans have made it difficult to develop clinical transplantation scenarios that are directly applicable to human health. A team of researchers at Iowa State University College of Veterinary Medicine (ISU CVM) are embarking on a mission to develop specific enteroid research strategies in dogs, with the hope of advancing both human and canine medicine for intestinal diseases.

Man's Best Friend

Animal research has been a crux of human medicine through the past few centuries, allowing for medical discoveries that have altered human health and shaped the world. The laboratory mouse is one of the best understood models for animal health – often chosen for its genetic homogeneity, small size, reliable breeding, and ease of husbandry in limited spaces.

While humans owe much to mice, many of the factors that make them reliable research models also make it difficult to directly translate findings from mice into human medicine. Differences in size, lifespan, anatomy, genetic variability, behavior, and living environments often mean that discoveries made in the mouse must undergo many iterations of trials before than can be confidently applied to humans. In the case of intestinal enteroid transplants, mice make a poor model because of their small body size, shorter lifespan and the fact that many mouse strains do not naturally develop gastrointestinal disorders similar to humans. In order to advance research in this area, it is critical to develop a large animal model that more closely captures human intestinal health and disease. The ISU CVM team argues that the domestic dog represents an ideal species in which to pursue this aim.

Dogs make a novel model for intestinal health for many reasons. First and foremost, they naturally develop many intestinal diseases highly similar to human conditions, including IBD and colorectal cancer. They share our living environments and often share our food, have genetic diversity similar to human diversity, and respond to medications in a similar manner. Their longer lifespans and larger body size make them better candidates for endoscopic procedures that are critical to monitor long term health following treatment. Further, discoveries made in the treatment of intestinal disorders in a dog model can be applied to both veterinary medicine and human health initiatives. The ISU CVM team plans to develop intestinal stem cell lines from dogs that can then be used in transplant studies, as part of the One Health initiative, aimed at advancing treatment options for both humans and dogs.

A Roadmap to Transforming Intestinal Health

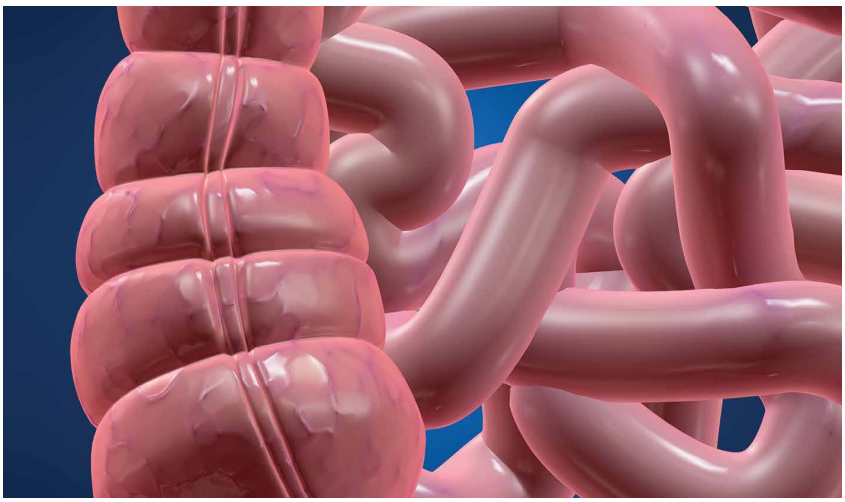
The first goal of the One Health initiative is to develop enteroid lines from the intestinal stem cells of both healthy and diseased dogs. After collecting stem cell samples from patients of the ISU Veterinary Hospital through endoscopic biopsy, researchers will carefully grow sections of intestinal lining that closely replicate the intestines of the donor dog. These lab-grown enteroids will give researchers the opportunity to observe and characterize different disease types of canine enteroids, and allow them to

optimize enteroid lines from an original healthy or diseased stem cell sample.

Using knowledge gained from successful attempts to grow mouse enteroids, the team will optimize techniques for canine enteroid growth. The researchers hope to characterize the different cell types present in the intestinal lining, and identify healthy versus diseased cell types within a complex tissue structure. They plan to develop assays to assess the functional behavior of the cells, particularly identifying the cell conditions and functions that contribute to diarrhea. They will be able to identify different intestinal disease conditions and study the cellular differences underlying why some individuals develop cancer or inflammatory disease, and begin to document these differences.

The second aim of the One Health initiative is to use the lines of enteroids they develop to test new drugs, prior to administering them to actual canine or human patients. Since enteroids develop into complex structures of functional intestinal lining, it will be possible to directly observe the effects that a given medication will have on the intestines and rate its efficacy in treating common gastrointestinal ailments affecting the intestinal lining. Using the assays developed in the first part of their roadmap, they will be able to use enteroids to determine if a particular medication would stop certain signs, such as diarrhea and weight loss. Further, they will complete genetic sequencing for each enteroid line, to begin to identify those gene differences that occur in some dogs with disease versus dogs that do not develop disease. Additionally, these studies will identify potential genetic differences in how individuals might respond to medications. These insights could lead to greater refinements in personalized medicine, and help to identify susceptible individuals before they ever develop disease, paving the way for optimized preventative care.

The ultimate goal of the One Health



initiative is to perform transplant trials in dogs with intestinal disorders. The researchers aim to grow healthy enteroids in the laboratory that can be medically applied to damaged areas of the intestine, with the hope of repairing the lining and reducing disease severity. In cases where the disease is genetic, they aim to use modern gene editing techniques to design disease free enteroids from the dog's original stem cells, providing a healthy transplant option for affected dogs. Following the transplant, dogs will be monitored long-term through periodic GI endoscopy checkups, to ensure that the intestinal grafts remain intact and healthy for the life of the dog, and identify potential problems that could arise with the procedure. The One Health researchers hope to test this procedure in dogs with numerous kinds of intestinal disorders, from congenital disorders present at birth to diseases such as colorectal cancer that develop later in life. Success in these trials could prove transformative to modern gastrointestinal medicine, benefiting both humans and dogs.

The Future is Bright

While the One Health initiative is still in its infancy, preliminary results developing enteroids are promising. Using intestinal samples from four healthy adult dogs, ISU researchers have been able to propagate successful enteroid lines following techniques similar to those used in mouse studies. Building on these results, the One Health team will continue developing veterinary enteroid technology in the pursuit of a world free of intestinal disease.

Further Reading

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Meet the researchers

Dr. Karin Allenspach
Professor

Dr. Karin Allenspach received her Doctor of Veterinary Medicine from the University of Zurich. She did an internship in small animal emergency medicine and critical care at Tufts University, and a residency in small animal internal medicine at the University of Pennsylvania. She was awarded a PhD in veterinary immunology from the University of Bern, Switzerland, for her work on canine chronic enteropathies. She is a Board-Certified Internist and currently appointed as Professor in Translational Health and Small Animal Medicine at Iowa State University. She is passionate about clinical research in small animal internal medicine, particularly inflammatory bowel disease in dogs. She is heavily involved in clinical trials and translational health research and is striving to improve comparative biology understanding.

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Dr. Albert E. Jergens
Professor

Dr. Jergens received his DVM from Texas A&M University performed a residency in Internal Medicine at the University of Missouri – Columbia. He has a broad background in clinical and basic science gastroenterology, serving as a board-certified veterinary internist (DACVIM) in the Department of Veterinary Clinical Sciences and as a collaborating clinician-scientist in the mucosal immunology laboratory of Dr. Michael Wannemuehler. Dr. Jergens has extensive post-graduate training in both Veterinary Pathology (MS degree) and Immunobiology (PhD degree) and is both proficient and experienced in murine, feline and canine clinical trials. His clinical interests include gastroenterology, GI endoscopy, inflammatory bowel diseases in dogs and cats, and participation in clinical trials. His basic science research interests focus on investigation of host-microbial interactions mediating GI health and disease.

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Dr. Jonathan Mochel
Associate Professor

Dr. Jonathan Mochel obtained a Masters in Pharmacology and Pharmacokinetics and his Veterinary Medical Degree from the National Veterinary School of Toulouse. He then went on to complete his Doctorate and Internship in Veterinary Neuroscience in Paris in collaboration with the College de France. His graduate work earned him the Silver Medal from the National Veterinary School of Alfort. Dr. Mochel did his PhD at Leiden University studying the biology of the renin-angiotensin aldosterone system. He is recognized as a European Specialist in Veterinary Pharmacology and Toxicology. He is also an expert in using computer modeling and simulation techniques to advance veterinary medicine, and co-founder of the Animal Health Modeling & Simulation Society (AHM&S). He currently serves as an Associate Professor in the Department of Biomedical Sciences at Iowa State University, specializing in the analysis of clinical data from pets participating in Clinical Trial Service studies, aiming to bridge the gap between laboratory animal studies and human health outcomes.

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Dr. Agnes Bourgois-Mochel
Clinical Trial Coordinator

Dr. Agnes Bourgois-Mochel graduated with a Doctor of Veterinary Medicine from the National Veterinary College of Maisons-Alfort (Paris, France) in 2009. After her graduation, she worked as a veterinarian in several private practices, both in France and in Switzerland, developing her interests and skills in Small Animal General Medicine and Surgery. Her professional interests include Small Animal Internal Medicine, as well as Theriogenology. Her interest in research motivated her move to Iowa State University, to join the new Clinical Trial Service at ISU as a Clinical Trial Coordinator and Clinical Assistant Professor. Her role is to facilitate the conduct of the clinical trials by operating as the connecting link between all the persons involved: the pet's owner, the clinicians, and the sponsors. She oversees the smooth running of the studies, enrolls animals, supervises the visits, interacts with the owners, discusses the patients and the protocols with the clinicians, and takes care of the administrative aspects of the studies.

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Dr. Chad Johannes
Assistant Professor

Dr. Chad Johannes received his DVM from Kansas State University in 1997. After completing his internship at Colorado State University, he entered a small animal internal medicine residency at the University of Missouri-Columbia and became board certified in Small Animal Internal Medicine (2002). Dr. Johannes obtained professorships of Small Animal Internal Medicine at Kansas State University (Clinical Assistant Professor) and at Mississippi State University (Assistant Professor). He completed his residency in medical oncology jointly at North Carolina State University and Sage Veterinary Specialty Centers in the San Francisco area and became board certified in Oncology (2013). Dr. Johannes joined Iowa State University in July 2015 as Assistant Professor of Small Animal Internal Medicine and Oncology. His areas of research focus include veterinary drug/therapeutic development, clinical trials and immunotherapeutics.

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