2018

Health Research Projects

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Novel shape memory polymer devices for optimal endovascular embolization of intracranial aneurysms

PI: Dr. Chung-Hao Lee, University of Oklahoma, Norman **Research Area:** Biomedical Engineering

OCAST Project: HR18-002

An intracranial aneurysm (ICA), is an abnormal focal dilation and weakening of an arterial blood vessel in the brain with a prevalence of 0.5%-6% in adults. Subarachnoid hemorrhage (SAH) occurs in approximately 30,000 Americans each year, which accounts for about 10% of all strokes. Incidental rupture of an ICA is associated with 50%-80% of the SAH cases, causing a mortality rate reaching as high as 40% within the first week. Endovascular embolization, aiming at complete and lasting occlusion of the treating aneurysm using micro-catheter deployed coils, has been an established therapy for treating ICAs. However, its long-term therapeutic outcomes have been disappointing, as for completely embolized aneurysms with recurrence rates approaching 41% by 3-5 years after initial coil therapy, of which 26% requiring retreatment. Thus, there is a critical need for a more comprehensive understanding of the biomechanical behaviors, morphological changes, and the hemodynamics of the arterial vessel interacted with the aneurysm and embolic devices.

Thus, the objectives in this project are (i) to develop and validate a patient-specific predictive simulation framework for systematic evaluating the ICA system, (ii) to identify essential biomechanical and hemodynamic factors for the design of embolic devices, and (iii) to prove the concept of using shape memory polymers (SMPs) for personalized treatment of ICAs under simulated endovascular conditions. Our central hypothesis is that increasing the packing density and maximizing the occlusion for endovascular embolization therapeutics will eventually lead to enhanced long-term durability. We will test our hypothesis and achieve our research objectives by pursuing the following three specific aims:

(1) To facilitate predictive simulations of the arterial blood vessel and aneurysm environment.

(2) To develop in vitro simulated endovascular experiments for SMP-based embolic devices.

(3) To validate the efficacy and occlusion performance of subject-specific SMP-based devices.

The endpoint of this project is expected to develop novel SMP-based embolic devices, which represent a new and substantive departure from the status quo by shifting the therapeutic management of intracranial aneurysms to a reliable, long-term durable personalized neurosurgical intervention. The development of such innovative technologies is expected to have an important positive impact because personalized therapy based on patient-specific aneurysm's geometry and pathological conditions could be achieved, which will likely advance neurosurgical management of intracranial aneurysms. It will also be beneficial to the healthcare of Oklahoma citizens, especially in the southwestern and eastern regions with a higher death rate (10-15% higher than other regions) and a higher percent of adults with a stroke history (1.5 times higher than the state average), and will reduce in-hospital expenditure for managing SAH-induced strokes.

OCAST

Nanocoatings for controlled drug release and improved biocompatibility

PI: Dr. Yu Mao, Oklahoma State University, Stillwater **Research Area:** Biomedical Engineering **OCAST Project:** HR18-005

Though drug-eluting stents have been widely used method in treating coronary artery diseases by opening up narrowed blood vessels, syndromes of restenosis and thrombosis after stenting remains problematic. Contemporary stent coatings rely on strategies to address drug efficiency and stent biocompatibility separately. The lack of comprehensive approaches in addressing drug delivery and surface biocompatibility limits the clinical success of stents. The long-term goal is to develop drug-eluting stents that significantly reduce restenosis and thrombotic response while supporting endothelialization after implantation.

The overall objective of this application is to identify strategies for simultaneous control of drug release and stent biocompatibility for the reduction of neointimal formation and initial thrombotic response. The central hypothesis is that the effectiveness of drug-eluting stents is determined by the drug, the drug release kinetics, the stent-vessel interaction, and the stent-blood compatibility. We will pursue three specific aims: 1) identify strategies for the preparation of dual-function stent nanocoatings with both drug release control and anti-platelet property; 2) determine factors that affect the vascular cell and blood compatibility of drug-eluting stents; 3) assess the vascular tissue response and inflammation reaction towards nanocoated drug-eluting stents.

Under the first aim, methods of vapor-based, sequential polymerization process will be used to combine controlled drug release and anti-platelet surface into structurally integrated nanocoatings. Under the second aim, the effects of drug, drug release rate, and coating surface on blood and vascular cell compatibility will be determined by studying the interaction of the nanocoatings with blood and human coronary artery cells. Under the third aim, a pilot animal study using rabbit model is expected to provide key information regarding the re-endothelialization and neointimal formation of nanocoated drug stents. The approach is innovative, because it departs from the status quo by 1) addressing drug release and stent biocompatibility comprehensively; and 2) introducing a novel diffusion barrier to eliminate burst drug release.

The proposed research is significant, because what is learned in this research will cast light on the optimal combination of drugs, delivery kinetics, coating composition, and surface design to improve the performance of drug-eluting stents in reducing in-stent restenosis and stent thrombosis.

Late-Stage C-N incorporation to bioactive cores

PI: Dr. Angus Lamar, University of Tulsa, Tulsa **OCAST Project:** HR18-013 **Research Area:** Chemistry & Biochemistry

The direct and selective transformation of chemical functionalities is a cornerstone of organic synthesis with respect to pre-clinical drug discovery and the synthesis of pharmaceuticals. Traditional strategy towards the production of a library of complex molecules to test for bioactivity and/or medicinal applications relies upon opportunities for "synthetic divergence". This involves the inclusion of intermediate compounds that can be easily modified to a broad range of related analogues on the pathway to a bioactive core.

Due to the fact that nitrogen is a key atom found in nature, materials science, and synthetic pharmaceuticals, it is of great desire in the drug discovery community to install nitrogen-containing functionality at late stages in the synthetic pathway to a bioactive core. Our research group has recently developed a novel method to accomplish this challenging goal by selectively inserting carbon-nitrogen (C-N) bonds into relatively complex molecules at a variety of reactive locations under incredibly mild reaction conditions.

Our method of C-N bond incorporation involves the visible-light-promoted generation of N-centered radicals (NCRs) from readily available, inexpensive sources. The system we are investigating is uniquely equipped to facilitate not only the activation of C-H bonds, but also distinctive reactivity towards a variety of substrates possessing previously inaccessible functionalities that can readily cleave to a relatively stable intermediate radical species.

Our goal in this investigation is to explore the untapped potential of NCRs and to apply this conspicuously overlooked, yet powerful method of C-N bond formation towards molecules of interest to human health.

Advancing therapeutic options for treating mood and anxiety disorders using a novel anti-inflammatory agent

PI: Dr. Randall Davis, Oklahoma State University Center for Health Sciences, Tulsa

OCAST Project: HR18-033

Research Area: Physiology & Pharmacology

About 30 million people in the U.S. suffer from mood and anxiety disorders and, as a result, shoulder enormous personal and economic burdens. Unfortunately, many of those who live with such disorders do not adequately respond to currently available medications, so developing new drugs and treatment strategies for such disorders is imperative. Inflammation in the brain (neuroinflammation) plays an important role in these brain disorders.

However, there are relatively few medications on the market that target neuroinflammation. We previously discovered a drug that inhibits activation in specialized brain cells called astrocytes that are instrumental in neuroinflammation. We then performed studies using mice and demonstrated that a single injection of the drug protected not just against neuroinflammation, but also reduced the sickness behavior that accompanied exposure to a bacterial product. The current proposal will significantly advance the therapeutic relevance of this drug as a neuroprotective agent, particularly in the context of extreme social stress or "bullying".

This project will involve subjecting a mouse to a larger and aggressive strain of mouse for 2h/day for 6 consecutive days. This form of social stress reliably produces both neuroinflammation and anxiety-like behavior in mice. We will test the hypothesis that our drug can reduce or prevent stress-induced neuroinflammation and anxiety. We first will examine whether drug treatment during the social stress prevents neuroinflammation and/or the behavioral deficits that follow "bullying". We then will examine whether the drug prevents or reduces the duration of neuroinflammation and/or behavioral deficits when it is administered after the social stress.

Overall, this project will significantly advance our understanding of the novel anti-inflammatory and neuroprotective actions of this drug, particularly, in terms of brain disorders associated with extreme social stress. Ultimately, the results of this project may lead to improved treatment options for addressing mood and anxiety disorders.

Development and evaluation of vibration-based wearable upper limb rehabilitation device

PI: Dr. Hongwu Wang, University of Oklahoma Health Sciences Center, Oklahoma City

OCAST Project: HR18-034

Research Area: Instrumentation, Data Sciences, Clinical Evaluation

Stroke often leads to significant impairment of upper limb function and is associated with decreased quality of life. Patients have difficulty moving out of the upper extremity flexion synergies that often dominate attempts to function after stroke. Change in muscle activation is the key underlying factor. Despite study results from several interventions for muscle activation and motor coordination, wide-scale adoption remains largely elusive due to the lack of sustainability of those interventions. The main reasons for the unsustainability are under-doses of the interventions and low patient compliance and participation.

Recent studies among individuals without disabilities as well as those with strokes have shown that with focal vibration there is greater potential to increase and coordinate muscle recruitment and build muscle strength and endurance. This form of treatment could widely benefit stroke patients and therapists who are in need of sustainable intervention that is effective and efficient for building muscle work capacity for function. Thus, the aims of this study are to design, develop and evaluate the usability and feasibility of a novel vibration-based wearable device for upper limb rehabilitation in stroke patients.

A user participatory design approach will be used for the design and development. Forty-eight stroke patients and 10 therapists working with those stroke patients will be recruited to evaluate the usability of the device. All stroke patients will participate in a 4-week in-home vibration treatment to evaluate the feasibility of the device. Patients will be randomized into four groups receiving vibrations with different frequency (60 Hz or 120 Hz) and amplitude (0.2mm or 2mm). All groups will follow a prescribed dose of vibration based on the therapists' recommendations. Strength and functional outcomes will be measured before and after the 4-week in-home intervention.

We hypothesize that all groups will show an increase in grip strength and upper limb function at the end of study compared to baseline and that the increases in outcomes will be different in different groups. We also expect all participants will tolerate the wearable device without adverse side effects and report high levels of satisfaction with the device. This pilot study may help to develop a novel sustainable wearable system providing vibration-based muscle activation for upper limb function rehabilitation. It may provide patients the opportunity to apply the prescribed vibratory stimuli in-home and/or at community settings. It may also allow therapists to monitor treatment usage and patient performance and to adjust the treatment doses based on progression.

Defining the role of the TMEFF2 transcript in androgen signaling in prostate cancer

PI: Dr. Maria Ruiz-Echevarria, University of Oklahoma Health Sciences Center, Oklahoma City

OCAST Project: HR18-037

Research Area: Cancer Research

PCa is the most common non-skin cancer malignancy diagnosed and the third leading cause of cancer-related mortalities in men in the United States. In Oklahoma, PCa mortality rates are particularly high in minority populations including Black and American Indian populations. In Oklahoma, PCa is the most common malignancy diagnosed in men, and the mortality rate is particularly high in Black and American Indian/Alaskan Native populations. PCa is a hormone driven disease, and the majority of PCa cells have a dependency on androgens for growth and survival. This dependency is exploited in the treatment of PCa with androgen deprivation therapies, which lower circulating androgen levels in PCa patients. Androgen deprivation is initially successful in the treatment of PCa, however most patients develop resistance overtime and the disease progresses to the currently incurable castration resistant prostate cancer (CRPC) form, often the cause of death in PCa patients. Many CRPC cells are able to maintain androgen signaling through re-activation of the androgen receptor (AR) function, even in the presence of low circulating androgen levels, allowing cells to grow in a low androgen environment. Therefore, identifying molecules and cellular pathways that regulate AR function, especially in the setting of CRPC, is of the upmost importance for the development of future PCa therapies and overcoming resistance to androgen deprivation.

The transmembrane protein with EGF-like and two follistatin like domains 2 (TMEFF2) is an androgen regulated gene that is primarily expressed in the adult brain and prostate, and its expression is altered during the progression of PCa. Here we show preliminary data indicating that the TMEFF2 RNA, but not the protein, functions as regulator of androgen signaling in PCa cells by modulating AR function. We show that the TMEFF2 RNA physically interacts with the AR. In addition, silencing of the TMEFF2 RNA, but not the protein, results in lower AR protein levels and a potent inhibition of androgen signaling in PCa cells. This function of the TMEFF2 RNA is maintained in CRPC cells, indicating that the TMEFF2 RNA/AR interaction could be a potential target for overcoming therapeutic resistance in PCa.

Here we propose a research plan to investigate the role and mechanism of action of the TMEFF2 RNA in PCa androgen signaling. We will seek to: 1) learn how TMEFF2 binds to the AR, 2) identify other molecules involved in the TMEFF2 RNA/AR interaction (which may provide new drug targets for PCa), and 3) investigate the consequences of the TMEFF2 RNA/AR interaction on AR function and ultimately in PCa cells (such as tumor growth). The broad long-term goal of our studies is to define novel molecular mechanisms involved in modulating AR activity with PCa progression and that affect clinical outcome and ultimately resistance to therapy. These results would have a positive impact on PCa patients in Oklahoma and worldwide.

Does glucose dysmetabolism contribute to Native American pain disparities?: A pilot study

PI: Dr. Jamie Rhudy, University of Tulsa, Tulsa **OCAST Project:** HR18-039 **Research Area:** Nutrition, Psychology, Public Health

Native Americans (NAs) have a higher prevalence of chronic pain than any other U.S. racial/ethnic group, yet there have been few attempts to understand the mechanisms contributing to this disparity. Diabetes also disproportionately affects this population. One of the many complications of diabetes is neuropathy (nerve damage) that affects peripheral and central nerves associated with pain and its regulation. Some of these neurotoxic effects can even occur in response to subclinical glucose dysmetabolism (eg, prediabetes).

Consistent with this, our preliminary data on 232 (NA=118, non-Hispanic white=114) healthy, pain-free, non-diabetic participants found a relationship between diabetes risk factors and pain promoting processes. Specifically, we found that participants with =3 diabetes risk factors (eg, family history of diabetes, overweight, sedentary) had: 1) deficits in peripheral small fibers that carry pain signals, 2) enhanced central sensitization (spinal hyperexcitability), 3) impaired descending pain inhibition (inability to dampen pain), and 4) decreased pain tolerance (enhanced pain sensitivity). Most in this group were NAs suggesting this pain risk pathway may be particularly problematic for this population.

We hypothesize these effects stem from individual differences in glucose dysmetabolism, but this can only be inferred because glycemic status (eg, HbA1c) was not measured. Thus, the relationship between glucose dysmetabolism and pain risk in NAs needs to be directly studied in persons with verified variation in glycemic status. The aim of this study is to determine the influence of glucose dysmetabolism on markers of pain risk in NAs. To do so, 50 NAs and 50 non-Hispanic whites who are normoglycemic (n=50) or type 2 diabetic without pain (n=50) will be recruited.

Testing will use state-of-the-art quantitative sensory testing methods that assess all levels of the nervous system. Peripheral fibers will be assessed from warm detection thresholds and contact heat evoked potentials. Central sensitization will be assessed from temporal summation of the nociceptive flexion reflex (NFR; physiological measure of spinal hyperexcitability). Pain inhibitory processes will be assessed from the conditioned pain modulation (CPM) task (ie, pain inhibits pain). Pain sensitivity will be assessed from cold pain tolerance.

This research is expected to impact minority health disparities in several ways: 1) identify mechanisms that contribute to NA pain disparities, 2) provide evidence that NAs have a unique pain risk pathway (eg, hyperglycemia) that warrants a tailored intervention approach, and 3) lay the groundwork for interventions that can be implemented prior to diabetes onset when they may be more effective in eliminating neurotoxicity and pain risk.

Central epigenetic reprogramming of amygdala receptor expression in stress-induced chronic pain

PI: Dr. Beverley Greenwood-Van Meerveld, University of Oklahoma Health Sciences Center, Oklahoma City **OCAST Project:** HR18-040

Research Area: Neurobiology

This grant focuses on understanding the basic mechanisms that underlie stress-induced chronic pain in order to improve the lives and the treatment options for patients suffering with chronic pain. It is my overarching hypothesis that changes in how nerves communicate with each other occur within an important area pf the brain known to be involved in the emotional responses to pain (the amygdala) lead to stress-induced chronic pain. In the current application I am building upon exciting and novel published preliminary data obtained in my laboratory in which we found that stress altered the way genes are expressed in the brain, particularly in an area of the brain involved in emotion known an the amygdala. In the current application I will examine the importance of external modification to DNA (epigenetic) by stress to turn on or off genes in the central nucleus of the amygdala without any change to the DNA sequence that lead to chronic pain.

Through the use of innovative methodologies, the project describes a logical combination of mechanistic and interventional aims that will: (i) advance our understanding of the neural and molecular level events responsible for chronic pain, (ii) raise awareness of sex differences in the mechanisms underlying visceral pain processing, (iii) determine whether key central pathways and molecular targets can be targeted to treat stress-induced chronic pain. A novel component of this application is the investigation of why females are more vulnerable to stress-induced pain. Furthermore, the results of this investigation will provide a comprehensive understanding of the beneficial effects of an enriched environment (EE) for the treatment of stress-induced visceral pain.

If my hypothesis is correct the data generated from this grant will result in an enhanced understanding of the mechanisms by which persistent changes in the brain prolong pain leading to chronic pain disorders. Importantly our findings may identify novel approaches and targets for new therapies directed at the brain to improve the treatment or even reduce the risk for the development of chronic pain.

Does prolyl oligopeptidase inhibiton suppress tumor growth?

PI: Dr. Victoria Christiansen, University of Oklahoma Health Sciences Center, Oklahoma City
OCAST Project: HR18-046
Research Area: Cancer Research

According to the Centers for Disease Control and Prevention (CDC) 19,044 new cases of cancer were diagnosed in Oklahoma in 2013 with 8,039 cancer deaths. Despite progress, there are still significant health issues due to cancer. One target for the control of cancer growth has been the inhibition of new vessel formation. All tumors need a supply of nutrients and oxygen and that need is met by the formation of new blood vessels. The majority of cancer treatments targeting new vessel formation focus on growth factor pathways such as VEGF, EGF and their receptors. However, delayed growth of tumors and no significant increase in life expectancy of the patients limit their use.

We propose to attack a different pathway that promotes new vessel growth, the prolyl oligopeptidase (POP) pathway. POP is found in virtually all tissues and is increased in cancer as opposed to normal tissue. POP only cuts proteins that have less than 30 amino acids. It cuts a shortened version of thymosin-ß4 (Tß4) to yield the vessel-promoting peptide, Ac-SDKP. We developed a compound that blocks the activity of POP and named it J94. It is effective at very low amounts. Blocking of POP activity by J94 greatly reduced the formation of tubules in a test for vessel growth. This effect could be reversed by adding Ac-SDKP. J94 markedly slows growth of human colon cancer tumors in a mouse model. J94 appears to work by reducing growth of new vessels. Mice treated with J94 showed slower tumor growth during a preliminary 28 day study.

The proposed work aims to establish that J94 slows colon cancer growth in a mouse tumor model. Several doses of J94 will be used to determine the best dose for slowing colon cancer tumor growth. J94 will also be tested in a mouse tumor model of human lung cell cancer. The CDC reports that breast cancer caused 23 deaths/100,000 women in Oklahoma in 2013, but these deaths were mainly due to cancer spreading and not the original tumor. This study will also use a mouse model of breast cancer that examines growth rate of the primary tumor and also the number and size of distant tumor growths when new vessel growth is slowed by our POP inhibitor, J94. Study of the proteins involved in the multiple steps of the POP pathway will provide more opportunities to affect the growth of new vessels. While it is known that Tß4 is shortened before POP can cut it to produce Ac-SDKP, this happens due to an unknown enzyme. We will explore the identity of these enzyme(s).

Our preliminary data has identified two possible enzymes and the literature identifies one other that may be involved. These enzymes as well as the products they yield will be tested for ability to increase vessel formation in a vessel forming assay. Inhibitors of these enzymes will also be tested for the ability to slow vessel formation in the same assay. Knowledge of the enzymes and products in this distinct vessel forming pathway will provide new targets for anti-cancer treatments.

Discovery of indolizidine (–)-237D analogs as selective a6* receptor antagonists

PI: Dr. Syed Raziullah Hussaini, University of Tulsa, Tulsa **OCAST Project:** HR18-049 **Research Area:** Physiology & Pharmacology

Annually, cigarette use causes 7,500 Oklahoma deaths. Better anti-smoking agents are needed. Current smoking cessation agents bind to many nicotinic acetylcholine receptors (nAChRs) subtypes. This nonspecific binding causes unwanted side effects. Compounds that target only a6* nAChRs could be more effective and may cause fewer side effects. The long-term goal is to discover analogs of (-)-237D that selectively inhibit a6* nAChRs. 237D has suboptimal physicochemical properties. Its pharmacokinetic profile is unknown. Hypothesis: Analogs of 237D can be found that have physiochemical properties suitable for in vivo studies while targeting only a6* nAChRs These analogs could inhibit the addiction-relevant behavioral effects of nicotine in animal models.

Objective: Discover analogs of 237D with favorable physiochemical properties. Such analogs could serve as probes of a6* nAChR function in both in vitro and in vivo. These probes could determine the role of a6* nAChRs in nicotine addiction.
Innovation: Novel analogs based on the structure of (-)-237D will be designed and evaluated for affinity and selectivity at a6* nAChRs.
Specific aims: Generate diverse 237D analogs in silico.

We will select analogs that score = 4 by the Central Nervous Systems Multiparameter Optimization (CNS MPO) algorithm. This algorithm uses six physiochemical parameters to identify compounds that are suitable for in vivo testing. We will perform virtual screening with these analogs to find ones that may bind tightly to a6* nAChRs. The lead compounds will be ranked by computation of their free energy of binding. Top leads will be made via metal-catalyzed reactions with thioamides and diazo compounds. Analogs will be tested for their potency at a6* nAChRs via inhibition of nicotine-evoked dopamine release from superfused rat striatal slices. Selectivity of the analogs will be determined in assays for three off-target interactions.

The first interaction is with the human ether-a-go/go channel. This interaction will be tested using cultured HEK cells that express this cardiac K+ channel. The second assay will assess dopamine uptake at the dopamine transporter using rat striatal synaptosomes. The third assay will assess interactions with predominant nAChRs (a4ß2 and a7) in the brain using radioligand binding assays. The milestone for the proposal will be the identification of leads with good physicochemical properties (CNS MPO score of = 4), high affinity (< 100 nM) for the a6* nAChR, and selectivity (> 30-fold) for the a6* nAChR target relative to off target sites.

In future studies, lead analogs will be refined to improve selectivity and potency. Pharmacokinetic profiles of emerging leads and backups will be determined. Their effects in addiction-relevant behavioral assays will be evaluated. These analogs will be used as probes to determine the role of a6* nAChRs in addiction-relevant behavioral models and may serve as new smoking cessation agents targeting a6* nAChRs.

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Testing the role of inflammation in aging and age-related diseases

PI: Dr. Deepa Sathyaseelan, University of Oklahoma Health Sciences Center, Oklahoma City
OCAST Project: HR18-053
Research Area: Cell & Molecular Biology

A common feature of aging and age-related diseases (e.g. type 2 diabetes, cardiovascular diseases, cancer, Alzheimer's disease etc) is low-level chronic inflammation, termed sterile inflammation (indicating inflammation in the absence of detectable pathogens) or inflammaging. Inflammaging is an important risk factor for both morbidity and mortality in older people and is characterized by high levels of proinflammatory cytokines (molecules that causes inflammation). Even though the association of inflammation with age and age-related diseases is well established, it is not known whether the increased inflammation that occurs with age is a causative factor in the increased incidence of age-related diseases and aging and what the molecular mechanism responsible for the increased inflammation that occurs with age. In other words, there is no direct evidence showing that inflammaging plays a role in causing aging or the diseases associated with aging. Our laboratory studies a mouse model that is deficient in an anti-oxidant enzyme, Cu/Zn-superoxide dismutase knockout mice (Sod1KO mice), which shows several accelerated aging phenotypes, have a shortened lifespan (~30% decrease) and increased inflammation. Thus, Sod1KO mouse gives us an excellent model that will allow us to determine if inflammation is a causative factor in age-related diseases and aging and begin dissecting out the mechanism(s) responsible for inflammaging.

Necroptosis is a newly identified pathway of programmed necrosis that plays a major role in inflammation through the generation of damage-associated molecular patterns (DAMPs). Necroptosis is initiated when necroptotic stimuli sequentially activate the receptor-interacting protein kinase 1 (RIPK1), RIPK3, and mixed lineage kinase domain like (MLKL) protein through phosphorylation. Phosphorylated MLKL binds to and disrupts the plasma membrane of cells, releasing DAMPs. Studies show that inhibiting necroptosis by knocking out Ripk3 reduces necroptosis as well as inflammation in several mouse models. My preliminary data shows that necroptosis was dramatically elevated in various tissues of the Sod1KO mice and inhibition of necroptosis using necrostatin1-s (pharmacological inhibitor of necroptosis) reduced necroptosis and transcript levels of pro-inflammatory cytokines in the brain and spinal cord of the Sod1KO mice. Based on this, I will test the hypothesis that the shortened lifespan and accelerated aging phenotype of the Sod1KO mice is due to increased inflammation that arises from necroptosis and that preventing necroptosis will improve lifespan and retard aging in the Sod1KO mice.

This will be the first comprehensive study into the role of necroptosis in aging phenotypes, and data generated from this study are translationally relevant because there are pharmacological agents than can inhibit necroptosis and potentially reduce chronic inflammation and improve healthspan.

OCAST

Fit-for-duty: An examination of the efficacy of the physical abilities test in determining physical readiness

PI: Dr. Roger Kollock, University of Tulsa, Tulsa **OCAST Project:** HR18-054 **Research Area:** Nutrition, Psychology, Public Health

Firefighters routinely face dangerous conditions and are at risk for injury or death from a variety of mechanisms such as heat strain, fire exposure, smoke inhalation and burns. The physical demand of firefighting evokes a significant activation of cardiovascular, metabolic and musculoskeletal systems increasing the physiological and mechanical strain on the body, thus, increasing the risk for fatal and non-fatal casualties at the fireground. Locally in Tulsa, Oklahoma during the years 2001-2011, the Tulsa Fire Department sustained >6,000 casualties for an estimated $19 million in total workers' compensation claims.

According to the most recent publically available records, in 2012 there were 80 occupational injuries per 10,000 full-time workers for Oklahoma local municipalities resulting in an average of 14 days missed from work. To help minimize the risk of fatal and nonfatal casualties, local municipalities often require firefighters complete an annual physical ability test (PAT) to determine if they are fit-for-duty. The PAT is normally a modified version of the nationally recognized candidate physical abilities test (CPAT). To date, there is no evidence supporting the validity of the CPAT as an indicator of physical readiness. Components of physical readiness include cardiorespiratory capacity, mobility, body composition, and muscular strength and power.

The proposed project for funding is Phase II of a three-phased investigation. Phase I of the investigation was designed to explore the percentage of firefighters injured within time-based quartile ranking of the CPAT. The specific aim for Phase II of the investigation will be to determine the percentage of shared variance between the CPAT and recognized scientific standards for assessing physical readiness. This project is novel because no other study has investigated the effectiveness of the CPAT, or modified versions of the test, on its ability to validate true physical readiness. Our University and its resources make it an ideal setting for this type of OCAST health related research project. This project aligns with the objectives set forth by OCAST to investigate causes, diagnosis, treatment, and prevention of human disease.

Currently, we have fostered a meaningful relationship with the Tulsa Fire Department and City of Tulsa. This project represents the University of Tulsa's commitment for community engagement to help address the needs of Oklahomans. Results of this project (Phase II) will directly benefit the City of Tulsa and Tulsa Fire Department by providing valuable insight into the effectiveness of Tulsa Fire Department's current standard of practice for determining physical readiness. Evidence obtained from this project will help support the ongoing measures to enhance physical readiness evaluation, reduce the overall casualty rate, and reduce worker compensation claims for the City of Tulsa and provide valuable insight to surrounding communities.

A mobile platform for clinical gait analysis

PI: Dr. Guoliang Fan, Oklahoma State University, Stillwater
OCAST Project: HR18-069
Research Area: Instrumentation, Data Sciences, Clinical Evaluation

This project seeks an innovative approach to develop a mobile platform for low-cost clinical gait analysis, which can (1) autonomously follow a walking subject in a free and natural setting and from three different perspectives; (2) reliably estimate full-body gait kinematics represented by skeletal joint angles and points, (3) robustly extract relevant biomechanical parameters for gait imbalance assessment. The proposed system is targeted on the limitation and constraints of the current motion capture (Mocap) systems, including "gold standard" optical Mocap systems, vision-based gait analysis tools, pressure sensor mats and wearable sensor networks.

The proposed system is designed to minimize the interference and constraints to the subject's motion pattern, while maximizing the subject's walking space and freedom and supporting multi-view motion capture. The system is economical (under $2,000 hardware), portable and fully integrated with a small footprint. The proposed mobile Mocap system has great potential to be applied for many motion-related clinical applications, gait disorder analysis, physical therapy and musculoskeletal surgery rehabilitation. The main system hardware includes a vision-guided robot, a RGB-D sensor, and a laptop.

This applied research is built on the past two OCAST projects that were about video-based motion analysis in clinical applications and the current NRI (National Robotics Imitative) project from NSF that is aimed at developing a considerate co-robot in an assisted-living environment. From the past success, we have learned two key insights which motivate the proposed project to further bridge the gap between motion/gait analysis and clinical/medical applications. One is that clinical Mocap should be done "on-the-go" in a free and natural setting and from multiple perspectives, and the other is the current Kinect-based Mocap capability needs major enhancements in the accuracy and sensitivity to be more clinically and medically useful.

The past and current efforts provide a unique opportunity for the PI to propose this project that resonates with (but is superior to) the two early preliminary attempts. In previous studies where vision capability was limited, the main research focus was on the robot design and hardware integration. In this project, the focus is on the enhancement, enrichment and engagement of the robot's vision capability for multi-view motion capture and extraction of biomechanical gait parameters.

The proposed research is translational in the sense that it bridges the gap between lab and clinic by creating a new mobile solution to advanced clinical gait assessment. This research involves one collaborator, Dr. Jerome Hausselle who is specialized in biomechanical analysis and musculoskeletal modeling, and he will be involved for system validation and evaluation in detecting gait imbalances related to long-term joint degeneration.

Regulation of RAG2-chromatin interactions during V(D)J recombination

PI: Dr. Karla Rodgers, University of Oklahoma Health Sciences Center, Oklahoma City
OCAST Project: HR18-039
Research Area: Immunology

In developing B and T lymphocytes, functional immunoglobulin and T cell receptor genes are produced by assembly of component gene segments through V(D)J recombination. The array of possible combinations for gene assembly is the basis for sequence diversity of the antigen binding receptors in the immune system. The first phase of the recombination reaction is catalyzed by the V(D)J recombinase, which consists of RAG1 and RAG2, proteins encoded by the recombination activating genes. Together the RAG proteins create double strand breaks at site-specific DNA sequences, referred to as recombination signal sequences (RSSs), which are located within the antigen receptor loci.

A critical step in this process is the selective binding of the RAG proteins to an RSS over the vast array of accessible DNA present in the human genome. Incorrect targeting of the RAG proteins to non-RSS sites is believed to lead to errors in the recombination reaction, which can result in genomic instability, such as chromosomal translocations. To understand the basis for correct versus incorrect targeting of the RAG proteins to genomic sites, it is important to deduce how these proteins are targeted to chromatin. In that regard, it is known that RAG2 specifically binds H3K4me3 (Histone H3 trimethylated on lysine 4), an epigenetic mark that is enriched at antigen receptor loci and transcription start sites. Significantly, binding of RAG2 to this modified histone activates the DNA cleavage activity of the RAG1-RAG2 complex, although the mechanism for this important regulation is not known.

Based on our recent preliminary results, we hypothesize that RAG endonucleolytic activity is regulated through a conformational switching mechanism of RAG2, which is twiggered by the opposing effects of RAG2 phosphorylation and H3K4me3 interactions. We propose that this mechanism would decrease the risk of RAG-mediated DNA cleavage activity at non-antigen receptor loci. To test our hypothesis, in Aim 1 we will determine if phosphorylation of RAG2 negatively regulates its interaction with chromatin. In Aim 2, we will elucidate the role of H3K4me3 in affecting conformational switching of RAG2, and how this conformational change favors RAG2-nucleosome interactions. In Aim 3, we will ascertain if misregulation of RAG2 conformational switching affects the activity and fidelity of V(D)J recombination at antigen receptor loci. Overall, this project will reveal previously unknown mechanisms that regulate association of RAG proteins with chromatin.

Investigation of impact of virtual reality based cyber learning approaches

PI: Dr. Joe Cecil, Oklahoma State University, Stillwater **OCAST Project:** HR18-077 **Research Area:** Biomedical Engineering

Autism and Autism Spectrum Disorders (ASD) are general terms for a group of complex disorders of brain development. The Center for Disease Control (CDC) estimates that one in 68 children in our nation have autism; Studies have also shown that autism is 4 to 5 times more prevalent in boys than girls. Current estimates are that it affects over 2 million individuals here in the US and tens of millions globally. Virtual Reality (VR) is considered one of the technologies that holds potential to help individuals with autism be better prepared to lead productive lives.

In this innovative project, our objective is to study the impact of using Virtual Learning Environments (VLE) to help children with autism learn science and engineering. We will adopt an Applied Behavior Analysis (ABA) based approach to investigate the impact of using such VLE based learning environments. We plan to develop unique VLEs using low cost immersive and haptic technologies and study the impact of such VLES on learning and engagement among children with autism in elementary, middle and high schools.

Identifying a direct path to emotion dysregulation in borderline personality

PI: Dr. Stephanie Sweatt, Oklahoma State University, Stillwater
OCAST Project: HR18-079
Research Area: Nutrition, Psychology, Public Health

Emotion dysregulation (ED) is related to serious maladaptive behaviors such as suicide, substance misuse, nonsuicidal self-injury, and risky sexual behaviors, all of which are associated with significant negative health outcomes. While there is a marked association between ED and detrimental consequences, the biopsychosocial mechanisms by which components of ED interact to produce negative outcomes and psychiatric disorders are unclear. Given that ED is a core feature of borderline personality disorder (BPD), delineation of the pathway from ED to negative outcomes within BPD is necessary in order to inform efficacious interventions aimed at regulating affect within BPD. Carpenter and Trull (2013) outlined a structural model with four distinct components proposed to result in ED within BPD.

The long-term goal of this study (Components of Regulating Emotion; CORE) is to identify the route wherein ED produces significant negative health outcomes, in order to inform targeted treatments. The first required step to identify the pathways of this model is to test the direct route from emotion sensitivity to heightened negative and unstable affect. To achieve this goal, CORE has two aims that will be addressed within a sample of individuals with emotional dysregulation (n = 100). The first aim is to demonstrate the extent of negative interpretation bias and heightened emotion sensitivity to facial expressions of emotions in individuals with borderline personality traits. This will be accomplished through laboratory tasks of emotion identification and intensity.

The second aim is to establish a direct model by which emotion sensitivity predicts subsequent heightened negative and unstable affect over time. This will be accomplished via ecological momentary assessment of mood. The impact of emotion sensitivity on changes in mood over time using advanced statistical techniques to model changes in affect will be examined. It is expected that heightened emotion sensitivity and negative interpretation bias will predict more negative and unstable affect. The use of EMA methodology is a major strength of CORE given that it is more precise than retrospective reporting of affect, which is often utilized in the extant literature. CORE will provide evidence for the path from emotion sensitivity to unstable affect within ED. Identification of this path will inform subsequent hypotheses isolating related components of the ED model within individuals with borderline personality traits.

This contribution is significant, as it will begin to address a specific path of ED that has not been tested, with an ultimate goal of understanding the mechanisms that translate ED into significant negative outcomes. This long-term research goal can then contribute to the identification and implementation of interventions targeting the detrimental process of ED. This research will broadly impact the field of psychopathology by gaining a precise understanding of the pathway to ED.

Non-contact, in vivo measurement of hyper-elastic response of bio-membranes for predicting traumatic injuries

PI: Dr. Shuodao Wang, Oklahoma State University, Stillwater **OCAST Project:** HR18-085 **Research Area:** Biomedical Engineering

The Medical device industry is expected to reach over $300 billion by 2021. To reduce cost and speed-up the regulatory approval required by the FDA, it is increasingly important to develop advanced modeling, simulation and analysis techniques, including creating models of the human anatomy to virtually test potential medical technologies or protocols. Building these models requires accurate experimental data of the physical and chemical properties of bio-tissues, but characterizations of bio-tissues are extremely difficult, especially for soft, thin bio-membranes such as tympanic membranes (the eardrum), meninges of the brain, thoracic diaphragm, and heart valves. It is desirable to obtain the full-field bio-membrane properties by developing non-contact, in vivo testing tools to accurately characterize properties of living tissues in their bio-contexts and environments. Unfortunately, there is no existing testing technique that is capable of performing this type of test, so the mechanical properties biomedical researchers use in existing simulations are usually not reliable or even contradictory among different studies.

The specific objective of this proposed work is to develop a novel non-contact, in vivo testing framework for measuring the hyper-elastic mechanical properties of soft bio-membranes. The PI proposes to use full-field three-dimensional (3D) fluorescent technique in connection with high-speed microscopic photography to detect the deformation of bio-membranes under bulge pressure loading. An inverse-problem methodology will be adopted by combining finite element method (FEM) simulation and numerical iterations to obtain the bio-membrane's full-field response so that a full 'map' of localized bio-membrane properties can be obtained.

Novel experimental techniques combined with finite element simulations will be developed in this project to accurately determine the hyper-elastic properties of tympanic membranes (TM). The proposed framework will be validated with artificially fabricated silicone membrane samples to assess the success of this project. Future projects will extend this work to measure more complex dynamic properties of TMs to capture their behavior under dynamic, fast-changing loads such as blast waves, or under traumatic conditions of fast bio-fluid buildups. These models can then be used to analyze and predict effects of different external stimuli, medical procedures, or interactions between tissues and biomedical devices, thereby aiding the development of new medical devices or diagnostic/ treatment procedures. In the larger scope, the research scheme can be applied to build accurate tissue models for other tissues such as the cerebral cortex, cornea, heart valves, human skin, etc. and study their dynamic responses under traumatic conditions.

Validating a clinical decision support algorithm developed with big data to diagnose, state, prevent, and monitor a patient's diabetic retinopathy

PI: Dr. William Paiva, Oklahoma State University, Stillwater
OCAST Project: HR18-087
Research Area: Instrumentation, Data Sciences, Clinical Evaluation

An estimated 29 million Americans aged 20 years or older have either been diagnosed or remain undiagnosed with diabetes. They incur $245 billion in annual health care cost. Diabetic retinopathy, a major complication for diabetics, is the most common cause of vision loss among people with diabetes and a leading cause of blindness for people aged 20 to 64. Diabetic retinopathy affects up to 80% of all patients who have diabetes for 20 years or more. Research indicates that at least 90% of diabetic retinopathy cases could be avoided with proper diagnoses, staging, and monitoring of each individual's condition. The traditional method utilized for detecting diabetic retinopathy is a comprehensive annual eye exam by an Ophthalmologist.

Despite the aforementioned intimidating statistics, the annual eye evaluation is one of the worst compliance index tracked. There are many reasons for this poor compliance: 1. Patients with diabetic retinopathy often do not experience symptoms and early warning signs to compel them to seek the evaluation, 2. Availability, and occasionally willingness, of ophthalmologists to perform the annual screening, especially in rural underserved areas thereby inhibiting convenient access to the evaluation. This is explicitly unfortunate because an extremely effective laser therapy exists if diagnosed early. With a growing diabetic population and continued increase of medical access barriers, it is imperative to develop a tool for preventing, diagnosing, screening, and managing diabetic retinopathy to cater to patients living with diabetes.

The proposed research lays the foundation for this kind of tool. Specifically, we propose to finalize and test a clinical decision support algorithm based on a patient's current lab results to decipher whether a patient has diabetic retinopathy. The effectiveness of this method is that diabetic patients are significantly more compliant with annual lab testing as it is a required diabetic management component. Ideally, primary care physicians would be empowered to assess patient diabetic retinopathy as part of a standard in-office primary care visit. This tool was developed by performing big data, descriptive and predictive bioanalytics on the largest relational HIPAA compliant health care database that was donated to OSU and is CHSI's competitive advantage. This donated dataset covers over 63 million patient's clinical records that has been collected over 16 years. The clinical decision support algorithm was developed over the last 18 months by performing descriptive analytics on over 1,422,134 unique diabetic patients, with 5,361,298 clinical encounters, and predictive analytics on 305,997 unique diabetic patients, with 822,019 encounters. Our algorithm will lead to a new standard of care for diabetic patients. It has the potential to make a significant health and economic impact for Oklahoma and patients nationwide. Furthermore, successful completion of this trial will enable larger grants.

Non-invasive liquid biopsy approach for using exosomes as a surrogate

PI: Dr. Rajagopal Ramesh, University of Oklahoma Health Sciences Center, Oklahoma City
OCAST Project: HR18-088
Research Area: Instrumentation, Data Sciences, Clinical Evaluation

Effective treatment of lung cancer remains a formidable clinical challenge. Standard of care has not improved patient survival and the overall five-year survival of lung cancer patients remains dismal at <16%. The advent of molecularly-targeted therapies and immune checkpoint inhibitors has shown promise in lung cancer treatment. However, occurrence of tumor heterogeneity results in only a subset of patients benefiting from these therapies. Further complication encountered frequently is the development of drug resistance. Therefore, apart from developing new therapeutics, there is an urgent need to screen for biomarkers that will enable in predicting treatment response. and allow oncologists in making quick treatment decisions, and improving patient survival.

To address and overcome some of the existing limitations, this application proposes a "novel and innovative strategy for monitoring and predicting response to immunotherapy" by utilizing a non-invasive liquid biopsy approach of isolating exosomes from urine and using them as a surrogate marker in lung cancer patients receiving immunotherapy, specifically pembrolizumab (anti-PD1). The scientific rationale is based on the following observations: First, exosomes have been shown to play a role in tumor metastasis and drug resistance; Second, a recent study reported programmed death ligand (PD-L)1 expression on exosomes isolated from head and neck cancer patients that correlated with disease progression; Third, development of resistance to immune check point inhibitors has recently been reported. Fourth, the most recent report demonstrates PD-L1 expressing exosomes derived from glioblastoma multiforme (GBM) suppress T-cell function and immune response; Fifth, majority of the studies reported till date examining PD-L1 or other exosomal markers have applied invasive to minimally invasive approach for isolating exosomes from blood and plasma; Sixth, preliminary studies from our laboratory demonstrate urine-derived exosomes from cancer patients express PD-L1, a marker that defines immune suppression in the tumor milieu.

Based on our preliminary studies, we hypothesize that PD-L1 expression levels in urine-derived exosomes will define response to immunotherapy, specifically pembrolizumab (anti-PD1) therapy. To test our hypothesis we propose conducting studies under two specific aims:
Aim 1. (a). Examine expression of PD-L1 and other immune checkpoint proteins in urine-derived exosomes from lung cancer patients receiving pembrolizumab (anti-PD1) as a single agent or in combination with chemotherapy and correlate with clinical response.
(b). Evaluate expression of PD-1 and other immune check point proteins on T-cells isolated from cancer patients.
Aim 2. Investigate the immune-modulating properties of urine-derived exosomes in vitro.
The study will be conducted by a multi-disciplinary team of investigators with expertise in lung cancer, patient care, pathology, immunology, statistics.

Neuroimmune activation and weight gain in a rat model of post-menopausal obesity

PI: Dr. Kathleen Curtis, Oklahoma State University for Health Sciences, Tulsa **OCAST Project:** HR18-089 **Research Area:** Neurobiology

Oklahoma ranks 6th in the US in incidence of obesity, with obesity in more than 30% of adults. As bad as this is, obesity only increases with age. Given the aging of our population, and diseases associated with obesity such as diabetes and hypertension, it is clear that better understanding and management of obesity is critical. Although important advances have been made in understanding how the central nervous system (CNS) controls feeding and body weight, current approaches have not been successful in reducing obesity. This failure is a particular concern for women's health, and especially for post-menopausal women since 38% of women over 60 are obese. It is well-known that body weight increases after removal of the ovaries in animals and after menopause in humans.

Accordingly, we propose to use female rats and examine inflammation in the CNS induced by weight gain after ovariectomy. This weight gain does not require special diet formulations or genetic manipulations, so we will be able to distinguish between changes due to obesity vs. changes due to dietary manipulations or to genetic manipulations independent of obesity. Importantly, the post-ovariectomy weight gain occurs rapidly and predictably, so we can investigate changes in the CNS that occur as obesity develops, and target specific factors in specific CNS areas.

These studies will allow us to identify factors that change early during post-ovariectomy weight gain, or at particular phases of the weight gain, rather than with established and extreme obesity. Ultimately, the information will be critical in effectively targeting these factors in attempts to manage—or prevent—obesity.

The UNIVERSITY of OKLAHOMA Health Sciences Center

Novel mechanism of age-related cerebromicrovascular dysfunction

PI: Dr. Anna Csiszar, University of Oklahoma Health Sciences Center
OCAST Project: HR18-092
Research Area: Physiology & Pharmacology

Moment-to-moment adjustment of cerebral blood flow (CBF) is essential for normal neuronal function in the brain. It is regulated via neurovascular coupling (NVC), which maintains the continuous supply of oxygen and nutrients to the neurons, however it becomes progressively impaired during aging, increasing the risk for vascular cognitive impairment. Our recent studies show that, in fact, impaired NVC responses and cognitive impairment are closely related. Although vascular causes of age-related cognitive decline are likely preventable, the age-related mechanisms that impair NVC responses, which contributes to a significant age-related decline in higher brain function, remain largely unknown.

Our recent studies show that age-related impairment of NVC is due to cerebromicrovascular endothelial dysfunction. Further, we recently demonstrated that rescue of endothelium-dependent NVC responses mitigates cognitive impairment in aged mice. The focus of this application is to identify reversible causes underlying cerebromicrovascular dysfunction in aging for the prevention of NVC dysfunction and vascular cognitive impairment. NAD+ is a rate-limiting co-substrate for anti-aging enzyme SIRT1, which is a key regulator of mitochondrial function, cellular redox homeo-stasis and eNOS activation. With age cellular NAD+ availability decreases, which is a critical driving force in aging processes.

There is increasing evidence that age-related overactivation of the poly(ADP-ribose) polymerase PARP-1, which is a critical NAD+ utilizing enzyme, contributes significantly to reduction of cellular NAD+ levels. Further, in aged mice enhancing NAD+ biosynthesis by treatment with nicotinamide mononucleotide (NMN; a key NAD+ intermediate) or decreasing NAD+ utilization by inhibiting PARP-1 reverses age-related dysfunction in multiple organs. The potential protective effects of NMN and/or PARP-1 inhibition on the aged cerebral microvasculature and endothelium-dependent NVC responses have not been investigated. The objective of the present proposal is to elucidate the mechanistic effects of age-related decline in cellular [NAD+] on NVC pathways and to develop novel therapeutic approaches for prevention/treatment of vascular cognitive impairment in the elderly.

Copper nanocatalyst as efficient heterogeneous photocatalyst for continuous syntheses of pharmaceuticals through cross-coupling reactions

PI: Dr. Mari Andiappan, Oklahoma State University, Stillwater **OCAST Project:** HR18-093 **Research Area:** Chemistry & Biochemistry

Approximately 25% of all the reactions performed in the pharmaceutical industry consist of cross-coupling reactions. The cross-couplings have been traditionally carried out by homogeneous palladium (Pd) catalyzed batch processes. The National Science and Technology Council (NSTC) has recently identified the continuous manufacturing of pharmaceuticals as one of five manufacturing areas of emerging priority. Continuous manufacturing of pharmaceuticals has the potential to (i) reduce manufacturing cost by up to 40-50 percent, (ii) improve product quality, (iii) reduce waste generation, and (iv) reduce the manufacturing facility space by 10 to 100 times. Additionally, continuous processes are safe, agile and robust. Therefore, pharmaceuticals manufacturing by continuous processes also has the potential to mitigate the public health threats arising from drug shortages.

Given these advantages, heterogeneously catalyzed cross-couplings have been of great interest since they can be used as platform to switch cross-couplings from traditionally used batch mode to continuous flow mode. It has been shown that metal nanocatalysts such as palladium (Pd) and gold (Au) nanocatalysts are promising heterogeneous catalysts for cross-couplings. However, these metal catalysts are expensive and require more drastic reaction conditions (e.g., high temperatures) because of their low catalytic activity. Another critical challenge that continues to hinder the applicability of these nanocatalysts in continuous flow reactor (e.g., packed bed reactor) is the poor stability of catalyst due to leaching of metal atoms under reaction conditions.

Therefore, there remains a critical need to develop a cheap metal nanocatalyst with high activity and long-term stability for cross-couplings. The objective of this project is to develop inexpensive, earth-abundant and comparatively less toxic plasmonic copper (Cu) nanocatalyst with activity superior to that of expensive, rare earth and toxic homogeneous Pd catalysts for cross-coupling reactions. Specifically, we propose to demonstrate visible-light mediated plasmonic Cu nanocatalyst as highly active and stable catalyst for cross-couplings.

We also propose to utilize a novel in-operando UV-Vis surface plasmon spectroscopic technique to identify stable heterogeneous catalytic systems and green solvents for cross-couplings. The heterogeneous photocatalytic approach proposed in this project has the potential to significantly reduce the manufacturing cost and increase the rate of production of pharmaceuticals. Successful completion of the project will have a major impact on the pharmaceutical industry in Oklahoma.

A novel virus-like-particle based RSV vaccine to generate broad and durable protection

PI: Dr. Antonius Oomens, Oklahoma State University, Stillwater **OCAST Project:** HR18-097 **Research Area:** Infectious Disease

Respiratory syncytial virus (RSV) is an RNA virus responsible for >100,000 deaths in children worldwide each year, and significant morbidity and mortality in the elderly. A past vaccine trial using inactivated virus failed to protect and instead caused virus-enhanced lung disease (VED) upon exposure to RSV. Absent of an approved vaccine, both live and non-live vaccine approaches are pursued. One major challenge for live vaccines is extensive dysregulation of the host response by viral proteins, resulting in poor immune memory. Non-live vaccines do not replicate and hence do not dysregulate the host response. Among the non-live approaches, virus-like-particles (VLPs) are gaining traction, due to recent successes with commercial VLP vaccines and reports showing that VLPs can induce protective anti-RSV immunity without VED and with improved immunological memory.

All current preclinical VLP approaches are based on foreign (non-RSV) VLPs, with most expressing a pre-fusion stabilized form of the RSV fusion (F) protein, termed preF. preF was shown to induce a high proportion of RSV-neutralizing antibodies, making it a critical target. However, a large body of work shows that other RSV antigens can significantly contribute to protection against RSV. Moreover, even a successful single-antigen RNA virus vaccine can induce resistant viruses in the population, as demonstrated in animals and humans. One avenue to overcome dependence on a singular antigen is to induce broad-based immunity with multiple RSV antigens, which could be achieved by using an authentic RSV VLP platform. However, the RSV VLP assembly process seemed unrobust and is poorly understood.

In the past years, we studied particle assembly and developed protocols for generating RSV VLPs in cell culture. These VLPs are indistinguishable from wildtype RSV, which makes them attractive for vaccine purposes. Recently, we generated two unique RSV-based VLPs, one displaying on its surface the preF protein, the other the conserved middle region of the attachment protein G, called G-CCR. The G-CCR is also a very important vaccine target, because it is conserved between strains and contains a receptor binding site, and because anti-G-CCR antibodies were shown to both neutralize the virus and reduce lung pathology caused by RSV. We have developed VLPs that exclusively, and recognizably, display the G-CCR on their surface, to augment the immune response to this important region.

We propose to vaccinate animals with a combination of authentic RSV VLPs displaying either the preF protein or the G-CCR. In addition to these important antigens, RSV VLPs include three additional, conserved, core RSV antigens for which antibodies or CD8 Tcell responses have been observed in humans. Such VLPs should therefore induce an across-strain, potent, response, broadly protective relative to F-alone approaches, and should lack the immune dysregulation observed with live virus and hence display an improved memory profile.

Tetherable glycosaminoglycan polymers for insights into matrix/cell/protein interactions

PI: Dr. Paul DeAngelis, University of Oklahoma Health Sciences Center, Oklahoma City
OCAST Project: HR18-104
Research Area: Cell & Molecular Biology

Phenomena from embryonic development to adulthood rely on molecular interactions at cell surfaces and the surrounding matrix. Certain polysaccharides called glycosaminoglycans [GAGs] and their protein-binding partners are critical for health and disease. While we can identify the minimal 'footprint' of a small GAG chain bound to a single protein active site, the basis for size interrogation and binding is not understood especially for larger physiological polysaccharide sizes. In addition, the organization, structures, and forces involved in GAG/protein complexes are not well understood. With respect to patient treatments, the design of inhibitors or activators typically requires molecular details of the players in the rational design process.

Our hypothesis is that we can use a series of very defined GAG chains with 'handles' for manipulations like atomic force microscopy to obtain insights into the molecular view at the scale found on cell surfaces. Our team has unique synthesis methods to create GAG probes that are tagged at one or both ends to tether GAGs in linear or looped topologies, respectively. This tethering strategy will solve a problem for integrating biological samples like GAGs into powerful instrumentation capable of peering down to the single molecule level. These very defined GAG probes will be rigorously characterized then analyzed for binding with various cell surface proteins. The data will include GAG complex sizes and binding strengths under physiological conditions.

Overall, this information should lead to better understanding of diseases including cancer, inflammation, and birth defects. In addition, these tetherable GAG reagents should be useful tools for other types of biophysical and biomechanical analyses to assist many other workers in the field.

The UNIVERSITY of OKLAHOMA

Two-component signal transduction in the human bacterial pathogen Clostridiodes difficile

PI: Dr. Ann West, University of Oklahoma, Norman **OCAST Project:** HR18-110 **Research Area:** Chemistry & Biochemistry

The bacterial human pathogen Clostridiodes difficile (Cd) is a leading cause of hospital-acquired infections and the CDC classified Cd as an "urgent" threat to human health due to the organism's acquisition of drug resistance, emergence of a hypervirulent strain (R20291) and increasing frequency of Cd infections (CDIs). In humans, this microorganism can colonize the lower intestinal tract, a unique anaerobic (oxygen-free) niche, and cause great discomfort ranging from mild diarrhea to life-threatening colitis. Due to its strict anaerobic lifestyle, the growth and study of this microbe is challenging because it requires specialized laboratory equipment such as anaerobic chambers (glove boxes). In recent years, the West research group at OU was involved in a collaborative project focused on anaerobic structural biology of potentially druggable protein targets in Cd (funded by the Price Family Foundation). Thus, our expertise in structure-function studies of Cd proteins and two-component signal transduction pathways place us in a unique position to significantly advance our understanding of Cd biology.

The genome of the hypervirulent strain of Cd R20291 encodes 54 histidine kinases (HK) and 57 response regulator (RR) proteins comprising two-component signal transduction pathways that allow the organism to sense and respond (adapt) to environmental changes. Many of the RRs are predicted to contain C-terminal DNA-binding domains that presumably bind promoter regions of downstream genes and either repress or activate gene expression. Despite a great deal of knowledge about how RRs function, the prediction, from sequence or structure alone, of which genes that one particular RR binds to and regulates remains a significant challenge in the field. We have adopted a bacterial one-hybrid screen to identify a DNA-binding motif that RR_1586, a response regulator of unknown function, recognizes and binds. Results from this screen as well as in vitro binding data leads us to hypothesize that RR_1586 binds to its own promoter and to promoter regions of genes that encode ion transporters important for sporulation.

Our long-term goal is to determine global signal-to-response regulatory circuitry in Cd from sensory HK function to RR-specific gene regulons since these represent potential protein targets for future development of new antimicrobial therapeutics. The specific aims of this proposal are to: (1) Characterize transcriptional regulation by RR_1586 and (2) Determine the role of phosphorylation in RR_1586 activation and its effects on gene regulation. We expect that successful completion of these specific aims will provide new mechanistic and regulatory insight regarding a heretofore uncharacterized two-component system, important for controlling sporulation in the human pathogen Cd, that could be exploited for therapeutic strategies.

OCAST

Define the role of Mpl in myelofibrosis

PI: Dr. Zhizhuang Joe Zhao, University of Oklahoma Health Sciences Center, Oklahoma City
OCAST Project: HR18-113
Research Area: Cancer Research

This study concerns myelofibrosis, a malignant blood disease caused by the malfunction of hematopoietic stem cells and their microenvironments. Myelofibrosis results from formation of scar-like tissues in the bone marrow, which disrupts normal production of blood cells and lead to severe anemia, weakness, fatigue, and an enlarged spleen and liver due to the mobilization of hematopoietic stem cells. So far, there is no effective treatment for myelofibrosis. Patients with myelofibrosis have a very poor prognosis. By expressing JAK2V617F, a mutant form tyrosine kinase JAK2, and Mpl, the receptor of thrombopoietin, we have generated a transgenic mouse model of primary myelofibrosis. In this study, we will find out how JAK2V617F and Mpl affect hematopoietic stem cells and their microenvironments thereby causing myelofibrosis at the cellular and molecular levels. We will further test if drugs that inhibit JAK2V617F and Mpl related cell signaling can effectively suppress myelofibrosis. This study defines the pathogenesis of myelofibrosis and may lead to identification of therapeutic drugs to treat the disease.

The role of vascular smooth muscle cell plasticity in age-related cognitive decline

PI: Dr. Shannon Conley, University of Oklahoma Health Sciences Center, Oklahoma City
OCAST Project: HR18-118
Research Area: Neurobiology

Cerebral microhemorrhages (CMH) result from rupture of small intracerebral blood vessels and progressively impair neuronal function. The incidence of CMH dramatically increases with age and hypertension and is a major cause for age-related cognitive decline and mobility deficits. Cognitive decline caused by CMH has severe impacts on quality-of-life, yet remains untreatable. CMHs occur due to increased blood vessel fragility but underlying mechanisms are unknown, and thus therapies to mitigate CMHs are not available. Blood vessel integrity requires plasticity of vascular smooth muscle cells (VSMCs).

In response to stress, VSMCs exhibit an adaptive switch from a highly contractile state to a protective anti-fragility state characterized by cell growth and proliferation as well as extracellular matrix remodeling. Aging fundamentally alters the ability of VSMCs to undergo this protective adaptation. In contrast, insulin-like growth factor (IGF)-1 has vasoprotective effects and promotes adoption of the protective anti-fragility phenotype. However, circulating IGF-1 levels are dramatically decreased with age. Low IGF-1 levels increase the risk for cerebromicrovascular disease and promote the development of CMH in our rodent models, supporting a role for IGF-1 deficiency in age-related vascular fragility.

Our hypothesis is that impaired ability of VSMCs to adopt a protective anti-fragility state switching due to deficient IGF signaling has a fundamental role in increased development of CMH and associated neurological and mobility deficits with age. Aim 1 will test the hypothesis that increased CMH in aging is due to vascular fragility arising from decreased IGF-1 signaling in VSMCs. Development of CMH, associated neurological/mobility defects, and VSMC phenotype will be evaluated in 1) mice with VSMC-specific disruption of IGF-1 signaling, 2) aged mice and 3) young controls. Aim 2 will use cultured aged and young cerebral VSMCs to evaluate the role of novel transcription factors Tbx15/18 in IGF-1 mediated adoption of protective VSMC states.

Our goal in aim 2 is to understand cellular mechanisms that regulate different aspects of the IGF-1 induced VSMC protective state, in order to identify future therapeutic targets to halt or prevent CMHs. The scientifically and technically innovative studies proposed here will significantly enhance our understanding of the role of IGF-1 deficiency in the development of CMH in aging, critical given the increased aging population and need to understand root causes for cognitive decline and mobility deficits.

Factors influencing the reproducibility of clinical trials and systematic reviews in addiction research

PI: Dr. Ben Matthew Vassar, Oklahoma State University Center for Health Sciences, Tulsa
OCAST Project: HR18-119
Research Area: Nutrition, Psychology, Public Health

The reproducibility crisis in biomedical and clinical research has raised serious questions about the credibility of study results, and factors contributing to this irreproducibility are not well understood. Absent such knowledge, the development of effective strategies to improve the reproducibility of research will likely remain difficult. The long-term goal is to improve the rigor of addiction science research and the reproducibility of its results to ensure a solid foundation for safe and effective patient care.

The overall objective in this proposal is to identify and evaluate factors contributing to irreproducibility in addiction studies, prioritize such factors, and create a foundation for subsequent interventional studies aimed at improving the reproducibility of addiction research. The central hypothesis is that both contextual (e.g., incentives, journal policies) and study-level factors (e.g., study bias, inadequate reporting) contribute to irreproducibility in addiction studies. The rationale underlying the proposed research is that reproducibility, as a cornerstone of scientific advancement, is essential for the validation of research and progress toward better patient care and clinical decision making.

The plan to evaluate the central hypothesis to achieve the intended objective of this application is to pursue the following specific, independent aims: (1) Appraise key study-level factors contributing to a lack of reproducibility in clinical trials in addiction science; (2) Reproduce the methodology and data analysis of systematic reviews and meta-analyses in addiction science to identify study-level factors contributing to irreproducibility; and (3) Prioritize contextual factors that promote reproducible scientific practices in addiction for the development of future interventions. The approach is innovative, in the applicant's opinion, because it departs from the status quo by taking a unified, collective effort by engaging multiple stakeholder groups to work toward solutions to mitigate irreproducibility. New horizons are expected to become attainable as a result.

The proposed research is significant, because completion of these aims is expected to allow for the diagnosis of key factors in study design, conduct, and reporting that contribute to irreproducibility in clinical trials and systematic reviews. From this information, reporting guidelines can be refined and training efforts strengthened. Until the factors contributing to the lack of reproducibility in addiction research are identified and addressed, unified efforts in the development and delivery of effective interventions to improve the reproducibility of scientific research will remain thwarted. Thus, the results from this proposal are expected to lead to better methodologies, increased transparency and reproducibility in research, and ultimately, better patient care.

Susceptibility to amyloid oligomers in response to aging and insulin/IGF-1 resistance

PI: Dr. William Sonntag, University of Oklahoma Health Sciences Center, Oklahoma City
OCAST Project: HR18-120
Research Area: Physiology & Pharmacology

Age is, by far, the single most important risk factor for the decline in memory, neurodegeneration and Alzheimer's disease (AD). Before 60 years of age the incidence of sporadic AD is rare; however, the risk of developing AD doubles every 5 years after 65 years of age and the age-group with the highest risk of AD are those older than 85, which is the fastest growing age-group in the United States. The cause for the age-related increase in risk for memory impairment and neurodegenerative disease remains unknown but if we are able to find the cause, we may be able to delay or even prevent the onset of the disease.

There are compelling data that Insulin and IGF-1 are involved in the increased risk for neurodegenerative disease with age. These factors that are known to protect brain cells either decrease with age or develop a resistance to the actions of these factors develops. IGF-1 replacement improves cognitive function in aged animals and humans. Insulin, a hormone that acts through a similar pathway, is effective in improving cognitive function in Alzheimer's patients.

Here we propose that insulin and IGF-1 have a key role in protecting neurons and astrocytes from the toxic effects of Amyloid-Beta (1-42) and that the decrease in IGF-1 (and insulin signaling) with age is part of the reason for the increased risk of AD with age. There is little information on this topic and the absence of this key information impairs our understanding of how these factors act to improve cognitive function with age and in AD and impedes progress in developing treatments for both age-related cognitive impairment and AD.

The overall hypothesis of this application is that a decrease in insulin and/or IGF-1 or their signaling pathways compromise energy production within the cell resulting in impairments in learning and memory and increased response to the toxic effects of Amyloid Beta. Two aims are proposed:

1. Establish the effects of astrocyte-specific insulin and IGF-1 receptor signaling on learning and memory and investigate whether responses to the toxic effects of Amyloid Beta are exacerbated by insulin or IGF-1 receptor deficiency.
2. Determine the effects of astrocyte-specific Insulin and IGF-1 signaling deficiency on mitochondrial metabolism and oxidative stress with age and in response to Amyloid Beta.

This application is designed to build on our existing preliminary data, provide proof-of-concept and data for initial publications in this area and collect the additional data required for an R01 submission to NIH. Our studies use state-of-the-art techniques and novel animal models and approaches to address critical topics related to the interaction between aging and Alzheimer's disease. If successful, our studies will provide information, for the first time, on mechanisms the contribute to the increased risk of neurodegenerative disease with age.

The UNIVERSITY of OKLAHOMA

Rational development of selective and potent inhibitors to pro-apoptotic Bax protein

PI: Dr. Yihan Shao, University of Oklahoma, Norman **OCAST Project:** HR18-130 **Research Area:** Chemistry & Biochemistry

Pro-apoptotic Bax/Bak proteins are key regulators of the intrinsic apoptosis pathway. The oligomerization of these proteins within the mitochondrial outer membrane is directly responsible for the pore formation in membrane, which eventually causes cell death. Therapeutic potential of inhibitors to anti-apoptotic proteins, such as Bcl-2, as anti-cancer agents has been extensively explored; whereas there are no potent and selective inhibitors to pro-apoptotic Bax/Bak, which could lead to the development of neuro- and cardio-protective agents. Our long-term goal is to develop potent and selective small-molecule inhibitors to pro-apoptotic Bax/Bak proteins. This will be achieved through a close collaboration between my computational chemistry lab and Dr. Indrajeet Sharma's medicinal chemistry lab at the University of Oklahoma as well as Dr. Jialing Lin's biochemistry and biophysics lab at the University of Oklahoma Health Sciences Center.

Our preliminary docking calculations suggested that ABT-199 and ABT-263, two anti-tumor drugs targeting Bcl-2, also bind Bax protein. Consistently these drugs inhibited Bax pore formation in vitro with moderate potency. Through analyzing the docking pose, we have identified a few favorable structural modifications to ABT-199, which led to several compounds with higher predicted binding affinity to Bax protein.

Based on these preliminary findings, we will build an automated workflow (combining the latest computer-aided drug design and binding free energy simulation techniques) to design a large virtual library of ABT-199/263 analogues. Most promising candidates will be synthesized using the convergent fragment-based approach from Dr. Sharma's lab, and their capabilities to selectively bind and inhibit Bax activation and function will be assessed in Dr. Lin's lab.

Our project will produce new potent and selective Bax inhibitors that will facilitate both basic and applied apoptosis research. Following this OCAST project, we will use resources at OU core facilities to conduct crystallization trials with the most active inhibitors and Bax proteins to obtain the structural information for further ligand optimization, and will also extend our study to develop inhibitors to the Bak protein. Our findings will constitute the basis for grant proposals on the development of neuro/cardio-protective agents, which aligns well with the funding priorities of multiple federal agencies.

OCAST

Neurocognitive Empowerment for Addiction Treatment (NEAT): A randomized controlled trial for opioid addiction

PI: Dr. Hamed Ekhtiari, Laureate Institute for Brain Research **OCAST Project:** HR18-139 **Research Area:** Neurobiology

Addiction to opioids is among the costliest and deadliest of mental health disorders in the United States. The US in general and the State of Oklahoma in particular face a crisis in opioid addiction. Opioids (including prescription opioids, heroin, and fentanyl) were involved in more than 42,000 deaths in 2016 in the US, more than any year on record and accounting for more deaths than road accidents and gun violence combined. Chronic opioid addiction is not only associated with increased mental health symptoms, such as anxiety and depression, but also with brain (neural and cognitive) deficits. Cognitive deficits in memory, attention, decision-making, and cognitive control disturb normal daily functioning and attempts for abstinence, and are associated with worse long-term outcomes. Current treatment programs for opioid addiction are mainly focused on abstinence, with the assumption that these neural and cognitive deficits will subsequently heal. However, these deficits are found to persist even after a long-term abstinence and are thought to contribute to relapse, decreases quality of life, and lack of reintegration into society. Brain rehabilitation programs focused on compensatory strategies and training exercises for cognitive deficits associated with traumatic brain injuries, stroke, multiple sclerosis and schizophrenia have consistently been found to improve functioning and long-term outcomes for these populations. However, there has been a relative lack of research focused on identifying interventions targeting cognitive deficits in the context of substance use disorder.

The aim of this study is to characterize clinical efficacy for an intervention targeting neural and cognitive deficits associated with opioid addiction by enhancing awareness and use of cognitive skills in the context of substance use recovery. This aim will be accomplished by randomizing 80 subjects with opioid addiction who are already enrolled in substance use treatment in the state of Oklahoma to also complete a novel "Neurocognitive Empowerment for Addiction Treatment" (NEAT) program. NEAT will be novel in (a) its use of cartoons, brain awareness games and real-life scenarios to ensure it is interactive and engaging, (b) the focus on the role of neurocognitive deficits in recovery from substance use and co-occurring mental health symptomatology, and (c) its incorporation of neuroscientific findings specific to substance use to the training and exercise strategies. Subjects will be followed for six months to explore the efficacy of NEAT compared to the control intervention on substance use and mental health symptoms, objective cognitive performance, and functional and structural brain changes using magnetic resonance imaging (MRI). This research study has the potential to identify a novel intervention that can be integrated into substance use treatment programs in Oklahoma and nation-wide to more effectively support recovery from opioid use disorder.