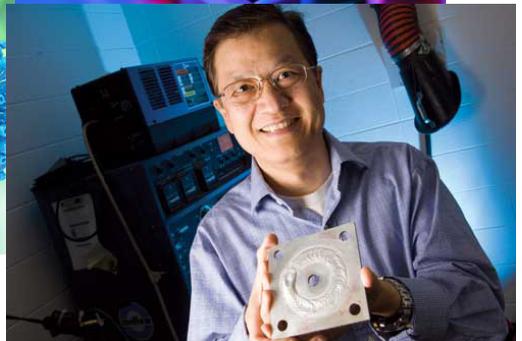
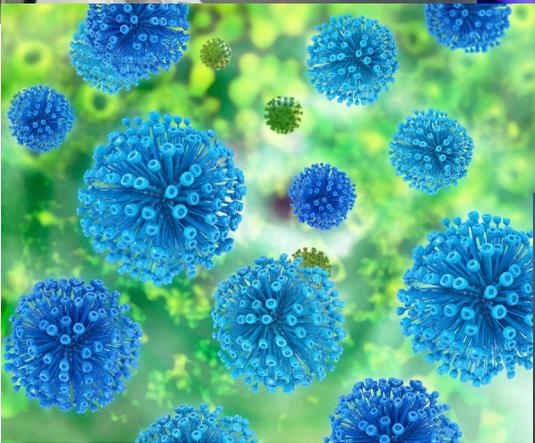
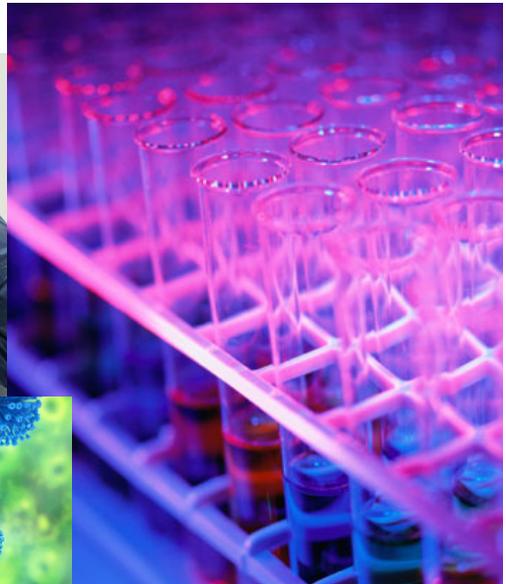


# 2016 Oklahoma Health Research Conference

Samis Education Center Auditorium  
OU Children's Hospital  
1200 Children's Avenue  
Oklahoma City, Oklahoma 73104

September 14, 2016



# 2016 Oklahoma Health Research Conference

## Agenda

- 8:00 a.m. Registration opens
- 8:00 a.m. - 9:00 a.m. Continental breakfast and networking
- 9:00 a.m. - 9:10 a.m. Welcome - **Dan Luton**  
*Director of Programs, OCAST*
- 9:10 - 9:30 a.m. Budget forecast for FY 2018 - **Chad Mullen**  
*Director of Government Relations, OCAST*
- 9:30 a.m. - 10:40 a.m. Keynote presentation and Q&A: How do I get a global biotechnology company interested in my work? - **Chad E. Eckert, Ph.D.**  
*Senior Scientist, Preclinical Affairs, Ethicon, Inc. (A Johnson & Johnson company)*
- 10:40 a.m. Closing remarks - **Mary Beth Humphrey, M.D., Ph.D.**  
*Chair, Oklahoma Health Research Program Advisory Committee; Professor of Medicine, McEldowney Chair in Immunology Division; Chief of Rheumatology, Immunology and Allergy, University of Oklahoma Health Sciences Center*
- 11:00 a.m. Adjourn

# Research Area: Biomedical Engineering

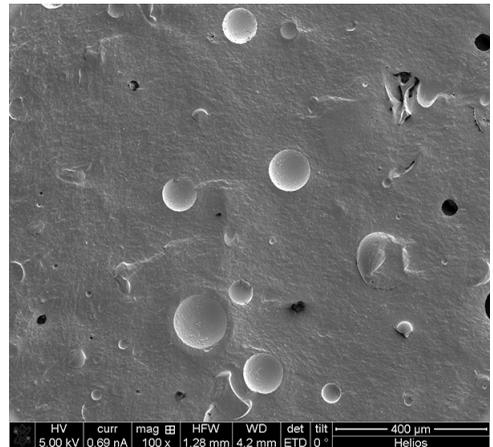
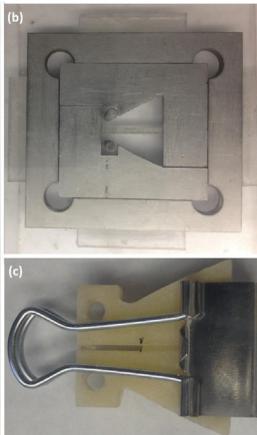
HR13-131

Development and testing of a tooth restoration that can self-heal if damaged

*Self-healing restorative resins*

Michael W. Keller, University of Tulsa

Resin-based composite materials are becoming the leading choice for the restoration of decayed and damaged teeth. These polymer composite materials offer improved appearance when compared to traditional metal-based restorations. Unfortunately, composite restorations are more susceptible to mechanical failure, such as cracking, than metallic repairs. Options for the repair of failed resin restorations are limited to removal of the damaged restoration and adjacent tooth structure and replacement of the repair. The number and cost of replacing restorations is increasing annually and is estimated to be in the billions of dollars per year. The long-term goal of this project is to reduce the frequency of mechanical damage-related failures and associated replacements by creating new, self-healing restorative resins that are capable of automatically repairing structural damage such as cracks.



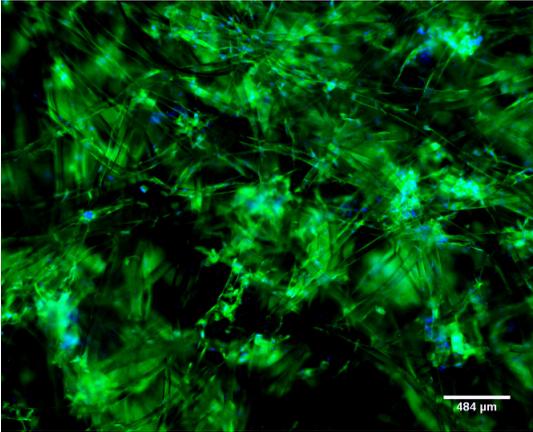
(a) Self-healing dental resin being tested (b) mold for making specimens, (c) self-healing specimen undergoing healing

SEM image showing microcapsules integrated into the self-healing material

## Monitoring the growth of bone replacements in the lab

*The development of a combined approach for the mid-culture monitoring and modelling of in vitro bone tissue engineered constructs*

Vassilios Sikavitsas, University of Oklahoma

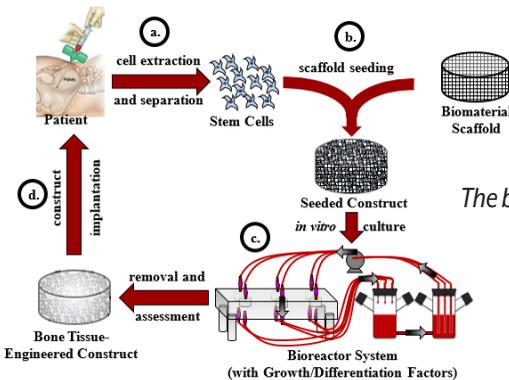


*Mesenchymal stem cells under a fluorescent microscope*

Every year, over \$2.5 billion is spent in the US on bone graft interventions to aid in the healing and regeneration of bone loss either from disease or injury. These grafts usually come in the form of bone taken from other parts of a patient's body or decellularized bone taken from cadavers. These methods are problematic with limited supplies, threat of infection, and donor site morbidity. Bone tissue engineering seeks to create new bone grafts in order to help fulfill this need. The end goal of our project is the creation of a system that will allow researchers and clinicians to grow bones on a mass production scale. Ultimately, this research may lead to a near-infinite supply of bones that can be grown for patients on demand, reducing the need for donor tissues.



*The bioreactor used for growing bones*



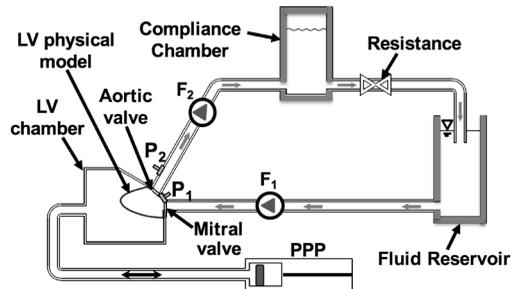
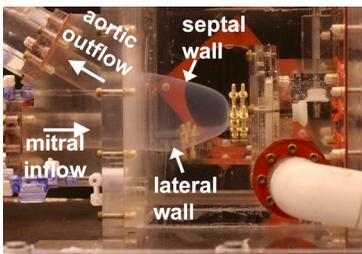
*The bone tissue engineering approach*

## Studying heart failure using physical models

*Left ventricular dyssynchrony in heart failure: Investigation of altered hemodynamics and diagnostic accuracy of MRI using an in vitro phantom model*

Arvind Santhanakrishnan, Oklahoma State University

Approximately 30% of heart failure (HF) patients exhibit loss of synchronization in left ventricular wall motion, a condition known as left ventricular dyssynchrony (LVD). The quality of life of LVD patients is negatively impacted from diminished heart function, as blood flow within the heart is ineffectively sloshed instead of following a coherent pattern. Cardiac resynchronization therapy (CRT) utilizing pacemaker leads is used widely as the clinical treatment, but 30%-40% of LVD patients do not show improvement after implantation. Clinicians administering CRT do not have any guidelines to help them to optimize where to place the leads. This is because there is no clear understanding of how mechanical alterations to the timing and coordination of left ventricular wall motion can impact blood flow inside the heart. We are interested in understanding how dyssynchronous wall motion can negatively affect the flow of blood inside the heart and improving LVD diagnosis using cardiac MRI. As it is not easy to conduct a systematic study with controllable heart wall motion patterns in animals or humans, we use an experimental physical model of the left heart for our study. The novelty of our experimental model is that it can be tested in an MRI-scanner. We will use our model using MRI to quantify accuracies of dyssynchrony diagnostic measures. This work is expected to potentially generate clinical translational impact in heart failure treatment by providing guidelines on resolution requirements for anatomical MRI data to accurately predict LVD severity and refine patient-specific CRT selection criteria.



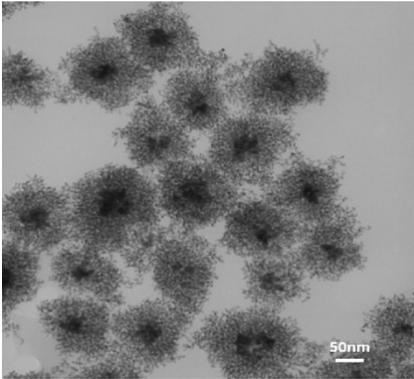
MRI-compatible left ventricle (LV) physical model (left), and diagram of the flow circuit (right) used to move blood mimicking liquid in flexible-walled silicone LV models. PPP=programmable piston pump; F<sub>1</sub>, F<sub>2</sub>=flow probes for measuring inflow and outflow; P<sub>1</sub>, P<sub>2</sub>=pressure taps for aortic and LV pressures

## HR14-160

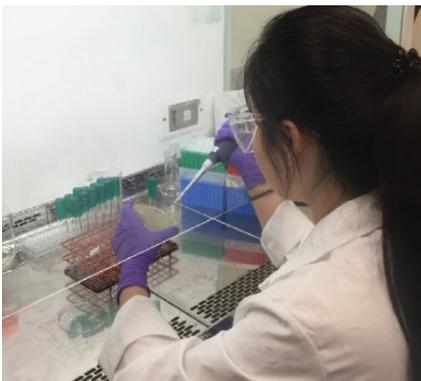
### Novel targeted gene delivery strategy by using nanomaterials

*Highly efficient non-viral VEGF gene delivery to human mesenchymal stem cells by phage-like nanoparticles*

Chuanbin Mao, University of Oklahoma



*Inorganic nanoparticles under the Transmission electron microscopy*



*Mengmeng, a graduate student from our lab, performs the screening of targeting-peptides.*

Vascular endothelial growth factor (VEGF) is a protein that can induce the formation of new blood vessels. Thus increasing supply of VEGF in tissues of cardiovascular diseases will help cure it. This will involve the delivery of VEGF gene into cells. Virus is a type of widely used gene carrier. However, because of their viral nature, there are plenty of safety concerns for clinical therapy. Thus development of a novel, safe, non-viral and efficient gene carrier is important. The proposed work will focus on the VEGF gene delivery to human mesenchymal stem cells (hMSCs) by using highly branched gold nanoparticles. To increase the delivery efficiency, a hMSCs-targeting peptide will be selected by a biological screening process. This peptide will guide the complex of gold nanoparticles and VEGF gene into hMSCs. Once successful, these cells will be able to stably produce fresh VEGF proteins. Then the hMSCs will be induced to differentiate into functional cells, such as cardiac cells, for disease therapy. The results of this proposed work may lead to a new method of transferring genes into cells with high efficiency by inorganic nanoparticles. In the long term, this research may provide a new site for the treatment of cardiovascular diseases through blood vessel formation.

## Using computer technologies to predict the treatment outcome of ovarian cancer patients at early stage

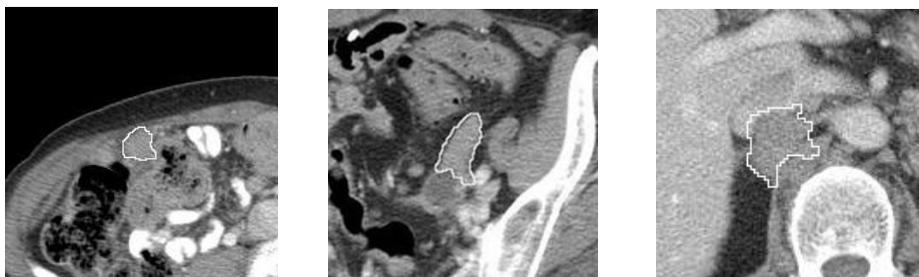
*Quantitative image analysis for predicting early response of ovarian cancer patients to chemotherapy*

Yuchen Qiu, University of Oklahoma

Ovarian cancer is the second most prevalent cancer in gynecologic oncology. Given that most of these patients are diagnosed at the advanced stage (Stage III-IV) with metastatic tumors on different organs inside the abdomen, chemotherapy is necessary to control the metastatic tumors after the surgery. For the chemotherapy, one of the major challenges is to accurately evaluate the treatment effectiveness at early stage (i.e. one month after the therapy).

In order to address this challenge, we in this project developed a quantitative image analysis scheme, which is able to objectively estimate the tumor characteristics depicted on CT images. Based on the pre-treatment and follow-up CT examinations, we first find the metastatic tumors and segment them from the background. Next, the tumor features are quantitatively estimated. For example, we will estimate: 1) How large the tumor is; 2) How dense the tumor is; 3) How uniform the tumor is; 4) Whether the tumor boundary is smooth or not; and so on. Using these features, we finally build a statistical model to predict the clinical benefit (i.e. whether the treatment will be effective after the therapy is finished).

The initial results demonstrate that our new quantitative schemes have potential to assist clinicians (i.e. radiologists, oncologists) to more effectively predict the clinical benefits of ovarian cancer patients. If successful, this method may have a significant impact on improving the efficacy of clinical treatment while minimizing the side effects.



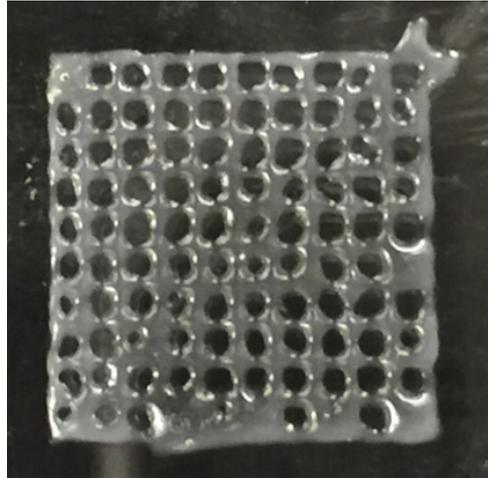
*Three examples of the tumor region segmentation*

## Printing synthetic liver for screening drugs

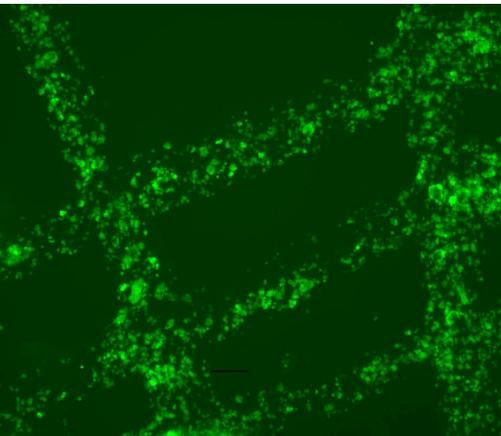
*Building 3D liver organoid from bottom-up for drug screening*

Sundar Madihally, Oklahoma State University

Drug-induced liver toxicity is the most common reason for the after-market withdrawal of a drug, despite effectiveness in treating a disease. In order to improve the screening and development of pharmaceuticals, synthetic liver that can provide similar metabolism is required. Our goal in this project is to use novel bioprinting technology to spatially locate different types of cells from the liver and develop such synthetic tissue. Bottleneck is the lack of biomaterials that provide a conducive environment for cells during



*Top view of a bioprinted structure*



*Fluorescent picture showing cells within the fibers*

printing. This proposal aims at using chitosan-gelatin thermosensitive hydrogel for developing 3D hepatic tissue and testing the developed construct for screen toxicity of routinely used acetaminophen. Successful completion will lead to large scale repetitive manufacturing of 3D synthetic liver that can be used in drug screening.

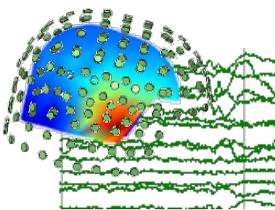
## HR16-057

### A new kind of brain image can tell us more about your memory function

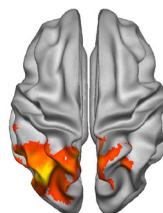
#### *Multi-modal imaging of brain networks in middle-aged and older adults*

Han Yuan, University of Oklahoma

Currently, 20 percent of the population in Oklahoma are over age 60 and about 34 percent are over age 50. In 2050 the number of people over 60 is expected to increase by 25 percent in the state of Oklahoma. The rapidly growing population of older adults puts an ever-increasing number of people at risk for cognitive decline. Characterizing physiological underpinnings in the human brain associated with both age- and disease-related cognitive changes is critical for promoting healthy aging. Understanding the mechanism of cognitive changes in normal aging is also an important first step in developing more sensitive methods for detecting abnormal aging process, such as Alzheimer's disease. Currently the procedures and tests to diagnosis Alzheimer's disease is not suited to be routinely applied on normal aging individuals. Therefore, a technology that focuses on assessing the functional domains of cognitive function and is built on broadly accessible tools, which can be used in outpatient clinical setting, is much needed in the study of aging. Our current project proposes to build such a technology based on an innovative, state-of-the-art imaging system that acquires simultaneous hemodynamic and electric signals of the brain through compatible near-infrared spectroscopy and electroencephalogram. We will study two groups of cognitively normal middle-aged and older adults based on a paradigm sensitive to cognitive function that has been established by the research team. Our study will characterize the brain networks using recent novel algorithms developed by the investigators and determine the relationship between brain network and cognitive changes. Successful completion of the project will establish the feasibility of a novel imaging technology in characterizing the cognitive changes in normal aging population and may discover a neuroimaging-based biomarker for the aging effect. In the long run, the established technology may aid in screening for abnormal cognitive aging in routine clinical settings and facilitate detecting early stages of deterioration, which will be critical in prevention of Alzheimer's disease.



*Dual measurements  
of hemodynamic  
and electrical signals  
acquired from a novel  
brain imaging system*



*A new kind of brain  
images that can assess  
memory function*

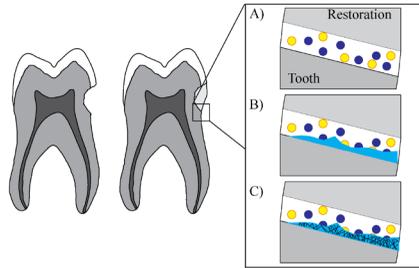
Automatic repair of the filling/tooth interface in dental restorations

*Interfacial healing in dental restoration*

Michael W. Keller, University of Tulsa

Resin-based restorations have become the primary choice of most patients requiring restorative dental work. This preference is based on appearance and a growing concern about the presence of mercury in dental amalgams. While these restorative materials provide benefits, composite resins are prone to failure. The primary cause of restoration failure is damage at the resin-tooth bond leading to the formation of new cavities. There have been several potential approaches for minimizing these failures. Researchers are looking at strategies for improving material performance and for minimizing the potential of new cavity formation. Material approaches are currently focused on the synthesis of new adhesive resin formulations that are resistant to degradation and attack by microbes. Based on this work,

several additives have been suggested by researchers that improve the resistance of the restoration-dentin bond to enzyme attack. These approaches use “passive” materials or processes to improve the durability of the resin-tooth bond. These passive approaches attempt to inhibit degradation processes in order to prevent failure of the interface and eliminate subsequent pathogenic attack on the remaining healthy tooth structure. In this project, we will synthesize and characterize an “active” material that will respond to interface damage by healing and sealing interfacial cracking and failure.



Photograph of a resin restoration with an interface failure at the gingival margin (indicated with arrow).

*Schematic view of a tooth with caries and subsequent restoration. Inset image shows the damage-healing process for the proposed adhesive resin material. A) shows the pristine, as-placed restoration, B) shows the onset of damage that ruptures capsules, C) shows the release and polymerization of the healing agent repairing and sealing the damage.*

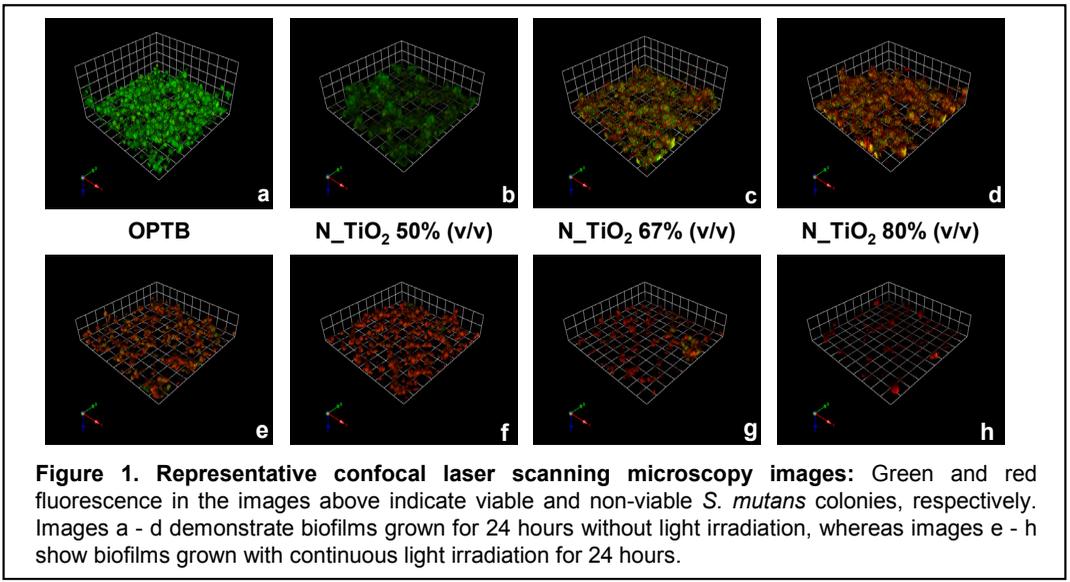
Smart adhesives with antibacterial and bioactive properties

*Real-time quantification of cells' viability and "smart" adhesive resins with antibacterial, bond-promoting and bioactive properties*

Fernando Luis Esteban Florez, University of Oklahoma Health Sciences Center

Secondary (recurrent) caries is the most common cause of failure of dental restorations. The etiology of secondary dental caries is related to the formation of bacterial biofilms at the adhesive interface between teeth and resin composite restorative materials. The problem is exacerbated further because posterior composite restorations tend to accumulate more biofilms when compared to other restorative materials. One approach to solving this problem is the addition of antibacterial agents within dental adhesive

resins. Toward that end, we will test the working hypothesis that addition of nitrogen-doped titanium dioxide nanoparticles in commercial adhesive resins (OptiBond Solo Plus) will promote the obtainment of experimental materials that present improved mechanical properties, that present improved antibacterial properties against *S. mutans* and that will be more resistant to biodegradation promoted by esterases commonly present in saliva.



## HR16-144

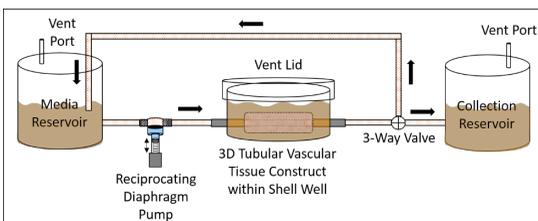
# Using an advanced tool to generate specialized immune cells for the treatment of a variety of diseases

*Ex vivo generation of dendritic cells from an advanced vascular tissue construct*

Heather Fahlenkamp, Oklahoma State University

What if a single key unlocked the cure to the treatment of cancer, viral infection, transplantation rejection and autoimmune diseases? One area that links all of these diseases is the immune system. The immune system protects the body by identifying and killing disease agents. A dysfunctional immune system is unable to protect against diseases and can destroy healthy cells. Dendritic cells are important cells of the immune system that play an integral role in the initiation and control of many diseases. Only a small number of these cells are required to stimulate the immune system, but it is a challenge to produce the quantity and/or type needed for treatment. The proposed project will develop a novel tool that can generate functional dendritic cells. The tool is described as a tissue-engineered model within a bioreactor. Tissue engineering is used to build models that mimic tissues or organs in the body. The process involves the combination of living cells and biologically active molecules within a scaffold material. A bioreactor is a vessel that can be used to control the environment for maintaining tissue-engineered models. The environment mimics the body. The design principles of the tissue-engineered model within the bioreactor are based on previous studies of dendritic cells. Dendritic cells have the ability to migrate between tissue and organs. This knowledge of dendritic cell trafficking will be used to design a novel vascular tissue-engineered model that mimics the interface between a blood vessel and its surrounding tissue. The tissue-engineered model will be designed within a bioreactor flow system. Just like blood vessels in the body, fluid containing cells will flow within the vascular tissue-engineered model. The cells will receive signals to change into dendritic cells. This project is innovative compared to other methods to generate dendritic cells by creating a tool to mimic the natural environment of dendritic cells in the body. The long-term goal of this research is to develop dendritic cell-based therapeutics to treat a variety of diseases

and that can be custom-made to meet the needs of an individual patient.



*3D vascular tissue-engineered model within the tubular bioreactor design*

# Research Area: Cancer

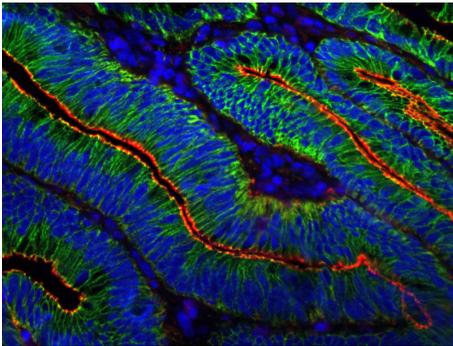
HR13-160

## A new colon cancer treatment strategy

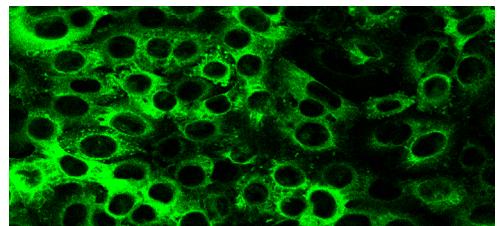
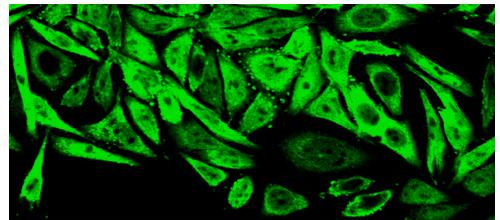
*Inhibiting Wnt signaling through Epsin depletion: A new anti-colon cancer strategy*

David Jones, Oklahoma Medical Research Foundation

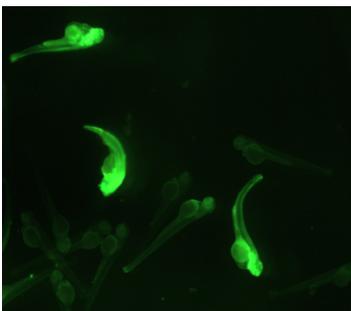
Colorectal cancer is a common cancer in terms of new cases and deaths among men and women in the United States. The past fifty years have seen only marginal improvement in survival from this disease. This improvement is largely due to improved early diagnosis and surgical treatment. The majority of colon cancers, however, are diagnosed at later stages when survival rates are dramatically reduced. Current statistics show that approximately 150,000 new cases of colon cancer emerge each year and that an estimated 56,000 people die from this disease annually. As such, the problem of colon cancer remains an important, unmet medical need that demands a better understanding of the disease as well as improved diagnosis and treatment. We have developed a novel strategy for blocking an important pathway that colon cancer cells rely upon for survival. Blockade of this pathway using a novel agent causes the tumors cells to function more normally and ultimately leads to the death of the cancer. We have determined that this new agent works through a previously unknown process and are studying this process in detail in an effort to exploit it as a new treatment target for colon cancer.



*Colon cancer remains a lethal disease*



*Testing anti-cancer drugs in human colon cancer cells*

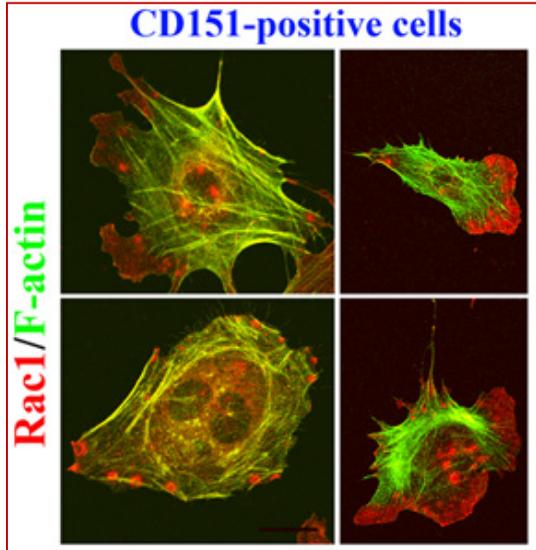


*Testing anti-cancer drugs in zebrafish*

## How tetraspanin CD151 promotes cancer invasion and metastasis

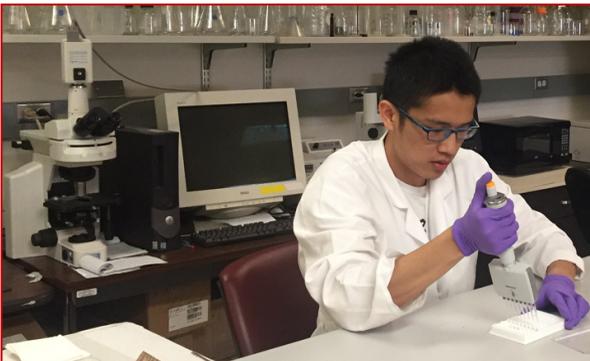
Xin Zhang, University of Oklahoma Health Sciences Center

The goal of this project is to elucidate how a cancer-facilitating protein called CD151 drives cancer metastasis. The rationale of our project is that CD151 directly promotes cancer cell movement to enhance the metastatic potential of cancer. We hypothesize that CD151 promotes cancer cell movement by changing the behaviors of its associated proteins, many of which are key players of cell functions. Specifically, we will first determine how CD151 promotes cancer metastasis by analyzing various animal cancer models. Second, we will determine how CD151 promotes cancer cell movement by using various advanced approaches at the molecular level. Because metastasis is the cause of fatality of cancer patients, the impacts of this project are enormous and will help reveal how cancers become metastatic, how cancer cells become



CD151 makes cells invasive.

invasive and how this cancer-facilitating protein functions. From the proposed in-depth studies, we will develop an integrated understanding of cancer metastasis and cancer cell movement, which will ultimately lead to the development of CD151 into a diagnostic marker and therapeutic target for cancer metastasis.



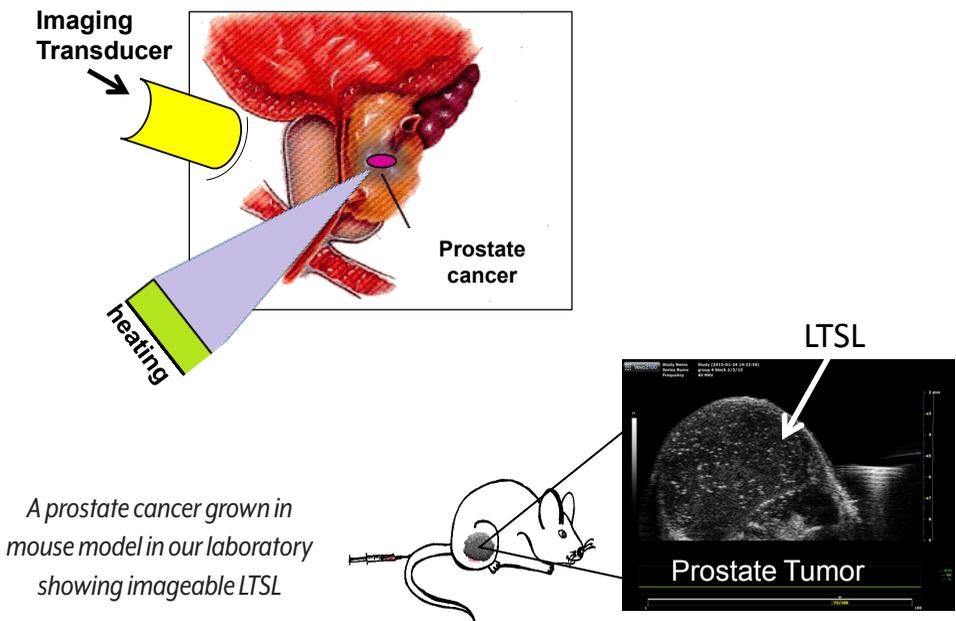
Dr. J. X. Chen examines cancer cell invasion capability.

## Mild heating of nanoparticles improve imaging and treatment of prostate cancer

*Dual-mode ultrasound-imageable thermosensitive liposomes for image-guided therapy*

Ashish Ranjan, Oklahoma State University

Prostate cancer is one of the most diagnosed cancers in males in the United States. There are three critical obstacles facing prostate cancer chemotherapy: 1. poor drug delivery and distribution into tumor, resulting in serious side effects, 2. absence of a reliable real-time method to non-invasively control drug delivery and 3. inability to synergistically enhance chemotherapy under multiple conditions resulting in tumor recurrence. The proposed work seeks to meet these challenges through a dual-mode Low Temperature Sensitive Liposome (LTSL) that co-encapsulate both Docetaxel (therapeutic agent) and imaging agent (Perfluoropentane [PFP]) to permit image-guided drug delivery. LTSL permits induction of docetaxel release using mild elevations (40-42°C) in local tissue temperature under ultrasound image guidance, thereby providing targeted prostate cancer therapy. Also, adding mild heating to docetaxel therapy significantly increases survival over treatments without heat in a mouse model of prostate cancer. Success of this all-in-one approach will be a milestone for providing real-time control of prostate cancer therapy.

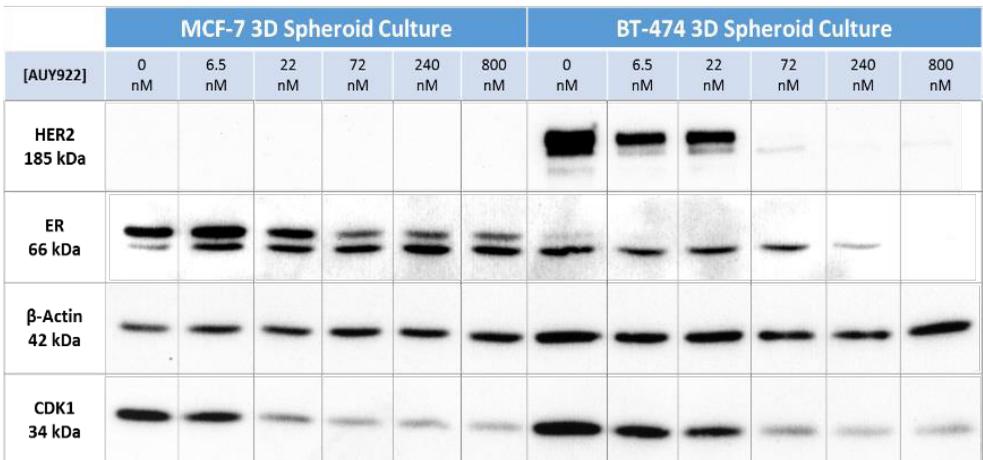


Changes in microRNA expression contribute to the anti-cancer activity of Heat Shock Protein 90 inhibitors

*Effect of Hsp90 inhibitors on miRNA expression in cancer*

Robert Matts, Oklahoma State University

Numerous proteins that play a role in tumor development require the molecular chaperone Hsp90 to function. Inhibitors of Hsp90 function are now under investigation as anti-tumor agents, as they inhibit the activity of Hsp90-dependent oncogenic proteins. Changes in the expression of microRNAs (miRNAs) also contribute to tumor initiation, progression and metastasis. Hsp90-dependent oncogenic proteins alter the expression of miRNAs in tumor cells. In addition, the insertion of miRNAs into argonaute proteins to form functional RNA-induced silencing complexes (RISC) requires Hsp90. This project uses cultured 3-dimensional breast cancer cell spheroids as a tumor model. We will determine how changes in the expression of miRNAs and their incorporation into RISCs contribute to the anti-cancer activity of Hsp90 inhibitors. Results from these studies will: 1) increase our understanding of the anti-tumor effects of Hsp90 inhibitors; 2) identify miRNAs that can be targeted to increase the effectiveness of Hsp90 inhibitors' anti-tumor activity; and 3) further support the development of Hsp90 inhibitors as chemotherapeutic agents that can be used in the clinic for the the treatment of cancers.



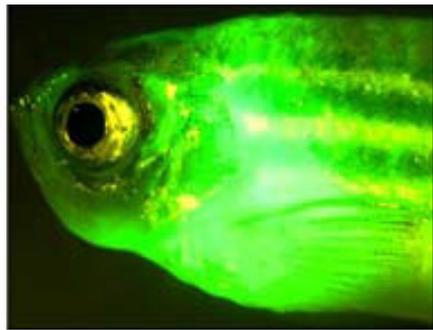
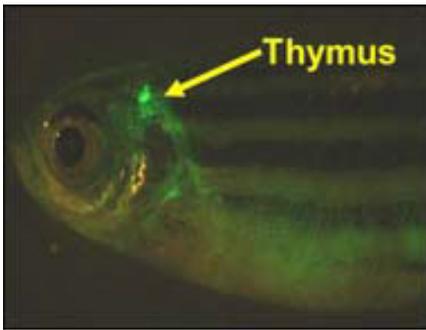
Western blot of extracts of MCF7 and BT474 spheroids demonstrating the depletion of the Hsp90-dependent oncogenic proteins: the HER2 tyrosine kinase, the estrogen receptor (ER), and the cyclin-dependent kinase Cdk1. Actin is the loading control.

Genes that cause childhood T cell cancers and govern treatment responses

*Oncogenic roles of TCF3 and ID3 in pediatric T cell cancers*

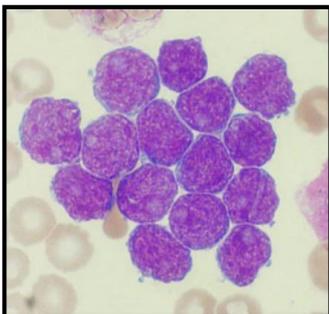
J. Kimble Frazer, University of Oklahoma Health Sciences Center

T cell leukemia and lymphoma are common pediatric cancers that kill ~20% of patients, and many surviving children are left with disabling lifelong health problems. Our lab uses zebrafish, a model animal, to study T cell cancer. Mutations in some genes and ‘misbehavior’ of other genes cause cancer. We genetically modified fish to make them prone to T cell cancer, and our studies in such fish suggest two genes, named TCF3 and ID3, have key roles. Our OCAST project is testing this by creating new zebrafish with ‘broken’ TCF3 and ID3, to see if they acquire cancer, and if so, how it differs from T cell cancers with normal TCF3 and ID3. We will also examine the effects of altering the function of TCF3 and ID3 in human T cell leukemia cells grown in petri dishes (i.e., tissue culture). Together, the experimental results from these studies will improve our understanding of the molecular basis of pediatric T cell cancer, test genes that may impact responses to treatment and identify new targets for therapeutic development. Ultimately, this has the potential to save lives and prevent long-term side effects in children with T cell cancer.



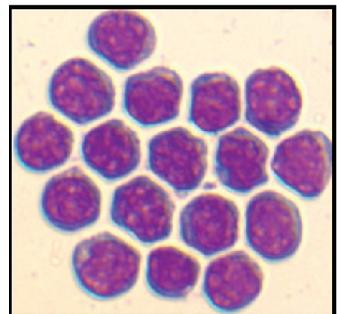
*Left: A normal zebrafish with fluorescent T cells in its thymus*

*Right: Zebrafish with a large fluorescent cancerous T cell tumor*



*Left: T cell leukemia of a patient*

*Right: T cell leukemia from a zebrafish*



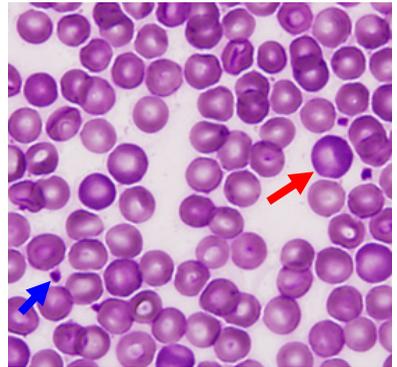
Development of combination therapeutic drugs to treat blood cancers

Targeting JAK2 and p53 to treat Myeloproliferative neoplasms

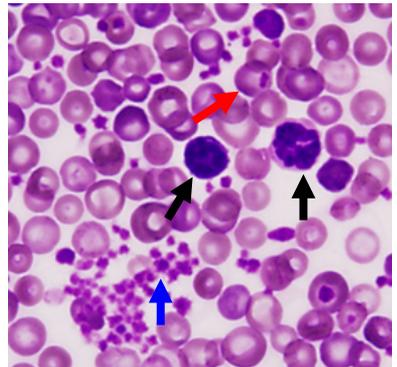
Z. Joe Zhao, University of Oklahoma Health Sciences Center

Blood cancers such as leukemia arise from uncontrolled production of certain types of blood cells. Myeloproliferative neoplasms (MPNs) represent a type of chronic blood cancer characterized by over-production of red blood cells, white blood cells and platelets. MPNs mainly affect older people with an average onset age of 55 years. MPN patients suffer from various symptoms including headaches, fatigue, blurred vision, dizziness, itching, bruising, abdominal pain, leg pain and gout. Complications associated with MPNs include thrombosis, hemorrhage, heart attack, stroke, persistent infections and acute leukemia. So far, there is no effective treatment. The major molecular lesion in MPNs is JAK2V617F, an acquired mutant form of the normal JAK2 gene. In earlier studies, we have generated a mouse model of MPNs by introducing JAK2V617F into mice. These mice display all the symptoms of human MPNs. We thus obtained a unique and valuable tool for identifying and testing drugs to treat MPNs. Our main goal to find drugs that suppress activity of JAK2V617F. We also intend to identify drugs that can elevate the level of tumor suppresser p53 that is often reduced in MPNs. By combining two types of drugs, we aim to develop more effective drug therapies. We have found several promising drug candidates. This study may allow us to convert MPNs into manageable diseases and to prevent many complications associated with MPNs.

Normal



MPN



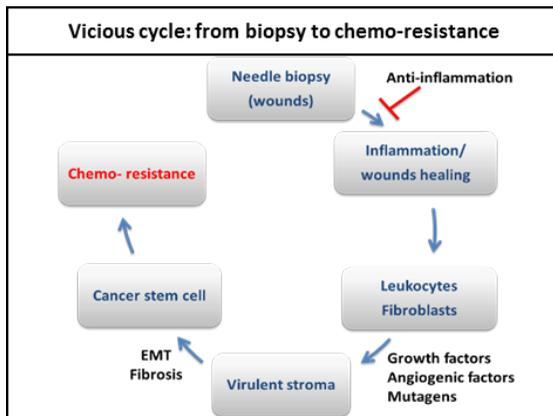
As found in human MPN patients, MPN mice have enlarged spleen and increased numbers of red blood cells (red arrows), white blood cells (black arrows), and platelets (blue arrows) in comparison with normal mice.



## Clinical impact of needle biopsy to tumor progression *Improvement of neoadjuvant therapy for breast cancer*

Takemi Tanaka, University of Oklahoma Health Sciences Center

A recent clinical study reported that the use of needle biopsy increases risk of metastasis to the axillary lymph nodes and neighboring tissues. In agreement with this clinical study, we have demonstrated in mice that a needle biopsy of breast tumors accelerates tumor growth and metastases in conjunction with severe inflammation inside the tumor. While inflammation is an aspect of the normal physiologic wound repair process, within the tumor it causes the development of new reactive stroma, rich in an array of growth factors that constantly stimulate cancer cells. Subsequently, the cancer cells acquired stem-like characteristics (Cancer Stem Cells: CSCs), which are the primary cause of chemotherapy-resistance. In the current standard of care, advanced breast cancer is surgically resected after the completion of neoadjuvant chemotherapy lasting 3-6 months. While chemotherapies are initially effective in controlling tumor growth, only about 10-15% of tumors achieve pathologic complete response, despite significant tumor size regression. This raises the question of whether a reactive stroma developed in the tumor following needle biopsy triggers the emergence of drug-resistant CSCs that in turn lead to metastasis. The rationale of this OCAST project is that needle biopsy of breast tumor and neighboring tissue predisposes the tumor to acute inflammation that will result in the development of a virulent tumor stroma that subsequently causes the emergence of CSCs, which may compromise the therapeutic efficacy of neoadjuvant therapy due to their chemo-resistant nature. We hypothesized that the implementation of post-biopsy care may mitigate post-biopsy inflammation and the emergence of CSCs, consequently improving response to neoadjuvant therapy.

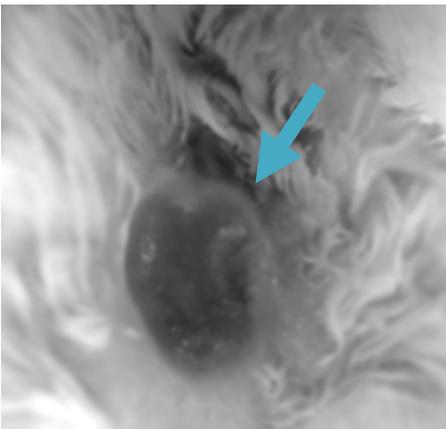


## Harnessing nanotechnology and the body's own immune system to fight cancer

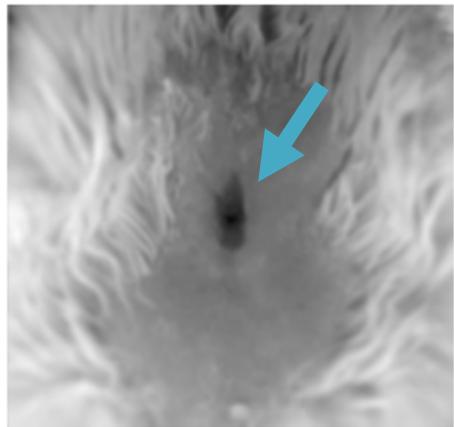
*Photothermal ablation of malignant melanoma using targeted carbon nanotubes combined with immunostimulation to combat distant metastases*

Roger Harrison, University of Oklahoma

Despite its rarity, malignant melanoma is the largest single source of skin cancer related deaths in America. Barely 1 in 20 patients will survive when malignant melanoma spreads from its original location on the skin to other organs. This process can potentially be reversed by destroying the tumor at its source and stimulating the immune system to attack any tumor metastases. We use tumor-homing carbon nanotubes to selectively destroy cancerous tissue while leaving healthy tissue unharmed. Carbon nanotubes are very small particles made entirely of carbon with diameters of one billionth of a meter. Light from a laser that is harmless to healthy tissue is used to heat the nanotubes, destroying the tumor. We are combining this treatment, known as photothermal ablation, with powerful immune system stimulants to train the body's own innate defenses to fight tumor metastases in organs far away from the site of treatment.



*A mouse tumor treated with cancer-homing carbon nanotubes and light from a laser. The laser light is harmless to the healthy tissue surrounding the tumor but kills tumor cells that have nanotubes attached.*



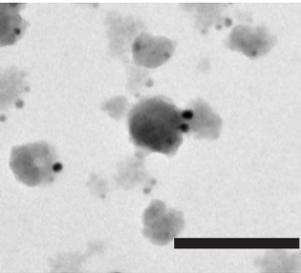
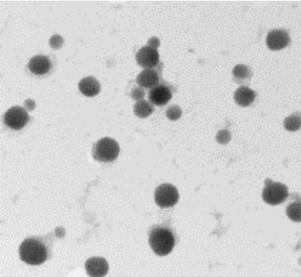
*A few weeks after treatment the tumor is completely eradicated. All that remains of the formerly prominent tumor is a small scar.*

New ways to target cancer

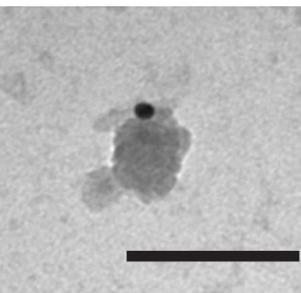
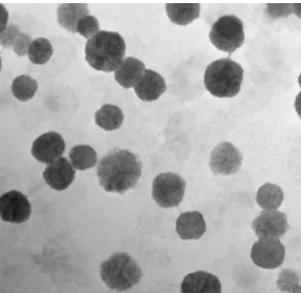
Targeting exosome-mediated intercommunication in breast cancer progression

Wei-Qun Ding, University of Oklahoma Health Sciences Center

MCF7



MDA-MB-231



Breast cancer is the second highest cause of cancer death among women in the United States. New approaches for breast cancer treatment are urgently needed in order to save lives. Docosahexaenoic acid (DHA) is a naturally occurring omega-3 fatty acid that can stop the growth of breast cancer and is currently being tested in clinical trials for breast cancer management. DHA can stop tumor growth by blocking the growth of new blood vessels (angiogenesis) in the tumor environment. How DHA stops tumor angiogenesis is not fully understood. Tumor cells can communicate with other cells in their environment. One way that tumor cells communicate is through the secretion of exosomes. Exosomes are small (40-120 nm) vesicles that contain a variety of proteins, mRNAs and microRNAs. Tumor cells release exosomes that can interact with blood vessel cells and promote blood vessel growth. Our goal is to determine whether DHA's anti-angiogenesis activity is facilitated by exosomes. This study will further the development of this natural compound as an anticancer agent against breast cancer. This will have significant impact on our understanding of how breast cancer cells communicate with other cells and may lead to new strategies for the development of tumor targeting agents.

*Exosomes from two breast cancer cell lines were visualized by electron microscopy (Left, Hitachi H-7600; ~100nm). DHA-treated exosomes of MCF7 cells suppress blood vessel cell branch point formation.*

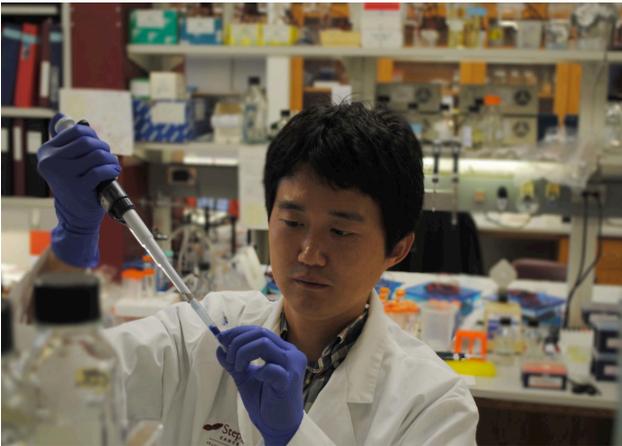
## HR15-072

A protein that becomes overexpressed in tumors may cause increased death in breast cancer patients

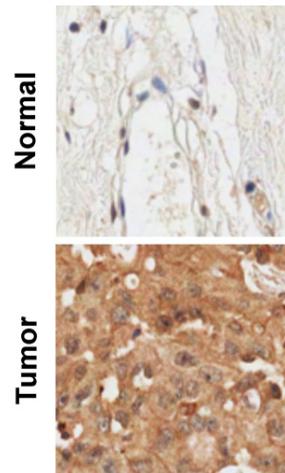
*Enzyme RCL is a novel promoter of breast cancer*

Ralf Janknecht, University of Oklahoma Health Sciences Center

The protein RCL is barely present in normal breast tissue, but often becomes highly expressed when breast tumors develop. So is RCL promoting this tumor development and thus reducing patient survival? Our preliminary data indeed suggest that this is the case; for instance, RCL seems to be required for efficient growth and metastasis in tumors of the HER2+ type, which account for 20% of all breast cancer cases. Our proposed work will define a tumor-promoting role of RCL not only in HER2+ breast tumors, but also in triple-negative ones that are even more aggressive and lethal. In addition, we will elucidate mechanisms by which RCL contributes to tumor development. Ultimately, this work will point out RCL as a novel valid drug target to improve the survival of the 40,000 females dying annually from breast cancer in the US. Also, such drugs could reduce morbidity of breast cancer patients and thereby decrease health care costs as well as lessen disease-caused absence from work and disabilities, which will be beneficial to Oklahoma's economy.



*Researcher Dr. Sangphil Oh isolates proteins from breast cancer cells to study the function of RCL*

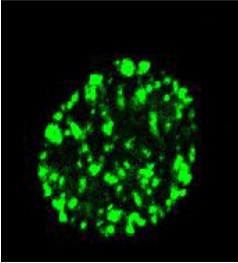


*RCL overexpression (brown color) observed in breast tumor cells under the microscope*

Aberrant DNA replication leads to genome instability and is a risk factor for cancer onset

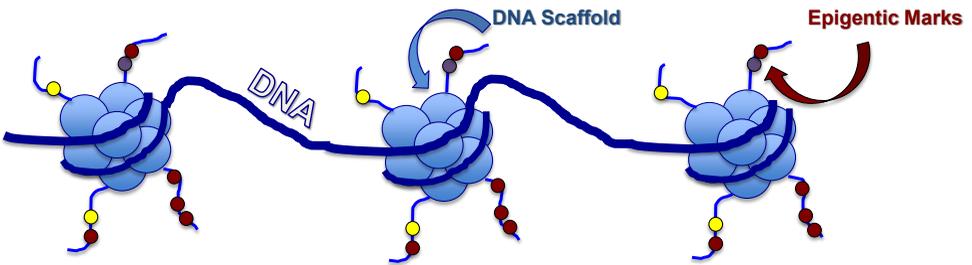
*Protein acetylation in the control of DNA replication initiation*

Christopher L. Sansam, Oklahoma Medical Research Foundation



*A human cell undergoing DNA replication*

Clinical evidence has shown that defects in DNA replication lead to genome instability and cancer. Chemical modifications to the DNA scaffold, termed epigenetic modifications, affect the ability of a cell to efficiently replicate its DNA, but the mechanisms by which epigenetic modifications affect DNA replication are unknown. Drugs that specifically disrupt the addition, modification, or removal of epigenetic marks are in development for the treatment of numerous diseases, but the extent to which their clinical efficacy is due to their effect on DNA replication is unknown. The long-term goal of the proposed work is to understand how DNA replication is normally regulated, thereby helping us better understand the specific molecular defects that lead to cancer. The specific goal of this project is to determine how epigenetic changes affect DNA replication.



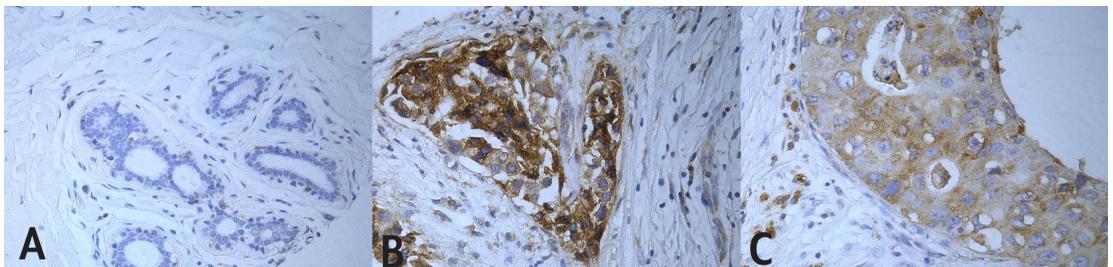
*Model of DNA bound to its scaffold. Epigenetic modifications are shown as dots.*

## Serum based biomarkers for breast cancer

*Breast tumor cells produce specific sugar modifications on glycoproteins detectable in serum*

Marie H. Hanigan, University of Oklahoma Health Sciences Center

Clinical evidence has shown that current markers for screening breast cancer are limited. Human breast tumor cells have been shown to produce modified sugars (high-mannose glycans) on the surface of certain serum proteins, termed glycoproteins. The high-mannose glycoproteins can be captured using Microvion (MVN), which specifically binds to the modified high mannose glycan and then are identified using Mass Spectroscopy. Once the breast tumor-derived glycoproteins are identified, antibodies are made. The antibodies are used to prepare a chip-based assay, which will be used to screen for cancer specific glycoproteins in patient serum. Patient serum can also be monitored for tumor response to treatment using the new chip-based assay detecting cancer-specific mammary-epithelial derived glycoproteins. Ongoing throughout this project, human serum is collected from 120 breast cancer patients including samples from benign breast disease patients and 120 normal human sera, to be used for assay design, validation and analysis.



*Expression of high-mannose glycans in normal human tissues and human breast tumors stained with Microvion (MVN). (A) Normal breast tissue. (B) Invasive ductal breast cancer. (C) Intraductal breast cancer. Brown staining is MVN positive.*

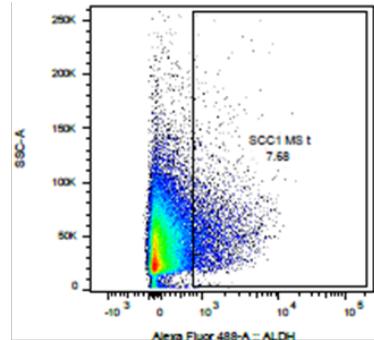
Studying the effects of tobacco smoking on oral stem cells

Lurdes Queimado, University of Oklahoma Health Sciences Center



*Scientists Jimmy Manyanga and Vengatesh Ganapathy discuss DNA damage results*

*Stem cells evaluated by fluorescence-activated cell sorting (FACS)*



Tobacco use is the main risk factor for oral cancer, the tenth most common cancer worldwide. The average 5-year survival rate for oral cancer has remained at about 50% for the last 30 years. Sadly, almost one-half of non-smokers are exposed to secondhand smoking. Recently, we have reported that a single puff of active (mainstream) or secondhand tobacco smoke can induce significant DNA damage leading to mutations which can cause cancer. Stem cells are a small subset of cells with unique properties essential for tissue homeostasis and tumor growth. The proposed work will focus on understanding the effects of mainstream and secondhand tobacco smoke on genes that regulate DNA damage and stem cell growth. We will also test novel gene targeted agents to treat oral cancer. Our results will provide the scientific support needed to improve tobacco control programs and might identify novel drugs that significantly improve the survival of patients with oral cancer. Ultimately, this will significantly reduce Oklahoma’s tobacco-associated disease burden and allocated funds can then be directed towards other wellness enriching programs throughout the state.

## PET imaged nanoparticles for targeted radiation therapy and cancer diagnosis

*Developing PET-detectable hybrid nanoparticles for radiotherapy and molecular imaging applications*

Jongmin Cho, Oklahoma State University

Gold nanoparticles (GNPs) have tremendous potential for cancer diagnosis and therapy. When irradiated by primary radiotherapy beams such as x-rays and protons, GNPs generate cascades of secondary radiation which are effective in killing cancer cells. Therefore, if cancer patients are injected with GNPs prior to radiation therapy, cancer cells suffer from double cell-kill: first, from the primary radiotherapy beams, then from the secondary radiation from GNPs. Despite its potential, the use of GNPs poses some challenges in terms of human applications. The lack of precision in GNP targeting can lead to GNPs being distributed in normal healthy tissues as well as in tumors causing unwanted damage during radiotherapy.

Therefore, the development of a non-invasive imaging tool for monitoring the distribution of GNPs is critical for a successful clinical transition. We are developing PET (Positron Emission Tomography; a very sensitive cancer

diagnosis tool) visible Zn@Au (zinc core and gold shell) nanoparticles (NPs). Zn@Au NPs are activated prior to patient injection and subsequently decay with the emission of positrons (also 511 keV gamma rays) while in the patient. Therefore, PET imaging can show the in vivo distribution of Zn@Au NPs. Zn@Au NPs are 98% gold and Monte Carlo simulations show near-identical secondary radiation (or secondary particles) as GNPs, indicating similar effectiveness in cell-kills as GNPs.

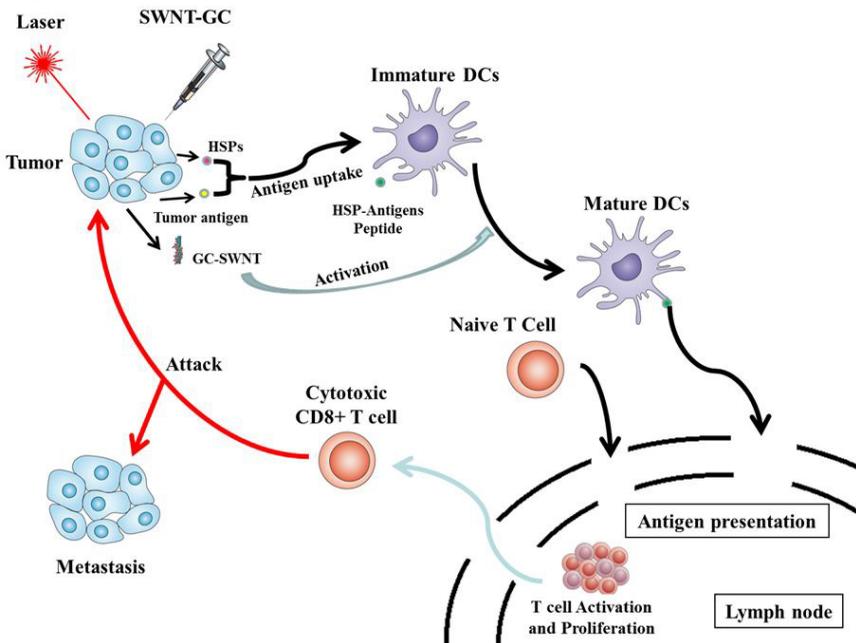
We envision that patients injected with Zn@Au NPs will be imaged with PET as verification prior to radiation therapy. The Zn@Au NPs are externally identical to GNPs and therefore can be beneficial for investigators developing various GNP tumor targeting methodologies. Additionally, Zn@Au NPs can function as PET tracers for PET mediated molecular imaging and cancer diagnosis.

Combining laser, nanotechnology and immunotherapy to treat metastatic cancers

*Phototherapy for metastatic breast cancer using immunologically modified carbon nanotubes*

Wei R. Chen, University of Central Oklahoma

Metastasis is the major cause of cancer-related deaths and treatment failure. We developed an immunologically modified single-walled carbon nanotube (SWNT), using a novel immunological stimulant, glycosylated chitosan (GC), as an effective surfactant. When SWNT-GC is administered into the target tumor and is irradiated by a laser of an appropriate wavelength, SWNT selectively absorbs laser light to induce tumor cell death and GC, combined with released tumor antigens, activates and enhances a tumor-specific immune response. This project is to use laser-SWNT-GC, a nanotechnology-based laser immunotherapy to non-invasively treat an aggressive, metastatic breast cancer in mice to induce a systemic antitumor immune response in order to eradicate the treated primary tumors and at the same time eliminate the untreated metastases at distant sites. We will also investigate the mechanism of laser-SWNT-GC induced immune responses. The results of the proposed work could lead to an effective therapy for patients with late-stage, metastatic cancers, who have severely limited treatment options.



*Hypothesized mechanism of laser-SWNT-GC-induced tumor-specific immunological responses*

## HR16-142

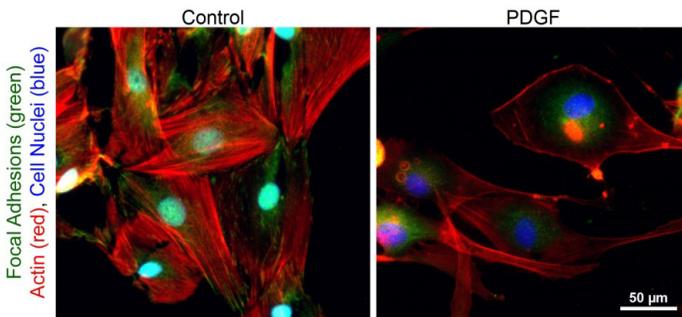
### Altering the tumor micro-environment to promote immune surveillance

*Rnd proteins promote a sentinel phenotype in fibroblasts*

Eric Howard, University of Oklahoma Health Sciences Center

Solid tumors consist of not only of tumor cells, but also a variety of other cell types that influence tumor viability, growth and invasion. Among those cells are fibroblasts, which are able to undergo a transition from a quiescent state to a highly contractile state—the myofibroblast. In this state, cancer-associated fibroblasts promote tumor progression through their ability to maintain a stiff mechanical environment. In response to specific cues, however, these cells undergo a transition to a migratory, non-contractile state, and we have found that migratory fibroblasts produce factors that prime the immune system to recognize and eliminate the tumor. This project focuses on the mechanisms involved in this transition, with an emphasis on the regulation of the myofibroblast to migratory fibroblast switch. In conjunction with ongoing studies on immune stimulation, we hope to determine how altering the tumor micro-environment can promote immune-mediated tumor elimination.

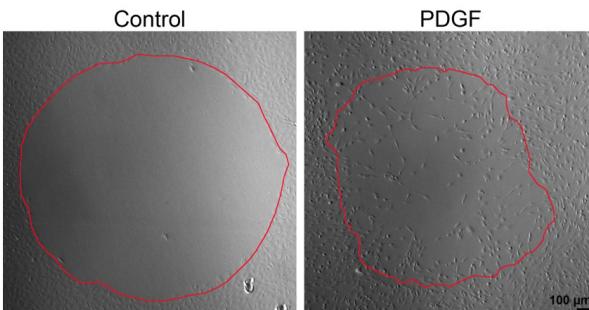
#### Fibroblasts adopt a migratory, pro-sentinel morphology with PDGF.



*Fibroblasts switch to a migratory state in response to the growth factor, PDGF. Part of this transition involves the loss of actin stress fibers (red), as illustrated in the top panel.*

*The bottom panel shows these cells migrating into a clear zone in a culture dish in response to PDGF.*

#### Fibroblasts migrate after 48 hours in response to PDGF.



Red line marks position of cells prior to treatment (0 hours).

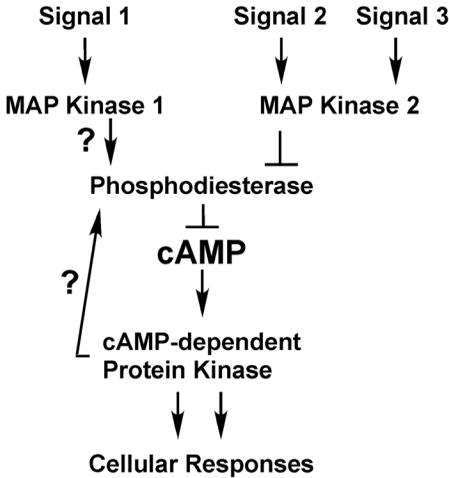
# Research Area: Cell & Molecular Biology

HR13-036

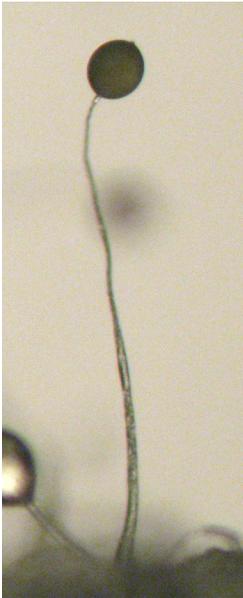
Understanding the mechanisms that protein kinases use to control phosphodiesterase function in cellular responses

*Specificity of MAP kinase regulation of phosphodiesterases*

Jeff Hadwiger, Oklahoma State University

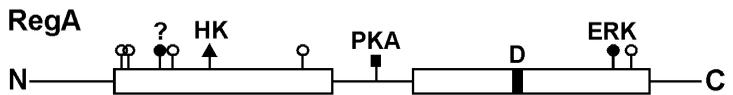


Kinase regulation of phosphodiesterase function



*Dictyostelium*, a model organism for studying signaling mechanisms

Immune responses and asthma-related diseases can involve changes to the levels of cAMP, a key signaling molecule inside the cell. These changes are often mediated by phosphodiesterases that turnover cAMP. Phosphodiesterases can be modified and regulated by protein kinases that function in response to changes in the environment outside the cell. The proposed research will examine the regulation of phosphodiesterases by protein kinases through identifying what sites on the phosphodiesterase are modified by protein kinases and how protein kinases and phosphodiesterases interact. These studies are being conducted in *Dictyostelium*, a model system for analyzing signaling mechanisms, because both genetic and biochemical approaches can be pursued. The results of the research may lead to new mechanisms to control cellular responses that impact human health through altering the levels of cAMP.



*Dictyostelium* phosphodiesterase (RegA) known modification sites (filled shapes) and kinase docking site (D).

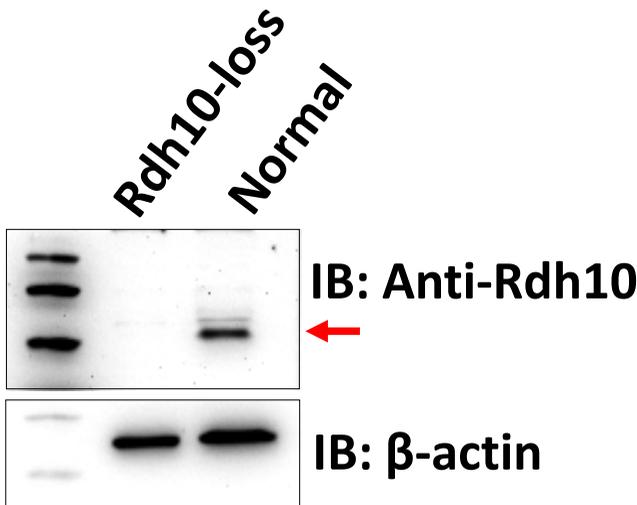
## Determining the function of an enzyme that is highly expressed in the eye

### *Defining the role of RDH10 in retinal pigment epithelium*

Krysten Farjo, University of Oklahoma Health Sciences Center

Retinol dehydrogenase 10 (RDH10) is an enzyme that is essential for fetal development due to its unique role in retinoic acid synthesis. In adults, RDH10 is present at high levels in the eye, although it is no longer present in most other tissues. Therefore, we seek to understand the function of RDH10 in the adult eye. Based on previous studies, we hypothesize that blocking RDH10 activity will significantly impair visual function by reducing the metabolism of Vitamin A in the eye. In order to test this

hypothesis, we are using sophisticated genetic tools that allow RDH10 to function normally during fetal development, but then specifically block RDH10 activity in the mouse adult eye. We then use specialized equipment to assess how blocking RDH10 activity affects visual function and ocular Vitamin A metabolism. This work will advance our understanding of the enzymes that function to maintain visual function, and could impact the development of therapeutic strategies to reduce and prevent blindness.

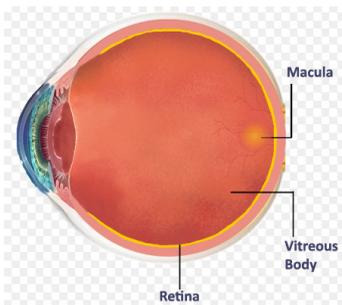


Western blot showing loss of RDH10 in eye tissue of experimental group

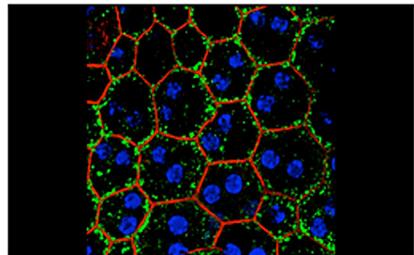
Understanding the preservation of visual health during aging  
*The role of mitochondrial dynamics in retinal health and disease*  
Scott M. Plafker, Oklahoma Medical Research Foundation

The incidence of age-related neurodegenerative diseases including Parkinson's disease (PD), Alzheimer's disease (AD) and age-related macular degeneration (AMD) is increasing at alarming rates in the US and other Westernized countries. The negative impact of these maladies on longevity, healthspan (quality of life) and the economics of healthcare will likely create a crisis in the near future if effective therapeutics and preventative measures cannot be brought to bear on these ailments. By way of example, it is predicted that AD will afflict 16 million Americans and AMD will afflict 20 million by the year 2050.

Research into the etiologies of these conditions has highlighted two common facets – (1) age is clearly the leading risk factor and (2) the specific lesions manifested in each disease have some similar characteristics. Among these characteristics is oxidative damage, which in the simplest terms can be thought of as the harmful interaction of oxygen molecules with cellular components. This is easy to appreciate if one thinks of what happens to an apple that has been bitten and exposed to the air in a room for 60 min; it begins to brown and decay. Fortunately, our cells have built-in defense systems that protect them from this type of stress and harm. These systems cooperate with one another when we are young but can fail as we get older. The work of this application is designed to better delineate how these defense systems cooperate with each other in the eye so we can understand how the deficits in these systems arise as we age. By figuring this out, we hope to ultimately design treatments that will maintain these systems and preserve visual health in the elderly.



*Cartoon of a human eye, highlighting the Macula region affected in the disease AMD*



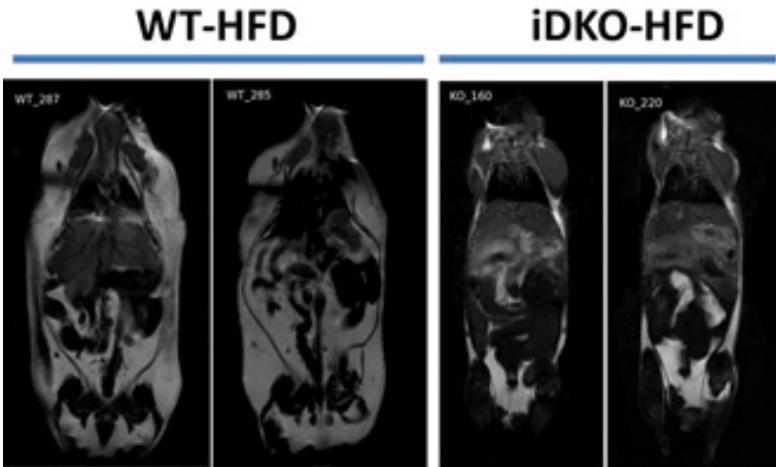
*Image of a layer of cells from a mouse eye. The green spots label the mitochondria that produce the energy for these cells.*

# Understanding the role of proteins called Epsins in the development of obesity

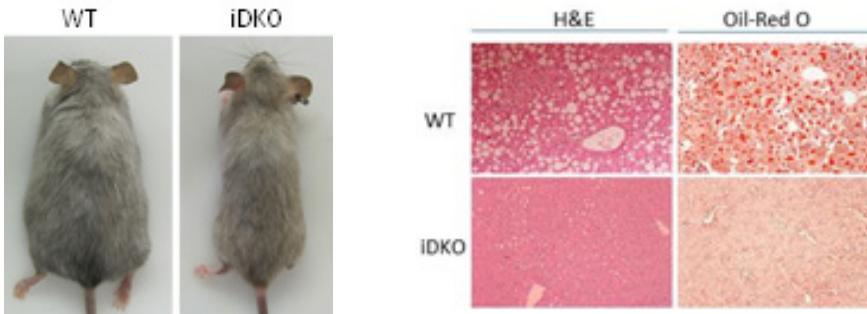
*Molecular mechanisms of Epsins in obesity*

Rheal A. Towner, Oklahoma Medical Research Foundation

Epsins are a family of highly conserved membrane proteins that play an important role in regulating adipogenesis, that is crucial for the development of obesity in humans. We are using Epsin knock-out mice (iDKO), wild-type (WT) mice and lean vs. high-fat diet (HFD) mice to understand the molecular processes associated with Epsins' role in obesity. Our data clearly indicates that Epsin alters fat deposits and fat metabolites and genes. The long-term goals are gaining a better understanding about the molecular changes associated with obesity and by altering the regulation of Epsins, reducing obesity and obesity-related diseases which currently burdens our health care system.



*Loss of Epsins significantly reduces adiposity in fat stores, as measured by MRI (magnetic resonance imaging).*



*Loss of Epsins decreases body weight.*

*Epsin decreases lipid content.*

We created a new animal model system to study kidney disease

*Role of Wtip in chronic kidney disease*

Tomoko Obara, University of Health Sciences Center

Chronic kidney disease (CKD) is characterized by progressive loss of function in the glomerulus filtration barrier. CKD progresses to end-stage renal disease requiring dialysis or a kidney transplant. Podocyte foot processes and the slit diaphragm play a crucial role in development of a healthy glomerular filtration barrier. Changes in podocyte morphology are contemporaneous with the onset of proteinuria. Genes, such as WTI, that are essential to podocyte function have been identified, but the mechanism by which mutations in these genes cause glomerulus filtration barrier failure is largely unknown. Our preliminary data using anti-sense morpholino-injected zebrafish larvae (morphants) demonstrated that depletion of Wtl interacting protein (Wtip), a basal body protein, causes podocyte foot processes to form two days early and also results in formation of the slit diaphragm at the onset of glomerulus filtration. We further searched for new interaction molecules for Wtip and discovered Podocalyxin. Interestingly, Podocalyxin was recently discovered as a candidate gene for focal and segmental glomerulosclerosis (FSGS). Patient with FSGS are challenging to treat, due to their frequently relapsing course and a high rate of progression to ESRD. Exome sequencing and in vitro studies have been performed to identify two PODOCALYXIN mutations for FSGS. These two transmembrane regions located in exon2 and exon8 are well conserved between humans and zebrafish. Therefore, we decided to create two zebrafish podocalyxin mutants: podocalyxin-exon2-HindIII and podocalyxin-exon8-PstI. We hypothesized that cilia are required for normal glomerulus filtration barrier development, and that Wtip, Wtl, and Podocalyxin are required for podocyte cilia function and podocyte development. To test these hypotheses, we proposed two specific aims: (i) determine whether cilia are required for podocytes' specification to assemble the glomerulus filtration barrier, and (ii) determine the mechanism by which Wtip signaling mediates glomerulus filtration barrier function. In this proposal, we aimed to understand how regulatory and signaling molecules function to establish a healthy glomerulus filtration barrier, thereby providing a framework for developing interventions to restore lost kidney function.

## Essential role of very long chain fatty acids in prevention of retinal degeneration

Martin-Paul Agbaga, University of Oklahoma Health Sciences Center

The long-term focus of our research is to understand the factors that contribute to vision loss in age-related macular degeneration (AMD) by studying an inherited early onset vision loss disease called Autosomal Dominant Stargardt Macular Dystrophy (STGD3). STGD3 patients have a gene mutation called Elongation of Very Long Chain

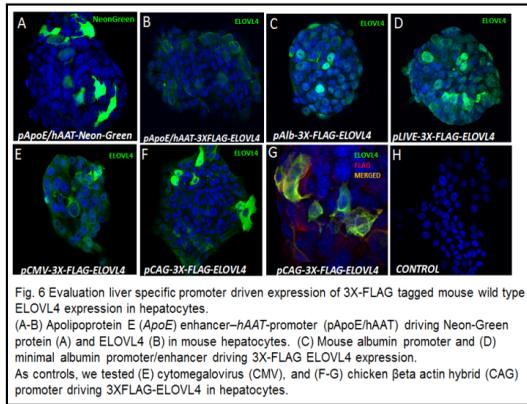


Fig. 6 Evaluation liver specific promoter driven expression of 3X-FLAG tagged mouse wild type ELOVL4 expression in hepatocytes. (A-B) Apolipoprotein E (ApoE) enhancer-hAAT-promoter (pApoE/hAAT) driving Neon-Green protein (A) and ELOVL4 (B) in mouse hepatocytes. (C) Mouse albumin promoter and (D) minimal albumin promoter/enhancer driving 3X-FLAG ELOVL4 expression. As controls, we tested (E) cytomegalovirus (CMV), and (F-G) chicken beta actin hybrid (CAG) promoter driving 3XFLAG-ELOVL4 in hepatocytes.

Fatty Acids-4 (ELOVL4). We discovered that the ELOVL4 is an enzyme that makes a unique group of fatty acids called very long chain fatty acids (VLCFA) found in the retina, testes, brain and the skin where they are essential for proper skin function. Mutations in the ELOVL4 results in decreased/loss of VLCFA biosynthesis which leads to loss of vision, severe neurological and skin problems and some cases cause death in childhood. Our current studies shows that absence/loss of retinal VLCFA results in age-dependent defects in retinal function (Fig. 1A-B). Mice expressing the mutant ELOVL4 protein that lacks VLCFA have reduced retinal function compared to wild type animals with full VLCFA complement (Fig. 1A-B). Hence we propose that dietary supplementation of VLCFA or introducing the wild-type gene into the liver of the mutant animals that have reduced VLCFA will result in biosynthesis and distribution of the VLCFA into multiple organs, including the retina, brain and testes to rescue vision loss as well as other neurological disorders associated with mutations in the ELOVL4 protein. We have generated a mouse model of Stargardt disease in which we show that loss of VLCFA leads to vision loss (Fig.1) We have crossed these mice with mice in which we expressed the mouse wild-type Elov14 in the liver (Fig.2) and are evaluating the ability of liver-produced VLCFA to correct the age-dependent visual defects we observe in the mice lacking VLCFA due to expression the mutant ELOVL4. Ultimately, the knowledge we will gain from these studies will greatly enhance our understanding of the role of VLC-PUFA in tissues in which they are found; more importantly, it will help in developing better therapeutic or dietary supplements for treating or attenuating the rate of retinal degeneration in STGD3 patients.

## HR14-150

### Understanding disease mechanisms for inherited forms of macular degeneration

*Identification of overlapping disease mechanisms for macular degeneration associated with different mutations in the RDS gene*

Shannon Conley, University of Oklahoma Health Sciences Center

Mutations in the photoreceptor-specific gene retinal degeneration slow (RDS) lead to blinding forms of inherited retinal degeneration in patients. The phenotypes in patients with RDS-associated disease can vary widely from retinitis pigmentosa (RP), a disease which primarily affects rod photoreceptor cells, to macular degeneration/pattern dystrophy (MD) a disease which often primarily affects cone photoreceptors. Developing a cure for these inherited diseases requires a clear understanding of the disease mechanisms, something that has been lacking for RDS-associated MD, especially for mutations that can cause both RP and MD. We are studying mouse models carrying one of two RDS mutations which cause either MD alone (R172W) or both RP and MD (Y141C) to determine what factors influence the development and severity of disease and how the disease process is regulated. Our work thus far has shown that a binding partner of RDS called rod outer segment membrane protein 1 (ROM1) can regulate the development of RP vs. MD. When ROM1 is present, mice carrying the Y141C mutation develop MD-like disease, while in the absence of ROM1, Y141C knockin mice develop RP. We have found that this change in phenotype is due to changes in the trafficking, assembly and stability of RDS complexes in the presence vs. absence of ROM1. This research is critical for our understanding of disease mechanisms associated with inherited retinal degeneration and may help develop novel genetic treatments or identify targets for pharmacological intervention.



*Electroretinography (ERG) is used to measure rod and cone function in both patients and mice.*

## How cone photoreceptors die in retinal degeneration

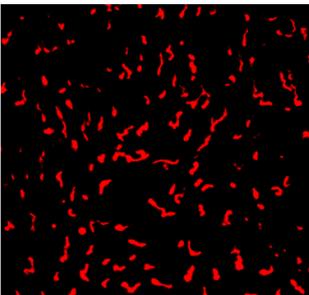
*The role of inositol 1,4,5-trisphosphate receptor in cone photoreceptor degeneration in CNG channel deficiency*

Xi-Qin Ding, University of Oklahoma Health Sciences Center

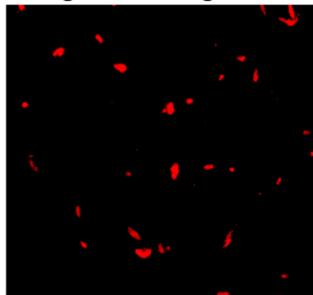
There are two types of light-sensing neuronal cells, rod and cone photoreceptors, in the retina. Cone photoreceptors are responsible for day-light vision, color vision and visual acuity. In retinal degeneration, it is the death of cone photoreceptors that eventually leads to the loss of vision/blindness. There are many pathological factors that can contribute to cone degeneration/death. Among them, the defects of the cone cyclic nucleotide-gated (CNG) ion channel represent a significant contributor. Defects of the ion channel account for about 80% of all cases of color blindness and are associated with progressive cone photoreceptor dystrophies. A better understanding of the mechanism(s)

of cone photoreceptor degeneration is essential for the development of therapeutic approaches. The proposed work focuses on the understanding of how cones degenerate when the normal functional channel is missing. Specifically, the proposed research will determine the contribution of some specific cellular organelles, including the endoplasmic reticulum. The results of the proposed work may help the development of the cellular organelles-based therapeutic approaches for cone protection. Indeed, even a small portion of remaining cones can provide useful vision and go a long way in helping people maintain their quality of life and independence.

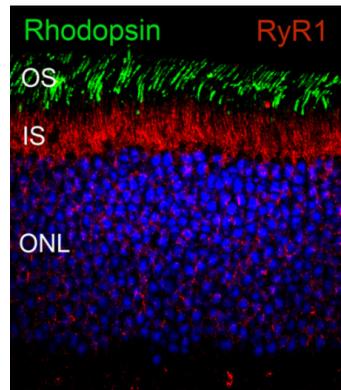
Normal retina



Degenerating retina



*Loss of cones in mice with CNG channel deficiency, analyzed by cone marker PNA labeling on a retinal flat mount*



*Labeling of endoplasmic reticulum on a mouse retinal section by Anti-RyR1 antibody*

New treatment for sight-threatening injuries and infections

Wound healing mechanisms modulated by novel antimicrobial peptide

Anne Kasus-Jacobi, University of Oklahoma Health Sciences Center

More than 2 million sight-threatening eye injuries and infections occur each year in the United States. Our long-term goal is to generate innovative ocular treatments with the dual effects of promoting wound healing and preventing or clearing infection of antibiotic-resistant bacteria. We have already identified a peptide (small portion of a naturally occurring protein) that has this dual effect and we are seeking to improve its wound healing activity to make it an even more powerful treatment. To do this, we first need to know the mechanism by which our peptide speeds up the process of wound healing. We know that when our wound healing peptide is applied to the surface of an injured eye, it binds to specific receptor molecules on the surface of the cells (Figure 1). This will in turn activate mediator molecules inside the cells, which will stimulate wound repair. In this project, we want to identify what specific receptors and mediators are activated by our peptide. First, we will use a variety of existing and newly developed tools to achieve identification of candidate receptors and mediators. One of these tools is depicted in Figure 2. It is based on an innovative reagent that will be used to identify the candidate receptors. Second, we will verify our findings by eliminating the candidate receptors and mediators one by one in mice. If by eliminating one candidate, we also eliminate the wound healing effect of our peptide, as shown in Figure 3, it will confirm the identity of this particular candidate. The next step will be to modify our peptide in order to improve binding to its specific receptor and improve activation of its specific mediators.

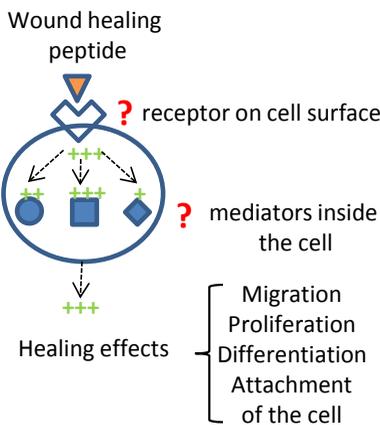


Figure 1: Mechanism of action of our wound healing peptide

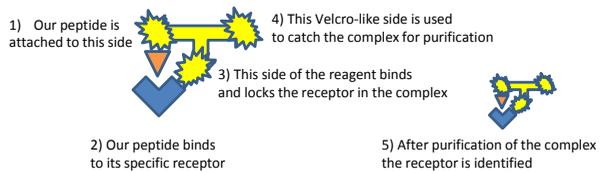


Figure 2: Innovative tool to identify candidate receptors of our

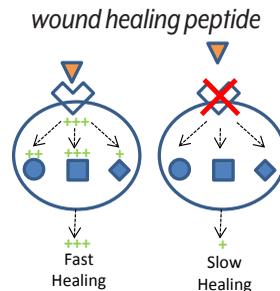


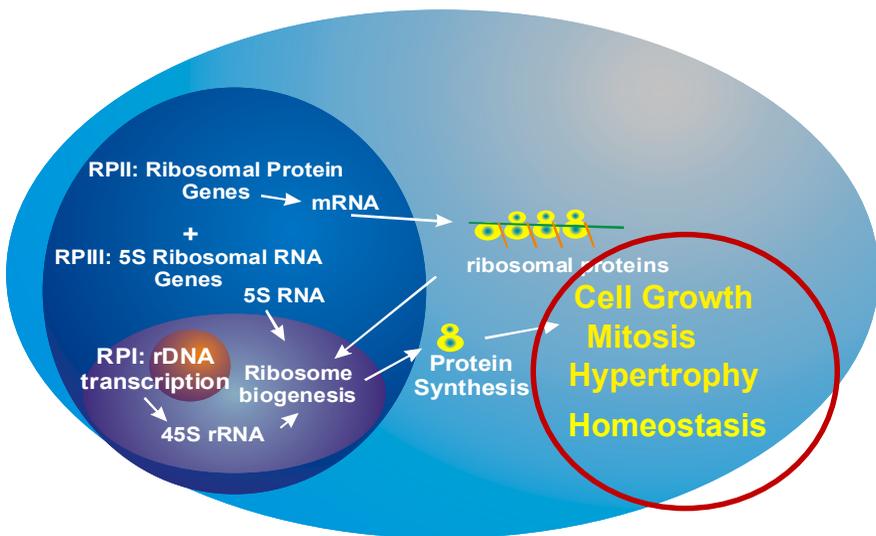
Figure 3: Confirming the identity of the receptor

Killing cancer cells by taking advantage of their addiction to growth

*Targeting cancer cells via ribosome biogenesis*

Lawrence Rothblum, University of Oklahoma Health Sciences Center

Cell growth requires the accumulation of proteins. This is made possible by the increased amounts of the basic protein synthesizing machinery in the cell, the ribosome. In order to accumulate ribosomes, the cell, particularly the cancer cell, must synthesize more of them. The rate-limiting step in this process, ribosome biogenesis, is the synthesis of ribosomal RNA, rRNA, by RNA polymerase I. When this process is inhibited, cancer cells die. Our study focuses on a novel and specific mechanism of inhibiting the synthesis of ribosomal RNA. We have found a peptide that can inhibit an essential interaction between two components of the rRNA synthesis machinery and that when this peptide is introduced into tumor cells, but not normal cells, it causes cell death.



**The Role of Ribosome Biogenesis in Cell Biology**

## HR16-014

The surface of your eye is vulnerable to injury and diseases which can threaten your eyesight

*Defense of corneal epithelial barrier integrity in homeostatic cell turnover and disease*

Allan F. Wiechmann, University of Oklahoma Health Sciences Center

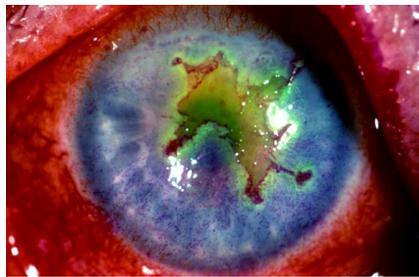
The transparent cornea comprises much of the anterior surface of the eye and is incessantly challenged by environmental assaults. A multi-layered corneal epithelium covers the corneal surface, with the outermost surface layer of cells providing the most crucial barrier to ocular infection. Deterioration of the corneal surface barrier integrity leads to loss of sight and is a major health concern for millions of people. We will create a corneal epithelium cell culture model that mimics the loss of corneal barrier function which is a hallmark of loss of function and infection in corneal diseases. With this model, we can identify drugs that are designed to protect intercellular connections. The long-term goal of this research is to preserve and restore sight to people with corneal trauma and disease, thus enhancing quality of life and productivity.



*Epithelium from human donor corneas are reconstituted in cell cultures to restore the normal tissue architecture for study.*



*The cornea of a healthy person is transparent to allow light to enter the eye to form visual images.*



*Loss of the protective barrier at the corneal surface enhances the risk of ocular infections and loss of sight.*

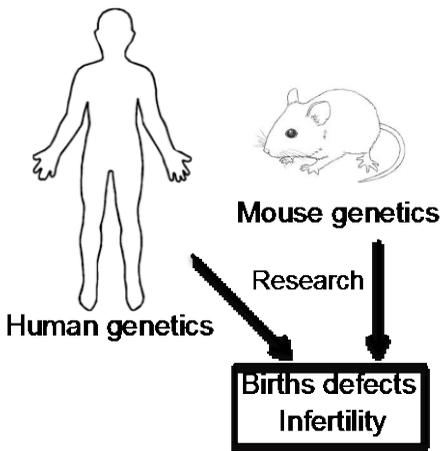
Understanding the causes of birth defects and infertility

*The Role of Psmc3 in homologous recombination*

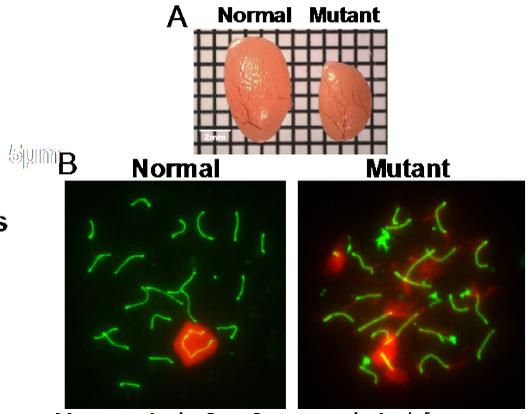
Roberto Pezza, Oklahoma Medical Research Foundation

Birth defects, which affect approximately 1 in 33 babies in the United States, have immediate social and economic consequences. Birth defects can be a result of genetic errors passed from the parents to the baby. Indeed, oocytes or sperm with the wrong number of chromosomes are a known leading cause of pregnancy loss and functional or developmental diseases such as Down, Klinefelter, Edwards and Turner syndromes. Our work focuses in identifying and understanding the function of the genes responsible for the formation of gametes with extra or lacking chromosomes. We use the mouse as a genetic model and biochemical in vitro approaches to reveal the origin

and the functional consequences of mutation in particular genes. Specifically, our results indicate that among the expression of 19 human genes that were different between fertile and infertile men, a gene named Psmc3 appears as a top candidate. More importantly, a mutation that deletes the Psmc3 gene in the mouse result in abnormal gonads and an increased number of gametes in which the number of chromosomes are altered. Our research has strong potential to accelerate approaches for the diagnosis, treatment and/or prevention of birth defects.



*Our approach to understand the origin and effect of mutations responsible for birth defects and infertility.*



Mutations in the Psmc3 gene results in defective testis development (A) and abnormal DNA repair (B). Chromosomes in green and DNA repair marker in red.

HR13-157

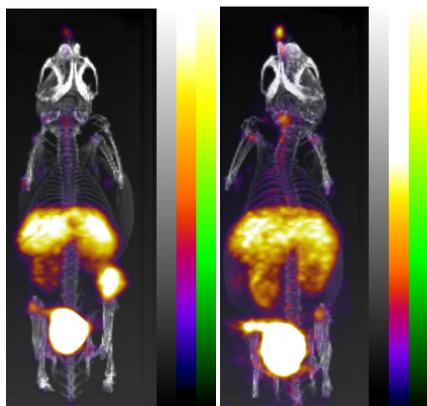
## Two birds with one stone: Targeting cancer twice with one drug

### *Dual CXCR4/CCR5 Chemokine Receptor Antagonists*

Tim Hubin, Southwestern Oklahoma State University

We want to prevent metastasis, the ability of cancer cells to travel to new locations from the original tumor. To do that, we want to block the signalling system that causes cancer cells to start migrating. Chemokines are small signalling proteins that bind receptors on the cell surface and activate the cell to move. CXCR4 and CCR5 are two different cell surface receptors that bind different chemokines that signal cancer cells to metastasize. There are more than 20 of these chemokine receptors and more than 20 chemokines, some of which can bind to more than one chemokine receptor. The sheer number and flexibility of the chemokine/chemokine receptor signalling system makes it difficult to completely inactivate metastasis by targeting only one chemokine or chemokine receptor. In order to stop metastasis we have

chosen to design potential drug molecules that can block, or antagonize, both CXCR4 and CCR5. We call these molecules Dual CXCR4/CCR5 Chemokine Receptor Antagonists. Our earlier research produced some of the most potent CXCR4 antagonists ever made, even better than the only CXCR4 antagonist currently approved by the FDA. These CXCR4 antagonists are made of two nitrogen-containing circular molecules linked together and bound to copper or zinc ions. They bind CXCR4 strongly because CXCR4 has lots of negative charge that is attracted to the positive charge provided by the copper or zinc metal ions. We are attempting to add CCR5 binding ability to these molecules by adding uncharged bulky organic groups that are the preferred structures for binding CCR5. Successful CXCR4/CCR5 antagonists may reduce cancer metastasis by interrupting the signalling system that initiates cancer cell movement.



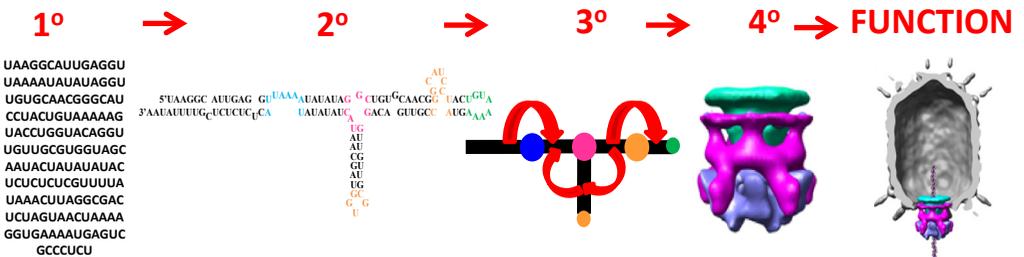
*PET/CT scans of mice bearing CXCR4-expressing (left) and non-CXCR4-expressing glioblastoma (right) tumors on their right flanks. This study shows strong binding of our CXCR4 antagonist to the CXCR4-expressing tumor, but little binding to non-CXCR4 expressing tumors.*

# Finding new shapes and drug targets in viral RNA genomes

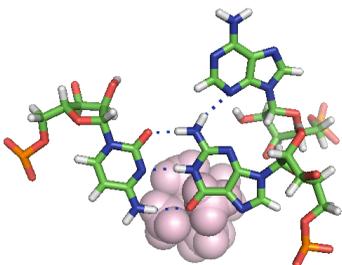
*Predicting viral RNA structure, function, and drug targets*

Susan J. Schroeder, University of Oklahoma

Extremely few drugs exist to treat or cure human viral diseases. Many viruses, such as HIV, Flu, Hepatitis, Zika, and Ebola, have RNA genomes. Viral RNA structure is a goldmine of undiscovered drug targets. The current challenge is to use the abundance of new sequence information to predict drug targets and thus convert sequence information into new drug development pipelines. The results of this research will generate new rules to predict the shapes of viral RNA and identify drug target sites in viral RNA. RNA can form base pairs to build helices or make other interesting shapes such as base triples and loops using unpaired regions in the RNA sequence. Binding metal ions is a key characteristic of RNA that also determines the overall three-dimensional shape. The long term goal is to predict RNA structure, function and drug target sites from sequence. Advancement requires more diverse RNA sequences and loops to be studied. The results of this research will provide benchmarks and test cases for computational methods development and improve predictions for all kinds of RNA. Amidst a deluge of sequence data and a tsunami of new RNA discoveries, these results will help guide the way to finding new drug targets in viral RNA.



*RNA structure builds up from sequence to helices and loops that bind metal ions and proteins in a virus that infects bacteria.*



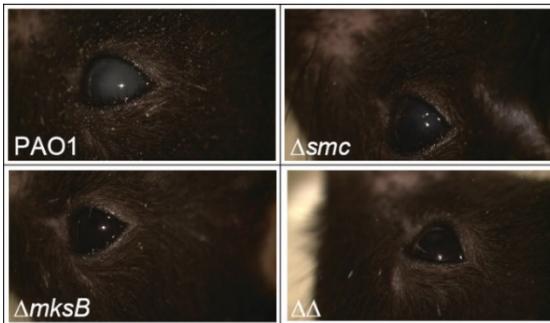
*A metal ion (purple) helps form an RNA base triple in a viral RNA bulge loop.*

## Developing a new family of antibiotics

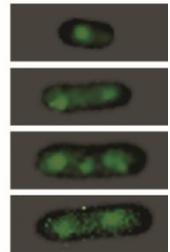
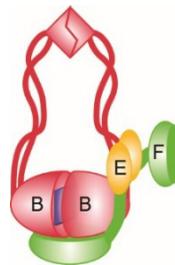
*Condensin dependent potentiation of antibiotics*

Valentin Rybenkov, University of Oklahoma

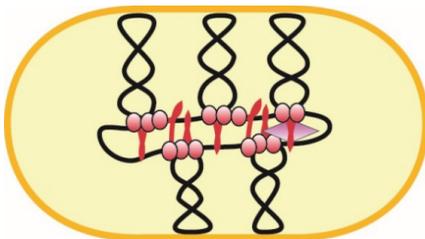
The emergence and spread of drug resistant bacteria requires the development of new antibiotics. This project seeks to develop such a family using a novel target for the drugs, condensins. Condensins play a key role in global organization of the chromosome in organisms ranging from bacteria in humans. However, they are sufficiently diverged to expect the development of organism-specific drugs. During the course of this project, we discovered that condensins are required for virulence in *Pseudomonas aeruginosa* during eye infection. We further developed a novel high throughput screen suitable for the search for condensin inhibitors. During pilot screening of a small library, we discovered two compounds that inhibit the protein. These are the first known inhibitors of condensins. Further development of this line of research will likely produce novel antibacterial and potentially anticancer drugs.



*Pseudomonas aeruginosa* encodes two condensins, *smc* and *mks*; both are required for eye infection in mice.



Condensins are multisubunit proteins (left) that localize at the core of the chromosome (right).



Condensins stabilize the core of the chromosome and thereby ensure stable transmission of genetic information.

## HR14-043

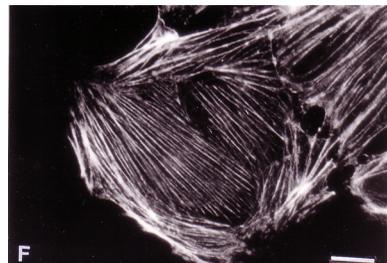
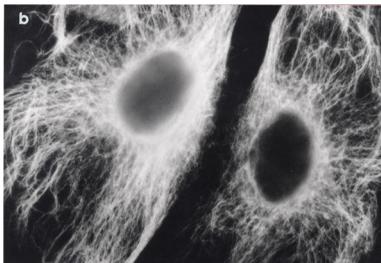
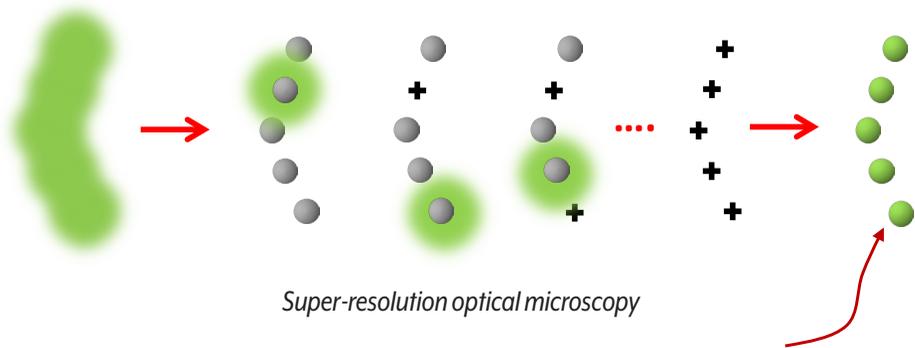
# Blinking protein-nanoparticle conjugates for imaging the inner structure of cells with a light microscope

*Protein-nanoparticle photoswitches for subcellular imaging*

Kaan Kalkan, Oklahoma State University

In 2014, the Nobel Prize in Chemistry was awarded to super-resolution optical microscopy. This technique makes use of blinking fluorescent molecules and allows imaging of the tiny organelles in a cell with a light microscope. Scientists need brighter and faster switching blinkers to best exploit this technique. To this end, we conjugate the green fluorescent protein (GFP), found in jellyfish, with a silver nanoparticle to develop such a switchable light emitter. Light scattered from silver nanoparticles can be thousands of times brighter and more stable than that

emitted from fluorescent molecules. Our objective is to turn this emission on and off (blink) using the energy transfer mechanism in a protein-nanoparticle conjugate. A potential application of the conjugate biomarkers is the intracellular imaging of cancer cells to reveal their therapeutic response to new drugs, which preferentially block cell movement and metastasis. The stability and brightness of our conjugate blinkers will enable these studies at the single cell level for longer periods.



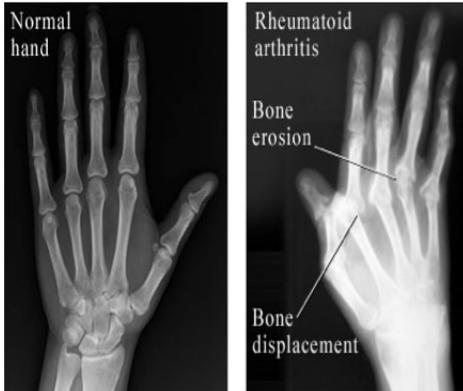
*Conjugates targeted to actin fibers in live cells*

Inhibiting human IL-18 for treatment of autoimmune diseases

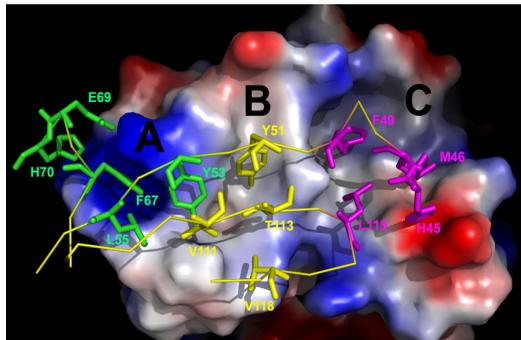
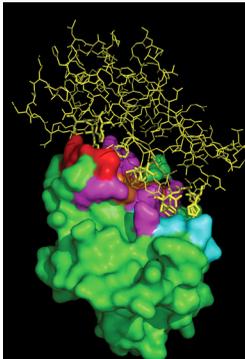
*Structure and function studies on the signaling complex of interleukin 18*

Junpeng Deng, Oklahoma State University

Interleukin 18 (IL18 plays an important role in host defense but also contributes to pathogenesis of inflammatory diseases such as rheumatoid arthritis and Crohn's disease. IL18 signaling is initiated by its binding to the IL18 receptor (IL18R)  $\alpha$  subunit, followed by the recruitment of the receptor  $\beta$  subunit to form a ternary complex. A naturally occurring inhibitory protein of IL18, IL18 binding protein (IL18BP), regulates IL18 activity through a negative feedback mechanism. We have elucidated the molecular mechanism by which IL18BPs function and have determined the crystal structures of two divergent IL18BPs in complex with IL18. The structures of the inhibitory complexes of IL18 provided key information for developing small molecule inhibitors against IL-18 signaling. We are also in the process of developing antibodies specifically blocking IL18 receptor signaling. These regents could be useful for further developing therapeutics against inflammatory and autoimmune diseases.



*IL18 has a direct correlation with the severity of autoimmune diseases such as Rheumatoid Arthritis (RA). [www.arthritis.org](http://www.arthritis.org)*



*Left, IL18:IL18BP complex. Right, the interface serves as structural basis for new drug design to inhibit IL18 as treatment of human diseases.*

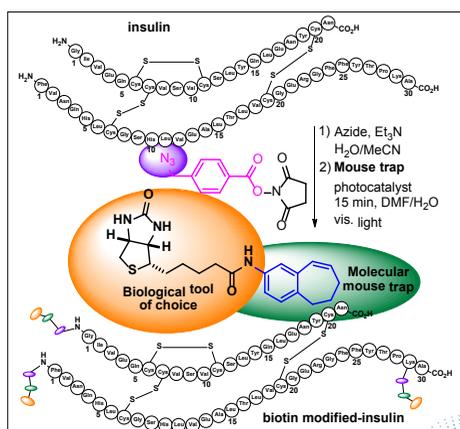
Tapping into the full potential of sunlight for energy storage, chemical synthesis, and building chemical probes for biology

*Photoredox catalysis for the rapid synthesis of diverse medically relevant motifs*

Jimmie Weaver, Oklahoma State University

Visible light carries with it an enormous amount of energy. In fact, it is equivalent to heating to a reaction to nearly 35,000 °C, a temperature that is not feasible. However, most molecules do not absorb this light and are unaffected by it. Furthermore, there are only a few strategies for harvesting this photochemical energy. While energy storage is an important issue, far less attention has been paid to exploiting this energy for the purposes of chemical synthesis and chemical biology. This is due, in part, to both the destructive nature of ultraviolet light (which is absorbed by organic molecules) and the optical transparency of nondestructive visible light. This proposed work capitalizes on the ability of photocatalysts to absorb

visible light and convert it into useable forms. Specifically, we aim to engineer small molecules which, along with a photocatalyst, can convert photochemical energy into ring-strain that can then be used to facilitate unprecedented reactions. Upon reaction, the strained molecules give off vast amounts of energy which results in fast and facile reactions. In essence, these molecules behave as molecular mouse traps. The proposed work will result in new strategies to synthesis small molecules of biological relevance, perform catalysis, perform conjugation chemistry with spatio-temporal control which is of great importance to many scientific fields. In the long run, the new strategies we develop will provide new directions to many scientific endeavors.



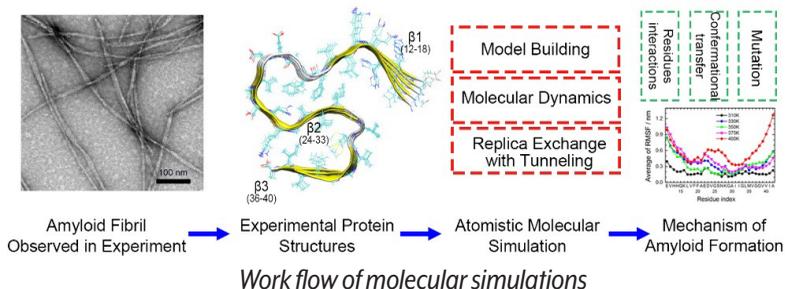
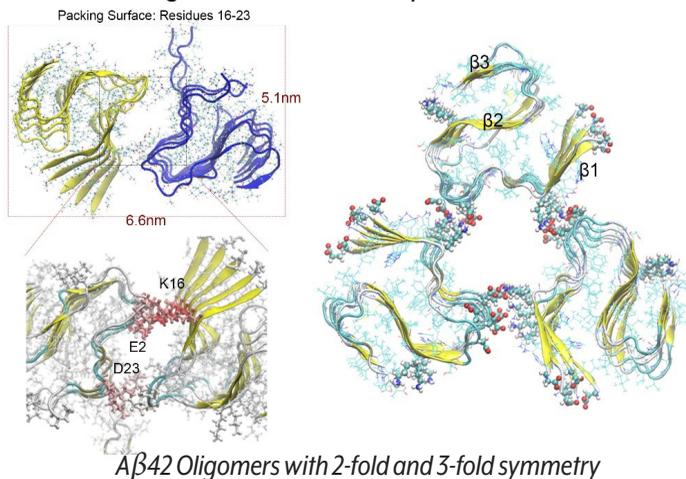
*Visible light mediated biotin conjugation of azide modified insulin. The benzo-fused cycloheptene serves as a molecular mouse trap capable of undergoing remarkably fast and selective reactions.*

# Molecules that cause Alzheimer’s Disease – a computer simulation study

*Modeling the molecular mechanism of amyloid oligomer and fibril self-assembly*

Ulrich H. E. Hansmann, University of Oklahoma

Over 20 human diseases are connected with the presence of amyloid fibrils. An example are Amyloid- $\beta$  peptides which are implicated in the pathogenesis of Alzheimer’s disease. An understanding of molecular mechanism of amyloid formation is crucial for developing therapeutic strategies to treat such diseases. However, it is difficult to study the amyloid structures, their formation and evolution in experiments. The PI uses molecular simulation, including the in-house developed replica-exchange-with-tunneling method to unveil the mechanism of amyloid formation of A $\beta$ 42 peptides, wild type and its mutations. The study of triple- $\beta$ -stranded A $\beta$ 42 fibril reveals that a different hydrophobic core in S-shape motif lead to a cross-propagation barrier to A $\beta$ 44 peptides with their U-shape motif. The driving force of stability in this triple- $\beta$ -strand conformation are hydrophobic interactions but not a K28-A42 salt-bridge. Various 2-fold/N-fold symmetries of A $\beta$ 42 are proposed that can serve as templates to study interaction of suitable drug candidates with amyloids.



## Single cell level mass spectrometry analysis for anticancer drug pharmacology

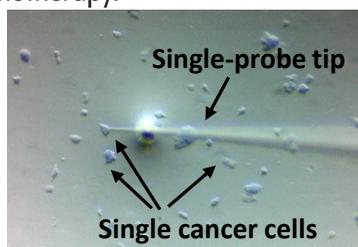
Zhibo Yang, University of Oklahoma

Mass spectrometry (MS) is a powerful analytical technique under a rapid development. MS has been widely used for sensitive detection and accurate identification of molecules in biological samples. Cell is the smallest unit of life, and each cell is unique. Traditionally, all analyses of the molecular pharmacology are performed from samples prepared from large numbers of cells (e.g. ~10 million), which can only provide the averaged results from a heterogeneous population of cells. A large amount of important information of individual cells is lost. More importantly, some cell samples (e.g. certain types of cancer cells obtained from individual patients) may be limited, eliminating the possibility of using traditional methods for studies. Single cell MS (SCMS) analysis of live cells is an emerging field, and these techniques can provide revolutionary approaches for molecular pharmacology studies.

We are advancing the development and application of the Single-probe, a miniaturized sampling and ionization device that can be used for MS analysis intracellular compounds of live single cells. A Single-probe is made from a laser-pulled dual-bore quartz needle, and each channel is connected to a

thin capillary. The Single-probe has a sampling tip that is smaller than a cell (10  $\mu\text{m}$ , i.e., ~10% of a human hair diameter). Using a computer-controlled motion system, the probe tip can be inserted into a target cell under microscopes. The sampling tip has two channels: one introduces solvent to extract molecules present in a cell, and the other transports the dissolved molecules for MS analysis, which is sensitive enough to detect molecules from one cell.

Our techniques can be used in many different types of studies. We are interested in the analysis of anticancer drugs inside cancer cells. In particular, we are developing quantitative SCMS methods that can be used to measure the amount of anticancer drug uptake by individual cells. These techniques can potentially provide guidelines for doctors to evaluate the effectiveness of specific anticancer drugs, and to optimize dosage for individual patients preventing any overdose during customized chemotherapy.



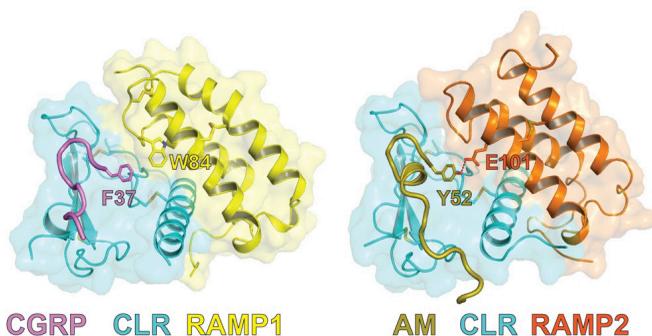
## HR16-005

Using powerful X-rays to visualize cardiovascular hormones and guide the development of new drugs for migraine headache and heart attack

*Rational design of potent and selective peptide ligands for the CGRP and Adrenomedullin receptors*

Augen Pioszak, University of Oklahoma Health Sciences Center

The hormones CGRP and AM control blood vessel relaxation in the brain and heart. Too much CGRP can cause migraine headache whereas extra AM seems to be beneficial for heart attack patients. CGRP and AM interact with receptors on the surface of cells to exert their control. This interaction process is analogous to a key fitting a lock. In previous work in our lab we used powerful X-rays to obtain 3-D pictures of CGRP and AM fitting their receptors, which significantly advanced our understanding of how these hormones work. In this project we propose to use the knowledge gained from these pictures to guide the design of new “super-hormones” that fit the receptors better than the natural hormones. The resulting super-hormones may lead to new therapeutics for the treatment of migraine headache and heart attack, which would benefit Oklahomans who suffer from these conditions.



*X-ray pictures showing how the hormones CGRP and AM that control blood vessel relaxation fit their receptors.*



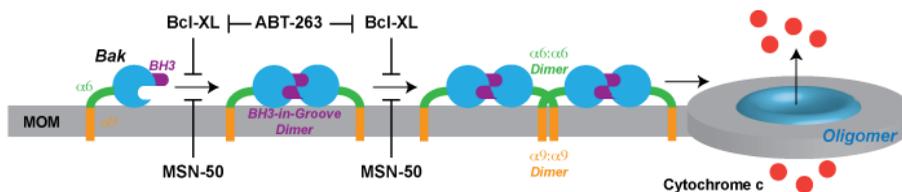
*Shooting powerful X-rays through these crystals of a hormone-receptor complex allows us to visualize how the hormone fits the receptor like a key in a lock.*

## Deadly pore formation in mitochondrial membrane: Mechanism and therapeutic potential

*Structure, function and inhibition of apoptotic Bak oligomers in mitochondria*

Jialing Lin, University of Oklahoma Health Sciences Center

The long-term goal of this project is to elucidate the molecular mechanisms for regulating programmed cell death. Understanding these mechanisms is the key to the development of effective treatments for a wide variety of human diseases such as cancer, stroke and heart attack, in which cell death is either inhibited or accelerated. Despite sequence and structural homology, pro-death Bak protein forms large pores in the mitochondrial outer membrane to induce cell death, whereas pro-survival Bcl-XL protein binds Bak to inhibit the deadly pore formation. This project will identify the key structural features of Bak pore and the molecular mechanisms for its assembly in the membrane and decipher the molecular mechanisms by which Bcl-XL and small molecules inhibit Bak pore formation. We will use a multidisciplinary approach, including molecular biology, biochemistry, cell biology and structural biology, to characterize the molecular interactions of these proteins and small molecules and the functional consequences. The anticipated outcomes from this rigorous investigation are the mechanistic details for (1) how Bak damages the mitochondria to kill the cell (2) how Bcl-XL inhibits Bak to preserve the mitochondrial integrity and save the cell, and (3) how small molecules bind Bak or Bcl-XL to regulate their respective pro-death or pro-survival activity. The impact of these significant outcomes to the cell death field will be vital because they will reveal or validate relevant target sites and provide lead compounds for developing the next generation of drugs to more effectively combat cancer, stroke and heart attack.



*Model for Bak oligomeric pore formation and regulations by Bcl-XL and small molecules ABT-263 and MSN-50. Active Bak forms the BH3-in-groove interface and then the  $\alpha6:\alpha6$  and  $\alpha9:\alpha9$  interfaces resulting in a tetramer and then a higher order oligomer that perforate the mitochondrial outer membrane (MOM) to release Cytochrome c. Bcl-XL and MSN-50 inhibit either or all Bak dimerizations and perhaps Bak interactions with the MOM to block the pore formation. ABT-263 neutralizes Bcl-XL so it cannot inhibit Bak.*

HR16-095

## Designing non-addictive analgesics to treat severe pain

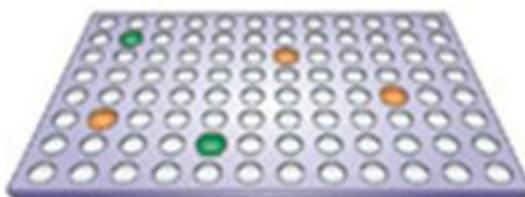
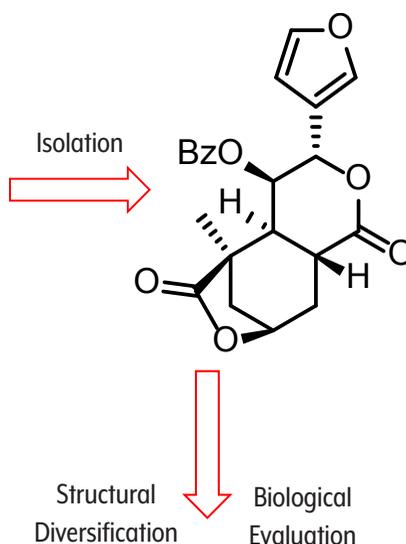
*Design and synthesis of collybolide analogues as probes in kappa-opioid pharmacology*

Indrajeet Sharma, University of Oklahoma

Pain is one of the most significant causes of suffering and disability worldwide. Chronic pain affects ~100 million American adults more than heart diseases, cancer and diabetes combined. While Mu-opiate analgesics such as morphine are effective for severe pain, their use is limited due to unwanted side effects such as respiratory depression, physical dependence, psychological addiction and abuse liability. Thus, a key gap and critical need for effective pain management is the development of selective kappa-opioid analgesics with reduced side effects. Collybolide, a natural product isolated from the mushroom *Collybia Maculata* has exhibited potent analgesics properties without the side effects seen in well-known analgesics such as morphine, due to its selectivity for the kappa-opioid receptor. This proposed work will focus on the synthesis and evaluation of collybolide analogues. This work will lead to a better understanding of the kappa-opioid receptor pharmacology to develop potential therapeutics for the treatment of pain with reduced addiction hazards.



*Collybia maculata*



# Research Area: Data Sciences

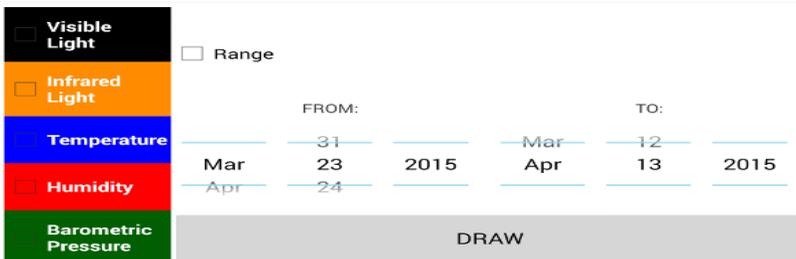
HR13-035

Integrating disease-correlated ambient information into reliable and privacy-preserving pervasive health monitoring

Eric Chan-Tin, Oklahoma State University

Privacy of health data is critical as it contains personally identifiable information. As health monitoring becomes common, there is an urgent need to secure this process. This project tackled several problems related to health monitoring and health data analysis. We deployed sensors to monitor the surrounding environment and wirelessly transmit the data. This data can be visually displayed on a smartphone app. This helps the patient easily understand how the environment has an effect on her health. Since sensors use low power, the wireless transmission can be easily masked by a stronger laptop or microwave transmission. We built an algorithm based on past history, called concordance, to predict when there will be no wireless interference to successfully transmit the sensor data. This conserves battery of critical medical devices. Medical data from different sources and hospitals sometimes need to be

compared. Medical data is encrypted. Decrypting the data to perform a comparison could leak private information. We developed an error-tolerant linking algorithm that allows for comparison of encrypted data without having to first decrypt the data. Since medical data needs to be transferred over the Internet, we also designed an algorithm that masks the medical data. This provides a private manner of sending medical data over the Internet while making it look like regular web data. The last goal of the project is to analyze the medical records of diabetes patients. In this study the effectiveness of different medicines is assessed. We also showed that this effectiveness can be evaluated based on the demographic information. This research project provides algorithms to protect the privacy of medical data and to analyze medical records. Results from our studies are beneficial to the medical community and society.



Screenshot of the smartphone app showing the different surrounding environment information recorded

# Research Area: Dental Biomaterials

HR15-021

Enzymes in saliva can worsen tooth decay under dental fillings

*Modulation of biofilm growth due to salivary biodegradation of resin restorations*

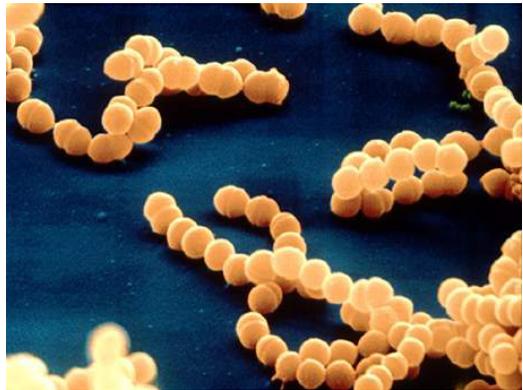
Sharukh Khajotia, University of Oklahoma Health Sciences

Center

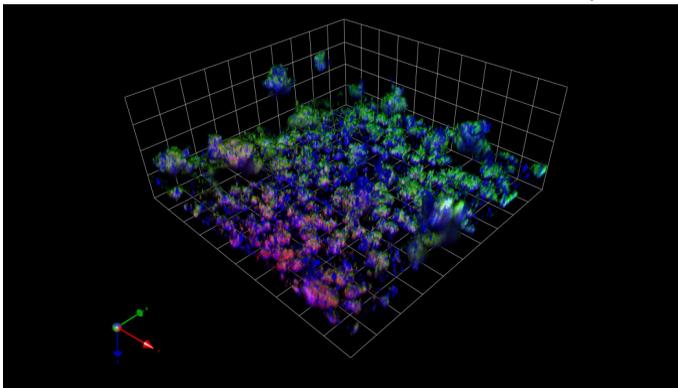
The bacterium *Streptococcus mutans* is a normal part of the human mouth. However, it can cause tooth decay when the diet contains sugars like sucrose and glucose that it can easily metabolize. A common reason for the replacement of tooth-colored (white) fillings is decay under the fillings. The proposed study will focus on understanding the role of enzymes in human spit (saliva) that roughen the surface of fillings. This creates a cycle where more plaque collects on the fillings and damages the fillings even more. The results of the proposed work may lead to potential solutions to improve the lifespan of dental fillings. In the long run, this research may ultimately lead to substantial reduction in oral health care costs because fewer fillings will need replacement, thus significantly benefiting the nation's economy.



*Junction between tooth and filling*



*The bacterium Streptococcus mutans under a microscope*



*Plaque grown on a filling material for two days*

# Research Area: Genomics & Gene Expression

HR14-174

## Persistent neuroepigenetic modifications caused by early-life endocrine factors

*How do changes to your genome across a lifetime contribute to brain aging?*

Willard M. Freeman, University of Oklahoma Health Sciences Center

Aging is characterized by a steady decline in organismal function across organ systems, including the brain. A common misconception about brain aging is that neurons – the primary cells that let us learn, remember and many other functions – are lost with aging. Neurons are only lost with neurodegenerative diseases like Parkinson's and Alzheimer's. Rather, detailed studies have demonstrated that neurons lose connections, called synapses, and have impaired function of a variety of other cell functions. These impaired functions appear to be driven by changing expression of genes in the cells. Why might these genes change in expression is not known. Our hypothesis is that epigenetic changes drive these gene expression changes.

What is epigenetics? Epigenetics is changes to the genome, the set of instructions for the cell, and how these instructions are organized and available for use. Epigenetics is different from genetics in that it is examining organization and structure of the genome rather than the sequence of gene itself and how mutations and other changes in the sequence of the

genome affect function. Epigenetics of the brain, neuroepigenetics, is of special interest as there are many examples of stimuli during development or other stages in life that cause persistent changes in brain function. How these stimuli/signals continue to effect brain function long after the stimuli has gone away is unknown but our hypothesis is that persistent changes in the brain are perpetuated by epigenetic factors.

To perform this research we have used OCAST support to develop a new technology called Bisulfite Oligonucleotide Capture Sequencing (BOCS). This new technology lets us analyze DNA modifications, a type of epigenetic mark, across the genome. This allows researchers to analyze the level of DNA modifications at millions of specific locations in the genome. Because the location of these DNA modifications in the genome is critically important, the 'where', and we are analyzing the levels of the modifications, the 'what', we can hopefully begin to understand the 'how' of the role of the epigenome in brain aging.

Do age-related increased mutations in mitochondrial DNA lead to cellular senescence?

*Single cell mitochondrial heteroplasmy*

David R. Stanford, University of Oklahoma Health Sciences Center

Aging is characterized by a steady decline in organismal function across organ systems. Aging is also a primary risk factor for a wide range of diseases from neurodegeneration (Alzheimer’s and Parkinson’s), to cancer, to diabetes. Understanding the aging process and how it contributes to disease has been termed geroscience. One of the goals of geroscience is to understand what aspects of aging contribute to organismal dysfunction and identify approaches to slow or reverse age-related cellular changes. Cellular senescence is one process that contributes to age-related tissue dysfunction across different organ systems. Cellular senescence is characterized as generally impaired cellular function and by induction of genes that cause a loss of replicative potential. Senescent cells are observed across almost all tissue and cell types with advanced age. Intriguingly only a portion of cells within a tissue become senescent with aging. Studies have provided compelling evidence that elimination of senescent cells has positive effects on tissue function and broadly speaking restore a younger phenotype to a tissue. A major gap in our understanding of cellular senescence is why do certain cells become senescent while others do not?

Previously published reports suggest that mitochondrial dysfunction may be a causative factor in cellular senescence. As the major source of energy (ATP) within cells and site of reactive oxygen species, dysfunctional mitochondria can impair and damage cells. Continuing on this pathway, the next question is why do mitochondria become dysfunctional? One potential mechanism is accumulation of damage to the mitochondrial genome (mtDNA). Because mtDNA replicates in the presence of high levels of free radicals it is especially prone to accumulate mutations and deletions over time. Numerous reports have detailed age-related increases of these mutations and deletions, termed mitochondrial heteroplasmy, and concomitant mitochondrial dysfunction. Broadly, this research program seeks to explore the hypothesis that mitochondrial DNA mutations and deletions lead to cellular senescence.

This hypothesis will be tested by determining whether senescent cells have higher levels of mitochondrial heteroplasmy than non-senescent cells from the same tissue. We have developed new techniques to comprehensively and quantitatively assess the level of mitochondrial heteroplasmy in a population of cells. In this research project we will extend this work to developing a method for single-cell mitochondrial heteroplasmy analysis and then apply this technique to a reporter mouse system that allows for discrimination of senescent and non-senescent cells within a tissue. These studies will not only provide definitive data on the level of mitochondrial heteroplasmy in senescent versus non-senescent cells but will identify the specific mtDNA mutations and deletions that are associated with cellular senescence.

## HR16-066

Changes in blood cell patterns in knee osteoarthritis patients may both diagnose the disease and predict how quickly it will progress

*Differential leukocyte epigenetic and transcriptomic patterns as diagnostic and predictive biomarkers in knee osteoarthritis*

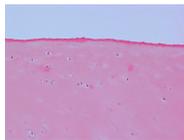
Matlock A. Jeffries, University of Oklahoma Health Sciences Center

Osteoarthritis (OA) affects nearly half of the population aged 70 and over. There is no treatment for people with this disease, which over time leads to severely diminished physical activity, quality of life and overall health. Reduction in OA patients' ability to exercise predisposes them to a variety of chronic diseases.

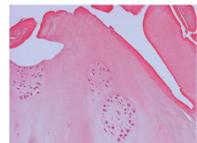
Over the past several years, we have begun to understand that OA is not simply a joint disease, but that inflammatory signals from all over the body can influence its development. Moreover, we have come to realize that it is not a purely inherited disease; other environmental factors are almost certainly involved.

The proposed work will recruit about 150 patients with early knee OA. Patients will donate a blood specimen, record their OA symptoms and have knee xrays every 6 months for 2 years. We will examine both the kinds and amounts of inflammatory cells present in their blood when they first enter the study and as time goes on and their OA worsens. Furthermore, we will look at epigenetic patterns within specific blood cells at each of these time points. Epigenetics is the study of particular markers which allow the environment to “interact” with genes by turning them on and off. Based on our prior experience, about one third of our patient population will experience rapid worsening of their OA over the course of two years. Once we have identified these patients, we will go back and determine if there were particular blood cell population or epigenetic patterns when they first entered the study that would have differentiated them from patients who did not go on to worsen over time. If successful, this project will produce the first accurate, blood-based diagnostic and prognostic test for people with knee OA and may offer insights into the ways in which blood-based inflammation may be contributing to OA. This may ultimately lead to the development of new treatments for individuals with OA and significantly benefit the economy of Oklahoma.

*Smooth, intact cartilage  
from an OA patient*



*Rough, eroded cartilage  
from an OA patient*



# Research Area: Immunology & Infectious Diseases

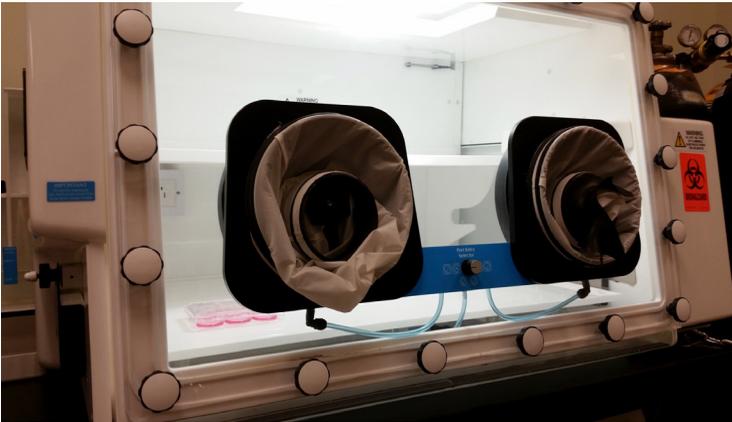
HR13-003

## Low oxygen levels control immune cell function

*The role of hypoxia on interleukin-22 (IL-22) secreting innate lymphocytes (ILC3s)*

Lauren A. Zenewicz, University of Oklahoma Health Sciences Center

Cytokines are small signaling molecules that control immune responses. Interleukin-22 (IL-22) is a cytokine produced by CD4 T cells and a specialized type of innate lymphocyte called ILC3s. IL-22 is highly produced during inflammation, such as in the intestines of inflammatory bowel disease (IBD) patients. IL-22 can be both bad and good for people. Therefore it is important for our bodies to have tight control on when and where the cytokine is made. We hypothesized that low oxygen levels are a signal for the immune cells to make IL-22 since low oxygen is one hallmark of inflammation. Our studies will help identify the environmental and cellular factors important for cells to make IL-22, allowing us to better design therapeutics to help IBD patients.



*To generate a low oxygen environment, we incubate cells in a special incubator.*



*Dr. Sudarshan Seshadri measures IL-22 levels using molecular biology techniques.*

## HR13-033

### Developing a vaccine against the most lethal virus in infancy

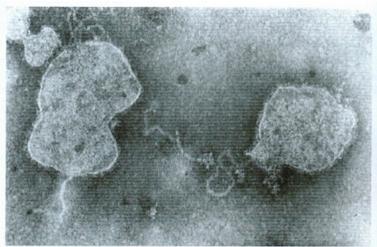
#### *Development of an M-null RSV vaccine in an infant baboon model*

Robert C. Welliver Sr., University of Oklahoma Health Sciences Center

Respiratory syncytial virus (RSV) is the most common cause of severe lung disease in human infants. Every year, RSV infections cause 150,000 deaths in infants worldwide. More than 120,000 infants are hospitalized with RSV infection annually in the United States. RSV infection in infants is associated with the development of asthma in later life. RSV also causes 10,000 deaths in elderly individuals in the US each year.

Remarkably, there is no effective vaccine to prevent RSV infection. Our research team has developed a live RSV vaccine that induces protective levels of antibodies against the virus. Our early studies show that the vaccine protects vaccine recipients against RSV infection, reducing the severity of breathing difficulties when vaccinated individuals are later infected with RSV. The vaccine appears to be safe, in that it does not cause any respiratory illness.

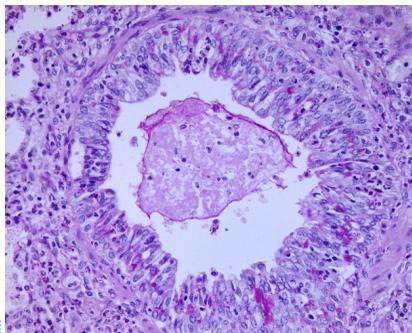
Further development of the vaccine may prevent deaths from RSV and reduce the high cost (> \$1 million annually) of caring for infants with RSV infection.



*Respiratory Syncytial Virus, in both its capsid (larger body) and filamentous (string-like) forms*



*Rachel Staats, MS adds RSV to a monolayer of human airway cells*



*An RSV-infected human airway, obstructed by inflammatory debris*

# Small molecules targeting mosquito midgut protein FREP1 block malaria transmission

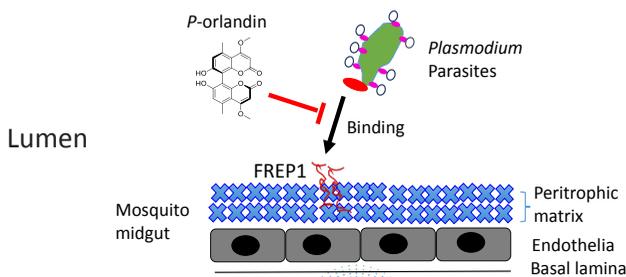
*Genomics analysis of mosquitoes to malaria infection*

Jun Li, University of Oklahoma

Malaria is responsible for two hundred million clinical cases worldwide and kills about one million a year. Malaria is caused by Plasmodium parasites and transmitted by mosquitoes. Inhibiting Plasmodium development in mosquitoes will block malaria transmission. This project aims to find target genes that are essential for malaria transmission in mosquitoes. Then, we aim to develop drugs targeting these critical genes to stop malaria transmission. Through genomic approaches, we discovered that fibrinogen-related protein 1 (FREP1) is critical for parasite infection in Anopheles gambiae and it facilitates Plasmodium invasion in mosquitoes through interacting with gametocytes and ookinetes. To test the hypothesis that small molecules disrupting this interaction will prevent parasites from infecting mosquitoes, we screened a fungal extract library and obtained a candidate fungal extract

of Aspergillus niger that specifically inhibited the interaction between FREP1 and P. falciparum infected erythrocytes by about 92%. Notably, feeding mosquitoes with the candidate fungal extract significantly inhibited P. falciparum infection in the mosquito midgut. A bioactive natural product that prevents FREP1 from binding to gametocytes or ookinetes was isolated and identified as P-orlandin, which is neither cytotoxic nor inhibiting the development of P. falciparum gametocytes or ookinetes. Importantly, P-orlandin significantly reduced P. falciparum infection intensity in mosquitoes. In summary, we discovered FREP1 as a key gene to mediate malaria transmission. Disruption of the interaction between FREP1 and parasites effectively reduces Plasmodium infection in mosquitoes. Targeting FREP1 with small molecules is thus an effective novel approach to block malaria transmission.

P-orlandin targeting mosquito midgut protein FREP1 blocks malaria transmission

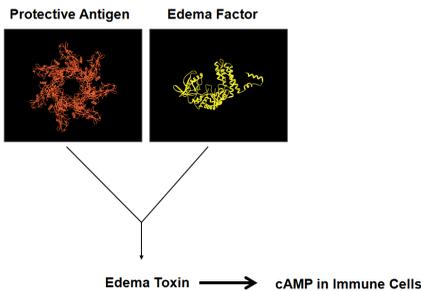


# Coupling PKA signaling to the adenomatous polyposis coli protein (APC) in macrophages

*Toxins produced by Bacillus anthracis cripple cells of the immune system*

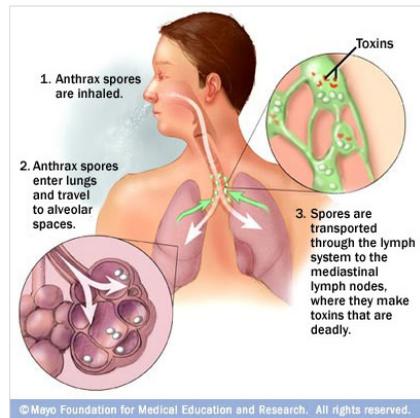
Jason Larabee, University of Oklahoma Health Sciences Center

Disease causing bacterial pathogens are a huge public health concern and developing treatments for these pathogens is a major goal of modern medicine. A key step in pathogenesis is linked to the ability of harmful bacteria to evade the immune system. Many pathogenic bacteria (e.g., Bacillus anthracis, Mycobacterium tuberculosis, Bordetella pertussis) have evolved strategies that cripple and remodel the immune system by increasing cAMP levels in macrophages. Signaling via cAMP is a major regulatory mechanism in macrophages and is often times connected to immunosuppression. An important goal of these studies is to dissect the signaling mechanisms used by cAMP in macrophages. Understanding these mechanisms will lead to the development of intervention that disrupt cAMP signaling and diminish the ability of bacterial pathogens to elude the immune system. Moreover, these studies will lead to a better understanding of the function of APC, which is a tumor suppressor protein frequently mutated in cancers.

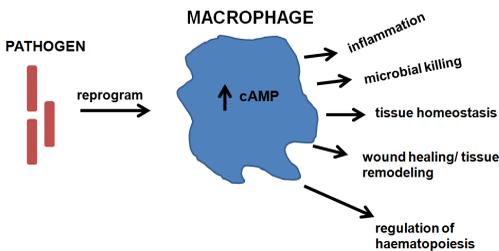


*Anthrax toxin that increases cAMP in immune cells.*

## Inhalation anthrax



*Example of disease depending on cAMP generating toxins.*



*Example of how pathogen uses cAMP to reprogram immune cells.*

## HR13-179

# Understanding how virus particles form to help future generation of viral vaccines with a defined protein composition and optimal immune response

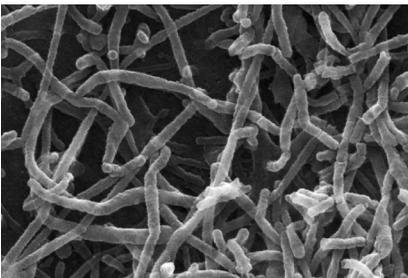
## *Structure-function analysis of the matrix protein hinge region in RSV assembly*

Tom Oomens, Oklahoma State University

RSV is a medically important virus. Respiratory syncytial virus (RSV) is a major human pathogen related to the Measles virus. Across the world, RSV is estimated to cause >200,000 deaths per year in children. RSV is also a serious threat for the elderly and the immune-compromised and may contribute to development of asthma. In contrast to Measles virus, and despite its medical significance, there is no licensed vaccine available for RSV.

Problems with production of RSV particles stands in the way of a future vaccine. Different vaccine approaches are being pursued in an attempt to lower the worldwide RSV-associated disease burden. Many of these approaches rely heavily on the production of RSV particles. To achieve a desired immune outcome, the composition of vaccine particles needs to be well controlled and defined. Production of RSV particles however, is

an inefficient process and the underlying mechanisms are poorly understood. We use molecular tools to improve our understanding of the RSV particle production process to overcome this hurdle and enable future vaccines. The viral matrix protein (M; indicated in purple in below right panel), is the most important building block in particle formation and hence the focus of our study. M interacts with other viral and host cell proteins to drive the formation of virus particles, but we do not know how. In this project, we mutagenize the M protein to identify the parts of M that control its function and to examine the mechanisms used by M to generate particles. Once we understand these mechanisms, we will be able to generate RSV vaccine particles with a defined and precise protein composition. Defined protein composition of vaccine particles will help control the level and quality of the induced immune response needed to provide children with a safe and lifelong protection against RSV.



*Electron microscopy image of RSV particles budding out of a host cell. Production of RSV in the lab is inefficient and hampers vaccine development.*

## HR14-060

# The activation of a cell membrane protein leads to inflammatory lung diseases

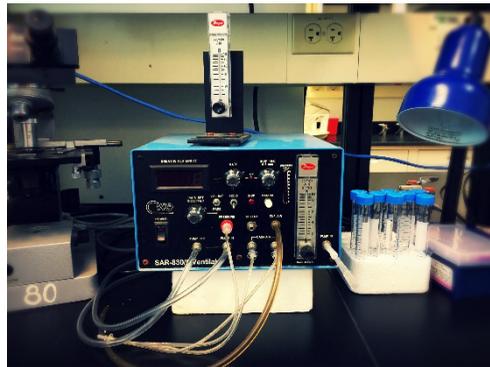
*Purinergic P2X7 receptor as a pro-inflammatory molecule*

Lin Liu, Oklahoma State University

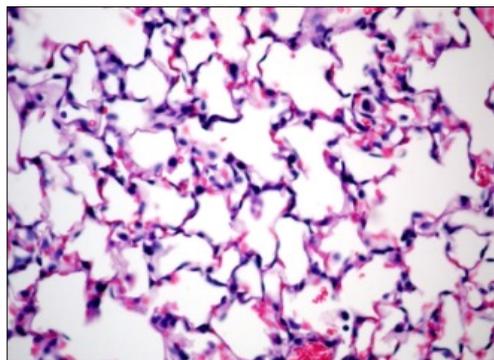
Acute lung injury (ALI) and its more severe form, acute respiratory distress syndrome (ARDS), is a life threatening disease that is often caused by lung infection. Pulmonary neutrophils are the initial inflammatory cells that are recruited during lung infection and are crucial for innate immunity. Recruitment of these neutrophils, however, can cause lung injury. This study aims to determine which molecule(s) recruit pathological levels of neutrophils to injury sites, amplifying lung inflammation during acute lung injury. By investigating the functions of a novel alveolar epithelial type I cell, purinergic P2X7 receptor, we hope to clarify the pathogenicity of ALI/ARDS. The results of this study will help to advance the development of pharmacological therapies as an alternative to supportive mechanical ventilation for ALI/ARDS.



*Bronchoalveolar lavage fluid being loaded into a centrifuge*



*A ventilator used during our research*



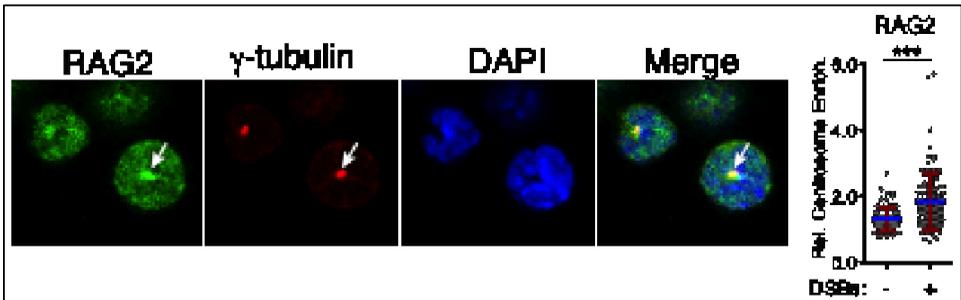
*Lung tissue section*

# Response of developing B and T cells in the immune system to DNA damage

*Novel functions of recombinase proteins in DNA damage response*

Karla Rodgers, University of Oklahoma Health Sciences Center

Our adaptive immune system is an essential line of defense against the onslaught of pathogenic organisms and viruses that our bodies are exposed to on a daily basis. B and T cells mediate the immune response through expression of diverse repertoires of antigen receptors. Functional antigen receptor genes are generated during B and T cell development through the action of the V(D)J recombinase, consisting of RAG1 and RAG2, which acts directly on specific DNA sequences in the genome. To protect the genome, the activity of the V(D)J recombinase must be limited to antigen receptor genes. However, this is a more challenging prospect upon the occurrence of excessive DNA damage, since the V(D)J recombinase activity could impede proper DNA repair. In this project, we will determine how the cell regulates the V(D)J recombinase in order to prevent the occurrence of genomic instabilities, such as chromosomal translocations, that can lead to certain types of leukemias and lymphomas.



*Fluorescence microscopy of pre-B cells expressing fluorescently tagged RAG2 following treatment with DNA damaging agents. The RAG2 (in green) is co-associated with  $\gamma$ -tubulin (in red), which is a marker for centrosomes, following DNA damage. The cell nucleus is stained with DAPI (in blue). Centrosomes help to partition chromosomes accurately during cell division, and are duplicated during every cell cycle.*

## HR14-138

### Different immune cells communicate with each other to cause disease flares in multiple sclerosis

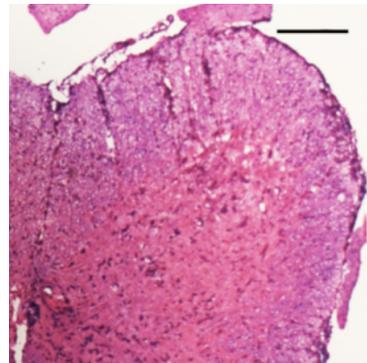
*Interplay between neutrophils and B-cells in neuro-autoimmunity*

Robert Axtell, Oklahoma Medical Research Foundation

Cells in the immune system communicate with each other to fend off infections and fight cancers. However, in multiple sclerosis (MS) the immune cells are misdirected and attack neurons causing inflammation in the brain and ultimately leading to severe disability in patients. Our research focuses on how the different immune cells are communicating with each other to cause the damaging inflammation of the brain in MS. Specifically, we use a mouse model of multiple sclerosis, called experimental autoimmune encephalomyelitis (EAE), which allows us to determine the interactions of these immune cells in fine detail which cannot be achieved using patient samples. Our research will lead to a better understanding of the processes that drive disease in multiple sclerosis and may lead to new strategies for therapies of this debilitating disease.



*Inflamed brain of MS patients*



*Inflamed nervous system in mice with EAE*

# Analysis of ribosomes in antibiotic-tolerant bacteria

*Translation complexes in E. coli persisters*

Kevin Wilson, Oklahoma State University

Many bacteria can survive exposure to antibiotics because the cells are physiologically dormant. Despite being rare, these persister bacteria can become genetically resistant to multiple antibiotics. They are responsible for many chronic infections in humans such as tuberculosis. Next-generation antibiotics are therefore urgently needed.

essential protein synthesis in the cells. The proposed research focuses on analysis of ribosomes from persister bacteria. The results of the proposed research may lead to new anti-persister antibiotics targeting ribosomes. In the longterm, this research may ultimately contribute to the treatment of chronic infectious diseases and the prevention of antibiotic resistance.

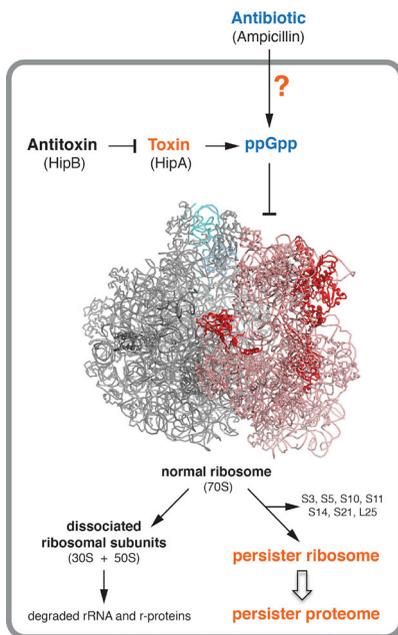
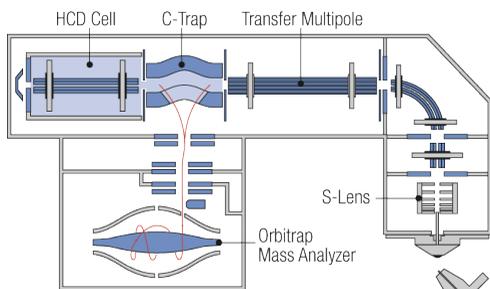
Many antibiotics kill bacteria by inhibiting their ribosomes, which perform

### Model of a persister cell.

We found that persister ribosomes are deficient in specific ribosomal proteins. This allows persister cells to survive exposure to antibiotics.

Reference: Cho et al. (2015)

*Molecular Microbiology* 95, 352



Ribosomes were analyzed using quantitative mass spectrometry.

## Vagus nerve stimulation for Lupus

### *Transcutaneous Vagus nerve stimulation for the treatment of SLE*

Aikaterini (Katherine) Thanou, Oklahoma Medical Research Foundation

Systemic lupus erythematosus (SLE) is a multi-organ autoimmune disease characterized by loss of tolerance to self, tissue inflammation and injury. Despite progress in understanding the complexity of lupus, there is a paucity of pharmacologic therapies for this disease, and those available have significant side effects even when clinically effective. Production of cytokines by immune cells can be inhibited by signals through the vagus nerve, and this circuit is known as the cholinergic anti-inflammatory pathway. Vagus nerve stimulation (VNS) inhibits inflammation, prevents tissue injury and improves survival in animal studies. VNS was also effective in ameliorating joint inflammation in mice and decreasing disease activity in patients with rheumatoid arthritis. Furthermore, VNS improves heart rate variability (HRV), a marker of vagus nerve signaling to the heart that can be easily measured in clinic and is commonly decreased in patients with inflammatory diseases like lupus. Transcutaneous stimulation of the auricular branch of the vagus nerve (tVNS) that innervates the external ear (Figure 3) is an alternative approach to VNS. This can be applied noninvasively by electrodes attached to the external ear (Figure 4). tVNS has been studied in patients with coronary artery disease, epilepsy and chronic pain with promising results.



Area of the external ear innervated by the auricular branch of the vagus nerve



Transcutaneous electrical stimulation unit used for vagus nerve stimulation

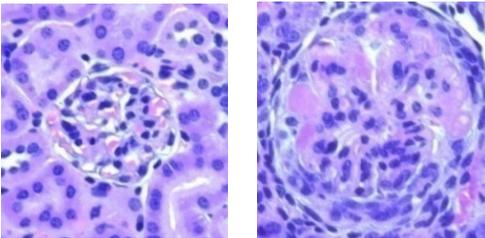
## Oral bacteria influence autoimmune disease

*Periodontal Disease: Cause or consequence of Systemic Lupus Erythematosus*

Harini Bagavant, Oklahoma Medical Research Foundation

In our laboratory, we study the chronic autoimmune disease, systemic lupus erythematosus (SLE). SLE patients develop immune responses that recognize their own cellular and nuclear proteins. This immune response against self (or autoimmunity) affects different organs like the kidneys, joints, skin, brain, heart and lungs. Our interest is to understand how the autoimmunity starts and how these autoimmune responses lead to organ damage. For our research we use mouse strains that spontaneously develop SLE and mimic the human disease.

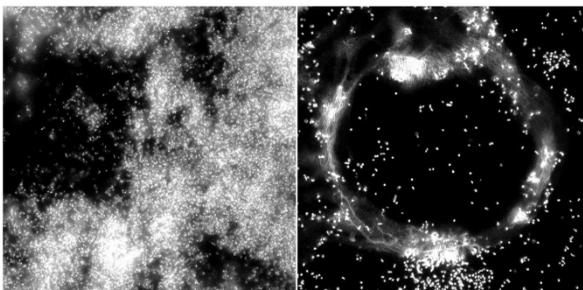
In this project, we are asking the question: Do bacteria in the mouth affect the onset and progression of autoimmune disease? If yes, how does this occur? This research will give us an understanding of how the immune system interacts with normal and disease causing bacteria in the mouth. It will investigate the contribution of oral health in the development of systemic autoimmunity. The results of the proposed work will help us to identify strategies that can reduce the severity of autoimmune disease in patients.



Normal

Diseased

*Images of normal and diseased kidney captured on a microscope*



Bacteria

Bacteria + neutrophils

*Microscopic image of immune cells (neutrophils) trapping bacteria in a dish*

## HR15-151

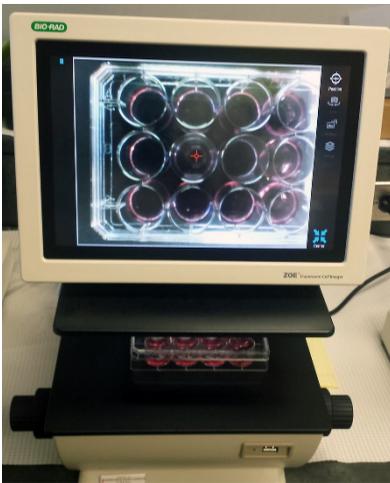
Excessive activation of your immune system by viruses can cause an autoimmune disorder responsible for dry eyes and dry mouth

*Innate immunity in pathogenesis of Sjogren's syndrome*

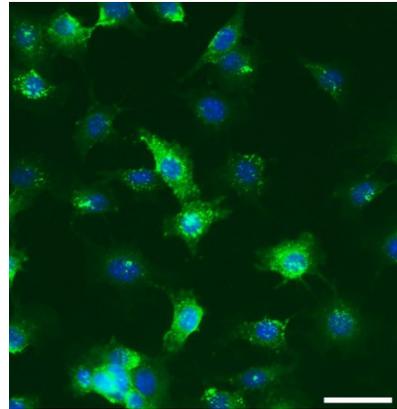
Umesh S. Deshmukh, Oklahoma Medical Research Foundation

Sjögren's syndrome, also commonly known as the dry eye and dry mouth disease, is a highly prevalent autoimmune disorder. In this disorder, the body's immune system mounts an attack on the exocrine, lacrimal and salivary glands. Destruction of these organs leads to reduced tear and saliva production, which translates into the dry eye and dry mouth symptoms of the disease. It is believed that excessive activation of the immune system by viral infections is responsible for initiating Sjögren's syndrome. The OCAST funded work investigates how viral nuclear material activates different immune

pathways inside the mammalian cells and contributes towards the development of Sjögren's syndrome. Understanding these pathways in detail is essential for developing novel therapeutic strategies to treat this disorder. Sjögren's syndrome mainly affects women at post-menopausal stage and significantly reduces the quality of life. The knowledge gained from the OCAST funded work may lead to the development of a newer generation of drugs that would contribute towards improving women's health not only in Oklahoma but all over the world.



*Live cell imaging is used to study the effects of chemicals mimicking viral nuclear materials on immortalized salivary gland cells.*



*Antibodies internalized by live salivary gland cells are shown in green. The project investigates how synthetic viral nuclear materials facilitate this process. Nuclei are shown in blue.*

# "Superbug" self-digestion: A new approach to eliminating hospital-acquired infections

*Exploration of bacterial ClpP as a treatment strategy for hospital acquired infections*

Adam S. Duerfeldt, University of Oklahoma

Carbapenem-resistant Enterobacteriaceae (CRE) represent a formidable challenge to long-term healthcare facilities. Recently, these multi-drug resistant gram-negative bacteria have infiltrated hospitals and infected vulnerable patient populations. Antimicrobial options are dwindling rapidly to address CRE, as these infections exhibit resistance to a number of "last-resort" antibiotics. The urgency for new antibiotics, especially those that operate through clinically unexploited mechanisms of action, has never been more apparent. The focus of this work is to develop antibiotic leads that "turn-on" a new drug target in bacteria (ClpP), causing the bacteria to self-digest and die. The results of the proposed work are expected to provide drug leads poised for optimization towards eradicating CRE hospital-acquired infections. Long-term, this research may lead to new treatments for infectious disease, a reduction in healthcare costs and an improvement in patient's lives.

JOURNAL OF  
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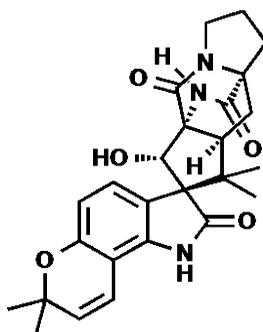
## Sclerotiamide: The First Non-Peptide-Based Natural Product Activator of Bacterial Caseinolytic Protease P

Nathan P. Lavey,<sup>1,†,‡</sup> Jesse A. Coker,<sup>1,†,‡</sup> Eliza A. Ruben,<sup>2,§</sup> and Adam S. Duerfeldt<sup>1,†,‡</sup>

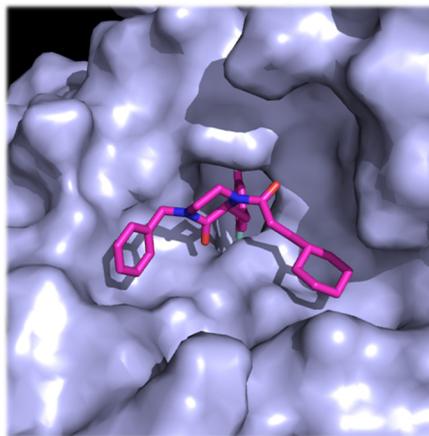
<sup>1</sup>Institute for Natural Products Applications and Research Technologies and <sup>2</sup>Department of Chemistry & Biochemistry, Stephenson Life Sciences Research Center, University of Oklahoma, 101 Stephenson Parkway, Norman, Oklahoma 73019, United States  
<sup>†</sup>Protein Production Core, University of Oklahoma COBRE in Structural Biology, Norman, Oklahoma 73019, United States

Supporting Information

**ABSTRACT:** Caseinolytic protease P (ClpP) maintains essential roles in bacterial homeostasis. As such, both the inhibition and activation of this enzyme result in bactericidal activity, making ClpP a promising target for antibacterial drug development. Herein, we report the results of a fluorescence-based screen of ~450 structurally diverse fungal and bacterial secondary metabolites. Sclerotiamide (1), a paraherquamide-related indolizone, was identified as the first non-peptide-based natural product activator of ClpP. Structure-activity relationships arising from the initial screen, preliminary biochemical evaluation of 1, and rationale for the exploitation of this chemotype to develop novel ClpP activators are presented.



*A new ClpP activating class of natural product discovered in our lab. OCAST funded research.*



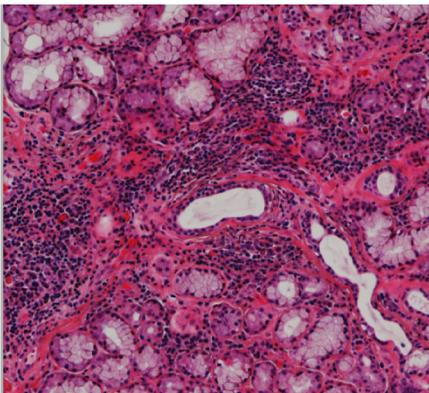
*Computational models are useful tools for structure-based drug design.*

## Immune cell studies from patients with Sjögren's syndrome

### *CD4+ T cells in oral pathogenesis of Sjögren's syndrome*

A. Darise Farris, Oklahoma Medical Research Foundation

Autoimmunity is the inappropriate response of our immune system to tissues and substances normally present in the body. Sjögren's syndrome (SS, pronounced "show-grinz"), which affects about 3 million Americans, is an autoimmune disease that targets the moisture producing glands of the body. SS patients suffer from long-term, severe dry eyes and mouth, resulting in rampant tooth decay, mouth infections, scarring of the surface of the eyes and lowered quality of life. About one third of patients also have complications elsewhere in the body, the most serious of which is cancer. The causes of SS are not known. There are currently no approved therapies for SS, and all treatments are designed to relieve symptoms but not treat their cause. However, research has shown that a variety of immune cells, including T cells, are found in the salivary glands of SS patients and may be involved in the disease process. Our group has unique access to salivary gland biopsy tissue from SS patients and has special knowledge of how to study the T cells found there. In our preliminary studies, we found that patients who have the most copies of certain immune cells (T cells) in their salivary glands have the lowest amounts of saliva and the highest degree of salivary gland damage. This means that these cells may be causing oral disease by attacking an important component of the salivary gland. Our research will identify the salivary gland target(s) of these T cells and use cutting-edge molecular biology tools to learn how genes are abnormally expressed in these cells. These studies will give us clues as to how salivary gland T cells cause SS and may lead to new medications to treat this debilitating disease.



*Stained tissue from salivary gland (SG) of SS patient showing high numbers of immune cells (small purple "dots").*

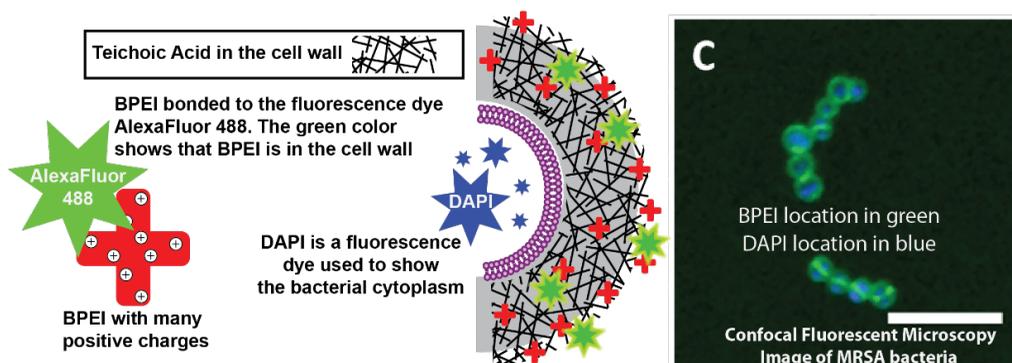
## HR16-084

### A low-cost high-impact route to kill MRSA with FDA-approved antibiotics

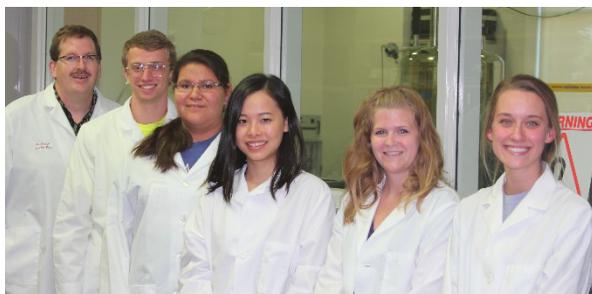
#### *Potentiating beta-lactams to treat MRSA infections*

Charles V. Rice, University of Oklahoma

New low-cost antibiotics that kill both susceptible and resistant bacteria will improve patient outcomes and reduce health care costs. However, antibiotic development is time consuming (>10 years) with a small chance of success. It may be possible to overcome these barriers with a discovery made in our laboratory. Low-cost  $\beta$ -lactam antibiotics that kill methicillin-susceptible *S. aureus* also prevent the growth of methicillin-resistant *S. aureus* (MRSA) if administered with a readily available and low-cost polymer: branched poly(ethylenimine), BPEI. We envision  $\beta$ -lactam + BPEI combinations as a potential low-cost antibacterial treatment. We have been able to demonstrate efficacy and low cytotoxicity. We have filed a full patent application that brings numerous off-patent antibiotics under patent protection.



*Fluorescence microscope image BPEI binding to the cell wall of MRSA bacteria*



*Rice Group Members. (L-R) Prof. Rice, Stoffel Strange, Natalia Roberts, Min Xiao, Melissa Foxley, Summer Wright*

## Testing of new drugs for the treatment of flu infection, a common respiratory problem due to influenza virus

A novel combination therapy for influenza pneumonia

Teluguakula Narasaraju, Oklahoma State University

Currently, influenza accounts for up to 500,000 deaths per year globally. The present study will be conducted to test the role of neutrophils in lung damage after influenza virus infection. We have found that a combination of a drug that blocks a surface protein on neutrophils together with an antiviral agent reduces lung damage and protects from influenza infection in mice. This proposal tests the protective effects of these drugs in a pig-model. The respiratory system in pigs is close to human respiratory system, thus positive results of this project will help in identifying new therapeutic drugs in the treatment of influenza virus infections in humans.



*Dr. Harshini Ashar, a team member preparing to test the antiviral effects of the drugs in cell culture.*

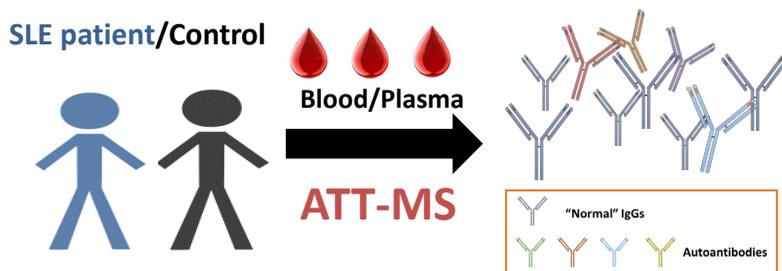
## HR16-125

### A novel diagnosis tool to find biomarkers from Lupus patient blood Characterization of serum autoantibody biomarkers through an antigen-targeted top-down mass spectrometry (ATT-MS) platform

Si Wu, University of Oklahoma

Autoimmune disease is a leading cause of death and disability, affecting more than 23.5 million Americans. Detecting systematic autoimmune diseases at an early stage is crucial for effective treatment and disease management to slow disease progression and prevent irreversible organ damage. However, this remains a significant clinical challenge due to the lack of biomarkers with both specificity and sensitivity. In many autoimmune diseases, including

Systemic Lupus Erythematosus (SLE), serum autoantibodies are produced at a very early stage in disease development, thus holding great potential as biomarkers for autoimmune disease diagnosis. Our ATT-MS platform on autoantibody analysis may provide foundations for new strategies in autoimmune disease prognosis, intervention, and prevention, which may lead to novel high diagnostic value biomarkers.



*The ATT-MS platform can be applied to provide autoantibody biomarkers for early diagnosis of autoimmune disease.*



*High resolution MS and home-made long capillary columns provide superior resolution and sensitivity for autoantibody detection.*

# Research Area: Neurobiology

HRI13-120

The nerve cell network for leg withdrawal can reset locomotion

Flexion reflex-selective spinal cord interneurons

Ari Berkowitz, University of Oklahoma-Norman

The spinal cord can generate many kinds of movements, even without input from the brain. These movements include leg withdrawal (flexion reflex) and locomotion, such as walking, swimming and flying. Turtles are especially convenient for physiological studies. We tapped each turtle's foot to trigger leg withdrawal during forward swimming, with input from the brain removed. We monitored spinal cord electrical outputs using wires around nerves that normally cause contractions of particular leg muscles (though contractions were chemically blocked here). We found that a foot tap during the hip-extension phase of swimming stopped hip extension abruptly and restarted the swim rhythm with an earlier flexion, like resetting a clock. This shows that the nerve cell network that produces leg withdrawal interacts strongly with or shares key components with the network that produces locomotion, as has been hypothesized. A better understanding of the spinal cord networks that produce different kinds of leg movements may advance the possibility that walking can be triggered through electrical stimulation in spinal cord-injured patients.

## Leg Withdrawal

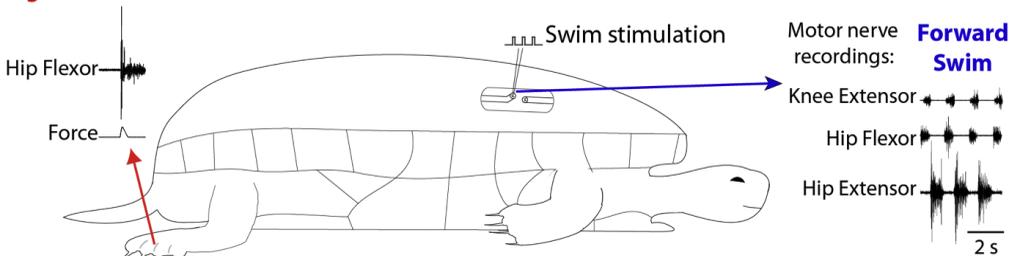
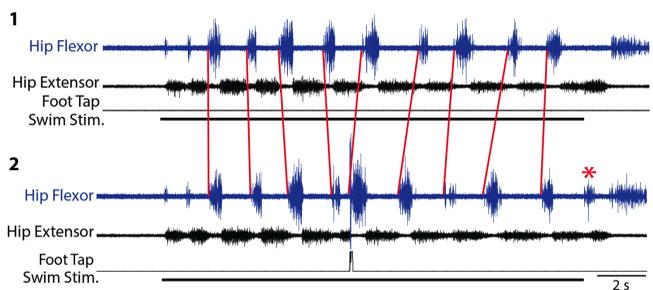


Illustration of turtle spinal cord production of leg withdrawal (flexion reflex) and swimming, monitored by electrical recording of the spinal cord output to particular leg muscle nerves.

The swimming rhythm can be reset by a foot tap: hip extension ends abruptly and hip flexion restarts with earlier onsets (red lines) after the foot tap in 2 than with no foot tap (1). From M.S. Elson and A. Berkowitz, *Journal of Neuroscience*, 36: 2819-2826, 2016.

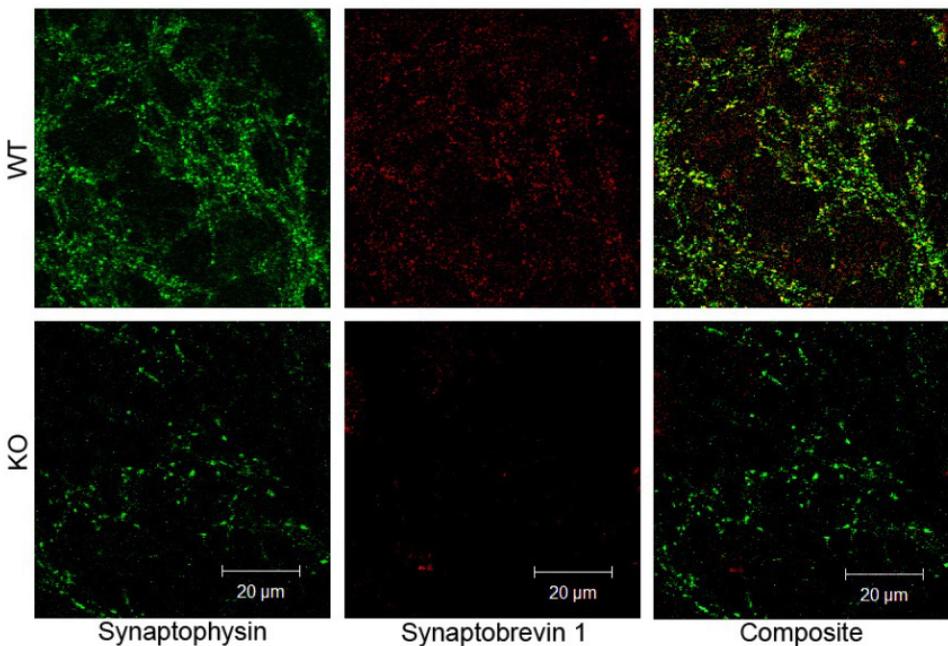


## Novel factor associated with risk for Alzheimer’s disease

*Role of synaptic neurotransmission in Alzheimer’s disease*

Ferenc Deak, University of Oklahoma Health Sciences Center

Cognitive impairment, and specifically Alzheimer’s disease, represents one of the most significant healthcare problems in the aging population of the United States, and development of effective therapy will be facilitated by understanding its underlying mechanisms. We are studying a protein called synaptobrevin/VAMP1 that has an important role in regulating the communication between nerve cells and presents a strong argument for the association of VAMP1 to disorders with cognitive impairment for instance to Alzheimer’s disease and beta-amyloid build-up in the brain of patients suffering from Alzheimer’s disease. After completion of the proposed research we will have developed a new model that will offer insight into the mechanism and potential treatment of the severe and common diseases leading to dementia.



*Immunocytochemistry. Fluorescence confocal images of cultured neurons from synaptobrevin(syb)1 KO mice after labeling with primary antibodies against synaptophysin and syb1 (Synaptic Systems) and secondary Alexa Fluor 488 and 633 antibodies (Invitrogen). Note the complete lack of syb1 labeling in KO synaptic connections (middle panel).*

## Keeping neuronal cargos on the right track

*Pathways controlling a newly discovered organelle gatekeeper in neurons*

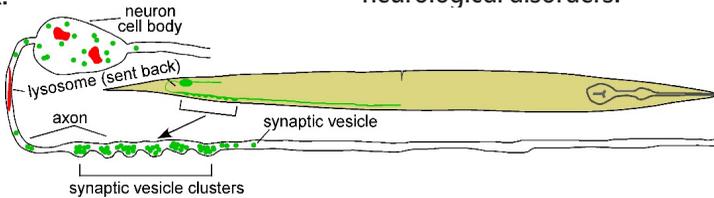
Kenneth Miller, Oklahoma Medical Research Foundation

Several human nervous system disorders arise from defects in cargo transport within neurons. Neurons have long extensions known as axons and dendrites. To transport cargos over long distances neurons use tiny motors that walk rapidly along tubular tracks, shouldering their cargo.

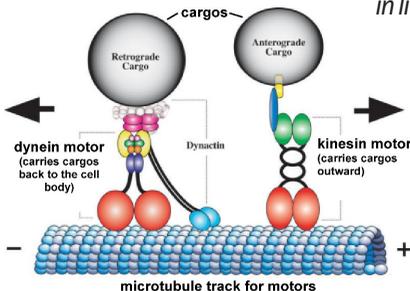
Neurons must transport an important cargo, synaptic vesicles, outward from the cell body of the neuron to specialized sites in the long axon where they accumulate in clusters known as synapses. The synaptic vesicle clusters are very important because they send chemical signals to other nerve cells and muscle cells to help us move and learn and think.

There are many different motors that carry specific cargos outward, but only one motor, known as dynein, that carries unwanted cargos back to the cell body. An example of an unwanted cargo is lysosomes, which can degrade synaptic vesicles.

So how do neurons use the dynein motor to send harmful cargos such as lysosomes back to the cell body without also sending back too many synaptic vesicles? We've been using genetic approaches in the model organism *C. elegans* to address this question and have made some completely new and unexpected discoveries that could be relevant to understanding some human neurological disorders.



*The model organism C. elegans is a roundworm that is about 1 mm long. By tagging neuronal cargos, such as synaptic vesicles (green) and lysosomes (red), we can image cargo movements in living animals.*



*Motors carry cargos by “walking” along microtubule tracks. Many kinds of kinesin motors carry cargos outward (one kind is shown), but there is only one dynein motor that carries neuronal cargos back to the cell body.*

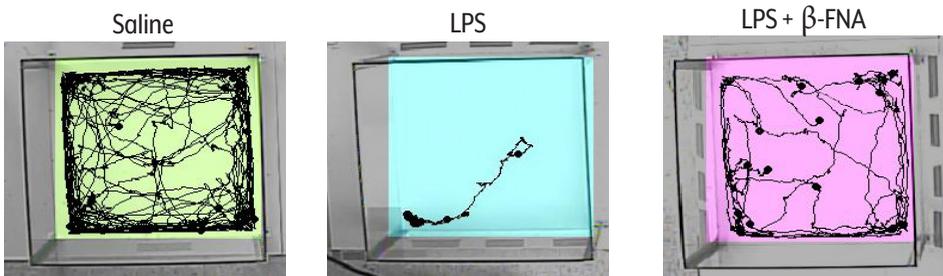
## HR14-007

### Advancing therapeutic options for treating major depressive disorders using a novel anti-inflammatory agent

Randall L. Davis, Oklahoma State University Center for Health Sciences

Brain disorders represent a huge burden, both in terms of human suffering and of economic costs. Indeed, major depressive disorder (MDD) is the leading cause of disability in the U.S. (ages 15-44); and Oklahoma is in the “top 10” in terms of percentage of adults suffering from depression. Neuroinflammation (inflammation in the brain) is present in MDD and in a wide range brain disorders, from neurodegenerative diseases to infection and trauma. Unfortunately, there are relatively few drugs on the market that effectively reduce neuroinflammation. Thus, it is of paramount importance that we identify anti-inflammatory agents that effectively reduce neuroimmune activation, thereby adding to or augmenting treatment options for these brain disorders. Importantly, several years ago we discovered that the compound  $\beta$ -funaltrexamine ( $\beta$ -FNA) inhibits inflammatory signaling in key brain cells (astrocytes) when experiments were performed in vitro. Discovery of these anti-inflammatory actions was both unexpected and exciting given that historically  $\beta$ -FNA is used for other purposes unrelated to inflammation.

This project is designed to gain a better understanding of the mechanism by which  $\beta$ -FNA exerts anti-inflammatory effects and test the effectiveness of this compound in a pre-clinical mouse model of sickness and depressive-like behavior. Overall, successful completion of the project will open a new line of inquiry into the potential of  $\beta$ -FNA (or modified forms of this compound) as an inhibitor of neuroinflammation to be included in combination drug treatment of MDD and other brain disorders.



Test chambers with tracings of mouse movements over 10 minute period. Green: mice treated with saline are very mobile and explore the chamber; Blue: mice treated with a bacterial component (LPS) are sick and are reluctant to move about; Pink: mice treated with LPS and the test compound ( $\beta$ -FNA) are more mobile and display less sickness behavior.

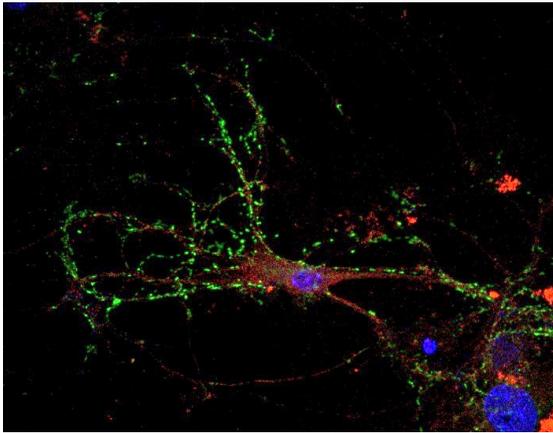
## HR15-089

A protein phosphatase important for the health of neurons

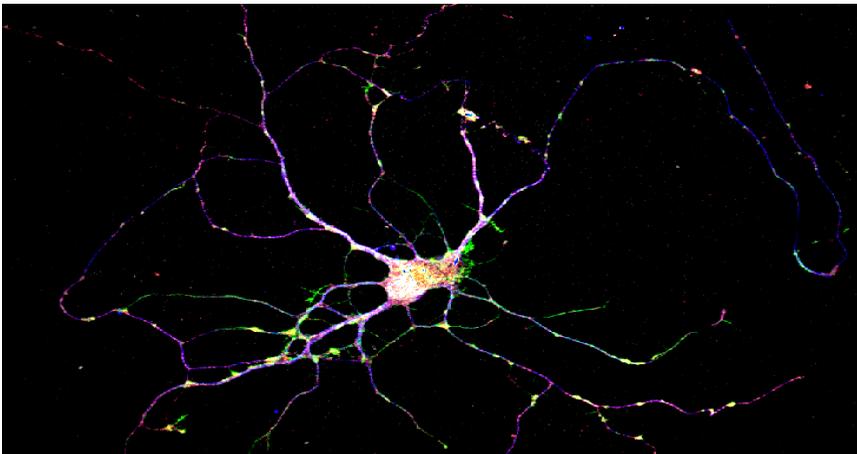
*PTP-MEG2 function in Trk trafficking and neurotrophin signaling*

Guangpu Li, University of Oklahoma Health Sciences Center

The health of neurons requires neuronal growth factors called neurotrophins and their interactions with receptors at the cell surface. Deficiency in neurotrophins and/or their receptors can lead to neurodegenerative diseases. This project focuses on a particular protein phosphatase (PTP-MEG2) and addresses how it can control the transport of neurotrophin receptors to the cell surface where they bind neurotrophins and promote neuronal differentiation and survival. The results may shed light on the regulatory mechanism of neurotrophin function and neuronal health and help develop therapeutics against neurodegenerative diseases.



A cortical neuron showing localization of PTP-MEG2 and the neurotrophin receptor TrkA



A cortical neuron showing Rab17 and actin and microtubule cytoskeleton

# Mechanism and treatment of dry age-related macular degeneration

## *Mechanism and treatment of atrophic AMD*

Yun Le, University of Oklahoma Health Science Center

Dry age-related macular degeneration (AMD) is the number one cause of blindness in people over 65 years of age in the US. The pathogenic mechanism of this multifactorial disease is poorly understood and there is no effective treatment. Experimental and clinical evidence suggests that this disease is associated with the abnormality of a single layer of cells, called retinal pigmented epithelium (RPE), which serves as the barrier between the sensory neurons (SNs) and underlying blood circulation (BC) system. Normal interaction between the RPE and this BC is thought to be responsible for the clearance of metabolic wastes of

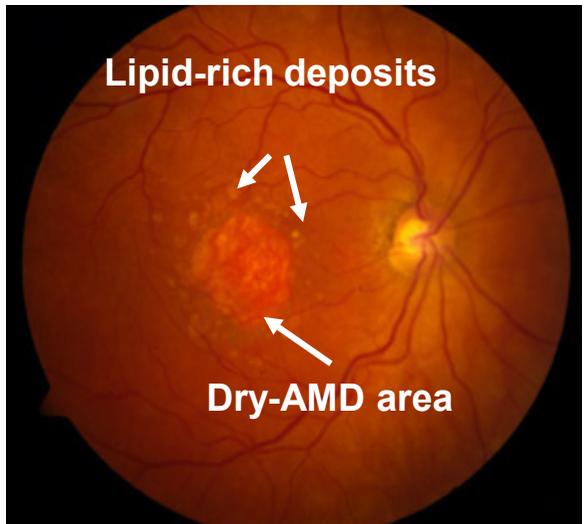
the SNs, including a high level of lipid metabolites. Abnormal lipid waste removal and altered lipid/lipoprotein metabolism during aging may be responsible for the excessive deposition of lipid-rich materials in the interface of the RPE and its underlying BC system, which induces inflammatory responses and leads to the loss of central vision in AMD eventually. In this study, we will 1) investigate the mechanism of lipid degradation in the RPE, 2) characterize dry AMD-like animal models with combined defects in lipid metabolism and lipid waste removal and 3) explore the therapeutic potential of altering lipid metabolism in the treatment of dry-AMD.



Normal vision



AMD vision



Fundoscopic image of dry-AMD

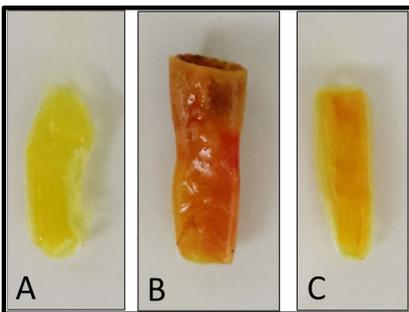
## HR16-003

### Colon inflammation can be reduced by blocking glutamate production

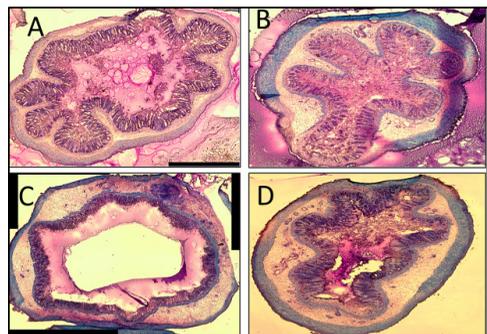
The role of glutamatergic sensory neurons in the initiation of and response to colitis

Kenneth E. Miller, Oklahoma State University Center for Health Sciences

Colitis is an inflammation of the bowel and is listed as an inflammatory bowel disease. The nervous system's connection with the bowel is an important component of colitis, but our understanding is limited about nerves that initiate and maintain colitis or types of sensory nerve cells that are changed during colitis. Our laboratory has determined that all sensory nerve cells use glutamate to communicate and they release glutamate into tissue. We have shown that glutamate release in injured tissue is an important part of inflammation and that sensory nerve cells go through changes in glutamate related proteins during inflammation. Our central idea is: Glutamate release from sensory nerves contributes to the initiation and maintenance of colitis. We have three aims using chemical induced model of colitis in rats during the first two days of colon inflammation. Our aims include: 1. Glutamate starts immune mechanisms in colitis. 2. Colitis affects sensory nerve cells. 3. Nerve growth factor contributes to colon inflammation and alters nerve cells during colitis. Molecular and protein techniques will be used to explore these aims. The results from our studies will give insight about inflammation in the colon and how nerve cells are changed. These results can be important for the development of novel therapies for patients with colitis pain by regulating glutamate in the colon.



A: Colon from normal rat; B: Colon from rat with colitis; C: Colon from a rat with colitis & pretreated with a glutamate blocker. Glutamate blockade decreases inflammation.



Histology. A: Colon from normal rat; B: Normal colon with glutamate blocker; C: Colon from rat with colitis; D: Colon from a rat with colitis & glutamate blocker. Glutamate blockade decreases inflammation.

## HR16-060

### Can nutritional interventions prevent neurodevelopmental disorders?

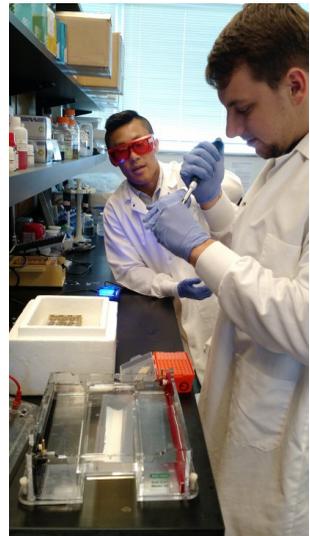
#### *Regulation of ZIP12- a candidate gene for neurodevelopmental disorders*

Winyoo Chowanadisai, Oklahoma State University

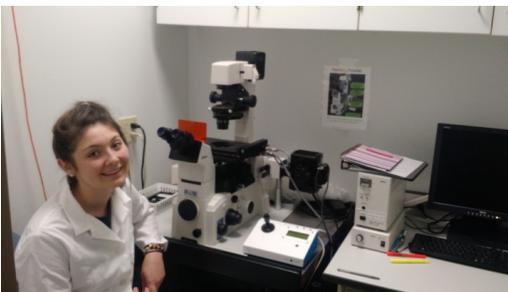
Both nutrients and genes are important for brain development. Impaired gene function and nutrient deficiencies can lead to neurodevelopmental disorders such as neural tube defects and autism. Because genes can encode proteins that control how nutrients enter the brain, mutations in these genes may impair brain development and possibly lead to neurodevelopmental disorders. The genes that control how zinc enters neurons and the brain are critical parts of brain development and function. The proposed work will demonstrate how upstream parts of brain development can turn on zinc uptake during brain development through a specific gene. The proposed work will also determine which downstream factors are affected by this specific gene that is important for zinc uptake during brain development. We hypothesize that the control of zinc in the brain by this gene, ZIP12, is a central part of brain development. Understanding these processes may identify which neurodevelopmental disorders are responsive to zinc. Ultimately, uncovering the connections between zinc and the brain may lead to nutritional strategies for preventing neurodevelopmental disorders.



*Cultured cells used to study brain development*



*Tony Tang, an OSU graduate student, and Matthew Hart, an undergraduate student, are working with DNA.*



*Mariah Nacke, an undergraduate student, at a microscope.*

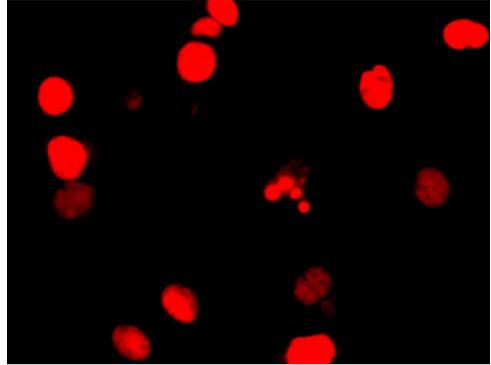
## HR16-074

### Protein finds a new way to protect brain cells from ischemic injury

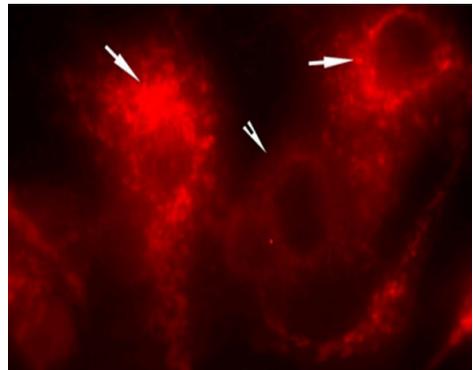
#### *Unconventional neuroprotective actions of sAATF in ischemic brain injury*

Qing Guo, University of Oklahoma Health Sciences Center

Apoptosis antagonizing transcription factor (AATF) is a protein often found inside the cell in cytoplasmic and/or nuclear compartments. However, we have unexpectedly noted that a significant amount of intracellular AATF was actively secreted extracellularly by brain cells under ischemic conditions. Secreted AATF (sAATF) was found to be highly neuroprotective. This extrinsic pathway mediated by secreted sAATF is unusual and suggests the existence of a non-classical secretory pathway where AATF was released extracellularly without a classical N-terminal signal peptide for secretory proteins. The proposed work will use multidisciplinary approaches to investigate the mechanisms of AATF secretion and how sAATF binds to specific cell surface receptors to block neuronal cell death. The results from the proposed studies may provide sAATF as a new therapeutic agent for ischemic brain injury in vivo. The long-term goal of the project is to find a truly effective and long-lasting strategy of neuroprotection to significantly improve the outcome of treatment and to substantially reduce the health care costs associated ischemic stroke.



*AATF transfected cells were largely rescued from apoptotic cell death induced by ischemia/reperfusion.*



*Fluorescently labeled siRNAs were introduced into the cells for gene expression studies.*

## HR16-108

Pain can be a preferred part of your experience of flavor during eating

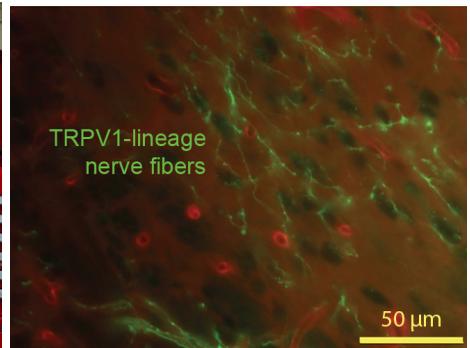
*Taste and oral sensory processing in the brain*

Christian Lemon, University of Oklahoma

Although sometimes called spicy or hot “tastes”, the burn of a jalapeño pepper in your mouth and the tingle of black pepper on foods are caused by the activation of brain circuits involved with pain. These and other mouth pain sensations, such as the heat of freshly hot coffee and freezing cold of ice cream, contribute to your experience of flavor during eating. Contrary to its usual negative association, pain can be a preferred sensory component of flavor, as evidenced in part by the popularity and wide consumption of spicy snacks and foods. However, only very little is known about how pain signaling in the brain contributes to flavor perception. The proposed work will use mouse models to focus on understanding the organization of brain circuits that support interactions between oral pain and the sense of taste. Taste is a more commonly studied flavor component that involves sensations such as, for example, the sweetness of sugar and saltiness of table salt. The results of the proposed work may lead to novel insight into how the brain combines pain signals from the mouth with other senses to generate the human perception of flavor. Understanding this process is important to define how flavor guides food selection and eating behaviors that affect nutritional status and can lead to health problems in humans, such as obesity, coronary artery disease and diabetes.



*Equipment for recording brain responses to flavor stimuli in mice*



*Projections of nerves associated with mouth pain (green) in brain tissue*

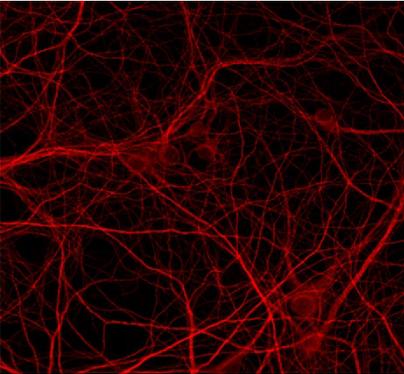
## HR16-116

### A novel protein's role in memory-forming mechanisms in the brain

#### *The role of AMPA receptor-interacting protein Prrt1 in synaptic plasticity*

Mohiuddin Ahmad, University of Oklahoma Health Sciences Center

The human brain contains billions of cells which are connected through trillions of connections. The formation of memories involves long-term strengthening or weakening of these connections. We have identified that a newly described protein called PRRT1 is required for animals to remember their paths in a water maze. The proposed work will focus on understanding how PRRT1 regulates the strengthening or weakening of brain connections to allow correct formation of memories. The results of the proposed work will lead to a better understanding of how memories are formed and provide important information for future investigations on the weakening of memories in old age and Alzheimer's disease.



*Brain cells (neurons) forming projections and connections in a culture dish*



*Electrophysiology equipment for recording the strength of brain connections*



*Shivani Mann, a researcher in our lab, analyzing electrophysiology data*

# Research Area: Nutrition, Psychology & Public Health

HR13-140

Tablet-delivered program can help improve medication adherence for people living with HIV (PLWH)

*Electronic Intervention for HIV/AIDS treatment adherence*

Thad Leffingwell, Oklahoma State University

Patients living with HIV who don't take their medicine as prescribed – on time and every dose – have worse health outcomes. Unlike other chronic illnesses, effective HIV treatment requires stringent adherence rate of 90% or better to maximize the chances of treatment success and reduce the likelihood of transmitting HIV to non-infected partners. Recent developments in intervention have found targeted intervention efforts using cognitive behavior therapy and motivational interviewing techniques to be effective at increasing adherence rates among patients with HIV. The effects of these interventions have proven superior to the long-standing educational and self-monitoring approaches.

Although the development of effective interventions is a promising step, several

practical barriers limit the likelihood of widespread dissemination and adoption of these methods. Clinic staff are busy and may not have the time or expertise to deliver the necessary information effectively. Electronic, computer-based interventions could overcome these barriers and aid dissemination of an efficacious, cost-effective and high-fidelity intervention in the clinic setting. The aim of this project is to develop and test the feasibility and effectiveness of an electronic intervention to improve adherence in PLWH. The results of this project may improve the availability of low-cost, efficacious interventions to enhance antiretroviral therapy (ART), thereby improving health outcomes for PLWH.



*Screen shots from our electronic intervention, Living Positive*

## Performing cognitive tasks improves immunity for older adults

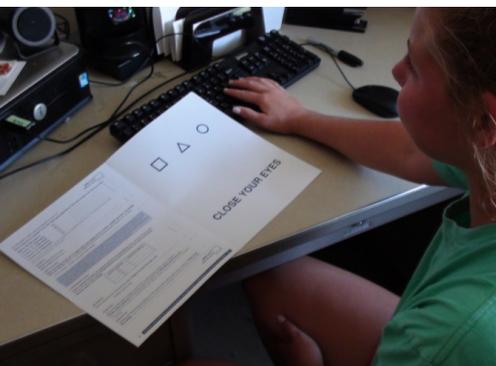
*Understanding the psycho-physiological dynamics of well-being and health in old-old age*

Alex J. Bishop, Oklahoma State University

Health decline is a normal part of human aging. The longer one lives, the greater the risk of being diagnosis with acute illnesses and chronic impairments. Recent evidence suggests that brain fitness exercises may help reduce and even slow the on-set and progression of varying age-associated symptoms leading to Alzheimer’s Disease. However, the extent to which cognitive activities act as a positive health intervention in old age has remained unclear. This proposed work aims to determine how cognitive task performance improves the health of older adults. Analyzing samples of saliva taken from research participants, initial results from this study indicate that performing cognitive tasks improves immunity for older adults. This finding suggests that cognitive exercises may provide added defense against potential illness and disease in old age. This has implications relative to promoting disease-free aging and healthy longevity. Inclusion of cognitive exercises within the care plans of older adults may ultimately help reduce acute as well as long-term healthcare costs.



*Sandy Peterson, technician from our lab, inspects a saliva sample with graduate research assistants Erin Harrington and Giavanna McCall.*



*Brooke Harris, undergraduate research assistant from our lab, works on coding and entering cognitive data collected from participants.*

## Understanding how bed bugs spread

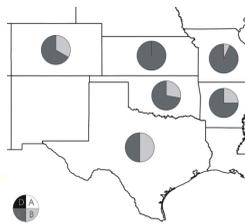
*Characterizing patterns of infestation and dispersal of bed bugs in the south central U.S.*

Warren Booth, University of Tulsa

The common bed bug, *Cimex lectularius*, is currently undergoing an alarming resurgence in the U.S and other developed countries. The reasons for this upsurge are not clear. While their presence within homes, hospitals and assisted-care facilities and the hospitality industry can be financially crippling, there is growing concern over their impact on physical and mental health of their victims. As a result, they have recently been recognized as an important public health problem by the CDC and EPA. In order to be able to develop region specific targeted control strategies, their origin, dispersal patterns and infestation dynamics must be understood. A large gap in our understanding of the rapid increase in bed bug infestations is a lack of such information. Resurgent bed bug populations could come from either local sources that have recently expanded, or they could be the result of one or a few source populations that have been spread globally through human transport. The proposed research addresses this and other questions regarding their spread by using three classes of genetic markers to investigate the genetic structure of bed bug infestations at increasing geographical scales from local aggregations to populations spanning seven U.S. states (Oklahoma and its 6 directly adjacent states). First, we seek to determine the frequency and distribution of insecticide resistance in south central populations. We then assess the link between insecticide resistant and non-resistant populations, providing additional information linking resistance in bed bugs to their recent resurgence. Finally we examine the extent of active dispersal of bed bugs in apartment buildings. Together, the results obtained under all three aims are expected to play a key role in developing more effective means of preventing bed bug outbreaks and for managing existing infestations.



*An aggregation of the common bed bug*



*Insecticide resistance profile for bed bug populations in the south central U.S. A) no mutations, B) 1st mutation only, C) 1st and 2nd mutations, D) 2nd mutation only. Having a B or C profile increases insecticide resistance 100 to 13,500 fold; thus a non-pyrethroid control strategy must be implemented.*

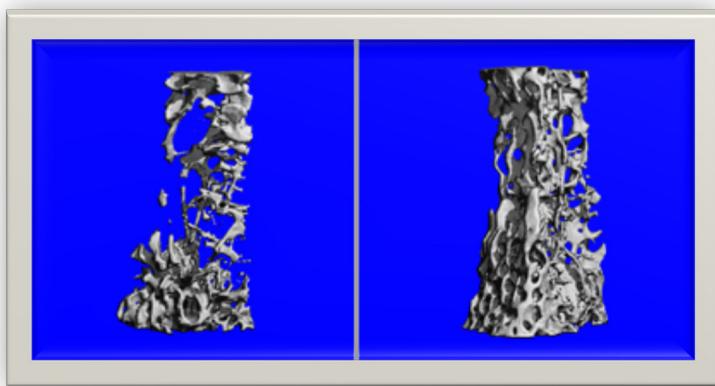
## Does improving gut health by consuming plums reduce the risk of osteoporotic fractures?

*Dried plum alters gut mucosal immunity and bone health in ovarian hormone deficiency model*

Brenda J. Smith, Oklahoma State University

Fractures are among the most common causes of pain and disability as people age. It is estimated that 1 in 2 women over the age of 50 will experience a fracture caused by osteoporosis. Bone loss that occurs in women is caused by immune cells that have become overly active. Certain foods such as dried plums are a good source of natural compounds known as phenolics that can alter immune cell activity in the body. Adding these compounds to the diet by consuming dried plums or a supplement has been shown to have unique effects on bone health. The phenolics not only prevent bone loss, but can even reverse it. However, it is not clear how these compounds work since they are known

to be poorly absorbed into the body. Our research will allow us to determine if the compounds in dried plums act by altering the microbes that live in a person's gut which in turn decrease the activity of nearby immune cells. These cells can then leave the gut and travel to sites such as the bone where they restore immune cells in the bone to normal and prevent bone loss. The results of this project will help us to determine if a person's gut could be a possible target for preventing bone loss. If compounds found in certain foods could target the gut they would provide new potential ways of treating or preventing the millions of fractures that occur each year.



*3-D images of bone in the spine of animals fed a normal diet (left) and those fed a diet supplemented with dried plum (right)*

## Improving sleep in trauma victims

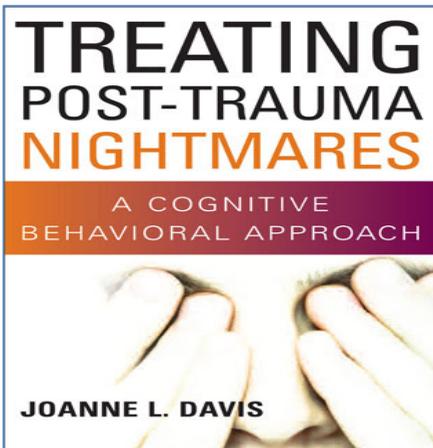
*Integrating sleep in PTSD treatment: Examining the role of emotion regulation*

Joanne L. Davis, University of Tulsa

Chronic sleep disturbances may result in significant mental and physical health problems for the individual and substantial costs to society due to lost worker productivity. Sleep disturbances, including insomnia and nightmares, are also considered the hallmark symptoms of PTSD. However, existing treatments for PTSD do not target sleep disturbances and nightmares and these symptoms often remain unresolved. This study combines two effective treatments, one for PTSD and one for post-trauma nightmares in an effort to improve both conditions and inform clinical guidelines for individuals suffering from both. The findings from this research may improve the mental and physical health of Oklahomans. In turn, this may decrease the state's expenditures on healthcare and hospitalizations due to sleep disturbances.

# SLEEP STRONG

*The collective phrase used to describe the ongoing nightmare research conducted at the University of Tulsa*



*Treatment manual for ERRT*

## TITAN

THE UNIVERSITY OF TULSA INSTITUTE  
OF TRAUMA, ADVERSITY, & INJUSTICE

*TITAN is the organization providing the space for this research trial.*

## HR14-131

### Do parents and peers influence the sleeping habits of teens?

#### *The impact of parents and peers on adolescent sleep*

Michael M. Criss, Oklahoma State University

Sleeping well is an important part of being a mentally and physically healthy person, especially during adolescence. Many teens today are not getting enough sleep due to electronic devices (cell phones, video games, computers) which delay bedtimes and disrupt sleep. This is not surprising, because about 75% of teens regularly talk with friends via texting (often at night). The current study focuses on how families, friends and the use of electronic devices influence the sleeping habits of teenagers. The results from this work will provide helpful information to parents who often struggle balancing the need for healthy sleeping habits while supporting their teen's need for independence. Moreover, this research will help in the creation of interventions for families with teenagers. Long-term benefits include improved school grades, reduced school drop-out, better job performance and reduced physical and mental health costs for adolescents. Thus, the findings can have significant economic impact on families and the local and state economies.



*Using electronic devices at night may delay bedtimes and affect one's ability to wind down and fall asleep.*



*Not getting enough and consistent sleep at night may lead to a variety of problems at school.*



*Reading and sending text messages often disrupt ongoing sleep at night.*

## HR15-084

Injured older adults are less likely to be treated at tertiary trauma centers regardless of injury severity or location

*Under-triage in the elderly trauma patient: An argument for tailored geriatric trauma triage criteria*

Tabitha Garwe, University of Oklahoma Health Sciences Center Level I and II trauma centers (tertiary trauma centers) offer the most comprehensive trauma care and have the resources to manage seriously injured patients. Yet, despite being at a higher risk of mortality and morbidity following traumatic injury, older adults (age  $\geq 55$  years) are less likely to be triaged to or treated at these type of facilities.

A major factor that has been attributed to the problem of under-triage in older adults is the ineffectiveness of the current adult trauma triage guidelines, in particular, the prehospital triage guidelines. These guidelines apply a universal criteria to all adults with no distinction between younger and older adults. Prehospital triage guidelines depend heavily on physiological parameters (heart rate, systolic blood pressure and altered mentation), parameters which are less reliable, especially in the pre-hospital evaluation of older patients. Older patients respond differently to trauma in part due to age-related physiologic changes, pre-existing morbidity and medication use and as such, the pitfall of using one triage criteria for all adult trauma patients becomes apparent and has been acknowledged.

The proposed work focuses on defining risk profiles for in-hospital mortality (low, medium and high) among injured older adults; variables defining the different risk profiles will then form the basis to propose a specific geriatric trauma criteria, which would have potential to be adopted nationally. While under-triage of injured older patients from the scene of injury has long been acknowledged, preliminary results from our proposed project also show significant under-triage between hospitals. This observation suggests that reasons for injury scene under-triage of injured older adults remain operative even after arrival at non-tertiary trauma centers.

If outcomes in this high-risk population are to be improved, evidence-based geriatric-tailored pre-hospital and inter-facility trauma triage guidelines are urgently needed. The overarching goal of our proposed work is to address this gap by proposing specific guidelines in the triaging of injured older adults and, ultimately, improve outcomes.

Mpower project:

Sexual health of peri-urban and rural men who have sex with men  
Randolph D. Hubach, Oklahoma State University

The HIV care continuum (i.e., HIV screening, linkages to care) is unreliable in rural areas of the United States. Geographic isolation and poverty may increase need for basic human services and further confound continuation in and linkages to care. Linkages to care are positively related with the course of disease and protects against disease transmission. Men who have sex with men (MSM) living within rural areas, including those in areas where suburban and rural areas are adjoining (i.e., peri-urban areas), are less likely to engage in routine HIV/STI testing and maintenance of HIV care. Thus, there remains a critical public health need to develop the HIV care continuum to meet the needs of vulnerable populations in rural, underserved areas. The long-term goal of this project is to reduce HIV transmission in rural communities through comprehensive community-based prevention programs that include holistic behavioral intervention targeting at-risk groups and people living with HIV/AIDS. The short-term goal of this project is to identify factors necessary for the development of appropriate HIV/STI prevention interventions in rural communities and to maximize the HIV screening and care in rural areas. Ultimately, this approach will inform specific prevention approaches relevant to rural MSM that are responsive to the complex layers and interplay of intrapersonal, interpersonal, community, healthcare system and healthcare policy factors that influence HIV screening and care. Investment in HIV and STI prevention efforts is financially sound policy that could lead to decreased sexual health-related medicals costs absorbed by government, health insurers and individuals in the future.



*A rapid HIV test which requires saliva or a single drop of blood from a finger-prick*

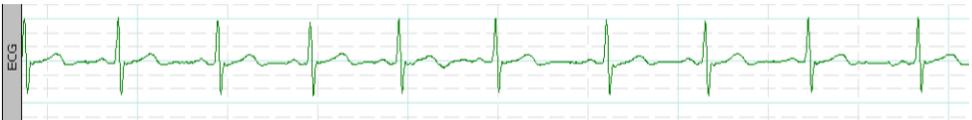
## Brain activity can tell researchers what leads to chronic anxiety

*Neural mechanisms of chronic worry*

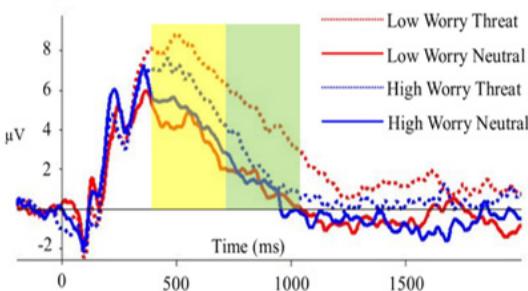
DeMond Grant, Oklahoma State University

Anxiety is a normal emotional reaction, characterized by physical sensations (such as increased heart rate) and negative thoughts. However, for some individuals worry can become chronic and uncontrollable. Research has found that worry interferes with our daily activities, such as taking a test, solving problems and falling asleep. People who experience excessive worry and anxiety also are at increased risk for medical problems, such as heart attacks, gastrointestinal problems and impairment resulting from medical diagnoses. Clinical psychologists have studied worry for over thirty years, but our current treatments do not work for everyone. Research is needed to help us understand the triggers for chronic and debilitating worry.

Although we know the consequences of worry, no research has found what causes worry. This study will examine how anxiety sensations affect our brain, leading to excessive and uncontrollable worry. We will measure brain activity using EEG, a specific measure of brain functioning. By identifying specific triggers for anxiety, we will be able to develop new treatments to stop people from worrying. Because worry increases the likelihood of developing both psychological and medical conditions, this research will be highly important to millions of people in the United States.



*Example measurement of heart rate*



*EEG data indicating reduced brain activity among worriers*



*Natalie Braden, a research assistant, wearing an EEG cap*

## What's my risk of getting a tick-borne disease in an urban area?

*Local and landscape-scale drivers of tick distribution and tick-borne pathogen prevalence in rapidly expanding urban and suburban areas*

**Bruce Noden, Oklahoma State University**

Most of earth's population lives in urban areas, and an urban lifestyle changes how different species, including humans, insects and wildlife, thrive and develop. These changes often lead to increases in infectious diseases, including diseases transmitted by arthropods (ticks, mosquitoes, fleas). Some studies have found ticks and tested them for tick-borne diseases in urban areas of the United States. However, no study has focused on how urban environments affect tick populations in a major US city. This study will evaluate how conditions in and around urban green spaces of Oklahoma City affect the type and number of ticks that could bite humans or their dogs. We will also assess what bacteria are present in urban tick populations. The information from this study will increase awareness about ticks and tick-borne diseases in U.S. cities, help public health officials to educate urban residents about avoiding tick exposure and focus resources on the urban 'hot spots' where the risk of transmitting tick-borne disease is especially high.



*Summer assistant Jennifer collecting ticks in an Oklahoma City park.*



*One of the sites in Oklahoma City where 4 species of ticks have been collected.*

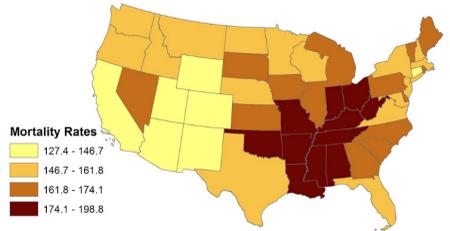
# Investigating the relationship between environmental exposures and cancer in Oklahoma

*Improving geocoding of cancer registry and development of a spatiotemporal database of environmental exposures*

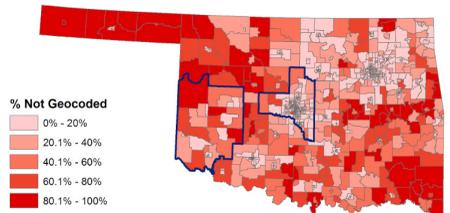
Naci Dilekli, University of Oklahoma

Oklahoma has the 11th highest age-adjusted cancer mortality rate in the US, and it is useful to investigate potential causes to inform relevant policy making. One of these potential causes is our environment, via the chemicals it contains and through the means (water, food and air) with which it interacts with us. To investigate such effects, we will do the following:

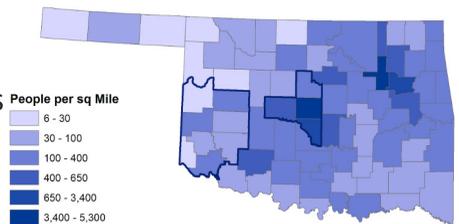
- 1.) We will increase the geographic accuracy of cancer cases in the Oklahoma Central Cancer Registry (OCCR) in two regions shown by blue boundaries in figures. This is done through generating the exact geographical location of each case using a process called geocoding. Despite the overall high quality of OCCR data, 23% of addresses between 1997 and 2013 were non-geocoded to the address level. Lack of complete data prevents useful analyses. We will use additional geographic reference data for this purpose.
- 2.) We will develop a database of environmental exposures that are potentially cancer causing. We will survey national and local data sources on chemical exposures and toxic releases. This database will include information on when and where these potentially cancer causing materials were potentially a danger to Oklahomans.
- 3.) We will establish preliminary linkages between these chemical exposures and cancer cases using geographic and statistical analyses.



National Cancer Mortality Rates (per 100,000)



Cancer cases not geocoded (%)



Population Density by County

## HR16-118

# Health-related quality of life benefits from advanced digital technology hearing aids

Carole E. Johnson, University of Oklahoma Health Sciences Center

Approximately 33 million Americans suffer from permanent sensorineural hearing loss (SNHL). Left untreated, SNHL can result in or contribute to a variety of problems including social isolation, depression and loneliness; dementia; reductions in self-efficacy and mastery; stress and frustration in relationships with family, friends and colleagues; and reduction of health-related quality of life (HRQoL). Only one in five persons with SNHL seek treatment with hearing aids; the average time between diagnosis and hearing aid fitting is seven years.

The three-year project is a single-blinded, randomized clinical trial that assesses the short- and long-term HRQoL benefits of entry-level, advanced digital technology (ADT) hearing aids. Eighty-six patients participating in a community hearing aid bank will be randomly assigned to a treatment or waiting list control group. The treatment group will complete self-assessment questionnaires before and eight weeks

after hearing aid fitting; the waiting list control group will complete the same surveys during two sessions, eight weeks apart. Short-term changes in HRQoL will be compared between the two groups. In addition, long-term benefit will be assessed in all patients at six-months and one-year postfitting in addition to identifying factors that predict positive outcomes with hearing aids.

The results of this study will provide information on the amount of and factors predicting benefits from entry-level, ADT hearing aids. This information will be helpful in counseling patients with SNHL who are considering hearing aids. In addition, findings will serve as pilot data for a federal grant application to the National Institutes of Health.



# Research Area: Physiology & Pharmacology

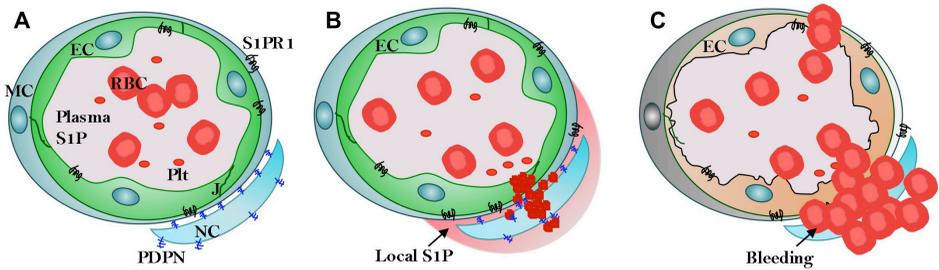
HR13-020

A critical platelet molecule prevents brain bleeding during development

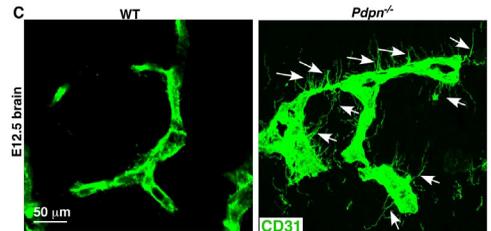
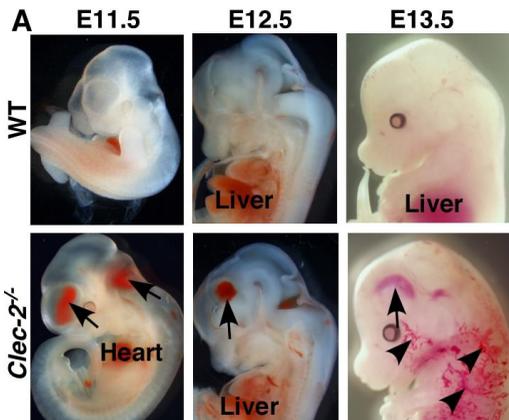
*Regulation of cerebrovascular integrity by platelet CLEC-2 signaling*

Jianxin Fu, Oklahoma Medical Research Foundation

Intraventricular hemorrhage (IVH), bleeding into the normal fluid spaces within the brain, affects around 30% of premature newborn babies in the US. However, it is not clear why IVH occurs. In a baby's fast-growing brain, blood vessels are very immature and fragile and easily rupture, suggesting additional protective mechanisms may be required to prevent bleeding. We previously showed that CLEC-2, a molecule on platelets, plays a crucial role in maintaining blood vessel integrity. In the current study, we demonstrated that platelet CLEC-2 signaling is required for normal vessel structure and for preventing IVH occurrence in developing brain. Mechanistically, upon activation through CLEC-2 signaling, platelets can release bioactive factors to promote endothelial barrier function. The identification of such a unique mechanism is predicted to stimulate new approaches, such as pharmacological agonists, to the prevention and treatment of some important human brain vessel diseases such as IVH.



*Working model: Normal quiescent vessel (A); Normal (B) and defective (C) fast-growing vessel*



*Abnormal vascular structure in mice lacking podoplanin, a CLEC-2 partner*

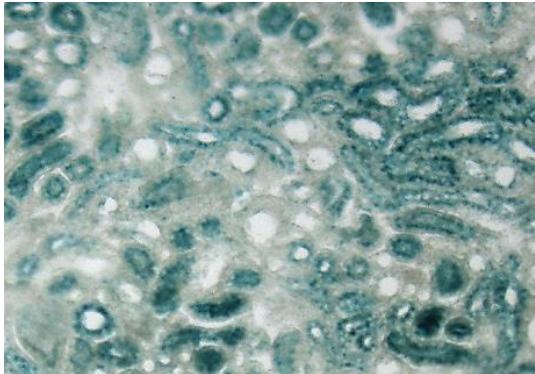
*Mice lacking platelet CLEC-2 develop IVH*

## Pathogenic role of Wnt signaling in diabetic nephropathy

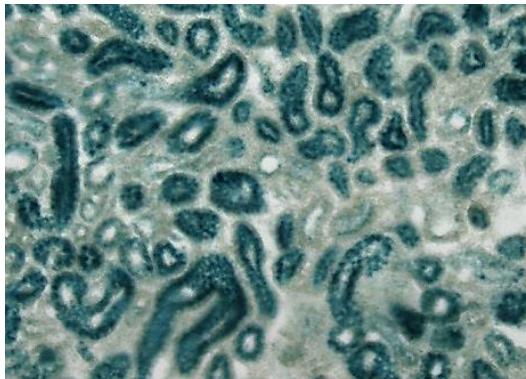
Jian-xing Ma, University of Oklahoma Health Sciences Center

Diabetic nephropathy is a common complication of diabetes and a major cause of kidney failure and lacks effective drug treatments since the cause is not very clear. Our previous studies have found a new signaling pathway, namely, Wnt signaling, that may mediate kidney damage in diabetes. This project will test if blockade of this pathway has therapeutic effects on diabetic nephropathy. This project has great potential to identify a new drug candidate for the treatment of diabetic kidney complication and benefit diabetic patients and the economy of Oklahoma.

*PEDF deficiency enhances Wnt signaling in the kidney*



*Wild-type mouse kidney*



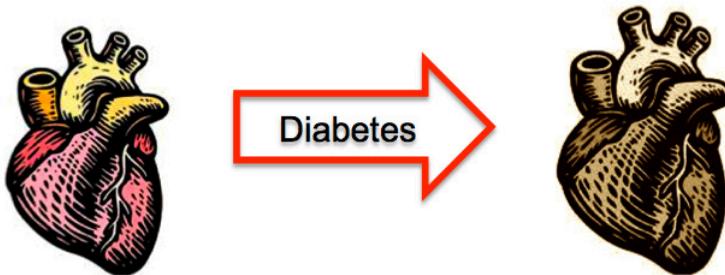
*PEDF knockout mouse kidney*

## Diabetes damages the heart by changing normal stress responses

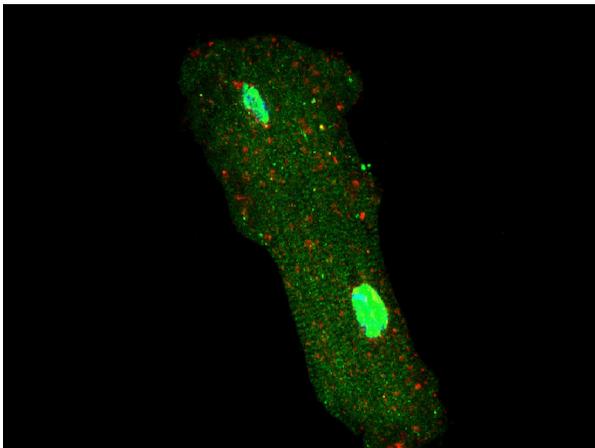
*Dysfunctional PKA signaling in the diabetic heart*

Kenneth Humphries, Oklahoma Medical Research Foundation

Diabetes increases the risk and occurrence of heart disease and heart failure. This is a serious health problem because of the prevalence of the disease. It is therefore important to understand how diabetes affects the heart. This research project is examining how diabetes increases stress on the heart by damaging an important molecular switch. This molecular switch normally acts to balance how hard the heart works with how energy is used. In this way, in a healthy person energy demand and energy supply are finely orchestrated. However, with diabetes this switch is unable to adapt and the heart is under a constant stress. This project is examining how diabetes causes this molecular change and how it affects the ability of the heart to work properly. Understanding how this occurs will allow us to develop therapeutic options to prevent diabetes induced damage to the heart.



*Diabetes can damage the heart, leading to an increased risk of heart disease and heart failure. It is critical to understand how this damage occurs so that better treatment options can be developed.*



*Heart cells are taken from control and diabetic mice. Cells are then stained and examined under a microscope to determine how diabetes affects cellular switches and processes. A typical heart cell is shown.*

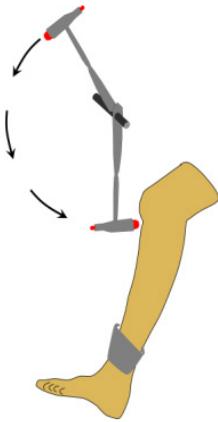
## HR14-023

### Are aging-related losses in sensory function the cause of motor deficits?

#### *Muscle spindle and motor unit function with aging*

Jason DeFreitas, Oklahoma State University

It has long been known that muscular weakness and a progressive loss of motor control is a “natural” part of the aging process. Recent research has shown that sensory function originating from muscle receptors (called “spindles”) plays a significant role during every voluntary movement. We hypothesize that aging-related losses in muscle spindle function may be one of the primary causes of motor deficits. Our first specific aim is to develop a clinically applicable, standardized index to quantify muscle spindle function. The second specific aim is to assess the magnitude of influence muscle spindles have on motor control. Multiple motor and sensory variables have been collected so far on over 150 subjects across the adult lifespan. This research will help define the extent of influence muscle spindles have on motor units and muscle function, and how that influence changes with aging.



*An older participant has her reflexes tested.*



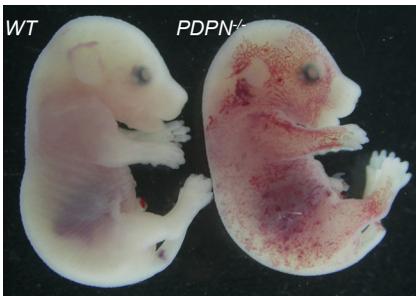
*Dr. DeFreitas, left, teaches his graduate students how to perform a balance assessment. This tests the integration between sensory and motor systems.*

A glycoprotein in regulating endothelial cell identity and malignant transformation of endothelial cell

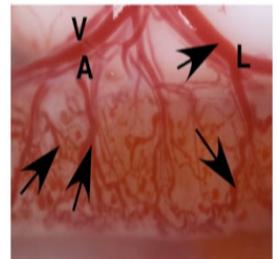
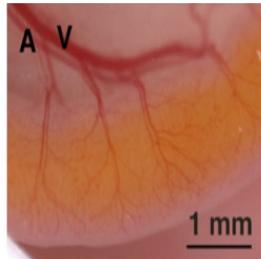
*Podoplanin regulation of vascular endothelial cell identity and tumor transformation*

Jianhua Song, Oklahoma Medical Research Foundation

Cells lining on the surface of lymphatic vessels (lymphatic endothelial cells, LECs) come from cells lining on the surface of veins (blood endothelial cells, BECs). Development of LECs as well as the maintenance of the LEC identity is tightly controlled and essential for development and functions of blood and lymphatic vascular systems. Podoplanin, a protein decorated with O-type glycans, is enriched on the surface of LECs. We found that lymphatic vessels in mice lacking podoplanin are filled with blood. Angiosarcoma is a blood vessel-originated vicious tumor that has high potential to invade other organs and therefore has very high mortality. It is widely accepted that angiosarcomas originate from BECs. There are lots of podoplanin on the surface of BECs and LECs in disorganized vessels in malignant, not benign, vascular angiomas. Also, podoplanin on the surface of LECs and/or BECs is closely associated with aggressive behavior of angiosarcomas. We hypothesize that podoplanin is critical in regulating endothelial cell identity and tumor cell formation. Therefore, understanding how lack of podoplanin causes abnormal LEC identity will provide basic insights into the mechanism(s) and role(s) of this molecule in formation and functions of the lymphatic vessel system. An understanding of how abnormal existence of podoplanin in BECs affects tumor cell formation will aid in revealing the pathways for the generation of malignant vascular tumors, and in developing novel therapies for these diseases.



Blood-filled lymphatics defect in *PDPN*<sup>-/-</sup> mouse (E16.5)



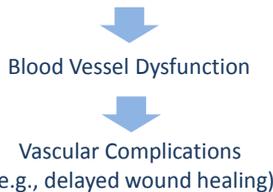
Blood filled lymphatic vessels in small intestine of *Pdpn*<sup>ΔEC</sup> mouse at postnatal day 5

## Blocking a vessel protein may improve wound healing in diabetes

### *Role of ULK1 in diabetic impairment of angiogenesis*

Jian Xu, University of Oklahoma Health Sciences Center

Lack of new blood vessel formation or angiogenesis delays wound healing in diabetes. Understanding how diabetes affects the vessel formation will help to find a cure. Diabetes reduces a key growth receptor protein in blood vessel cells both in patients and experimental animals. Although the reduction is strongly associated with diabetic complications, mechanism of the reduction is unknown. Autophagy is a self-eating process in cells necessary for whole body function. We found that an aberrant autophagy reduced the protein levels of the receptor. Our pilot studies further supported this idea in diabetic mouse models of wound healing. Building on these data, we generated a new mouse strain lacking an autophagy starter protein ULK1 only in the blood vessels. We hypothesize that diabetes activates autophagy that reduces the receptor and impairs blood vessel functions. The present project is to determine whether blocking the starter protein facilitates wound healing in mouse models of diabetes. If successful, this study will reveal a novel pathway connecting selective autophagy with blood vessel function. The findings hold a promise to develop therapeutic protocols for diabetic complications associated with defective blood vessel formation.



*Blood vessel dysfunction is the culprit*



*Wounds heal faster in Ulk1-KO mice*

## Development of diamond nanoparticle based therapy for treating urinary tract infections

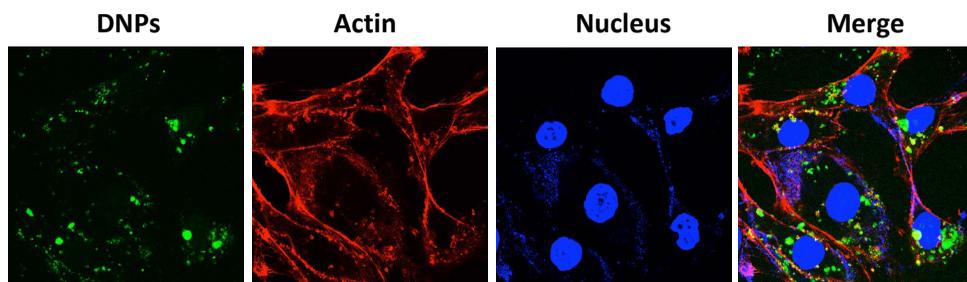
*Nanoparticles for drug delivery and treatment of urinary tract infections*

Dr. Rashmi Kaul, Oklahoma State University Center for Health Sciences

Co-PIs: Dr. Anil Kaul, Oklahoma State University Center for Health Sciences

Dr. Raj Singh, Oklahoma State University - Tulsa

Urinary tract infections (UTIs) are the second most common bacterial infection in the United States costing about \$6 billion annually in treatment. *Escherichia coli* (*E. coli*) are the primary infectious agents in >80% of UTIs. Dr fimbriae bearing *E. coli* (Dr *E. coli*) are responsible for causing persistent UTIs that can infect the upper urinary tract leading to acute or chronic kidney infections. These infections are commonly treated with an antibiotic regimen but frequent use of antibiotics has resulted in the evolution of drug-resistant bacteria. Therefore, there is an urgent need to develop new strategies for the treatment of persistent UTIs. Diamond nanoparticles (DNPs) are becoming popular as drug delivery agents as they are biocompatible, internalized by human cells and can be chemically modified for drug or antibiotic loading and thus ready to kill the bacteria hidden inside the cells. Therefore, in the current study we will investigate how DNPs interact with the bladder cells and study their antibacterial properties against Dr *E. coli*. The aim of this project is to develop DNP based antibacterial therapy for resolving bladder infections. These studies will help us to develop new ways of treating persistent infections of the urinary tract by delivering drugs inside the cells and cure the infection. These new treatments will have a significant impact on health care costs in the state as well as in the nation.



*Diamond nanoparticles (DNPs, green) are able to enter the human bladder cells where bacteria try to hide and thus can be targeted by DNPs. Visualized by confocal microscopy.*

## A therapeutic for reconnecting the cochlea and the brain

*Restoring synaptic connections in the cochlea using a novel brain metabolite*

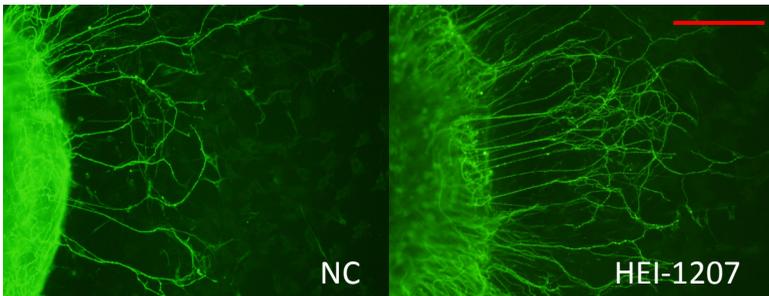
Richard Kopke, Hough Ear Institute

Deafness as well as tinnitus or the perception of a sound in the absence of any external source are human disorders with no known cures affecting over 1 billion people world-wide. A major component underlying these pathologies is loss of the specialized nerves that relay the signals from the sensory hair cells in the cochlea to the auditory centers in the brainstem. Exposure to loud sound, age-related attrition, or other cochlear insults can result in permanent loss of these specialized auditory nerves. Our aim is to find a way to regrow these neurons and restore normal auditory function. To this end, our initial study focused on a natural metabolite, LKE, which has neurotogenic potential; however, our focus changed when we discovered a compound, HEI-1207, had already passed FDA trials and was also able to stimulate re-growth of cochlear neurites. Since HEI-1207 has

already passed FDA trials, the path to the clinic will be much shorter than with a novel compound. Preliminary studies have been very successful. If further studies also prove successful, this project could yield a drug that may revolutionize the standard care of sensorineural hearing loss and tinnitus for the general public and military personnel alike by restoring lost hearing function and reducing chronic tinnitus.



*Dr. Kopke connects research with his clinical practice.*



*HEI-1207 induces robust auditory nerve outgrowth in auditory nerve explants compared to normal control (NC).*

HR15-017

How men with above-knee amputation perform work tasks

*Work performance in men with transfemoral amputation*

Carol P. Dionne, University of Oklahoma Health Sciences Center

Despite advances in medical and rehabilitation intervention intended to return adults with above knee, or transfemoral amputation (TFA), to the labor force, potential workers with TFA are disproportionately among the unemployed, chiefly due to painful residual limb injury suffered during performance of work-related activities. To understand mechanisms of musculoskeletal pain and injury and prevent debilitating injury in this working age group with TFA, we aim to characterize the mechanical loads and muscle activity within the prosthetic socket during actual work-related activity as well as quantify the alterations in bone metabolism and inflammation in the residual limb at 2 visits, 12 months apart. No translational, contextual studies have been undertaken with this working-age population. Investigators expect to isolate unwanted forces to be addressed in future rehabilitative approaches, prosthetic designs and technologies and to generate data and methodology that will inform larger studies planned to be submitted to national funding agencies (American Diabetes Association & National Institutes of Health) with different amputee groups and specific groups with illness, such as diabetes.

UPDATE: As of July 15, 2016: We have collected data on 25 participants. We have 2 additional subjects appointed and 6 identified to participate. Visit 1 controls' data-completed.



Can we train healthy people to turn on pain reduction circuitry?

*Biofeedback training in conditioned pain regulation*

Jamie Rhudy, University of Tulsa

Pain is a significant public health problem and current treatments do not adequately relieve pain-related suffering. Moreover, many pharmacological treatments have side effects, including addiction. Human neurocircuits exist for regulating pain, and psychological factors can engage them. Unfortunately, current treatments for chronic pain (psychological and pharmacological) do not do enough to reduce the burden of pain. The aim of this study is to develop and test an innovative intervention that harnesses the body’s natural ability to reduce pain. It combines two effective pain reduction strategies: relaxation/biofeedback and conditioned placebo analgesia. The treatment provides the patient with real-time biofeedback of their arousal level to promote control over arousal and pain. However, the current treatment differs from traditional biofeedback in two ways: 1) patients practice biofeedback during painful stimulation and 2) it includes a second feedback mechanism that allows trainees to physically control the painful stimulation with their arousal level. This novel treatment is being tested in a randomized controlled trial that compares it to two other control interventions. Pain-free patients are

being recruited for this initial study before it is tested in persons with chronic pain. The treatment involves three training sessions spaced 1-week apart and each session involves three 10-20 min trials. Subjective and physiological markers of pain are being assessed before and after each training session to determine whether the treatment affects pain processing. If successful, this novel treatment will: 1) provide a low-cost way to naturally reduce pain and pain signaling that can be adapted for chronic pain patients (especially those with high addiction potential) and 2) reduce the need for medications that have the potential for abuse/misuse.



*A sensor is applied to the back of the leg to record a physiological marker of pain processing that is assessed before and after biofeedback training.*

## New possible causes and potential therapies against cancer: What is the role of the important growth factor called IGF-1?

*Susceptibility of cancer: Novel mechanisms*

Anna Csiszar, University of Oklahoma Health Sciences Center

The growth factor called Insulin-like growth factor 1 (IGF-1) is very important in humans regarding many health aspects including life-span, diseases of age and development of cancer. In most people, IGF-1 levels decrease with age. However, studies in a naturally occurring mutation in a population of Ecuadorian individuals that have lower-than-normal level of a hormone called growth hormone (GH) has proved that low levels of IGF-1 during the whole life-time resulted in a strong immunity to cancer development. Despite we already know that IGF-1 has a very important job in the vasculature, the heart and the brain, the contribution of IGF-1 in adjusting resistance to cancer is not well-known yet. This study aims to investigate the function of low IGF-1 in cancer resistance and additionally study the importance of how low IGF-1 levels in different times can change the likelihood to develop cancer. The results of this proposed work will lead to a better understanding on the causes of cancer and the ability of IGF-1 deficiency to alter cancer development. Additionally, the results of this work could potentially provide helpful information to develop new anti-cancer therapies.



*Andriy Yabluchanskiy, M.D., Ph.D., a scientist from our lab, is studying cellular responses to cancer cells.*



*The millipore cell flow cytometer allows our lab to analyze and quantify different population of cells.*

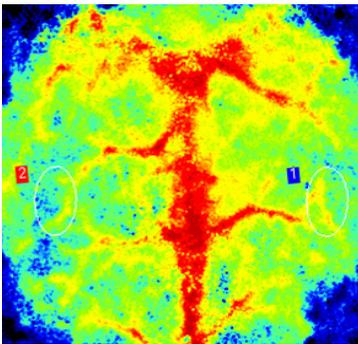
## HR15-106

The loss of an important growth factor with age leads to small blood vessel problems in the brain causing cognitive impairment

### *IGF-1 and cerebrovascular dysfunction*

Zoltan Ungvari, M.D., Ph.D, University of Oklahoma Health Sciences Center

Our abilities to think and to remember depend upon a close match-up between the supply and demand of oxygen and nutrients in the brain. This match-up is called neurovascular coupling and depends on a tight regulation of the blood flow in the brain that is responsible for providing oxygen and nutrients while removing waste from brain cells. The growth factor called Insulin-like growth factor 1 (IGF-1) is very important to maintain good cognitive health and it is known to dramatically decrease with age. Despite we already know that IGF-1 is very important for the vasculature and the heart, the contribution of IGF-1 in keeping a good balance between blood flow supply and demand in the brain is not well-known yet. The proposed work aims to study the relationship between this hormone and the blood flow balance in the brain. The results of this proposed work will lead to a better understanding on the causes of cognitive deficits and dementia in the elderly, as well as potentially provide the required knowledge to attempt therapies to slow down the onset of cognitive impairment with the progression of age.



*The vessels with most blood flow are shown in red in this non-invasive image obtained using the Laser speckle.*



*The Laser Speckle contrast imager from PeriMed: the instrument used to measure the blood flow in the mice brain is shown above.*