INTERACT
INSTITUTE FOR TRANSLATIONAL AND EMERGING RESEARCH IN ADVANCED COMPARATIVE THERAPY

ADVANCING ONE HEALTH

INTERACT RESEARCH SYMPOSIUM
TUESDAY, OCTOBER 12
McKNIGHT CENTER FOR THE PERFORMING ARTS
One-health and one-medicine can transform the landscape of global medicine

Colleagues and Guests,

Now more than ever, the research we do at Oklahoma State University is making a difference in the world. This public impact is at the core of our modern land grant mission, and your work that advances one health — both human and veterinary medicine — is vital to solving society’s most pressing needs.

As part of today’s symposium, Oklahoma State University is proud to host Nobel Laureate, Dr. Bruce Beutler. We are fortunate to learn of his scientific discoveries that have reshaped our understanding of critical immunological pathways.

The diverse symposium presentations and the abstracts in this compendium showcase this work. By bringing together a wide range of disciplines from across the university to foster team science, INTERACT is truly a model for other universities to follow and exemplifies collaboration among some of our brightest research stars.

I commend all of you in your pursuit of new therapeutic and diagnostic products. Congratulations to our accomplished faculty and students for presenting such meaningful and impactful research today.

Thank you.

Dr. Kayse Shrum
President, Oklahoma State University
Greetings,

Thank you for attending the inaugural INTERACT Research Symposium. The College of Veterinary Medicine (CVM) has an established and nationally renowned program of animal health and comparative biomedical research. The idea for INTERACT came from our long successful history in conducting novel research and clinical trials that are focused on developing and discovering new therapeutic approaches and diagnostic modalities for the treatment of a variety of diseases in large and small animals. Through INTERACT, the college is focusing on creating a university-wide network of investigators from various colleges to develop a platform that supports interdisciplinary and translational research in a collaborative team-based approach. This approach of merging basic and clinical sciences not only augments the research capacities but also helps develop specific expertise focused on one-health-related disciplines. I am glad to see a wide range of speakers for this symposium in line with those expectations. CVM will continue to work with other colleges to strengthen the INTERACT program. I look forward to more such meetings and new collaborative research programs in the coming years.

Again, thank you to all the faculty, staff and students for their dedication to conducting cutting-edge research that results in new technologies to improve the wellbeing and health for Oklahomans and throughout the world.

Sincerely,

Carlos Risco, DVM, DACT
Dean and Professor
Greetings,

The Institute for Translational and Emerging Research in Advanced Comparative Therapy (INTERACT) is a university-wide initiative led by the College of Veterinary Medicine. Human and veterinary medicine converge on a variety of chronic diseases, and there is a significant commonality in the therapeutic and diagnostic approaches employed to target those indications. INTERACT aims for a one-health and one-medicine approach that hopefully will increase the translational pace of diagnostic and therapeutic modalities for patient use. I am honored to direct INTERACT in its formative years. Since its establishment, INTERACT has focused on recruiting a wide range of disciplines on its platform. We periodically organize networking events that act as a perfect breeding ground for strengthening the OSU bench-to-clinic research mission.

The INTERACT Research Symposium reflects the cutting-edge research being performed by our researchers. As you will find, existing research capacities of OSU can play an instrumental role in advancing fundamental and translational medicine. Our symposium also features a keynote talk from Nobel Laureate, Dr. Bruce Beutler. It is an honor for INTERACT and OSU to host him, and we are very fortunate to hear him. Surely, he will motivate and inspire our researchers to do next generation science.

I look forward to continued interactions among INTERACT members and to developing interdisciplinary programs supporting our mission.

Best Wishes,

Ashish Ranjan, BVSc, Ph.D.
Professor, Kerr Endowed Chair
Director, INTERACT
College of Veterinary Medicine
Nobel Laureate Bruce Beutler: A transformative figure in the field of Innate Immunity

Bruce Beutler, MD is Regental Professor; Raymond and Ellen Willie Distinguished Chair in Cancer Research at the University of Texas Southwestern Medical Center in Dallas, Texas. He also serves as the director of the Center for the Genetics of Host Defense. Dr. Beutler received his undergraduate degree from the University of California at San Diego, and his MD degree from the University of Chicago. After his residency and postdoctoral fellowship, he started as an Assistant Professor at the Rockefeller University (1983-1986). In this role, he isolated mouse tumor necrosis factor (TNF) and was the first to recognize its role in inflammatory response. Later at UTSW, he leveraged recombinant inhibitors of TNF to enhance treatments of rheumatoid arthritis and other inflammatory diseases. His pioneering contributions on using TNF to identify the receptor for bacterial lipopolysaccharide (LPS) has played a crucial role in signatures of infection, especially those involving Toll-like receptors. In addition to the Nobel Prize, he has also been awarded the Shaw Prize (2011), the Albany Medical Center Prize in Medicine and Biomedical Research (2009), election to the National Academy of Sciences and Institute of Medicine (2008), the Frederik B. Bang Award (2008), the Balzan Prize (2007), the Gran Prix Charles-Leopold-Mayer (2006), the William B. Coley Award (2005), the Robert-Koch-Prize (2004), and other honors.

Keynote Seminar Timing: 11.00 am – noon

Watch the INTERACT Research Symposium live at https://ostate.tv/playlist/0_ccwxiq0r.
INTERACT RESEARCH SYMPOSIUM
COMMITTEE MEMBERS

College of Veterinary Medicine
Giovanna Paloma, Drs. Joao Brandao, Clinton Jones, Todd Holbrook, Véronique Lacombe, Jerry Malayer, Fabio Pinaffi, Joshua Butcher and Jennifer Rudd

College of Arts and Sciences
Tyrrell Conway

College of Engineering, Architecture and Technology
Josh Ramsey

School of Biomedical Sciences at OSU Center for Health Sciences
Dolores Vazquez-Sanroman

Symposium Moderators
Rosslyn Biggs, Dolores Vazquez-Sanroman, Erik Clary, Véronique Lacombe
Watch the INTERACT Research Symposium live at https://ostate.tv/playlist/0_ccwxiq0r.


Follow us on Twitter at https://twitter.com/OKStateVetMed.

Or visit the INTERACT webpage at https://vetmed.okstate.edu/interact/.

Closing Ceremony/Awards/Drinks
West Lobby, McKnight Center at 4pm
### INTERACT SYMPOSIUM AGENDA
October 12, 2021, OSU McKnight Center, Stillwater

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<td>Dr. Rudra Channappanavar, College of Veterinary Medicine</td>
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<td>Dr. Josh Butcher, College of Veterinary Medicine</td>
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<td>1:47 – 2:00</td>
<td>Dr. Kelly S. Harrison, College of Veterinary Medicine*</td>
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<td>Dr. Jimmie Weaver, College of Arts and Sciences</td>
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<td>Alejandro Torres, Center for Health Sciences*</td>
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<td>Dr. Sai Narayanan, College of Veterinary Medicine*</td>
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<td>Dr. Kaushalya Jayathilake, College of Veterinary Medicine*</td>
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*Graduate/postdoc Awards category
A Multilayer Network-Enabled Ultrasonic Image Series Analysis Approach for Online Cancer Drug Delivery Monitoring

Yuxuan Li¹, Joshua VanOsdol², Ashish Ranjan², Chenang Liu*¹
¹The School of Industrial Engineering & Management, Oklahoma State University
²College of Veterinary Medicine, Oklahoma State University

Presenter’s email: yuxuan.li@okstate.edu

ABSTRACT

The objective of this study is to develop an effective data-driven methodology for the online monitoring of cancer drug delivery guided by the ultrasonic images. To achieve this goal, effective image quantification and accurate feature extraction play a critical role on image-guided drug delivery (IGDD) monitoring. However, the existing image-guided approaches in such area are mainly focused on the analysis for individual images rather than the image series. In fact, the temporal patterns between consecutive images may contain critical information and it is necessary to be considered in the monitoring analysis. In addition, the conventional approaches, such as the pure intensity-based method, also do not sufficiently consider the effects of noise in the ultrasonic images, which also limits the monitoring sensitivity and accuracy.

To address these gaps, this paper proposed a novel multilayer network-enabled IGDD (MNE-IGDD) monitoring approach to analyze the ultrasonic image series. Through a proposed multilayer network community detection-based image feature extraction approach, the progress of drug delivery after cancer drug treatment can be accurately monitored. To validate the effectiveness of the proposed method, a simulation study was conducted and this method was also applied to a real-world mouse colon tumor treatment case study under three temperature conditions. Both simulation and the real-world case study demonstrated that the proposed method is promising to achieve satisfactory monitoring performance in clinical trials.
Developing the Next-Generation Elastic Whole-Lung Model using Computational Fluid Particle Dynamics

Yu Feng
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ABSTRACT
Nowadays, “personalized medicine” is starting to replace the current “one size fits all” approach. The goal is to have the right drug with the correct dose for the right patient at the right time and location. An example of personalized pulmonary healthcare planning is the targeted pulmonary drug delivery methodology. However, traditional in vitro and in vivo studies are limited and not sufficient for the personalized treatment plan development purpose. Specifically, due to the invasive nature and imaging limitations, most animal studies and clinical tests lack operational flexibility and cannot provide high-resolution patient-specific data. Therefore, alternative methods should be developed to conquer these bottlenecks. Models based on the computational fluid-particle dynamics (CFPD) method play a critical role in exploring alternate study designs and provide high-resolution data in a noninvasive, cost-effective, and time-saving manner. The in silico methodologies can fill the knowledge gap due to the deficiency of the traditional in vitro and in vivo methods, as well as make breakthroughs to pave the way to establish a reliable and efficient numerical investigation framework for pulmonary healthcare on a patient-specific level. CFPD models can provide high-resolution local dosimetry of inhaled aerosols to address the public health concern, i.e., “What type of inhaled aerosol deposits where at what surface concentrations in the patient-specific respiratory system under what operational conditions?” In this presentation, the speaker will discuss the research progress and challenges on creating the individualized digital twin for in silico pulmonary healthcare planning, with details on using computational fluid-particle dynamics to simulate inhaled aerosol transport, deposition, and translocation in human respiratory systems. The presentation will cover: (1) the development of the unique elastic whole-lung model that can recover the disease-specific airway deformation kinematics simultaneously with tracking pulmonary air-particle flow dynamics from mouth/nose to alveoli; (2) inter-species scale-up method from rat to human respiratory systems, (3) applications of such virtual whole-lung models on targeted drug delivery, occupational exposure assessment, and noninvasive diagnosis of airway obstruction locations.
Interactive Effects of Diisopropylfluorophosphate and Atropine on Cholinergic Signs of Toxicity, Forced Swim Behavior and Monoamine Signaling in Rats

Landon Butler Pierce, Dr. Carey Pope
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BACKGROUND
Acute exposure to diisopropylfluorophosphate (DFP) leads to cholinergic toxicity and long-term increases in immobility in the forced swim test (FST).

METHODS
As the FST is used to model depressive-like behavior in drug development (e.g., monoamine uptake inhibitors), the effects of acute DFP on serotonin and dopamine signaling were evaluated. The anticholinergic antidote atropine (16 mg/kg, sc) was given shortly after DFP in subsets.

RESULTS
Atropine transiently decreased early functional toxicity (1 hr) but not later (4-120 hr). Immobility increased at 1 and 4 mo after DFP, but atropine had no significant influence. At 4 hr, neither dopamine (DA) nor serotonin (5HT) levels were affected by DFP, but their turnover was increased. DFP-induced changes in DA turnover were reversed, but increased 5HT turnover was unaffected by atropine. At 4 mo, DA levels were similar in control and DFP-treated rats, but lower in animals post-treated with atropine. While DA turnover was similar between control and DFP treatment groups, rats post-treated with atropine showed an increase in DA turnover. 5HT levels were unaffected by DFP but were significantly reduced in rats post-treated with atropine. 5HT turnover was markedly higher in DFP-treated rats post-exposed to atropine.

CONCLUSIONS
We interpret these findings to indicate that DFP induces acute toxicity and long-term neurobehavioral changes related to stress coping. Atropine provides transient protection from acute toxicity but has little influence on persistent behavioral changes. In contrast, atropine markedly increased DA and 5HT turnover months after the acute intoxication. These results may suggest strategies for further non-cholinergic countermeasure development.
Targeting Neuroinflammation with Novel Anti-inflammatory Agents

Randall L. Davis, PhD
Oklahoma State University, Center for Health Sciences
Presenter’s email randall.davis@okstate.edu

ABSTRACT
My laboratory has a long-standing interest in neuroinflammation, and its role in CNS disorders such as Parkinson’s disease, HIV-dementia and mood/behavior disorders. We are particularly interested in inflammatory signaling in astrocytes and microglia and modulation of these signaling events by novel pharmacologic agents. We discovered that β-funaltrexamine (β-FNA), a selective, mu-opioid receptor (MOR) antagonist, has anti-inflammatory actions in vitro and in vivo. However, these anti-inflammatory actions are not related to classically defined actions through MOR. We have obtained key insights into the effects of β-FNA on inflammatory signaling in human astrocytes and established fundamental evidence that β-FNA also inhibits neuroinflammation and sickness behavior in mice. Our overall goal is to further define the anti-inflammatory effects of β-FNA and open a new line of inquiry into the potential of β-FNA (or modified forms of this compound) as an inhibitor of neuroinflammation to be included in combination drug treatment of neurological conditions, including mood and anxiety disorders. A more recent line of investigation in my lab involves a collaborative effort with my departmental colleague, Dr. Hugo Arias. This project is expected to advance positive allosteric modulators (PAMs) of α7 nicotinic acetylcholine receptors as non-opioid agents in the treatment of chronic pain.
Recombinase deficiency in P. aeruginosa sensitizes cells to antibiotics and stimulates interbacterial killing

Nina Baggett¹, Adam Bronson, Matthew Cabeen
¹College of Arts and Sciences, Oklahoma State University
Presenter’s email matthew.cabeen@okstate.edu

BACKGROUND
Pseudomonas aeruginosa is an important and treatment-resistant human pathogen that conducts interbacterial warfare using phage tail-like killing complexes termed pyocins. Pyocin production is stimulated by DNA damage, and pyocin release requires lysis of producer cells via pyocin-associated lysis enzymes.

METHODS
We found that deficiency of a tyrosine recombinase, XerC, strongly upregulates pyocin production via a novel pathway that is separate from the DNA damage-induced pathway.

RESULTS
XerC-deficient cells are more sensitive to clinical fluoroquinolone antibiotics, which further stimulate pyocin production. At the individual-cell level, pyocin upregulation manifests as a greater proportion of cells turning pyocin production on and then explosively lysing. Surprisingly, inactivation of the pyocin-associated lysis enzymes blocks explosive lysis but not producer cell death. Released pyocins can effectively kill other P. aeruginosa strains.

CONCLUSIONS
Our results imply that chemically targeting XerC can increase the antibiotic sensitivity of P. aeruginosa while simultaneously inducing it to kill other nearby bacteria.
Humanimal Trust

Roberto La Ragione
Professor of Veterinary Microbiology and Pathology in the School of Veterinary Medicine and Head of the School of Biosciences and Medicine, University of Surrey
Presenter’s email r.laragione@surrey.ac.uk

BACKGROUND
Humanimal Trust drives collaboration between veterinarians, doctors, and researchers so that all humans and animals benefit from sustainable and equal medical progress, but not at the expense of an animal’s life. This is One Medicine.

As a charity, we are unique leaders and drivers of this vision in research and clinical environments.

The pursuit of One Medicine is not the sole preserve of professionals; we can all influence those with the responsibility of achieving change. Inclusivity and accessibility are crucial to progress.

In this presentation, Professor La Ragione, Chair of the Trustees Board of Humanimal Trust will describe how their ongoing work contributes to bringing together multiple disciplines on one platform to further one-medicine goals.
Therapeutic Applications of Extracellular Vesicles in Tuberculosis

Yong Cheng
Department of Biochemistry and Molecular Biology, Oklahoma State University
Oklahoma Center for Respiratory and Infectious Diseases, Oklahoma State University

Presenter’s email  ycheng@okstate.edu

ABSTRACT
Mycobacterium tuberculosis (M.tb), the causative agent of tuberculosis (TB), has been a major source of human suffering since antiquity. Presently, over 2 billion people are infected by M.tb across the world, leading to an estimated 10 million active TB cases and 1.4 million deaths in 2020. Drug-resistant TB is becoming a major threat in the global TB control. Multidrug-resistant/rifampicin-resistant TB (MDR/RR TB) was diagnosed in an estimated 4.1% of new cases and about 19% of previously treated cases. Among these, approximately 6.2% of cases were extensively drug-resistant TB (XDR-TB). An estimated treatment success rate for MDR/RR-TB and XDR-TB is 54% and 30%, respectively. Additionally, treatment for MDR/RR-TB and XDR-TB requires a longer therapeutic duration with less effective, more expensive and toxic drugs, leading to a higher rate of treatment failure and mortality. To stop the global spread of MDR/RR-TB and XDR-TB, new anti-TB drugs or combined regimens are urgently needed. Recently, a combined therapeutic strategy consisting of an adjunct immunotherapy and anti-mycobacterial drugs has been proposed and investigated. In our study, we found that extracellular vesicles isolated from M.tb-infected macrophages synergistically increased M.tb clearance in macrophages in combination with moxifloxacin, a key antibiotic against MDR-TB, in in vitro cell culture infection model and in vivo mouse model. We further demonstrated that extracellular vesicles isolated from M.tb-infected macrophages inhibited M.tb growth in host cells by activating host cytosolic RIG-I/MAVS RNA sensing pathway and LC3-associated M.tb-containing phagolysosome maturation. Taken together, our results shed light on the development of extracellular vesicle-based host-directed therapy against tuberculosis in humans.
Applications of a naturally occurring animal model to study SARS-CoV-2-induced acute respiratory distress syndrome

Jennifer M. Rudd¹, Miruthula Tamil Selvan¹, Shannon Cowan¹, Eva Kao¹, Cecily C. Midkiff², Jerry W. Ritchey¹, Craig A. Miller*¹

¹Department of Veterinary Pathobiology, College of Veterinary Medicine, Oklahoma State University; Stillwater, OK, USA; ²Division of Comparative Pathology, National Primate Research Center, Tulane University; Covington, LA, USA

Presenter’s email: craig.miller@okstate.edu

ABSTRACT

The emergence and worldwide dominance of COVID-19 has emphasized the urgent need for efficient animal models to develop novel therapeutics and assess immune responses to SARS-CoV-2 infection. In these studies, we establish a naturally occurring feline model for SARS-CoV-2 infection that results in clinical disease and histopathologic lesions consistent with acute COVID-19 in humans. Specific-pathogen-free domestic cats were intratracheally inoculated with both wild-type (WA isolate) and delta variant (B.1.617.2) of SARS-CoV-2 to evaluate clinical disease, histopathologic lesions, and viral infection kinetics. Intratracheal inoculation of wild-type SARS-CoV-2 produced significant clinical disease (lethargy, fever, dyspnea, dry cough) consistent with the early exudative phase of COVID-19. Pulmonary lesions (diffuse alveolar damage, hyaline membrane formation, fibrin deposition, and proteinaceous exudates) were also observed with SARS-CoV-2 infection, replicating lesions in people hospitalized with COVID-19-induced ARDS. Viral loads and ACE2 expression were quantified in nasal turbinates, trachea, lung, and other tissues, and there was a significant correlation between the degree of clinical disease and pulmonary lesions in infected cats. Intratracheal inoculation of SARS-CoV-2 B.1.617.2 produced severe clinical respiratory disease and histologic lung lesions that were most pronounced at day 4 post-inoculation, even at 1/10 the dose of wild-type SARS-CoV-2. While current studies investigating mechanisms of immune dysfunction contributing to disease progression are pending, our preliminary results indicate marked activation of inflammatory pathways and systemic cytokine upregulation during SARS-CoV-2 infection in cats. Natural ACE2 expression, paired with clinical and pathologic correlates between this feline model and human COVID-19, encourage use of this model for future translational studies.
Cohen’s Restaurant Hypothesis of Intestinal Colonization

Tyrrell Conway
Regents Professor of Microbiology, College of Arts and Sciences, Oklahoma State University
Presenter’s email tconway@okstate.edu

ABSTRACT
Competition for resources defines community structure and determines the success or failure of introduced species. According to David Tillman’s theory of equilibrium competition, stable co-existence of two species is possible when competing for different resources. Rolf Freter sought to understand how competition for resources in the intestine resulted in stable multispecies communities. Freter postulated that for many species to coexist each must use one limiting nutrient better than all others. However, recent experiments showed that different *E. coli* biotypes occupy distinct niches. We therefore postulated that *E. coli* reside in “restaurants” where they grow on sugars that are served locally by polysaccharide degrading anaerobes in mixed biofilms. Accordingly, the resident microbiota, which serves as a barrier to colonization by invaders, resides in mixed biofilms, taking up nutrients almost as rapidly as they are released by adjacent polysaccharide degrading anaerobes. Hence, only the small amounts of sugars that escape the mixed biofilms would be available to invading *E. coli*. The invaders must compete directly with planktonic residents that have left the biofilms. Consequently, an invader might initially compete in a “Freter-like” niche, in which nutrients are mixed and equally available to invaders and planktonic residents, and if it can remain long enough in the intestine, then enter a “restaurant” and become stably colonized. Invading pathogens and commensals alike must acquire nutrients to initiate infection or engage in the succession of microorganisms that make up a stable healthy community, respectively. Understanding how enteric pathogens compete for nutrients to overcome colonization resistance should lead to strategies to prevent intestinal infections.
Differential replication and antiviral response to SARS-CoV-2 and it’s variant viruses of concern (VoCs)

Rudragouda Channappanavar1, 2, Muneeswaran Selvaraj1, and Debarati Chanda3

1Department of Veterinary Pathobiology, College of Veterinary Medicine, Oklahoma State University
2Oklahoma Center for Respiratory and Infectious Disease (OCRID), Oklahoma State University
3Graduate Program in Comparative Biomedical Sciences, Oklahoma State University College of Veterinary Medicine

Presenter’s email rchanna@okstate.edu

ABSTRACT
Emerging human pathogenic coronaviruses (hCoVs) are a threat to public health and global economy. This is evidenced by the ongoing pandemic caused by SARS-CoV-2 and its variant viruses of concern (VOC) such as alpha, beta, gamma, and delta SARS-CoV-2 VOCs. Recent clinical data demonstrate increased transmission and severity caused by VOCs, but whether the differential outcomes are caused by robust virus replication and or excessive inflammation following infection with VOCs is not well understood. Additionally, SARS-CoV VOCs are differentially susceptible to neutralization by vaccine induced antibodies. Consequently, we examined replication kinetics and host response in different cell lines infected with wile-type (WT) SARS-CoV-2 and its VoCs. Our results show that WT and beta (South African) variant viruses replication to similar levels with peak titers observed around 48hr-post infection. These viruses replicated to significantly (10-100-fold) elevated titers as compared to alpha (UK variant, B117) and gamma (P.1, Brazilian) variants in immunocompetent A549 alveolar epithelial cell line. Of note, P.1 variant showed a lag in peak titer, reaching peak replication around 72hr post-infection. In stark contrast to these results, WT and VOC SARS-CoV-2 viruses replicated to comparable titers in interferon deficient Vero-E6-hACE2 cells. These results suggest differential susceptibility of SARS-CoV VOCs to interferon-induced antiviral response. Further evaluation of our results showed that WT and SARS-CoV-2 VOCs induced differential host immune response. Collectively, our results highlight a potential basis for differential outcomes observed following infection with WT and SARS-CoV-2 VOCs.
Utilization of an Exercise Mimetic as a Buffer Against Influenza

Joshua T. Butcher, PhD, MS
Department of Physiological Sciences, College of Veterinary Medicine, Oklahoma State University
Presenter’s email  joshua.butcher@okstate.edu

INTRODUCTION
Viral infection is well known for its ability to significantly compromise cardiovascular health, and elevate morbidity and mortality in healthy (and unhealthy) patients. Even modest amounts of exercise (pre, post, and during infection) are protective against influenza, influenza severity and mortality, and additionally enhance immunization efficacy in both human and rodent models. However, exercise is contra-indicated in those with viral infection, due to potential contagiousness and a weakened immune state. Further, a significant patient population is unable to exercise at a rate that confers cardiovascular benefit (ex: the aged, obese, those constrained by a pandemic). Thus, it would be inherently valuable to determine if an exercise mimetic can protect and preserve function, independent of increases in activity or exercise. To address this question, our lab manipulates the muscle myokine myostatin (GDF-8) in mouse models. Myostatin is a potent negative regulator of skeletal muscle growth that is upregulated in human and animal models of obesity, influenza, and downregulated following regular exercise. Our hypothesis is that targeting myostatin in a rodent model of influenza will prevent mortality via a mechanism that mimics exercise.

METHODS
Influenza infection was induced via Intranasal administration of Influenza A/PR/8/34 in WT mice with and without myostatin deletion. Assessed variables included weight, survival, coat score and inflammatory factors in the lung.

RESULTS
Myostatin deletion significantly improved survival in mice compared to infected controls, despite similar weight loss. Assessed inflammatory factors showed elevated IL-2, MCP-1, and IL1B in myostatin KO mice, as well as NOX1 and NOX2, compared to infected controls. Taken together, our data suggests that myostatin may be an effective target for improving outcomes in influenza infection.
BACKGROUND
Orofacial infections with Herpes simplex virus 1 (HSV-1) lead to lifelong latent infection in trigeminal ganglia (TG). Reactivation from latency may cause serious recurrent disease including blindness and encephalitis. Stress is a trigger for reactivation from latency, yet the mechanism of action is poorly understood. Physiological stress increases corticosteroids levels, which activate the glucocorticoid receptor (GR). We hypothesize stress-mediated GR activation induces viral gene expression, culminating in reactivation from latency.

METHODS
WT C57Bl/6 mice and a functionally impaired GR mutant mouse strain containing an Alanine mutation in Serine 211 (GR-S211A) were ocularly infected with HSV-1 strain McKrae, a highly virulent strain. Ocular swabs were collected to monitor virus shedding during acute infection and establishment of latency. 30 days post infection, TG were harvested and explanted to induce reactivation, which was quantified by virus shedding.

RESULTS
Male GR-S211A mice exhibited reduced virus shedding during acute infection. Conversely, female GR-S211A shed virus like WT C57Bl/6 mice. Virus shedding from the ocular cavity of infected male and female GR-S211A was undetectable 6 dpi. Conversely, WT mice shed high levels of virus for the first 6 dpi; however, virus shedding was not detected at later times confirming latency was established. Explant induced reactivation was significantly reduced in female GR-S211A mice relative to WT and male GR-S211A mice.

CONCLUSIONS
Mutation of GR Ser211->Alanine impaired virus shedding in males and females, and explant induced reactivation in females. Conversely, HSV-1 acute explant-induced reactivation in male GR-S211A mice was similar to WT C57Bl/6 mice.
The Development of Contrathermodynamic Catalysis; Applications to Photo-Click Reactions and Unfavorable Isomerizations

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BACKGROUND
The primary objective of the Weaver group is the elevation of the field of synthesis as it is the quintessential central science and positively impacts many fields of study. We have primarily focused on the advancement of two concepts, contra-thermodynamic catalysis and fluorine sculpting. Today’s talk will focus on the former.

Traditional catalysis has the effect of lowering energy barriers and facilitating reactions but ultimately does not alter the thermodynamics, or the spontaneous direction, of the reaction. Well-trained chemists quickly learn the bounds of thermodynamics. Our long-term aspirations are to realize a system that makes formerly energetically impossible reactions possible. In other words, we seek to make endergonic reactions synthetically feasible. Achieving this objective will require the development of reactions which are not subject to the principles of microscopic reversibility, irreversible reactions, that can serve to pump energy into the system, and translation of this potential energy into useful forms that can serve as harvested energetic currency. Finally, we must learn how to drive reactions with our newfound energetic currency. Realizing these goals will result in new tools for the study of large molecules, and the development of new synthetic methods that have long been ignored, specifically because of the energy issue. More specifically, we hope to utilize the cis-to-trans photoisomerization of cycloalkenes to serve as energy pumping reactions that quickly and efficiently convert visible light photons into useful energetic currency that can be used as a driving force to make formally impossible reactions possible.

METHODS
We probe this problem by the study of different cycloalkenes and their propensity to undergo Dexter energy transfer from Ir-dyes, and then ultimately study the behavior of the alkene. In other words, does it show evidence of undergoing cis-to-trans isomerization and conversion of the triplet state energy into strain energy on the ground state surface? If so, how does the strained species behave? What is its lifetime? What is its reactivity?

RESULTS
We have investigated a number of different strategies for harvesting photochemical energy. As a result, we have developed several novel and highly useful chemical reactions that are impossible on a simple energetic standpoint.

CONCLUSIONS
We have seen that it is feasible to 1) efficiently capture photochemical energy in the form of ring strain, 2) shown some simple strategies for driving energetically unfavorable reactions, 3) have demonstrated the utility of contrathermodynamic catalysis.
Validation of a Novel ADAMTS13 Substrate to Characterize Patients With Thrombotic Thrombocytopenic Purpura

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BACKGROUND
Thrombotic thrombocytopenic purpura (TTP) is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and microvascular thrombosis. TTP is caused by genetic or autoimmune deficiency of ADAMTS13, an enzyme that prevents excessive platelet adhesion and thrombi formation by regulating the von Willebrand factor (VWF) multimeric size. ADAMTS13 activity <5% is confirmatory for TTP. Most ADAMTS13 assay substrates are peptides derived from the human VWF A2 domain but their applicability is limited. We serendipitously discovered a peptide (Cattle-VWF71) from the cattle VWF (Bos taurus) which is extraordinarily cleaved by ADAMTS13. The Cattle-VWF71 would be therefore ideal for developing a quicker and sensitive assay to diagnose TTP. However, Cattle-VWF71 has not been validated with clinically relevant samples.

METHODS
Cattle-VWF71 peptide was prepared recombinantly and dyes conjugated following established protocols. Calibrant pooled normal plasma (heparinized) from >35 healthy donors was obtained from BioIVT. Biobanked human plasma samples (100) were previously obtained under the protocol approved for the ART study (Adjuvant Low Dose Rituximab for Acquired TTP with Severe ADAMTS13 Deficiency; NCT01554514).

RESULTS
For over 90 heparinized plasma samples, Cattle-VWF71 substrate assay precisely and accurately differentiated samples with low, moderate, and high ADAMTS13 activity. Comparing to a similar ADAMTS13 assay (FRETS-rVWF71), Cattle-VWF71 assay was faster (~15 vs 60 minutes assay time), used less plasma and substrate (economical), and was very effective in detecting the residual ADAMTS13 activity (<5%).

CONCLUSIONS
Cattle-VWF71 accurately confirmed all TTP plasma samples, indicating specificity. Also, it was very effective in detecting residual ADAMTS13 activity, which would be useful for monitoring TTP therapy.
Deciphering Viral Components in Coronavirus Replication and Pathogenesis

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ABSTRACT
Since the first coronavirus (CoV) was discovered in the 1930s, the CoV family has grown dramatically with over a hundred members. CoV infection has been posing a significant threat to the health of animals and humans, as exemplified by the ongoing CoVID19 pandemic. Unfortunately, limited preventive and therapeutic agents are available. Investigating what and how viral component(s) involves in CoV infection and pathogenesis is vital for identifying antiviral targets and developing effective treatment. In our research, we aim to decipher the genetic codes of coronaviruses and identify key viral components that are essential for CoV infection. By employing reverse genetics approaches in a combination with animal models, we identified multiple viral proteins involving in viral RNA synthesis and evasion of antiviral innate immunity. One of these proteins is non-structural protein 15 (nsp15), which possesses an endoribonuclease (EndoU) activity that cleaves RNA molecules at uridine nucleotides. We reported that nsp15/EndoU cleaved the poly-uridine of the negative-sense viral RNAs and prevented the latter from acting as dsRNA-like molecules that activate the host antiviral immunity. We found that knocking out the EndoU activity significantly crippled CoV infection in macrophages and animals. The EndoU-deficient mutant CoVs were severely attenuated but still elicited protective immunity in animals. Conclusively, our research discovered that nsp15/EndoU is a conserved viral component and a major virulence factor that limits the host sensing of viral dsRNA and contributes to CoV-induced diseases. Our findings demonstrate that nsp15/EndoU may be a promising target for antivirals and vaccine development.
Tularemia: an Oklahoma perspective

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BACKGROUND
Tularemia is a reportable, fatal and sporadic zoonotic disease caused by the bacteria Francisella tularensis. Multiple animal species are naturally infected and modes of transmission include arthropod bites, skin or mucus membranes, inhalation, or ingestion of contaminated materials. Two cases of tularemia, in a horse and a cat, were recently diagnosed at OADDL. Infection in horses is rare and prompted this retrospective study to review the cases diagnosed at OADDL.

METHODS
Necropsy examination and histopathology were performed at OADDL. PCRs were performed on various organs. Archived case materials were obtained from the OADDL database. Data on human tularemia cases were obtained from the Centers for Disease Control and Prevention website (https://www.cdc.gov/tularemia/statistics/index.html).

RESULTS
Since 2014, twenty cases have been diagnosed in different animal species at OADDL. Cats (15) accounted for most of the cases followed by rabbits (3) and one case each for horses and dogs. These cases were spread among 16 Oklahoma counties. Common macroscopic postmortem findings included necrotic foci in the spleen, lymph nodes, and liver. Histopathological lesions were characterized by necrotizing inflammation and intralesional bacteria. Furthermore, between 2010-2019, 226 human cases were reported in Oklahoma (ranked 3rd in the U.S.), and 2,108 cases were reported in the United States. More than 52% of human cases in the U.S. were concentrated in the states of Oklahoma, Arkansas, Kansas, and Missouri.

CONCLUSIONS
Given the public health significance, animal handlers and veterinarians should be vigilant against tularemia in domestic animals especially in endemic areas.
Impact of Social Stress in Adolescent Oxycodone Dependence and Withdrawal: Is the Microbiota-Gut-Brain Axis Implicated?

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BACKGROUND
In the United States, 9.5% of high school age students developed chronic oxycodone use leading to the development of dependence. Predictors of oxycodone dependence included early life stress (ELS). On the other hand, the formation of the gut microbiota is a crucial process in early life and influences several aspects of brain-behavior responses. However, the effects of ELS and oxycodone addiction in the adolescent gut microbiome remain unknown. Brain-derived neurotrophic factor (BDNF) is essential in stress and response to opioids, also, enhances gastrointestinal motility.

METHODS
1) we investigated the effects of oxycodone-induced withdrawal under ELS in the adolescent gut microbiota and 2) brain/gut BDNF levels. Adolescent male Sprague-Dawley rats were raised in an isolated (IE), standard (SE), or enriched environment (EE). On a postnatal day 51, oxycodone dependence-withdrawal was initiated using a passive injection model (1, 2, 3, and 5 mg/kg) every 12 hr for five days. On the sixth day of administration, rats received a naloxone injection (1 mg/kg), for precipitating withdrawal. Brains were collected for BDNF immunoassay analyses. Gut microbiota compositions were analyzed using 16S rRNA gene amplicon sequencing in baseline and time-course fecal samples and intestinal samples.

RESULTS
ELS increased all withdrawal and anxiety-like features compared to controls. ELS followed by oxycodone withdrawal enhanced proBDNF and mBDNF expression in the Prefrontal Cortex and a Periaqueductal gray area. Oxycodone dependence/withdrawal and differential rearing conditions correlated with compositional changes in the gut microbiota.

CONCLUSIONS
Our study provides insight how the bidirectional microbiota-gut-brain communication may be affected by ELS and drug misuse.
Hyperplexed Computational Protocols for Metagenome-based Infectious Disease Diagnosis

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BACKGROUND
Current approaches for pathogen detection and disease diagnosis are limited in their multiplexing capabilities and require prior knowledge of disease manifestations. Metagenomic sequencing and data analysis offer an avenue to develop protocols that are pathogen-agnostic with unlimited multiplexing capability. With technological advances, sequencing has become more accessible, but the availability of rapid and user-friendly data analysis tools continues to be a major hurdle. We are exploring the use of different computational algorithms including machine learning (ML) and neural network-based tools for rapid and reliable diagnosis of infectious diseases.

METHODS
The proposed deep learning framework leverages a novel, attention-based structural reasoning framework to learn robust representations for distinguishing between plausible pathogens and host sequence reads in metagenome data. We used Bovine Respiratory Disease (BRD) as a disease model for algorithm evaluation. Metagenome sequences from 25 known positive and 25 known negative samples were analyzed using the algorithm for pathogen detection. Detection sensitivity was assessed from the metagenomes of known negative lung samples that were spiked with decreasing amounts of BRD bacteria.

RESULTS
The algorithm was successful in detecting multiple bacterial pathogens in metagenomes from clinical samples. We are able to separate host genome from BRD-specific pathogen sequences with a sensitivity of 98% and specificity of 99%. The algorithm was also able to discriminate BRD-specific pathogen sequences with an average sensitivity of 65% and an average specificity of 62%.

CONCLUSIONS
Initial studies indicate our ML based metagenome sequence classification algorithm out-performs existing algorithms. The algorithm will be further developed for automated detection of multiple pathogens.
Equine insulin dysregulation induces upregulation of inflammatory proteins in a tissue-specific manner

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BACKGROUND
Equine metabolic syndrome (EMS) causes insulin dysregulation leading to debilitating sequelae including laminitis. The pathophysiological mechanisms underlying EMS are not well elucidated. Using two unique equine models, we hypothesized that insulin dysregulation induces an increased expression of inflammatory proteins in a tissue specific manner.

METHODS
Striated muscle and lamellar biopsies were obtained from horses, given a 48-hr euglycemic-hyperinsulinemic-clamp (pEHC) or an electrolyte infusion (control, n=4/group). Biopsies from skeletal muscle and adipose tissues were collected from insulin-resistance (IR) or insulin-sensitive (control) horses based on intravenous glucose tolerance test (n=3-5/group). Expression of proteins was quantified by Western blotting.

RESULTS
HSP90 protein expression was significantly higher in lamellae of pEHC group, as well as in visceral adipose tissue and skeletal muscle of IR horses (p=0.039, p=0.046, p=0.017 vs. controls, respectively), but not in subcutaneous adipose and cardiac tissue. Alpha-2 Macroglobulin protein expression was higher in lamellae of pEHC group and in visceral adipose of IR horses (p=0.018, p=0.039 vs. control, respectively) but not in subcutaneous adipose tissue or striated muscles. Fibrinogen protein expression was significantly higher in the lamellae of pEHC horses and in subcutaneous adipose tissue of IR horses but not in striated muscles. IL1-beta expression was higher in lamellae and visceral adipose from pEHC horses (p=0.015, p=0.0009 vs. controls, respectively), but not in striated muscles.

CONCLUSIONS
Upregulation of inflammatory proteins in lamellae and adipose tissue during equine insulin dysregulation may reveal novel biomarkers and potential therapeutic targets for EMS. Further, the lack of increase of inflammatory proteins in the heart could underscore potential cardioprotective mechanisms.
Downregulation of Astrocytes induced pro-inflammatory markers via modulation of the $\alpha_7$ nicotinic acetylcholine receptors

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BACKGROUND
Chronic pain (e.g., neuropathic pain) is a major health problem with high economic burden. Add to that the widespread opioid epidemic crisis consuming lives and devastating the health system. In that focus, developing an effective and adequate medication that acts on central and peripheral pain targets without inducing tolerance or addictive behaviors is an urgent need. Glial cells are viable targets for pain therapy, considering their contribution to sensory and/or non-sensory aspects of neuropathic pain. In fact, targeting glial cells may attenuate upregulation of inflammatory mediators in the spinal cord and brain, and reverse nociceptive behaviors. $\alpha_7$ nicotinic acetylcholine receptors (AChRs) are expressed in glial cells, and $\alpha_7$-selective positive allosteric modulators ($\alpha_7$-PAMs) decrease pain in animal models. Our group is particularly interested in identifying novel agents that target the cholinergic inflammatory pathway, particularly in astrocytes, as a potential therapeutic strategy.

METHODS
To assess the anti-inflammatory activities of PAM-2, an $\alpha_7$-PAM, the levels of inflammatory chemokine/cytokines (e.g., IL-6, CCL2, CXCL10) were measured in activated normal human astrocytes (NHA) using the enzyme-linked immunosorbent assay (ELISA). The modulating activity of PAM-2 (0-2.5 µM) was determined in the absence and presence of (-)-nicotine (5 µM). NHA cells were exposed to interleukin-1β (IL-1β; 1 ng/µL), to stimulate the release of inflammatory mediators.

RESULTS
IL-1β-induced expression of inflammatory mediators was inhibited by (-)-nicotine (0-100 µM) or PAM-2 (0-5 µM), whereas PAM-2 potentiated the inhibitory effect of (-)-nicotine. The most pronounced effect was on IL-6. Interestingly, methyllycaconitine (MLA; $\alpha_7$-selective antagonist) inhibited the observed activity of PAM-2/(-)-nicotine, supporting a mechanism involving $\alpha_7$ AChRs.

CONCLUSIONS
The current work supports a role for $\alpha_7$ AChRs in the regulation of glial cells as a therapeutic strategy for alleviating neuropathic pain.
Host Cytosolic RNA Sensing Pathway Plays a Critical Role in Mycobacterial Killing in Macrophages

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BACKGROUND
Non-tuberculous mycobacteria (NTM) are opportunistic pathogens, predominantly causing pulmonary infections in susceptible populations including the elderly and in patients receiving immunosuppressive drugs, or with pre-existing conditions such as cystic fibrosis and chronic obstructive pulmonary disease (COPD). The most commonly isolated NTM species are Mycobacterium avium complex (MAC) (M. avium and Mycobacterium intracellulare) and Mycobacterium abscessus complex (MABSC) (M. abscessus, M. massiliense and M. bolletii), which account for >90% of the total cases reported. Despite their increased clinical importance, we still have a limited knowledge of NTM pathogenesis and host immunity.

METHODS
In our current study, we investigated the engagement of the MAVS-dependent RNA sensing pathway in host defense against M. avium infection using macrophage culture and mice as our study model.

RESULTS
We identified that CD4+ T lymphocytes mediate mycobacterial killing in NTM-infected alveolar macrophages in ex vivo cell culture infection model and mice. We further found CD4+ T lymphocyte-mediated mycobacterial killing in alveolar macrophages depends on host RIG-I/MAVS/TBK1 RNA sensing pathway by regulating ICAM-1 production, a key component in the formation of immune synapse between armed CD4+ T lymphocytes and NTM-infected alveolar macrophages.

CONCLUSIONS
Our study demonstrates a previously undefined mechanism by which a host cytosolic RNA sensing pathway contributes to the interplay between mycobacteria-infected macrophages and antigen-specific T lymphocytes, and shed light on the development of host-directed therapy against NTM infections in humans.
β-Funaltrexamine protects against lipopolysaccharide-induced behavioral impairment and inflammation

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BACKGROUND
Neurological disorders often involve inflammation in the brain. However, many medications available do not have potent anti-inflammatory properties. Consequently, identification of therapeutic options for such disorders is crucial. We previously discovered that a selective mu-opioid receptor (MOR) antagonist, beta-funaltrexamine (β-FNA), inhibited inflammatory signaling in vitro in human astroglial cells. In a preclinical model, β-FNA was also found to inhibit lipopolysaccharide (LPS)-induced sickness behavior and neuroinflammation in mice when administered immediately post-LPS. In the present study, we explore the extent that β-FNA is protective when treatment occurs 4-hours after LPS administration.

METHODS
Male C57BL/6J mice were administered LPS (0.83 mg/kg, i.p.) followed by β-FNA treatment (50 mg/kg, i.p.) immediately or 4hr post-LPS. Sickness behavior was assessed using a 10-min open-field test, followed by collection of brain, spleen, and plasma. Levels of inflammatory chemokines/cytokines (CXCL10, CCL2; and IL-6) in tissues were measured using an ELISA.

RESULTS
β-FNA treatment immediately after LPS administration inhibited LPS-induced CCL2 and CXCL10 levels in the brain/plasma at 24hr; whereas only CCL2 was inhibited in the spleen. LPS-induced sickness behavior at 24hr was also reduced by immediate β-FNA treatment. β-FNA treatment 4hr post-LPS was less protective. β-FNA was not protective at 8hr post-LPS regardless of the timing of treatment. Whereas at 24hr post-LPS β-FNA was protective against sickness behavior and inflammation, when administered immediately after LPS.

CONCLUSIONS
The results show that the timing of β-FNA treatment is critical for neuroprotection. Further examination of β-FNA’s anti-inflammatory and neuroprotective actions is still necessary.
Pulmonary glucose dysregulation leads to increased influenza viral replication

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BACKGROUND
Hyperglycemia is an independent risk factor for severe respiratory infections, including influenza. We hypothesize that hyperglycemia predisposes diabetic subjects to excess glucose in the airway, allowing for greater viral replication.

METHODS
To test this hypothesis, type 1 (T1Dx) and type 2 (T2Dx) diabetic mouse models were intranasally infected with influenza. Subsets of T1Dx and T2Dx mice were treated with insulin or metformin, respectively, to restore euglycemia. Glucose concentrations of the bronchoalveolar lavage fluid (BALF) were measured with a glucose oxidase assay. Human bronchial epithelial cells (HBECs) were incubated with varying glucose concentrations, 2-deoxyglucose, insulin, or AMPK modulators, then infected. Viral loads were determined by immunofluorescence and/or qrtPCR for the viral protein hemagglutinin.

RESULTS
In vivo, diabetic and infected mice demonstrated increased glucose concentrations in the BALF. Viral load was significantly greater in lung homogenates of both T1Dx and T2Dx mice, which was rescued by insulin or metformin, respectively. In vitro, HBECs incubated in high [glucose] had a significantly greater percentage of cells infected than those incubated in normal [glucose]. Conversely, cells treated with 2-deoxyglucose demonstrated reduced viral replication. Activation of glycolysis using insulin or AICAR (AMPK activator) increased viral replication, while inhibition of AMPK decreased viral replication.

CONCLUSIONS
These novel findings suggest that: hyperglycemia increases BALF [glucose], thus H1N1 replication capacity in diabetic lung, and influenza viral replication is dependent on host-cell glycolysis. Better understanding of the mechanisms altering glucose metabolism during viral infection may lead to the discovery of novel therapeutic targets for diabetic patients infected with influenza.
Targeting Myostatin as an Adjunct Treatment for Preservation of Cardiometabolic and Skeletal Muscle Function in Type 1 Diabetes

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BACKGROUND
Type 1 Diabetes Mellitus (T1DM) is a disease characterized by the destruction of insulin-secreting pancreatic beta cells and results in hyperglycemia, muscle wasting, and vascular dysfunction. Patients afflicted with T1DM suffer from increased morbidity and early mortality, largely driven by an inability to appropriately maintain glucose homeostasis. Skeletal muscle is the body’s largest metabolic reservoir, absorbing significant amounts of glucose from the blood stream and physical exercise is known to improve all of the above outcomes, but many T1DM patients are unable to exercise at a level that conveys benefit. Thus, directly targeting muscle independent of exercise may prove beneficial for improving T1DM outcomes. Myostatin is a myokine that is a potent negative regulator of muscle growth and is upregulated in T1DM patients. Our hypothesis is that genetic deletion of myostatin will preserve glucose homeostasis, maintain muscle function, and protect against vascular dysfunction in a mouse model of T1DM.

METHODS
T1DM was induced via streptozotocin (STZ) in adult male mice with (WT) and without myostatin (MyoKO). Multiple variables were assessed including glucose homeostasis (plasma glucose, HbA1c, IGTT), fluid dynamics, muscle function (in vivo plantarflexion), and vascular function (ex vivo pressure myography of gracilis arteriole).

RESULTS
Myostatin deletion inhibited STZ-induced increases in plasma glucose, preserved fluid dynamics, and prevented decreases in muscle function, independent of insulin. Further, endothelial function was protected with myostatin deletion.

CONCLUSIONS
Taken together, this data suggests that myostatin inhibition may be a target for effective treatment and management of the cardiometabolic and skeletal muscle dysfunction that occurs with T1DM.
The INTERACT Steering Committee will accept proposals focusing on multi-investigator team building from members for support of research activities aligned with the goals and mission of the INTERACT program. The goal is to initiate development of activities to establish and build programs that integrate researchers throughout OSU. Projects should focus on a specific theme of interest to a specific external sponsor, which may be described in a program/application announcement from that agency (e.g., Program Announcement, Request for Applications/Proposals), and should address outcomes that will enhance the competitive position of individuals/program areas for external funding. Please email INTERACT@okstate.edu for additional details.