

BioMed Insider

College of Veterinary Medicine
Research Newsletter

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Research and the Change that brings to the World

Letter from Kelley Marchbanks, Director of Development

There was a time when supporting research was not as exciting as many other giving opportunities. Research support was left to groups and government agencies such as the National Institute of Health (NIH). Though, the times they are a changing! People give for many different reasons. I think there is an underlying desire to, above all, make a difference. I have had the pleasure of working in the advancement field for over a decade and although every dollar has an impact, gifts given to support research can have far-reaching effects on the world in truly meaningful ways. Giving can also be one of the most engaging and fun ways to connect with a college and a cause.

I have worked with individuals who are passionately interested in a specific area. That passion is often derived from a personal experience of tragedy or loss. Emotions of frustration, pain, and anger are equally as passionate as joy, love and gratitude. A gift can be the tool used to “fight-back.” It can be used as a weapon against problems too big to tackle alone. It can also be a resounding thank you.

Over the last year, I have met with each and every faculty member and listened as they answered three very specific questions: Who are you? What do you do to make the world a better place? If you had additional funds, how could you make the world an even better place? Their responses were not only enlightening but also inspiring. They are working on everything from using mathematical analysis to determine which flu type should be included in the next year’s flu shot, to healthy aging, to extending not only life-span but also health-spans (keeping us healthy longer is often more important than just keeping us alive longer).

Individuals who choose to support research at the OSU College of Veterinary Medicine have the opportunity to be a part of something bigger than one person while having the chance to connect in very personal ways with the brilliant scientists doing incredible work. Donors have spent days in the lab peering through microscopes to see the results of the work they have supported, scrubbed in to a surgery to see a new procedure used to treat a dog who would have otherwise been untreatable, and met the cat who was the beneficiary of a clinical trial they supported. Investing in research can have an impressive ROI (return on investment) regardless of the size of the gift. At Oregon State’s College of Veterinary Medicine, we are doing remarkable things. Join us as we seek to change the world in ways yet to be discovered!

*Kelley Marchbanks, Director of Development
College of Veterinary Medicine
Oregon State University*

The Scope

The Future of Veterinary Anatomy



***Radiographic Imaging Application**

***Interactive Online Learning**

***Improving CVM Student's Test Scores**

Canine Thorax



Unpublished Work, ©, 2017, Sarah Nemanic, OSU

Front Limb/Equine

Unpublished Work, ©, 2017, Sarah Nemanic, OSU

The current anatomy curriculum at Oregon State University's College of Veterinary Medicine employs lecture, lab and textbook imaging as the main methods of study. Though still effective, a challenge naturally exists when it comes to examining 3-dimensional tissues and organ structures in a 2-dimensional setting. In association with Open OSU and Technology Across the Curriculum, Dr. Sarah Nemanic, Assistant Professor in the Department of Clinical Sciences, College of Veterinary Medicine and her team have spent the past 3 years developing a radiographic imagery based web application that allows students to view the

canine, feline, and equine anatomical systems from a near 3-dimensional standpoint. The application creates an interactive learning environment, allowing users to directly highlight the differentiated structures in each bodily region (front/hinds limbs, thorax/abdomen and skull/spine) from multiple body planes and angles to create an optimal visual experience. "The difficulty is time. Trying to teach students the disorders of certain structures when they are not fully aware of the anatomy makes is difficult" says Dr. Nemanic. She conducted a recently accepted study testing the effectiveness of student learning before and after using the

app and found that test scores increased approximately 18% for the combined regions which suggests a significant increase in student comprehension. Dr. Nemanic's goal is to have this new method of study implemented not only at Oregon State University, but other universities around the nation alike; allowing students to better understand the curriculum and ultimately improve the knowledge of future Doctors of Veterinary Medicine.

- ❖ *The application is accessible for all users and can be found at: <https://veterinary-radiographic-anatomy.oregonstate.edu/>. Contact Dr. Sarah Nemanic at (541)737-4812, Sarah.nemanic@oregonstate.edu*

The Scope

Inhalation Vaccine for Bovine Tuberculosis



Bovine tuberculosis (BT) is a serious disease of farm animals. Due to its high contagion rate, the USDA policy is to kill infected animals without any attempt of treatment. Epidemiologically, BT is frequently transmitted to farm animals from direct contact with wild life, making the control very challenging. BCG vaccine, a possible prevention strategy, has been shown ineffective. Now, Dr. Luiz Bermudez's laboratory has determined that the surface antigens exposed by *Mycobacterium bovis* upon the lung infection are present in bacteria expelled from infected animals.

By identifying the antigens, Dr. Bermudez's group has developed a potential vaccine to be delivered via inhalation. Studies in laboratory mice have confirmed that airway immunization induced lung specific antibody of the Immunoglobulin A class and was protective against the infection. The group's next endeavor is to test the vaccine in cows.

The Untapped Potential of Marine Probiotics

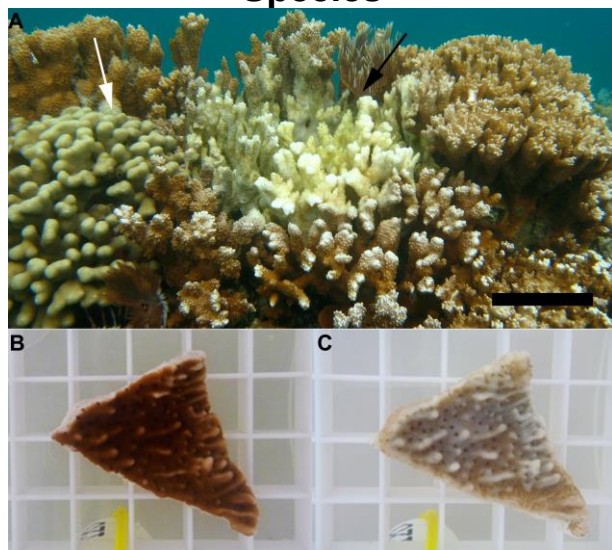


- **Motive-actions of marine probiotics**
- **The race against Methicillin-resistant *S. aureus* (MRSA)**
- **Carla Schubiger seeks to explore the frontier**
- **Oceans may hold the potential to treat antibiotic resistant bacteria**

Oregon State University's Carla Schubiger, a DVM and Ph.D. at The Department of Biomedical Sciences in the College of Veterinary Medicine is focused on discovering how to harness probiotic based antimicrobials, naturally produced by marine-life, for both human and animal pathogens, including MRSA. Her recent findings of a marine *Pseudoalteromonas* sp. has shown "strong inhibiting activity" against pathogens such as *Staphylococcus aureus*, *Salmonella* sp., *Pseudomonas aeruginosa*, *Yersinia pestis* and various *Vibrio* species. Some bacterial species also affect marine ecosystems such as coral reefs who are at risk of infections. If the mechanisms of inhibition can be uncovered, then research can be focused towards a new treatment for MRSA; as well as discovering ways to preserve the oceans valuable ecosystems.

The Scope

***Vibrio* Upregulation Affecting Coral Species**



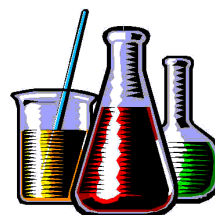
Coral Reef after bleaching

The effects of climate change have become evident once again in a valuable marine species. Coral species provide a nursery environment for thousands of coral reef dwellers, but due to rising sea surface temperatures (SST), their survival is endangered. The well documented coral bleaching epidemic of 2009 caused by the increased SST resulted in the death of nearly one-third of wild coral species, as estimated by some marine-researchers. The increase in temperature and ultimately susceptibility to rising bacterial concentration has also put coral species at risk. *Vibrio coralliilyticus*, an increasingly studied pathogen has been found to have a higher concentration in coral reefs, mainly near tropical climates (due to higher temperatures). *Vibrio* related infection of coral species has only recently been accepted in the mid to late 1970's and therefore minimal data have been published on the issue. Oregon State University's Dr. Blake Ushijima (a post-doctoral researcher in Dr. Claudia Hase' laboratory) may be at the forefront of coral species and *Vibrio coralliilyticus* pathogenesis. As one of the leading researchers in coral-*Vibrio* virulence factors, Blake's goal is to find differentiable genome expressions and mechanisms of pathogenic interaction. By using a transposon technique (insertion of genetic material into the genome) and consequent inactivation of genes, he has identified transcription activators toxR and mannose-sensitive hemagglutinin as key factors in reducing virulence of *Vibrio coralliilyticus* in certain coral.

Continued:

As Dr. Ushijima attempts to further contribute data, he encourages the broadening of study towards this growing issue. His results may help to find novel treatments and ultimately contribute to the protection of the invaluable coral species.

Chemistry to Discover Novel Treatments for Infectious Diseases



Oregon State University's Dr. Deidre Johns is an Assistant Professor of Medicinal Chemistry who is currently aiming to discover new medicines for the treatment of infectious diseases.

Her most recent research projects involve staphylococcus infections including MRSA, leishmaniasis, mycobacterial infections, and biofilm formation. "We are especially interested in using chemistry to discover medicines with new and novel mechanisms of action" says Johns. This research is the study of how chemical structures can be modified to improve their medicinal properties with the use of cutting-edge approaches to design compounds with improved drug-like properties. The medicinal chemistry and drug discovery approaches are based on the chemical structure of proteins to guide the design combined with computational chemistry tools. Inspired by natural products, the molecules from Dr. Johns' and her collaborators' research serve to advance the discovery of novel medicines and also serve as tools to better understand disease biology.

The Scope

Bighorn Sheep and Susceptibility to Infectious Diseases



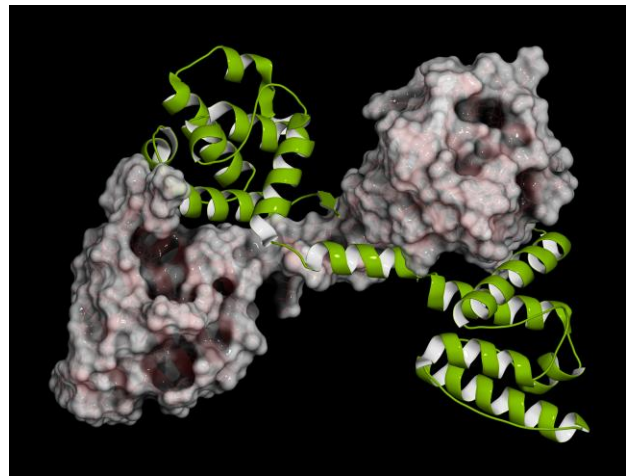
Marked females in the Southern Oregon study area with their lambs. Photo by Rob Spaan, Ph.D. student working on Sheep project.

Bighorn sheep (*Ovis canadensis*) a native of North America, are highly susceptible to ovine pneumonia caused by a bacterial infection that can devastate wild sheep populations, and result in drastic population declines for years following initial invasion. They live in large herds and inhabit a vast range, from the Rocky Mountains to Central America.

Dr. Brian Dolan, Dr. Anna Jolles and Dr. Brianna Beechler at the College of Veterinary Medicine are part of a large multidisciplinary team trying to understand how these charismatic animals respond to infection, and how the disease spreads through populations. They are combining genetic, immunologic, nutrition, microbiome and movement data in populations of bighorn sheep in California, Oregon and Washington to ask what factors can successfully halt disease spread, and which factors may exacerbate infections.

They have found that genetically isolated populations of Bighorn Sheep may have more disease, possibly because of altered immune response. Future work will explore the role of the microbiome and nutrition.

Improving Therapeutics for Duchenne Muscular Dystrophy



Defects cause Duchenne muscular dystrophy (DMD). Cartoon representation combined with semi-transparent molecular surface. Shutterstock:369113942

Duchenne Muscular Dystrophy is a rare disease commonly known for its crippling effects on the muscular system. The disease occurs due to the improper transcription of a dystrophin gene, resulting in the improper development muscle fibers to the surrounding tissue.

A recently published study by Oregon State University's Dr. Hong Moulton, uses a therapeutic treatment called Eteplirsen (Phosphorodiamidate Morpholino Antisense Oligonucleotide or PMO), generalized by the splicing or replacement of the mutated exon with within the dystrophin gene with an alternative exon so that the gene can be more adequately transcribed.

Dr. Moulton and the researchers involved in this study found some clinical efficacy in terms of certain patients' ability to retain muscular function as well as repair damaged cells. The issue is the ability to increase uptake of the PMO; dosage is high and treatment is frequent. In an effort to solve the uptake dilemma, Dr. Moulton continues to research new methods for delivery.

If an optimal delivery method is discovered for Duchenne Muscular Dystrophy, then a potential platform can be set for a multitude of other disease research surrounding PMO's therapeutics.

The Scope

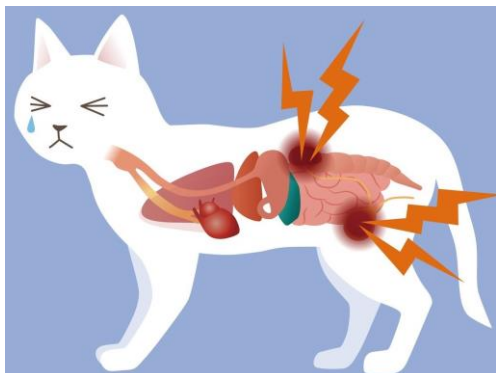
Cats and kidney stones: a new method for diagnosis?



It is known that cats develop kidney stones with high frequency. The problem is that if stones go without being detected they can cause irreparable damage to the kidneys. A more precise way to tell if a cat has kidney stones would mean a major advance in the clinical field with intact in the outcome of the patients.

Dr. Jean Hall and her collaborators at Hill Pet Nutrition and IDEXX laboratories, had just published in PLoS ONE journal their study showing that serum concentration of symmetric dimethylarginine correlates with renal function of cats, and can serve as an early indicator of decreasing health of kidneys.

According to Dr. Hall the use of blood concentration of symmetric demethylarginine as a routine test for mid-to-old age cats would likely facilitate the introduction of treatment and preventive measures before kidney function declines further.



Cat's organ and urologic disease, vector illustration
Shutterstock:412498588

Reversing the HIV Epidemic



HIV in blood vessel with red blood cells. Human immunodeficiency virus, AIDS virus. Shutterstock: 339306944

Since its first reported appearance over three decades ago, the Human Immunodeficiency Virus (HIV) has infected an estimated 75 million people globally, with no sign of slowing. In the United States as of 2014, approximately 87% of the newly infected patients have been diagnosed; unfortunately, only 50% of the diagnosed have been treated for the infection. With the rates of HIV and progressive development of AIDS growing annually, the need for a new method of treatment is essential.

Despite the extraordinary advances in the treatment of HIV infection the global pandemic is still active. Dr. Medlock and his collaborators at Yale School of Public Health developed a mathematic model for 127 countries components of the joint United Nations Program to evaluated the added benefit of a HIV vaccine. The researchers, in an article just published in PNAS estimate that out of the 49 million cases predicted to be diagnosed in the next 20 years the program is expected to avert 25 million cases of new infections and an additional 6.3 million cases reduction would occur if a 50% efficacious vaccine is introduced in 2020. The information would likely stimulate new energy in the field for vaccine discovery.

The Scope

Finding the Tricks of Tuberculosis



Therapy of tuberculosis is prolonged and requires a multitude of antibiotics. In an article to be published in Antimicrobial Agents and Chemotherapy (American Society of Microbiology), Dr. Lia Danelishvili and her co-authors describe how *Mycobacterium tuberculosis* (the bacterium that causes tuberculosis) when treated with effective antibiotics, shifts to metabolic pathways which delay the lethal effects of the drug and allows the bacterium to develop resistance. By discovering the enzymes required for bacterial metabolism once exposed to the antibiotics, the authors were able to show that the inactivation of these enzymes resulted in rapid death of the pathogen. Future identification of compounds that inactivate key enzymes of *M. tuberculosis* may lead to a rapid killing of the pathogen and decreases the chance of developing resistance to therapy.



**Tuberculosis bacillus in the lungs.
Tuberculosis is caused by the bacterium
Mycobacterium tuberculosis.
Shutterstock:393854935**

Intestinal Bugs, Inflammation and Diabetes



Diabetes has always been considered a problem based on increased glucose in the blood. Now, Dr. Natalia Shulzhenko and her team are discovering that bacteria in the intestinal tract can influence inflammation and glucose metabolism. In an article recently published in Nature Communications, the group of researchers from Oregon State University, Duke University, North Carolina University, Brazil and the National Institutes of Health describe that an intestinal bacteria *Akkermansia* is capable of mediating glucose metabolism. The level of bacterium in the intestine is regulated by the Irgm-1 gene, which is under control of interferon-gamma, an inflammatory protein produced by many cells in the body. In the presence of interferon-gamma, the number of *Akkermansia* in the intestine increases, enhancing glucose tolerance. The observation suggests a connection between interferon-gamma, inflammation, *Akkermansia* and glucose tolerance, and may explain why microbiota health can impact the development of diabetes.



Gut Bacteria Shutterstock:400088722

Paws for the News



Feline Injection Site Sarcoma (FISS)

is a rare, but life threatening disease, typically associated with the site of an administered adjuvant vaccine in the feline species. FISS is a subcutaneous mass with a range of projections or lesions known to penetrate multiple layers of tissue. When the site of injection develops a malignancy the sensitivity of the tumors location and its associated projections renders the tumor inoperable in most cases.

Approximately 7-21% of feline neoplasms are diagnosed as FISS, for which the standard treatment involves surgical removal and possible amputation depending on the site and severity of the tumor invasion. Complete removal of the tumor is essential to patient survival due to high sarcoma recurrence rates. It has been reported that incomplete excision of FISS tumors leads to 10 times greater likelihood of site specific reappearance, which consequently has been shown to correlate with decreased survival times (499 vs. 1461 days in cats with and without recurrence). Studies at OSU have provided evidence that as high as 80% of the associated projective lesions seen during MRI scanning, which in many cases renders the patient inoperable, are either benign or associated with the tumor (i.e. inflammation, vessels, etc...). This makes it difficult for pathologists as well as surgeons to accurately differentiate malignancies from benign or other excised tissue. This combined with a varying approximation of one in 1,000-10,000 cases per vaccinations each year in North America alone, FISS has gained traction at Oregon State University.

Dr. Sarah Nemanic in The Department of Clinical Sciences at OSU's College of Veterinary Medicine whose efforts in the fight against Feline Injection Site Sarcoma have focused on post-excision marginalization. After surgical removal, FISS tumors have a tendency shrink in overall size, creating a communicative challenge between radiographers and pathologists in regards to the specific sarcoma sites.

Dr. Nemanic recently conducted a study to characterize FISS shrinkage by determining the average reductions at different stages post-excision. The research created a platform for the development of her recently patented fiduciary marker. When placed over the tumor-body, the marker allows surgeons and pathologists to more accurately marginalize the location of given tumor lesions from center mass. Based on the studied shrinkage percentages, Dr. Nemanic and others can approximate sarcoma lesions at certain time intervals post-excision.

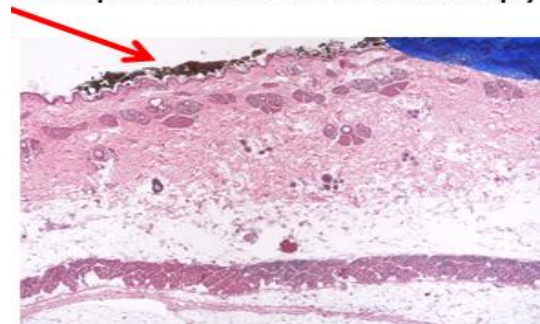
Dr. Christiane Löhr is the leading pathologist collaborating in the FISS study at OSU. Dr. Löhr's focus is on what role micro and messenger RNA plays in the defense against FISS. It is estimated though that only 25% transcripts are translated into proteins. The rest of these 'non-coding' RNA molecules play key roles in certain biological regulations, including the proliferation of cancer cells. Though little is known about the FISS' mechanisms, Dr. Löhr is able to implement a form of advanced transcriptomics, the study of a range of messenger RNA in a given tissue, to identify the type of mRNA's-microRNA's associated with FISS as well as characterizing their mechanisms. Her central hypothesis is that "FISS has cancer-specific epigenetic signatures that are predictive of altered metabolic and cellular function".

Since microRNA's are an advantageous biomarker, using them as a target for novel therapeutics is optimal if their role in FISS can be further understood. Ultimately the goal of both Dr. Löhr and Dr. Nemanic is to contribute to the knowledge of Feline Injection Site Sarcomas; long term facilitating sustainable surgical and therapeutic methods, providing patients with longer and more fulfilled lives.

Unpublished Work, ©, 2017, Sarah Nemanic, OSU



Tissue ink applied to surgical sample visible on microscopy



Paws for the News

Chlamydia trachomatis

When many of us think “Chlamydia”, we commonly think of the sexually transmitted disease. While this is correct, it turns out that the different chlamydia also cause disease in a wide variety of animals, including reptiles, birds, koala bears, bighorn sheep, and many domestic animals. Dr. Dan Rockey is a Professor in the Biomedical Sciences Department who explores chlamydial infections in different animals, including humans.

“While species diversity within the chlamydiae is a challenge to researchers interested in these pathogens, there are many aspects of the infections that are similar. Thus, studying one species of chlamydia often leads to an understanding of all of them. Our laboratory has a strong focus on infections in humans and infections in other important species,” says Dr. Rockey.

Dr. Rockey’s interest in *Chlamydia* originated during his time at the Rocky Mountain Laboratories branch of the National Institutes of Health, located in in Hamilton, MT. After finishing his graduate program at OSU primarily working with diseases of fish, Dan had the opportunity to work with a plethora of sexually transmitted diseases in mammals while in Montana, which is what led him to working with *Chlamydia*. “*Chlamydia*’s ability to develop within cells, and the use of fluorescence microscopy to explore these infections, is what really piqued my interest,” says Rockey.

His 25 years of experience has led him to a new study involving not just sexual transmission, but persistence of different chlamydial species within a host. With antibiotics providing a viable treatment for many infections, the mechanisms of latency by *Chlamydia* is an understudied and perhaps underappreciated strategy used by the pathogen. Rockey intends to change the narrative by contributing viable data to why

these strains are resistant to antibiotics and the pathogenesis of their persistence.

Chlamydia trachomatis is a bacterial species that infects mucosal epithelial cells with the ability to alter its phenotype and function. Long term infections, such as those persistent or untreated, can lead to ocular trachoma, pelvic inflammatory disease and reactive arthritis. The asymptomatic nature of infection makes initial prognosis tough unless patients are carefully tested.

As mentioned above, all chlamydiae not only infect the host but can only grow in the host’s cells. Dr. Rockey described their behavior as “the most virus-like behaviors of any bacterial pathogen.” Prior to infection of the cell, *C. trachomatis* takes the form of an elementary body (EB), whose primary role is attachment and infiltration of the surrounding epithelial tissue.

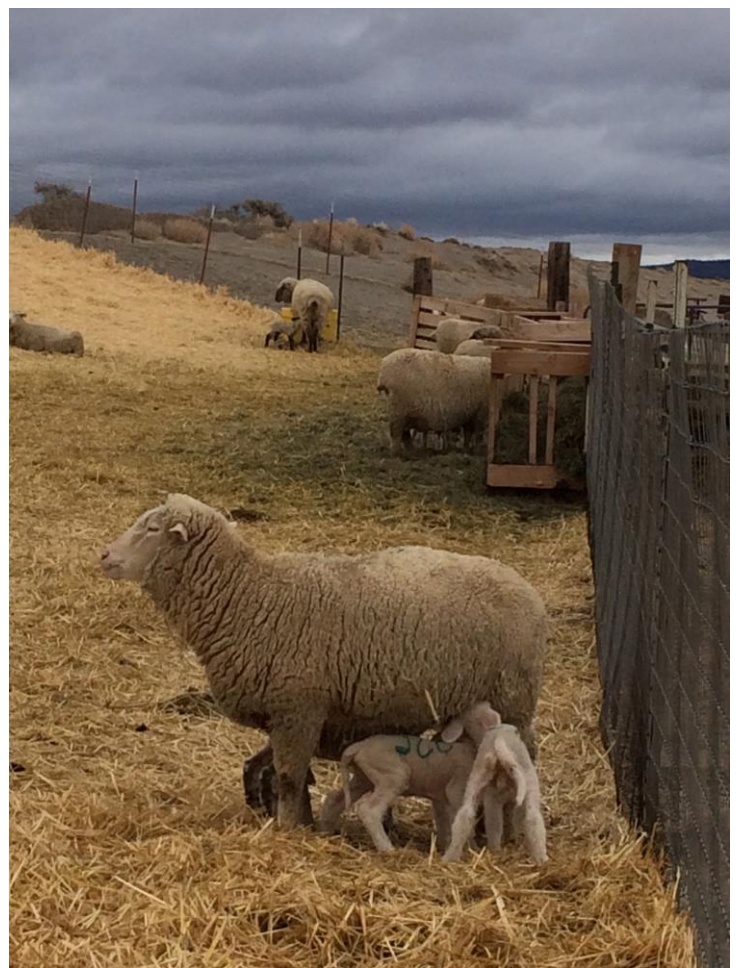
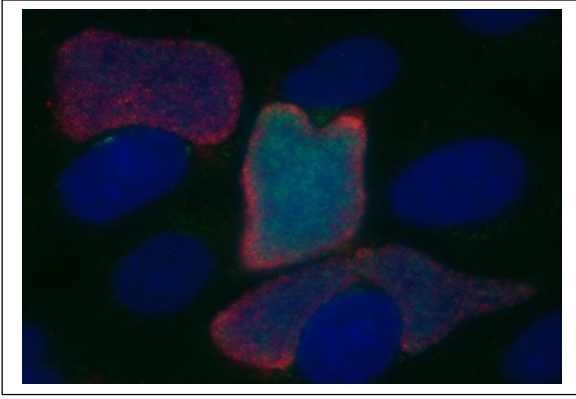


Figure 1. Healthy sheep from a farm in Oregon undergoing an outbreak of chlamydia-induced abortion. While the chlamydia that infect these animals are generally similar to those infecting humans, both its disease and its transmission mechanisms are quite different. The sheep pathogen can infect humans however, and pregnant women should not work with birthing sheep that are suspected to be chlamydia-infected.



After infection of a cell, the *Chlamydia* then transform from an EB to a reticulate body (RB), capable of division within the cell. Though the mechanisms of this transformation are poorly understood, the knowledge of the activity once within the cell has grown over the past decade. After penetrating the cytoplasmic membrane, *Chlamydia* develops within a host-derived vacuole, termed the inclusion, where they proliferate until lysis of the cell occurs. Just prior to escape from the cell, the bacteria resume the form of an EB capable of infecting a new host cell. It is a general hypothesis that the inclusions provide a source of nutrients for the replicating bacteria as well as a protective environment that helps avoid host immunity.

Before studying the mechanisms of latent *Chlamydia*, members of the Rockey laboratory and colleagues worked to provide definitive evidence for *Chlamydia trachomatis* persistence within hosts. “My graduate student Tim Putman and an undergraduate student-turned-technician worked very hard with a colleague at the University of Washington, Bob Suchland, to explore the genomics of *Chlamydia* inside people who appear to be persistently infected,” Says Dr. Rockey. There has been a lasting debate between some clinicians and researchers on validity of latent *Chlamydia*. It is a prominent assumption that the reactivation of the bacteria is entirely due to repeated infections and therefore few studies have provided evidence towards the theory that certain *Chlamydia* can persist after antibiotic treatment. To contribute evidence towards the latter, Dan conducted a study in which he obtained patient samples from the University of Washington Chlamydia Repository. Individuals in the University of Washington School of Medicine

have produced a database containing thousands of *Chlamydia* strains to cross reference with their genotypic variations, which allowed Rockey to verify any relations between mutations in his study. The *Chlamydia* samples were from seven different patients who were sexually active and had high recurrence rates; all receiving treatment over a span of 1-6 years. The Rockey Laboratory generated genome sequences for all of the patient samples to examine variation within strains found in individual patients. He found that even after antibiotic treatment, some of the individuals remained infected with a nearly identical strain that had been found before, indicating persistence, even in the face of regular, effective antibiotic treatment. Dr. Rockey adds, “This is not antibiotic resistance as we typically think about things. These individuals were infected with completely antibiotic-sensitive strains that had somehow survived in the face of what was considered to be effective therapy.” <https://www.ncbi.nlm.nih.gov/pubmed/?term=28368459>

After providing evidence towards latent *Chlamydia*, Professor Rockey's focus has turned towards how latent bacteria persist within the host. Thanks to support from the College and the OSU Agricultural Research Foundation, Dr. Rockey, visiting scholar Rajesh Chahota and student Emaan Khanare working to translate some of these studies to problems in Oregon agriculture, primarily chlamydial infections in sheep. In these infections, *Chlamydia abortus* remains completely hidden until the fetus is well developed and delivery might be just around the corner. *Chlamydia* then attack the sheep's placenta, resulting in the abortion of the fetus. “This is a great example of how our work in human disease will help studying these important veterinary pathogens, and vice versa. Tools developed in the study of human chlamydia persistence are directly applicable to the sheep problem, and these will be used to investigate how the pathogen resides silently in sheep until it arises and leads to abortion.”, says Dr. Rockey. One important note: while the chlamydiae that cause diseases in humans and in sheep are different and cause very different diseases, pregnant women need to completely avoid working with sheep that are at risk of abortion. The sheep chlamydia are very abundant in ovine abortion products, and these can lead to serious disease and human abortion.

By taking samples of the sheep chlamydia at different stages of infection both in the sheep and in the laboratory, Dr. Rocky is able to examine and compare any genotypic differences in the bacteria. The sequencing data provided from the study may provide genotypic evidence as to why the bacteria resist antibiotic treatment and remain silent in the host, prior to expanding in the pregnant ewe and causing abortion. Dr. Rocky hopes an effort to understand latency, both in the human and in the sheep, will lead to effective and novel therapeutic options in both systems.

Paws for the News

Viruses and the Honeybee



The honeybee is an ecologically and economically important pollinator species worldwide. The honeybee provides pollination services to 90 commercial crops worldwide. In the United States alone, honeybee pollination is valued at \$14.6 billion annually. Healthy and strong bee colonies and beekeeping industry are critical for Oregon's agricultural economy. More than 700 of the 4,000 native bee species in North America and Hawaii are believed to be inching toward extinction. Recent annual honeybee colony losses (averaging 30%) are alarming to both beekeepers and growers, who are interdependent for their economic viability. There has been much concern throughout the world over the steep decline in populations of honeybees due to Colony collapse disorder (CCD), a mysterious malady that abruptly wiped out entire hives of honeybees across the United States, exacerbating the already dire situation for honeybees. RNA viruses, alone or in conjunction with other pathogens, have frequently been implicated in colony losses. No single cause has been identified for the sometimes dramatic overwintering losses of honey bees but rather multiple interacting factors, such as pesticides, malnutrition, habitat loss, parasites and pathogens have been suggested as causing chronic sublethal stress.

The brood of the honeybee is susceptible to infection by a wide variety of pathogens, including *Deformed wing virus* (DWV), *Paenibacillus larvae* (*P. Larvae*) and *Varroa destructor* mites, the causative agents of some of the most important diseases affecting bees. Deformed wing virus is a honeybee viral pathogen either persisting as an inapparent infection or resulting in wing deformity. The occurrence of deformity is associated with the transmission of DWV through *Varroa destructor* mites during pupal stages. Such infections with DWV add to the pathology of *V. destructor* and play a major role in colony collapse in

the course of varroosis. The bacterium *P. larvae* is the causative agent of the honeybee disease American foulbrood (AFB). AFB causes significant economic losses to beekeepers, because it is the most harmful pathology of honeybee brood. If untreated, it can lead to the demise of an entire hive. The highly social nature of bees also leads to easy disease spread, between both individuals and colonies. The antibiotics oxytetracycline and tylosin are used both prophylactically and to treat symptoms; however, widespread drug resistance is evident and their registered use is being withdrawn in many countries since residues can show up in honey that is consumed by humans.

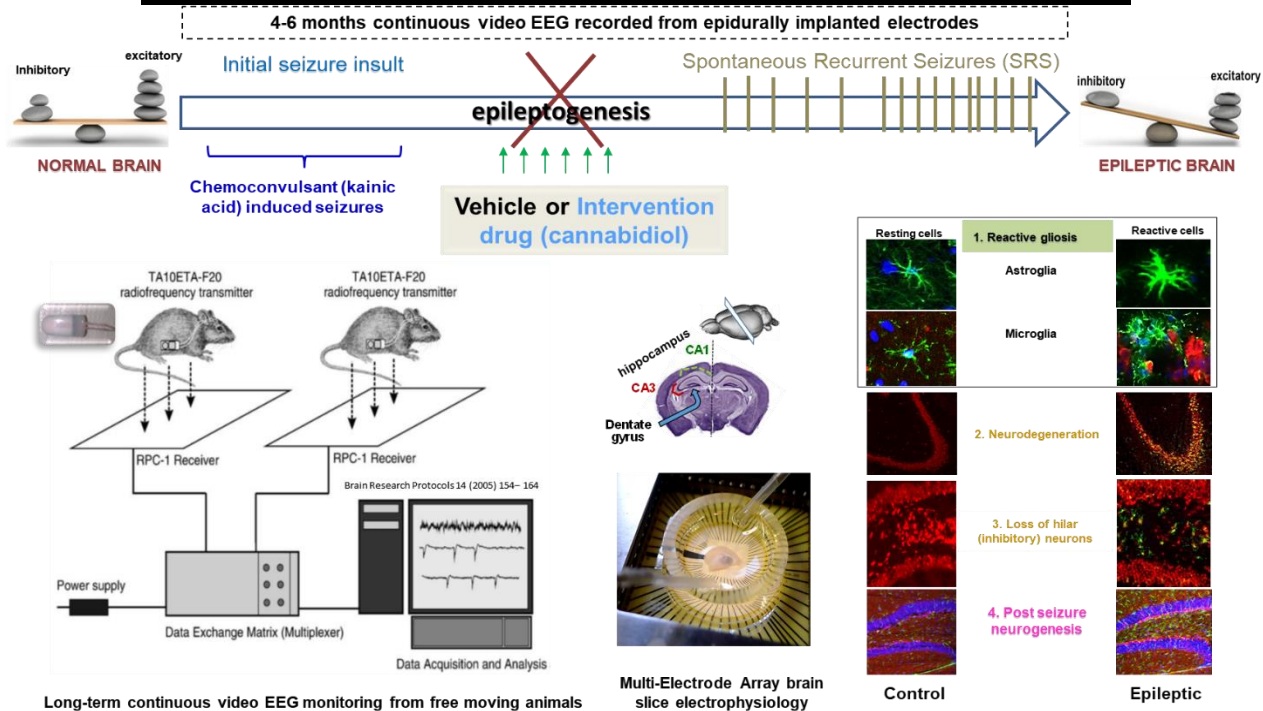
Current diagnostic methods such as culture and conventional PCR are not sensitive and specific and time consuming. There is an urgent need for a rapid, highly sensitive and reliable diagnostic test to detect the above pathogens. Therefore Dr. Pastey's goal in this project is to develop a rapid, selective, with low detection limit, sensitive, specific and quantitative real time probe-based PCR assay to detect DWV and *Paenibacillus larvae*. The knowledge of infectious pathogens in honeybees is of great importance because they can serve as possible reservoirs, resulting in pathogen spillover towards honeybees and native bumblebees. A better understanding of the epidemiology of pathogens is vital to know the dynamics of out-breaks and may shed light on the current crisis of the world's pollinators.

Dr. Pastey also plans to develop methods to monitor the health of honeybee colonies. Honeybees deposit vitellogenin molecules in fat bodies in their abdomen and heads. The fat bodies apparently act as a food storage reservoir. The vitellogenin has additional functionality as it acts as an antioxidant to prolong Queen bee and forager lifespan as well as a hormone that affects future foraging behavior. The health of a honeybee colony is dependent upon the vitellogenin reserves of the nurse bees - the foragers having low levels of vitellogenin. Vitellogenin levels are important during the nest stage and thus influence honeybee worker division of labor.

Dr. Pastey's group envisions that their molecular test strategy to detect DWV, and *P. larvae* would have significant impacts in diagnosis, surveillance and prevention of two of the most important infectious pathogens and also help to monitor the overall health and lifespan of honeybees. Information obtained from this study will enable the Oregon Veterinary Diagnostic lab to serve clients such as stakeholders (growers and beekeepers) and avoid risks to bee colonies that potentially will strengthen the economic sustainability of both beekeepers and producers.

Paws for the News

OSU epilepsy researcher aims to slow down or prevent development of epilepsy using Cannabidiol



Targeting CB1 receptor to inhibit or prevent epileptogenesis

CORVALLIS, Ore.- Exciting anecdotal reports in human patients and a burgeoning research in rodent models of epilepsy reveal a hope that derivatives marijuana may soon provide a therapeutic potential in treating drug resistant epilepsies. One of the least psychoactive compound, Cannabidiol, has been shown to act as an agonist at presynaptic Gi/o protein coupled cannabinoid receptor-1 (CB1 receptor). Activation of CB1 receptors has been shown to reduce vesicular neurotransmitter release by interfering with calcium dynamics and excitability thus, benefiting epileptic patients. However, not enough is known, especially from long-term rodent studies, to draw any conclusion whether CB-1 receptor activation addresses root cause of epilepsy or provides any sustained long-lasting benefits. Sreekanth Puttachary's lab at the Biomedical Sciences Department, OSU campus is focused on investigating the effect of drugs that target the endocannabinoid system (such as Cannabidiol) administered during epileptogenesis to validate their short-term and long-term impact on the disease progression.

We asked few questions to understand epilepsy and how his lab is contributing to the preclinical research using rodent models to achieve a cure for epilepsy.

What is epilepsy? What is its prevalence in US and Worldwide?

Even after a century of research to find a cure, epilepsy still remains a disease that is not well understood. Epilepsy is a chronic neurological disorder characterized by the occurrence of spontaneous recurrent seizures that affects both humans and animals. In simple terms, seizures are just the symptoms/manifestation of a disease referred to as epilepsy. People of all ages, gender, socio-economic background and demography are susceptible to this disease. More than 2.9 million people in the US suffer from epilepsy which accounts for \$15.5 billion in annual medical costs with loss of productivity of patients (cdc.gov). Nearly 50 million people (among them 80% of patients from developing countries) are affected worldwide with 200,000 new cases are being diagnosed each year.

I see many medications available in the market. Why we need research to find new drugs to treat/prevent epilepsy?

Currently there are more than 25 antiepileptic drugs (AEDs) available in the market to provide a symptomatic relief by suppressing the seizures. These drugs have side effects that affect patient's daily performance and also increase a risk of seizure relapse when drugs are discontinued. In addition, these drugs are not safe during pregnancy. Further, 1/3rd of patients worldwide don't even respond to the existing AED medications (referred to as drug resistant epilepsy) and continue to have uncontrolled seizures with no effective treatment options.

All right. What research direction that you are heading?

A major burning question that needs to be answered is, how initial seizure insult to the brain transforms a normal brain into an epileptic brain that continues to produce spontaneous recurrent seizures (SRS). There may be many causes that may result in seizures. For example, head injuries (traumatic brain injury), stroke, brain tumors, central nervous system infections, exposure to toxic chemicals (such as pesticides), prolonged fever (febrile seizures in young children) and so on. What becomes interesting here is, some of the patients who show initial seizure episode later progress into a latent period (epileptogenesis with no overt symptoms) that rewires the brain to produce spontaneous recurrent seizures (referred to as established epilepsy). Once epilepsy is established, it becomes extremely difficult to cure although, we can certainly manage its symptoms by available AED medications. However, AED treatment does not prevent the progression of initial seizure episode towards epilepsy. Hence, there is a critical window of opportunity available during epileptogenesis to explore and develop viable drug targets to slowdown or prevent progression of the disease.

In your quest, what tools do you have to identify and validate drug targets during epileptogenesis to slowdown/prevent epilepsy?

In my previous work at Iowa State University as a Post-Doctoral researcher (Dr. Thippeswamy lab), I have successfully tested intervention drugs using chemoconvulsant mice and rat models of epilepsy. I want to build on this experience to test drugs that target cannabinoid receptors using various research tools (please refer the figure).

- 1) A state-of-the-art long-term continuous video EEG monitoring in rodents- This tool gives us valuable continuous long-term data (4-6months) that reflects the effects of neurobiological changes such as hyperexcitability that occur during epileptogenesis that later leads to spontaneous seizure episodes. We can also test whether our intervention drug (such as cannabidiol) when given soon after initial seizure episode provide any sustained benefits in preventing hyperexcitability and later, the spontaneous recurrent seizures.
- 2) We can use fresh brain slices from control and intervention drug treated rodents collected at various end-points to test the effects on hyperexcitability using Multi-Electrode Array brain-slice electrophysiology.
- 3) Common molecular biology tools such as immunofluorescence, immune blotting and RT-PCR can further assess neurobiological changes, protein and mRNA expression in the brain tissue samples to further validate the short-term and long-term impact of an intervention drugs.

What is your long-term goal?

My long-term plans will be to develop a dedicated EEG facility at Oregon State University to serve nationally and globally to provide expertise in identification, testing and validation of intervention drugs to prevent/cure epilepsy.

CVM CUTTING EDGE NEWS

Clinical trials bring new forms of therapy to treat tumors

Clinical trials with the OSU Oncology Service are gaining regional and national attention. Well-designed clinical research in dog and cat patients has the opportunity to benefit both veterinary and human oncology by enabling the practice of evidence-based medicine and improving patient outcomes. The goal of the Oncology Service at OSU is to offer clinical trials as an additional treatment option when a pet is diagnosed with cancer.

OSU is now an active member of the National Cancer Institute Comparative Oncology Trials Consortium (COTC). The COTC is an active network of academic comparative oncology centers that functions to design and implement clinical trials in dogs with cancer. We currently have two clinical trials available through the COTC for patients with osteosarcoma, and an additional trial will likely open this summer.

Dr. Curran says that currently, we have a total of 6 clinical trials that are actively enrolling patients and one clinical trial that has closed enrollment. The trials are enrolling canine patients with a range of tumor types including osteosarcoma, lymphoma, histiocytic sarcoma, transitional cell carcinoma, and other carcinomas. Approximately 30% of the OSU Oncology case load consists of clinical trial patients.



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