Project Title: Development of a vaccine against human immunodeficiency virus (HIV-1).

Principal Investigator(s): Michael Cho

Collaborating Investigator(s):

Veterinary Scholar Focused Abstract: (300 words or less):

Since the start of the pandemic nearly four decades ago, AIDS has claimed 35 million lives. About 1.8 million people have been newly infected just in 2017, and nearly 37 million are currently living with AIDS. To date, there is neither a vaccine nor a cure. A vaccine is urgently needed against HIV-1, the virus that causes AIDS. Although neutralizing antibodies (nAbs) can provide effective prophylaxis against the virus, eliciting those that are broadly reactive against many antigenically diverse HIV-1 isolates has been a major scientific challenge and it remains a critical roadblock for the AIDS vaccine development. In my laboratory, we use multidisciplinary approaches to generate immunogens, characterize their biochemical, antigenic and immunogenic properties, and evaluate their ability to induce broadly neutralizing antibodies (bnAbs). We are currently evaluating a number of novel immunogens based on HIV-1 glycoproteins gp120 and gp41 and testing a few vaccine strategies in rabbits and mice. Through participating in these research projects, students will gain better understanding of virology molecular biology, protein biochemistry, vaccinology and immunology. Although HIV-1 is not a veterinary pathogen, students can apply the learned knowledge to develop vaccines against many veterinary pathogens.
Project Title: Development of a universal influenza virus vaccine.

Principal Investigator(s): Michael Cho

Collaborating Investigator(s):

Veterinary Scholar Focused Abstract: (300 words or less):

Influenza virus is a major public health concern as it causes significant morbidity and mortality worldwide. The U.S. CDC estimates that the virus infected 9.2-35.6 million people, of which 140,000-710,000 required hospitalizations and 12,000-56,000 died annually since 2010. The total economic burden related to influenza infections in humans is estimated at more than $86 billion per year. Influenza virus can also cause of acute, severe respiratory diseases in many animal species, such as swine, horses, cattle, dogs, cats, sea lions, bats and poultry. Currently, influenza vaccines are produced annually, based on circulating virus strains predicted to be most prevalent during the following flu season. The overall protection of current vaccines is conferred by antibody responses against the globular head domain of HA (HA1), which is highly variable. Thus, the efficacy of the vaccines is quite low (41% ± 15%, ranging between 10% to 60%). Besides the low efficacy, there are significant drawbacks and limitations with the current vaccine approach, including having to produce and immunize every year, slow production process, and inability to provide protection against new pandemic strains. Thus, a universal influenza vaccine that is administered only two or three times and provides a long-term protection against all or most influenza strains is highly desirable. We recently generated a novel immunogen that provides hetero-group protection in mice. We are currently working on generating a second-generation immunogen to improve protective efficacy. We plan to evaluate in mice as well as in pigs. Through participating in these research projects, students will gain better understanding of virology molecular biology, protein biochemistry, vaccinology and immunology. Students can apply the learned knowledge to develop vaccines against many veterinary pathogens.
Project Title: Diagnostic evaluation of Misfolded proteins in Animal and Human Brain Neurodegenerative Diseases

Principle Investigator(s): Dr. Anumantha Kanthasamy

Collaborating Investigator(s):

Veterinary Scholar Focused Abstract: (300 words or less):

Protein misfolding is a key pathophysiological process of many neurodegenerative diseases including prion disease, Alzheimer’s disease, and Parkinson’s disease but the diagnosis of these disorders remains to be developed. We have developed a new sensitive method to specifically detect misfolded toxic using a recombinant protein-based amplification technique that can be readily applied to various neurodegenerative diseases affecting both human and animals. We intend to further expand the new assay platform by determining whether the extracellular vesicles present in biofluids can be used as a diagnostic markers of neurodegenerative diseases including prion diseases. Thus the specific objective of this project is to characterize and evaluate the diagnostic efficiency of these extracellular vesicles in the diagnosis of prion diseases as well as human protein misfolded diseases. Biofluid samples from a wide host species form captive and wildlife as well as humans will be used in this project. Some of the skills a student will learn to pursue this project include, cell culture, recombinant protein extraction and purification, protein analysis, advanced plate reader assays, qRT-PCR and Western blot. The students will be trained in data analysis and manuscript preparation.
Veterinary Scholar Focused Abstract: (300 words or less):
Collagens are the major component of connective tissues. Mutations in collagen genes cause various types of connective tissue disorders such as osteogenesis imperfecta (OI), chondrodysplasias, and Ehlers-Danlos syndrome. Studies on OI have revealed the proteins that play a critical role in synthesis, folding, processing, post-translational modification, and secretion of type I collagen, which demonstrates fundamental importance of every stage of the life cycle of collagens in bone formation. Despite the progress, new genes are still being found in disorders having significant clinical overlap with OI. These new genes are also implicated in the life cycle of collagen, exemplifying our incomplete understanding on the life cycle of collagens. There is, therefore, a critical need to identify additional molecules that affect a stage of the collagen life cycle. Without such understanding, treatment strategies will be limited for OI and related diseases. Our preliminary data suggest that CRL3s, E3 ubiquitin ligases, regulate COL1A1 synthesis in a complex way. A BTB-domain protein serves as a substrate-specific adaptor of a CRL3. There are 204 genes encoding a BTB-domain in the mammalian genome. The overall objective of this project is to identify different mechanisms by which CRL3s regulates collagen synthesis. Our overarching hypothesis is that multiple BTB-domain proteins govern COL1A1 synthesis in different ways. The rationale that underlies the proposed project is that once we achieve the goal we will be able to provide new regulatory strategies for COL1A1 synthesis.
Project Title: Bovine Mucosal-Associated Invariant T (MAIT) cells and their role in health and disease

Principal Investigator(s): Jodi McGill

Collaborating Investigator(s):

Veterinary Scholar Focused Abstract: (300 words or less):

Mucosal-Associated Invariant T cells (MAIT) cells are a population of innate-like T cells that circulate in the peripheral blood and reside in mucosal sites such as the lung and gastrointestinal tracts. MAIT cells respond to bacteria-derived metabolites and host-derived damage associated molecular patterns (DAMPS). They have been described to respond to several bacterial infections in mice and humans, including *Klebsiella*, *Salmonella* and *Mycobacterium* infection. Some reports also suggest they respond during viral infections, although their role is less clear in this context. To date, there is only a single description of MAIT cells in cattle and there is no information regarding their role in the immune system. Our preliminary data suggest that MAIT cells circulate at relatively high frequency in the blood of both calves and adult cattle, and that they expand during respiratory infection. We hypothesize that bovine MAIT cells are recruited to the lungs during respiratory infection, and that they play a role in the immune response to both viral and bacterial infections in the lung. The objectives of our proposed project include: 1) defining the phenotype of bovine MAIT cells in the blood and lung; 2) defining antigen-specific and antigen-nonspecific responses of bovine MAIT cells; 3) determining the response of bovine MAIT cells to a respiratory viral infection. The proposed project will rely primarily on samples which have been cryopreserved from previous animal studies, but may require collection of fresh peripheral blood samples from adult cows housed at the ISU Dairy. Innate-like T cells have been shown to play a critical role in shaping the adaptive immune response in other species. The results of our proposed studies will be novel and are expected to contribute significantly to our understanding of mucosal immunity in agricultural species.
Project Title: Use of a gnotobiotic mouse community to understand host/microbiome interactions

Principle Investigator(s): Gregory Phillips, Ph.D.

Collaborating Investigator(s): Michael J. Wannemuehler, Ph.D.

Veterinary Scholar Focused Abstract: (300 words or less): Recent experimental evidence reveals that the bacterial communities (microbiota) that comprise the mammalian gastrointestinal (GI) tract can have a profound influence on the health of the host. Diseases ranging from colorectal cancer to inflammatory bowel diseases (IBD) have been linked to an abnormal microbiota (dysbiosis) in humans and animal models. Despite the importance of bacteria to the wellbeing of humans and animals alike, how the microbiota influences health and disease is the subject of current research efforts. To better understand how specific bacteria interact with the host, we are using a unique gnotobiotic mouse community, the Altered Schaedler Flora (ASF), which is comprised of animals colonized with only 8 known bacterial species. Despite the low complexity of the microbiota, ASF mouse exhibit normal immune system development and growth. Use of this resource includes monitoring the changes in relative number, spatial distribution and gene expression in response to alterations in diet and following infection with bacterial pathogens. Independent student projects include, but are not limited to, use of quantitative PCR to measure changes in the abundance of individual ASF community members in response to infection with bacterial pathogens, as well as identifying genetic changes in the ASF that occur in response to perturbations to the GI tract. The ASF model also offers the potential to study new results that indicate that the composition of the GI microbiota may actually influence animal behavior. The overall impact of these studies will lead to a better understanding of how the GI microbiota influences human and animal health and disease.
Project Title: The Role of Avian Thrombocytes in Innate and Adaptive Immunity and the Enhancing Potential of Beta Glucans

Principal Investigator(s): Jay Reddy, MVSc., PhD

Collaborating Investigator(s): Donald Reynolds, DVM., PhD

Veterinary Scholar Focused Abstract: (300 words or less):

An increasing trend in modern poultry production is to raise birds with no antibiotics. The new movement to decrease the use of antimicrobials has increased the focus on more efficient, efficacious and targeted methods of enhancing the bird’s immune system. An important component of the bird’s immune system is the often unnoticed innate immune response. Innate immunity is characteristically nonspecific, rapid and the very first line of immune defense. A cell type that has until recently been overlooked but has been increasingly recognized for its role in innate and adaptive immunity is the avian thrombocyte. Beta-glucans (β- 1,3 / 1,6 glucans) are derived from extracts of the cell walls of plant and yeast cells. Glucans have been used for various health promoting effects in humans and other animals. When glucans are consumed orally they have been shown to have immune enhancing effects primarily on the innate immune system. The overall goal of this project is to improve the bird’s ability to protect itself from infectious diseases through modulation and/or conditioning of the bird’s immune system. To this end, we have chosen to focus on the much overlooked avian thrombocyte and determine its contribution to the immune response. We hypothesize that a never before recognized way in which beta glucans enhances the bird’s immune response is through thrombocytes. We propose to prove this hypothesis by using avian thrombocytes from chickens. This work will be beneficial to the growing poultry industry in Nebraska and to other animal species including humans.
Project Title: Investigating the glial source of nitric oxide as a target for mitigating the long-term effects of organophosphate-induced neurotoxicity

Principle Investigator(s): Thimmasettappa (Swamy) Thippeswamy

Collaborating Investigator(s): None

Veterinary Scholar Focused Abstract: (300 words or less):

Organophosphate (OP) pesticides are seizurogenic neurotoxins to humans and animals. Acute OP intoxication, in the long-term, will cause irreversible brain damage due to hyperexcitability of neurons, reactive gliosis, and neurodegeneration. If these are not adequately controlled at a very early stage, they will lead to the development of epilepsy, cognitive dysfunction, and other neurological deficits. Currently there is no treatment for the long-term neurotoxic effects of OP. The symptomatic drugs atropine, oxime, and diazepam (DZP) are inadequate to prevent OP-induced long-term brain injury. DZP controls seizures, but not neuropathology. We have found that OP-induced seizures cause reactive gliosis and increase the levels of reactive oxygen/nitrogen species (ROS/RNS) in the hippocampus. We have also discovered inducible nitric oxide synthase (iNOS) as a major source of RNS production in glial cells in the rats that were exposed to neurotoxins. Incidentally, our studies in the rat suggested that 1400W, a potent and highly selective iNOS inhibitor, is blood-brain barrier permeable and ameliorates long term neuropathology in the rat kainate model of epilepsy (PMID: 27208748). Therefore, our overarching hypothesis is that 1400W, if given soon after the symptomatic drugs, will prevent OP-induced long-term brain pathology. To test the hypothesis, we will use our established diisopropylfluorophosphate (OP agent) rat model to replicate a real life scenario of OP poisoning. In the proposed study, Veterinary Scholar will perform cognitive (the Morris water maze) and motor function tests, video-EEG analyses for seizures, and utilize various histological and biochemical assays from serum and brain samples to investigate the pathogenesis of OP-induced brain toxicity, and the long-term neuroprotective effects of 1400W in OP poisoning.
Project Title: Structural based design of a multivalent vaccine immunogen against bovine respiratory disease

Principal Investigator(s): Dr. Shi-Hua Xiang

Collaborating Investigator(s):

Veterinary Scholar Focused Abstract: (300 words or less):

Bovine respiratory disease (BRD) is the leading cause of death in the US cattle, and is estimated to result in over $1 billion loss yearly. Although the tremendous efforts have been made in understanding and treating this disease during the past thirty years, we are still not able to control or cure this disease. BRD is caused by various pathogens which include viruses such as bovine viral diarrhea virus (BVDV), bovine respiratory syncytial Virus (BRSV), parainfluenza 3 (PI3) and bacteria such as *Mannheimia haemolytica*. It is obvious that developing a multivalent based vaccine would be more effective since it can be able to combat various pathogens at the same time. This project is to design a multivalent vaccine immunogen to induce various immune responses against different pathogens that caused BRD. We will utilize bioinformatics approaches to search for conserved epitopes from different antigens and then utilize protein structural based approaches to combine these epitopes into an epitope focused multivalent immunogen. The designed multivalent immunogen will be immunized mice and the antisera can be analyzed for immunogenicity evaluation, such as antibody titers and pathogen neutralization capabilities. If this designed multivalent vaccine immunogen is promising from the immunogenicity test in mice, further study is to conduct a directly vaccination test in cattle for the protection efficacy.