OCAST

2020

HEALTH RESEARCH PROJECTS

Table of Contents

Cell & Molecular Biology

Chemistry & Biochemistry

A new polymer to modify nanoparticles and suppress toxic immune reactions

Immunokinetics of superhydrophilic polymer-modified liposome encapsulated hemoglobin

PI: V. Awasthi, University of OK Hlth Sci Ctr **Project: HR17-054** **Research Area: Bio Med Eng**

Liposomes are commonly used nanoparticles for drug delivery and vaccine formulation

PROBLEM

Naked or plain liposomes can cause severe toxicity in people

SOLUTION

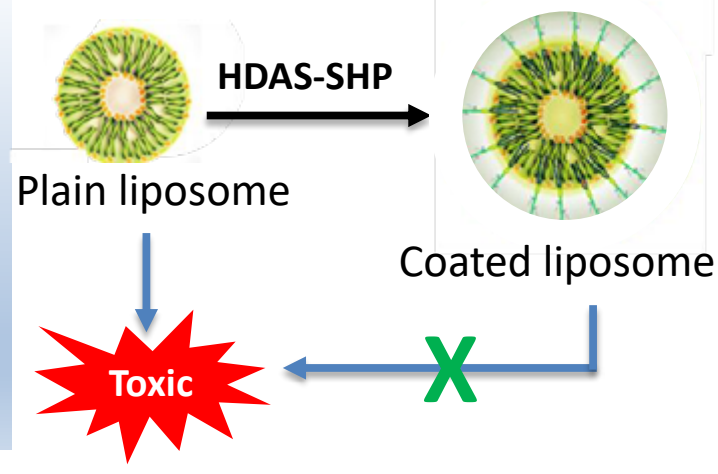
Coating of liposomes with special polymers can prevent this toxicity

OUR RESEARCH

A new polymer called HDAS-SHP for coating liposomes

ADVANTAGES OF HDAS-PEG

- Better protection than customarily used polymers
- Completely synthetic and potentially not immunogenic
- Helps liposomes circulate in blood for long period of time



FINDINGS

- Evaluated stability of HDAS-SHP on liposomes
- Tested HDAS-SHP liposomes in cells
- Assessed immune reactions in mice

CONCEIVED APPLICATIONS

Use HDAS-SHP to coat liposomes containing hemoglobin for use as a blood substitute

Replace traditionally used polymers in present-day liposomes to improve their effectiveness

A Smart Skin to prevent Bed Sores

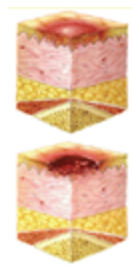
Develop a Liquid Crystal Elastomer (LCE) skin to redistribute stress and prevent pressure ulcers

PI: Aurelie Azoug, Oklahoma State University OCAST Project: HR20-086-1 Research Area: Biomedical Engineering

When patients are **IMMOBILIZED** for **TOO LONG,**

their skin gets injured.

BED SORES



They can die just by staying in a hospital bed.

Treating bed sores costs $11bn/year.

Immobility has a heavy price.

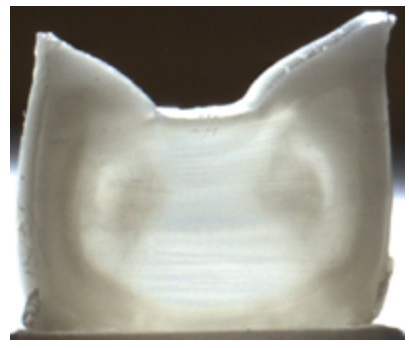
The only treatment is to move patients every 2 h.

Benefits of the Smart Skin

- Reduced treatment costs
- Improved quality of life
- Lesser need to move patients

We believe LCEs can help us.

We study LCEs and their unique mechanical properties.



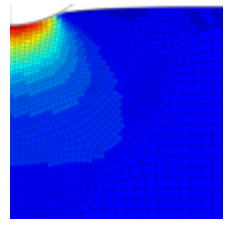
LCE during compression

They can change shape without adding force.
They come back to their original shape.

Recent accomplishments

- Observing changes of properties inside LCE
- Developing a model under compression for simulations

Simulation compressed LCE



Understanding the Effects of Sphero-Cylinder Drug Particle Shape to Enhance Small-Airway Drug Delivery for Better Emphysema Treatment Outcomes

Elongated Sphero-Cylinder Particles Can Enhance Delivery from Dry Powder Inhalers to Human Lung

PI: Yu Feng, Oklahoma State University OCAST Project: HR19-106 Research Area: Biomedical Engineering

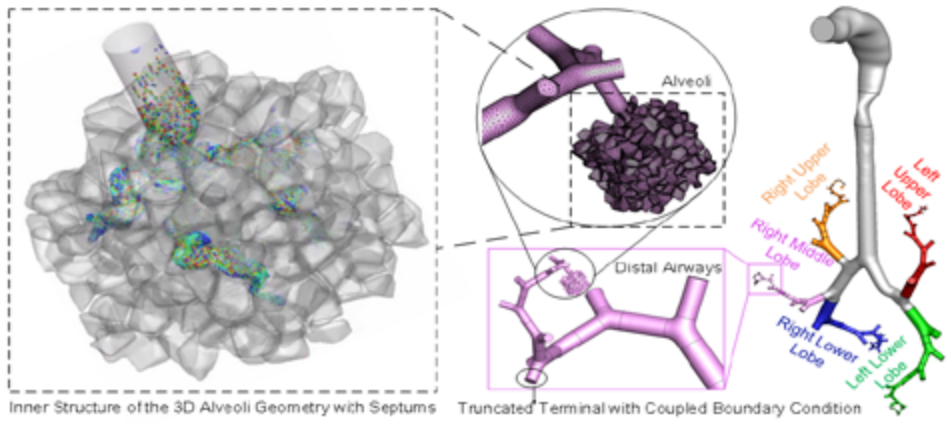


Fig. 1. A Newly Reconstructed Elastic Whole-Lung Model

OVERALL GOAL

To model and determine how particle shape features can influence the emitted particle size distributions at the mouthpiece of a representative dry powder inhaler, and enhance drug deposition in emphysematous whole lung airways and therapeutic outcome using a computational fluid dynamics (CFD) and discrete element method (DEM).

RECENT ACCOMPLISHMENTS

- We developed and validated a CFD-DEM model for sphero-cylinder particles transport and interactions in Spiriva™ Handihaler™
- We developed a new reconstructed elastic whole-lung model and a S-D rate model ready for the CFD-DEM simulations of drug particle dynamics through the pulmonary routes.
- We found that particle shapes and actuation flow rate can both influence the delivery efficiency and distributions of the dry powder particles emitted from Spiriva™ Handihaler™.

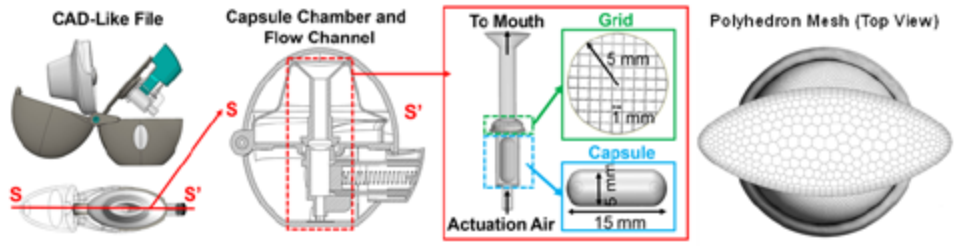


Fig. 2. The reconstructed Spiriva™ Handihaler™ geometry and the hybrid polyhedral mesh including the flow channel, grid, and capsule with pierced holes

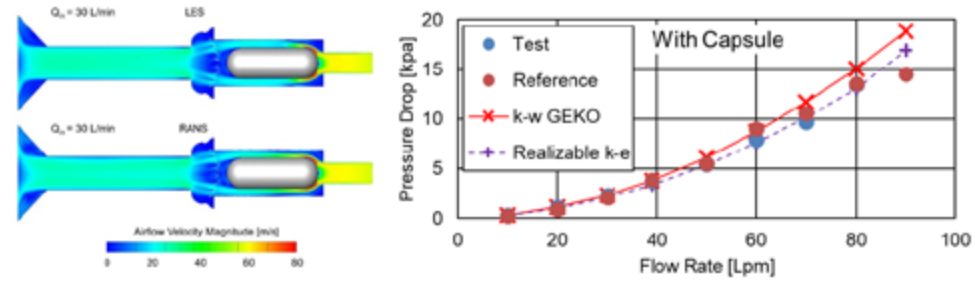


Fig. 3. CFD-DEM model validations with the comparison of airflow field and pressure drop in Spiriva™ Handihaler™

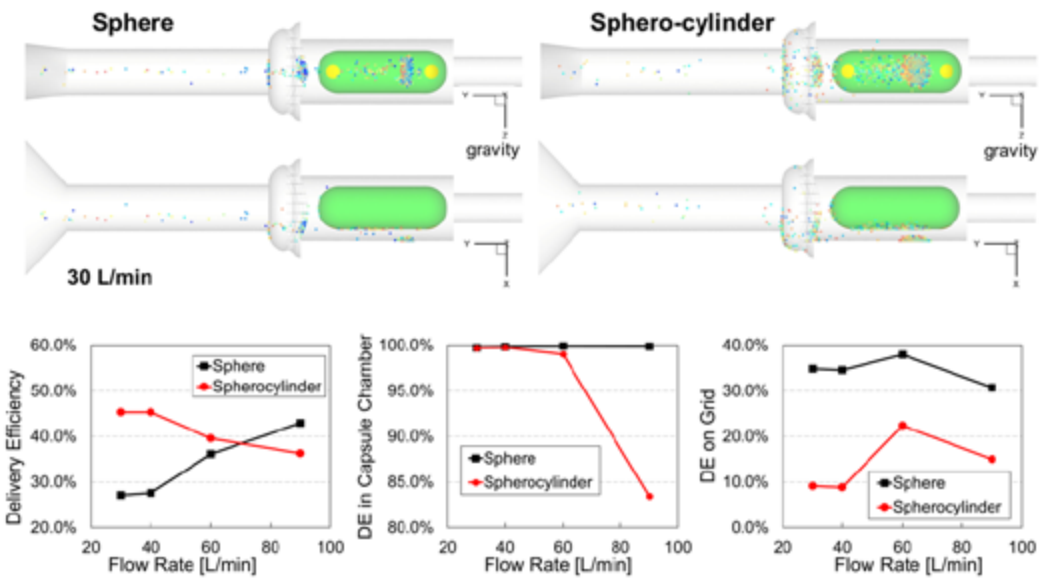


Fig. 4. Comparisons of particle transport dynamics and delivered doses between spherical and sphero-cylinder particles through Spiriva™ Handihaler™

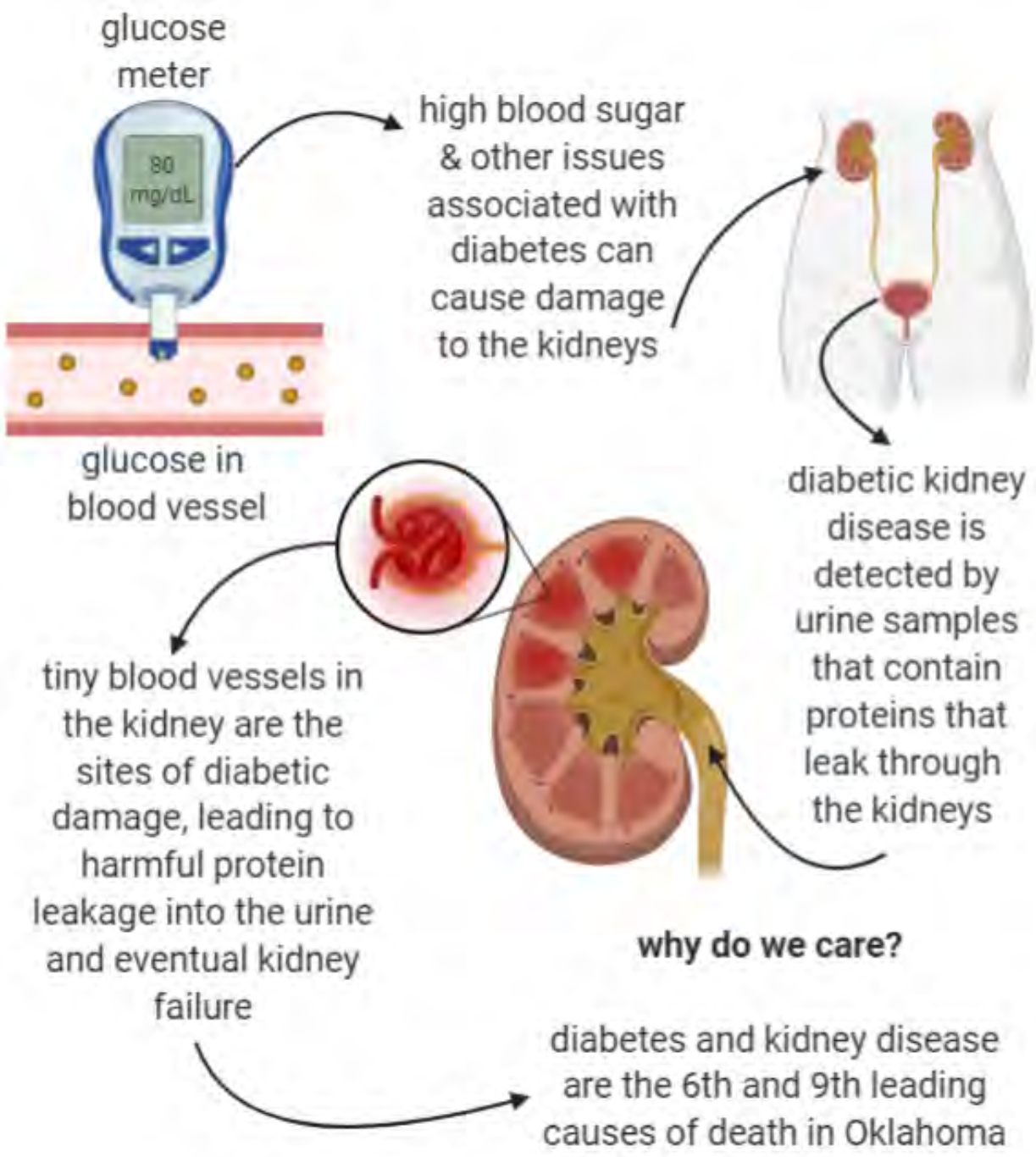
BENEFITS

- Provide a noninvasive and cost-effective *in silico* tool to evaluate the delivery efficiency of inhaler designs and drug formulations.
- Accelerate the innovation and optimization processes of dry powder inhaler, pulmonary drug formulation, etc.
- Enhance the therapeutic outcome and reduce the side effect of pulmonary drug delivery treatment.

Determining How Diabetic Kidney Disease Starts

Computational Modeling of the Onset of Diabetic Kidney Disease

PI: Ashlee N. Ford Versypt, Ph.D., School of Chemical Engineering, Oklahoma State University
OCAST Project: HR17-057
Research Areas: Biomedical Engineering, Chemistry, Physiology, & Computational Biology



this OCAST project has enabled the Ford Versypt Lab at OSU to develop the first prototype computer simulation of the biochemical processes that start kidney damage due to diabetes before protein leakage is detectable

A new method for targeting and treating triple negative breast cancer with commonly used drugs linked to a protein

Novel targeted protein-drug conjugates for treating metastatic breast cancer combined with immunostimulation and mTOR inhibition

PI: Roger Harrison, Ph.D., University of Oklahoma

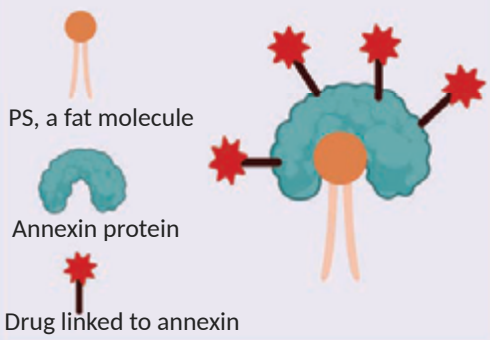
OCAST Project: HR19-148

Research Area: Biomedical Engineering

Delivering targeted chemotherapies to triple negative breast cancer (TNBC) remains a major challenge for oncologists and scientists. But we can overcome this challenge by targeting a fat molecule called phosphatidylserine (PS) with the protein annexin to deliver drugs to the tumor.

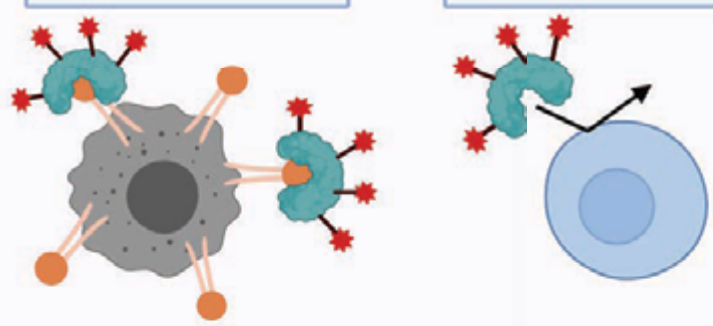
Annexin Targets PS

PS is like a parking place on the surface of cancer cells, that is only reserved for annexin.
Annexin is like a delivery vehicle that delivers drugs to the tumor.



TNBC cells have an excess of PS parking places for annexin to deliver drugs to the cancer cells.

Healthy cells have no PS parking places, and annexin will not park on these cells.



Benefits

Decrease in chemotherapy side effects

Increased survival of patients with metastatic breast cancer

Less drug needed to kill cancer cells

Recent Accomplishments

1. We confirmed the appropriate dosing schedule for both annexin-drug conjugates in mice.

2. Annexin-DM1 conjugate significantly increased survival in mice.

3. Annexin-chlorambucil conjugate significantly decreased tumor volume in mice.

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Automatic Repair of the Filling/Tooth Interface in Dental Restorations

Interfacial Healing in Dental Restoration

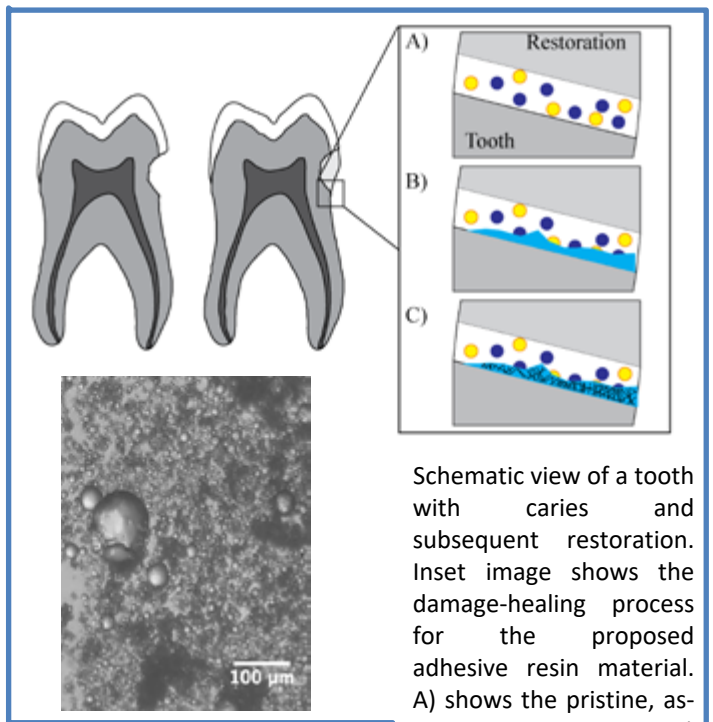
PI: Michael W. Keller, The University of Tulsa **OCAST Project: HR16-100** **Research Area: Biomedical Engineering**

Project Summary

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. A major research area is new 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.

Accomplishments

- Synthesized micron and submicron (nanoscale) microcapsules for inclusion at the tooth-restoration interface.
- Developed specimen preparation procedure to enable testing of the new self-healing material.
- Fracture testing of interfacial specimens is ongoing to determine efficacy of self-healing.



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. Image below the tooth is a micrograph of 1 micron and smaller capsules intended for self-healing.

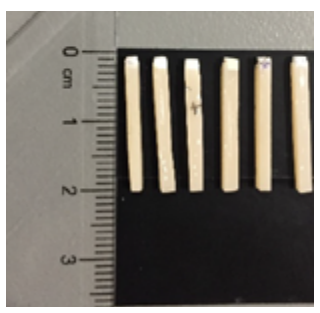


Image of initial fracture specimen to test interfacial self-healing

PERSONALIZED TREATMENT OF BRAIN ANEURYSMS

HR-18-002: Novel Shape Memory Polymer Devices for Optimal Endovascular Embolization of Intracranial Aneurysms
Research Area: _____
Dr. Chung-Hao Lee, Dr. Yingtao Liu & Dr. Bradley N. Bohnstedt, The University of Oklahoma

BRAIN ANEURYSMS

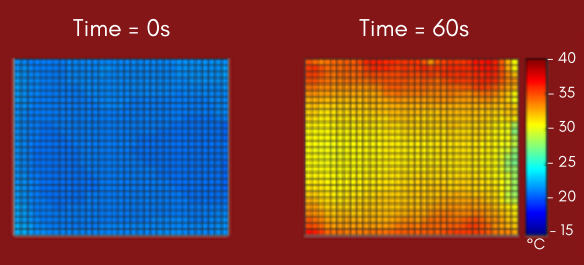
Balloon-shaped deformation of arteries in the brain

Occur most frequently at the circle of Willis

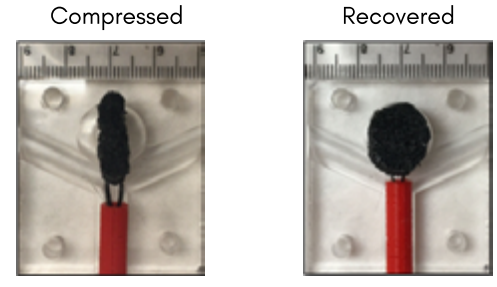
Aneurysms can be clipped off or filled with coils

We want to create personalized foams that fill the aneurysm

Shape memory polymers (SMPs) can be compressed and recover their shape using heat stimulus

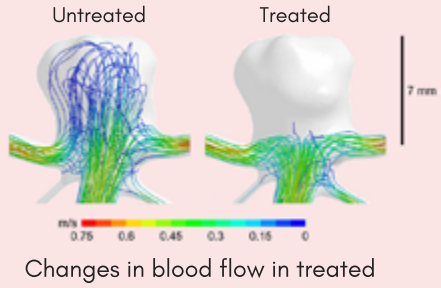


Our SMPs release heat when short electric currents are applied to them

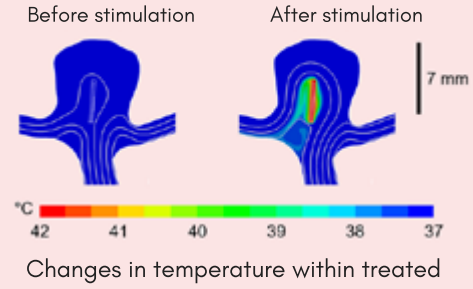


Our SMPs recover their shape and occlude aneurysm models after electric stimulation

COMPUTARIZED SIMULATIONS ALLOWED US TO UNDERSTAND INTERACTIONS BETWEEN OUR DEVICE AND THE BODY



Changes in blood flow in treated aneurysms



Changes in temperature within treated aneurysms during foam delivery

NEXT STEPS

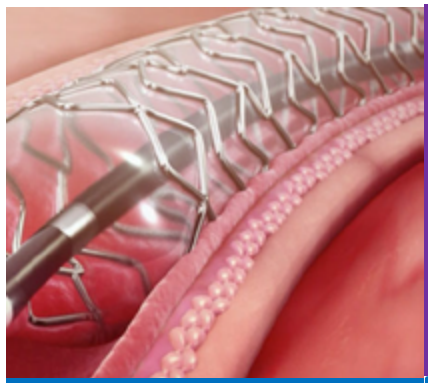
Development of a device to transport the foam into the aneurysm (catheter).

Assessment of interactions between the foam and aneurysm environment (*in vivo*).

Dual-function Nanocoatings with Drug Release Control

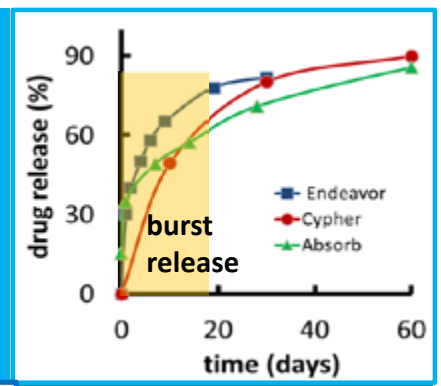
Nanocoatings for Controlled Drug Release and Improved Biocompatibility

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

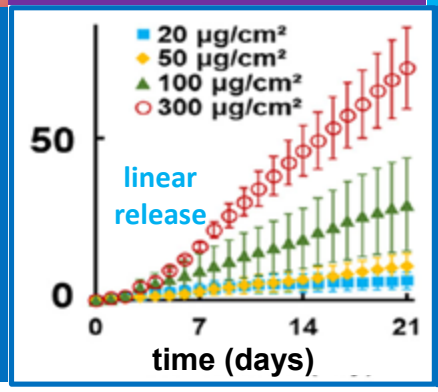


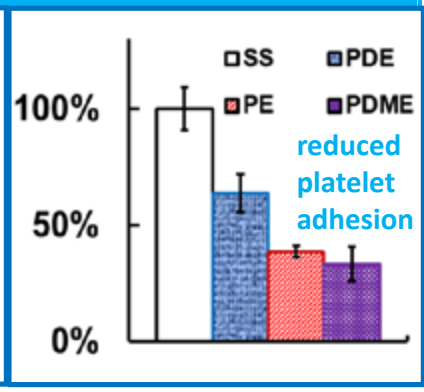
Drug-eluting stents widely used in treating **coronary artery diseases**.

But burst drug release and lack of biocompatibility **limits** the clinical success.



Our research focuses on simultaneous control of **drug release** and **stent biocompatibility**.





Accomplishments

Linear drug release, no burst.

Regulation of drug release kinetics.

Improved biocompatibility with less platelet adhesion.

Increasing the Efficiency of Cancer Therapy Drugs Using Smart Nano-Scaled Materials

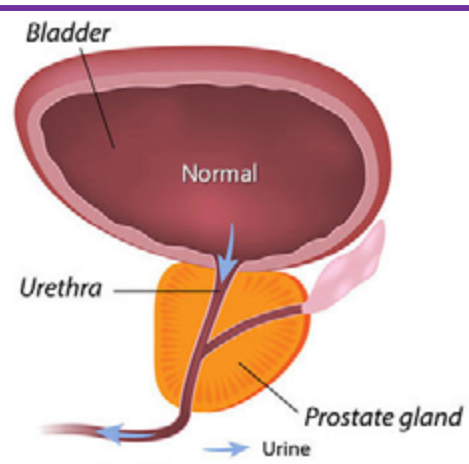
Targeted Delivery of a Reactive Oxygen Species Generator for Treatment of Hormone Refractory Prostate Cancer

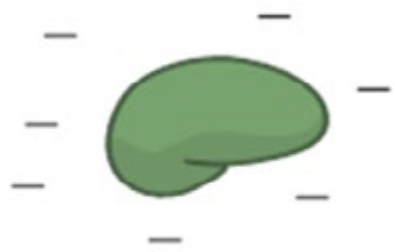
PI: Joshua D. Ramsey, Oklahoma State University

OCAST Project: HR19-104

Research Area: Biomedical Engineering

Prostate cancer affects more than 1 in 10 men at some point in their lifetime and is the second leading cause of death among men.

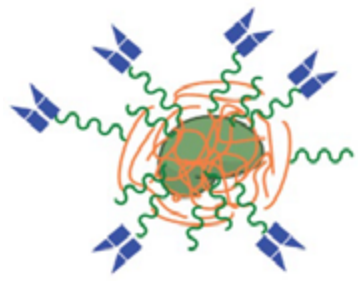




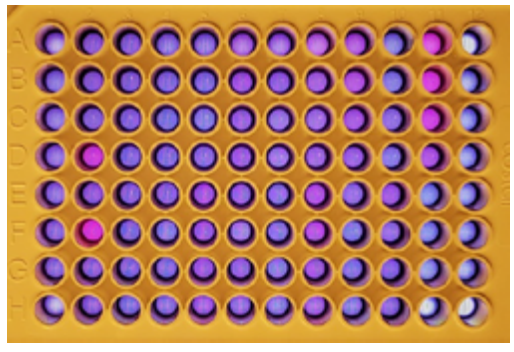
Glucose oxidase (GOX) is a cytotoxic protein that can be used for treating prostate cancer.

Treatment options are limited and the side-effects of using a reactive oxygen species generator, such as glucose oxidase, are high due to poor targeting and retention.

Our approach is to encapsulate GOX within a polymer matrix that is targeted to prostate cancer cells, thereby limiting the side-effects and protecting the enzyme.



Encapsulated GOX targeted to prostate-specific membrane antigen.



Live cell assays compare the effectiveness of encapsulate GOX vs unencapsulated GOX.

GOX encapsulated in our novel drug carrier is six times more efficient than unencapsulated GOX.

A novel wearable vibration therapy device for treating upper limb functional impairment in stoke

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

PI: Hongwu Wang, University of Oklahoma (HSC) **OCAST Project: HR18-034** **Research Area: Biomedical Engineering**

Project Highlights

Functional recovery from neurorehabilitation only lead to 20% of patients' fully resumption of their social life and job activities mainly due to **underdoes**.

Focal vibration (FV) therapy, a non-pharmacological, non-invasive treatment, has had satisfactory outcomes as a useful tool in neurorehabilitation.

We are developing and evaluating a wearable and mHealth technology that delivers **individualized** and **precise** vibration to target muscles.

The device provides patients opportunity to apply the prescribed vibratory stimuli in-home and/or at community settings to **sustain the dosage** needed. It also allows therapists to monitor usage and compliance and to adjust based on progression.

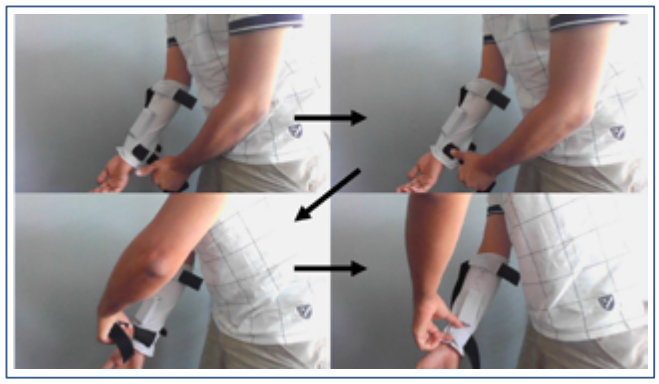
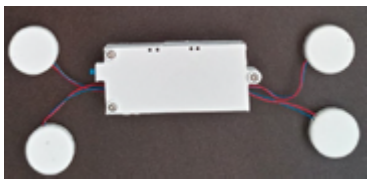
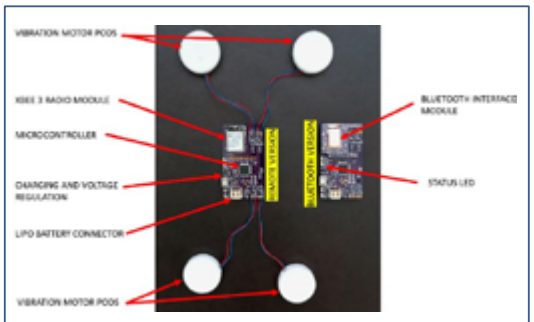


Illustration of wearing the device to right arm by patient him/her self

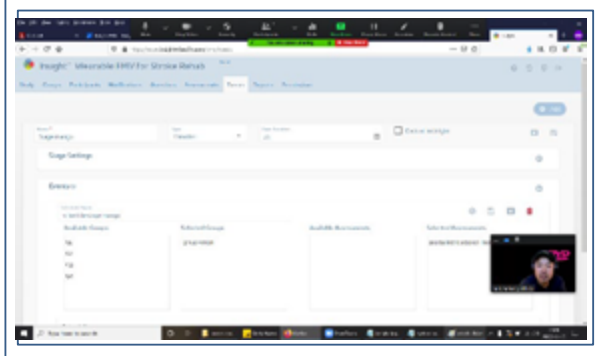




The final prototype of the wearable vibration device and its hardware components

Recent Accomplishments

- Patients, caregivers and therapists met virtually during COVID-19 pandemic to finalize the design and development.
- A **final prototype** was fabricated and assessed by the patients, caregivers and therapists.
- **An app and web portal** was developed to track the device usage and remotely monitoring and adjusting the vibration
- Wearable Focal Vibration Device and Methods of Use (2020), **Provisional Patent**: 62/991,562.



The web portal that allows therapist to remotely monitor and adjust the vibration regimen

Aravindan

RD3 protein, an unsung hero that can control the development of the deadly infant cancer

Cre-Conditional RD3-Loss Driven Neuroblastoma Mouse Model: Novel Tool for Preclinical Studies on Disease Evolution

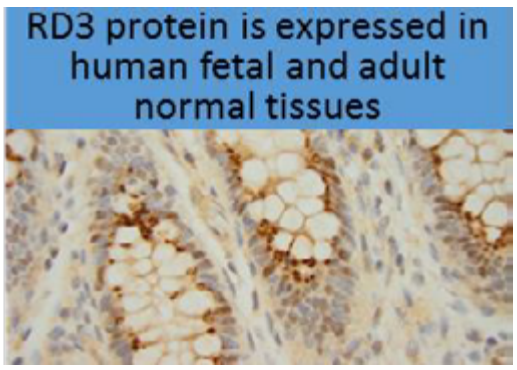
PI: Natarajan Aravindan, OUHSC OCAST Project: HR19-045 Research Area: Cancer Research/Biology

Project Highlights: Despite four decades of clinical and research efforts to combat *neuroblastoma, the most common cancer in infants*, cure for aggressive disease is challenging. Neuroblastoma contributes to one-tenth of all childhood cancer deaths. We recognized the loss of a protein called Retinal Degeneration Protein 3 (RD3) in aggressive tumors and, also indicated that such loss plays critical role in cancer progression.

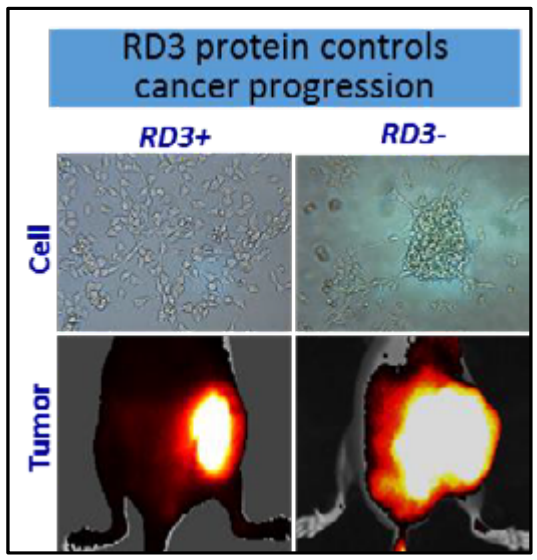
Here, we are developing a novel preclinical mouse model by *knocking out RD3* gene in select neural crest cells (NCC, unique cells in which this cancer arise) during early development to study whether RD3 loss is required for onset of neuroblastoma and for its progression.

In the long run, this research will lead to recognize the mechanism(s) of cancer initiation and progression and, will allow us to develop improved therapeutic strategies for the cure of this deadly disease.

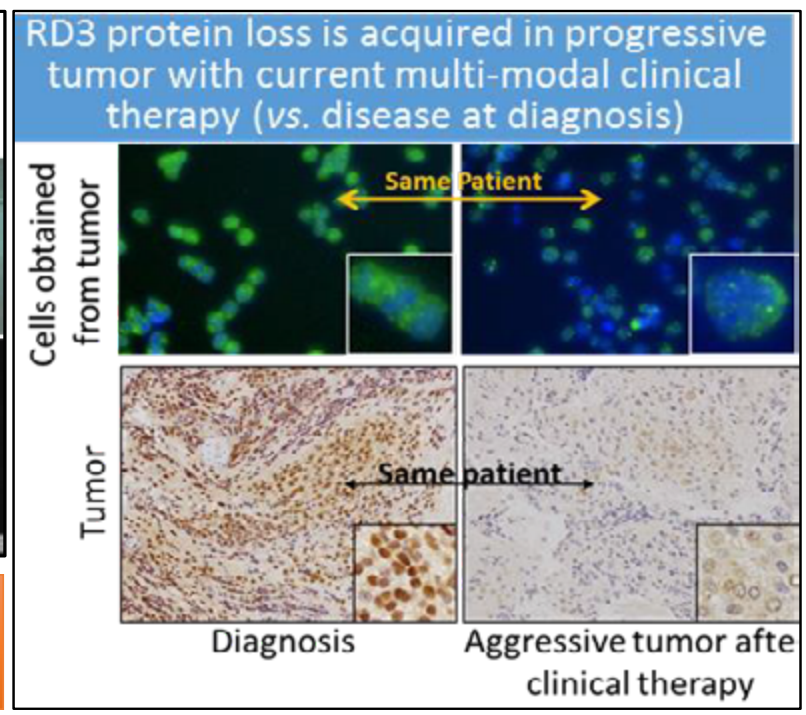
Recent Accomplishments



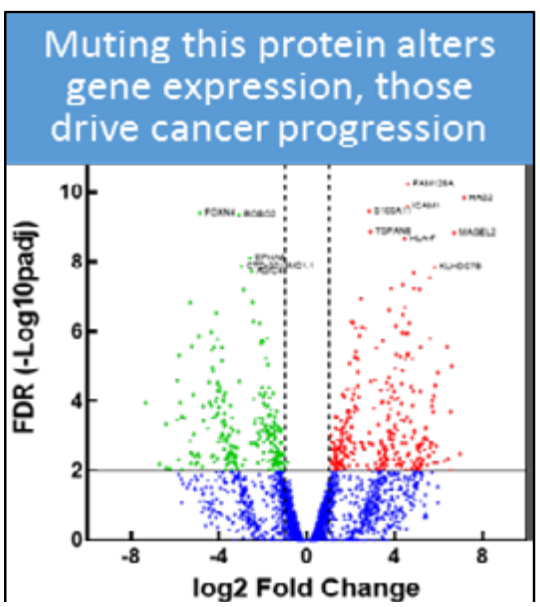
Establishing preclinical mouse model to study whether loss of RD3 in select cells during development prompts the genesis of neuroblastoma

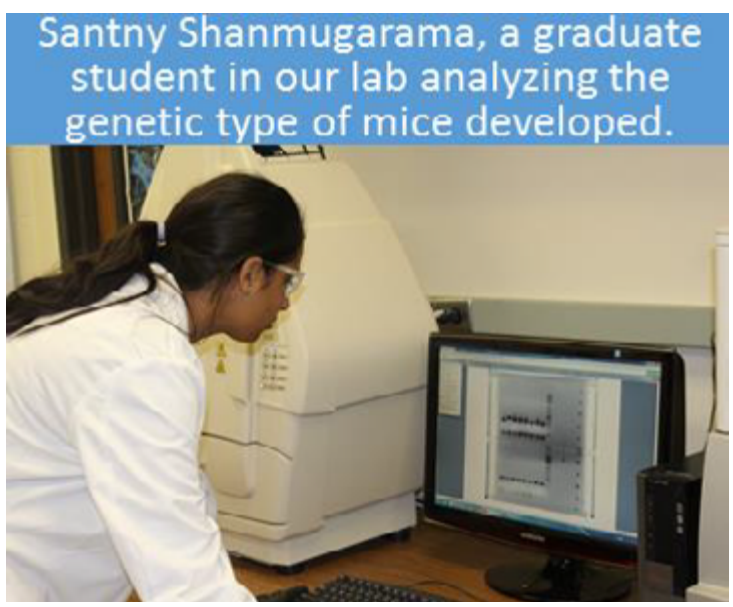


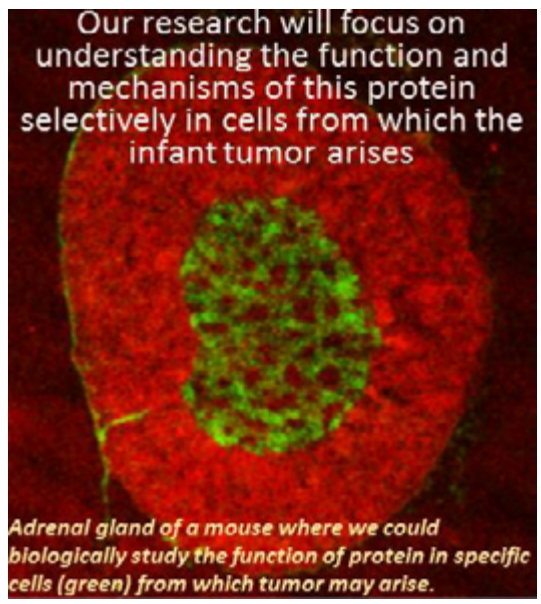
Mechanisms how RD3 control tumor evolution



Generating clinical disease mimicking mouse model to study whether RD3 loss aggravates neuroblastoma progression







A dual functional small protein identified by phage-based biotechnology can smartly home to tumor sites and trigger the antitumor immune responses

Cancer immunotherapy by tumor-homing immune checkpoint-blocking dual-functional peptide

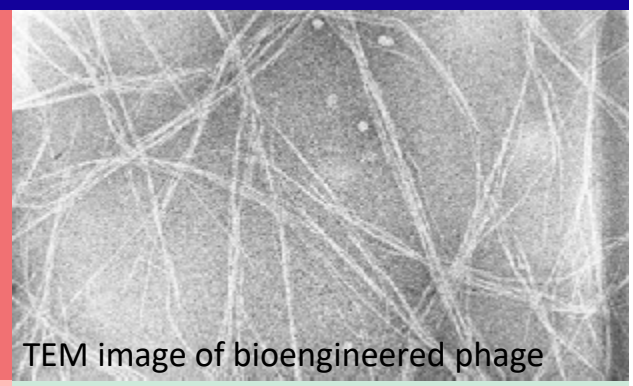
PI: Binrui Cao, University of Oklahoma

OCAST Project: HR17-043

Research Area: Cancer Research

CANCER CELLS avoid immune responses

by interacting with the **"SWITCHES"**



TEM image of bioengineered phage

Liwei Zhang, a student in our lab constructs bioengineered phage

Our research is to develop a medicine with both tumor targeting and "switch" blocking capabilities

The Benefits:

Smart cancer therapy

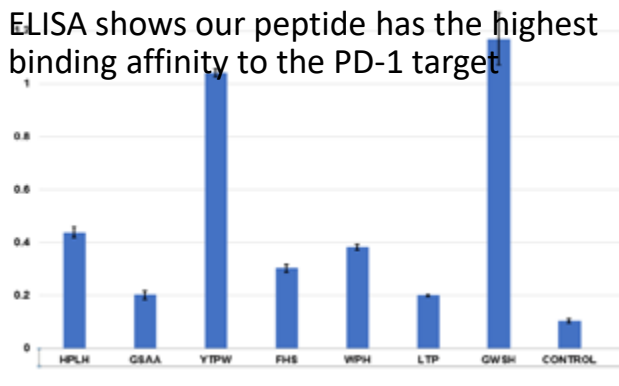
Low side effects

Low production cost

Recent accomplishments:

- Tumor targeting molecule was identified
- "Switch" blocking molecule was identified

ELISA shows our peptide has the highest binding affinity to the PD-1 target



- A bioengineered phage displaying two molecules was constructed.
- The phage could inhibit tumor growth.

Does Stopping Blood Vessel Generation Slow Tumor Growth?

Does Prolyl Oligopeptidase Inhibition Suppress Tumor Growth?

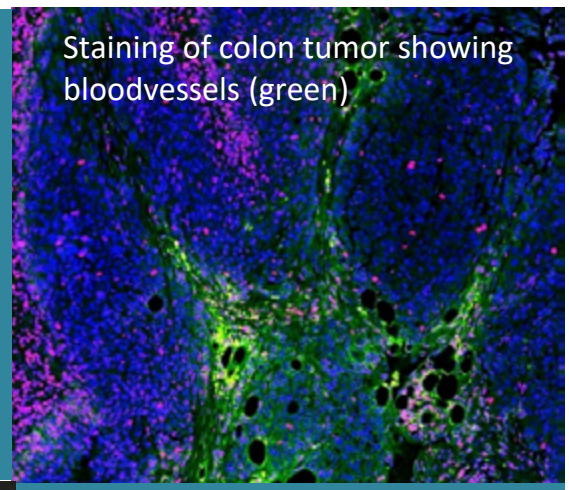
Victoria Christiansen, OUHSC, Warren Research HR18-046 Cancer Research/Cancer Biology

Blood vessel growth is

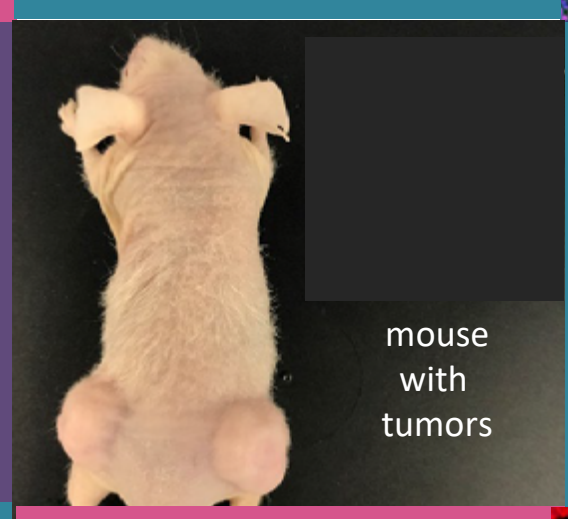
NORMAL

But in tumors It can lead to

INCREASED Tumor growth



Slowing vessel growth = SMALLER Tumor size



Our research focuses on understanding vessel growth and reducing

tumor formation

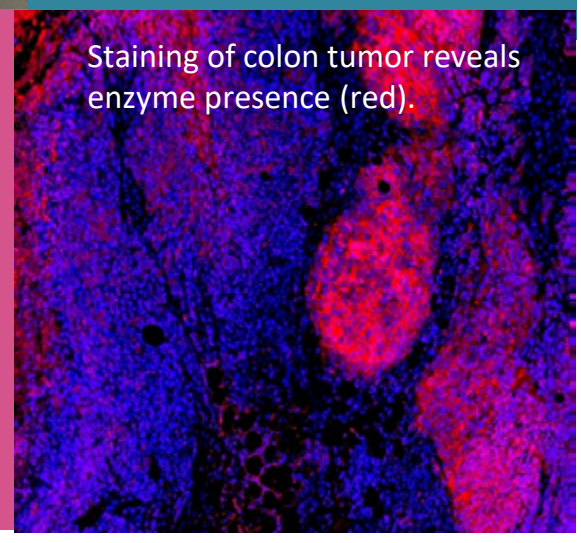
Benefits:

New cancer treatment

Understanding vessel growth

Recent accomplishments:
Animal experiment showing reduced tumor growth

Staining tumors to show vessels , cell death and enzyme presence



Breast cancer cells secrete a protein that may regulate cancer migration

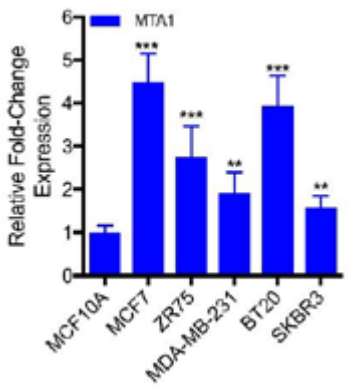
Exosome Mediated Transfer of Metastasis Associated Protein 1 in Metastatic Breast Cancer

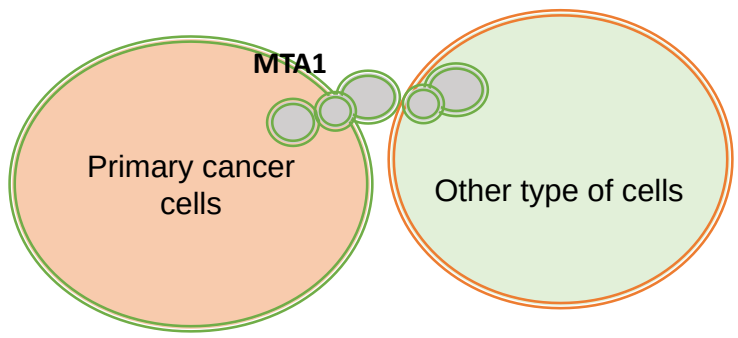
PI: Wei-Qun Ding, University of Oklahoma Health Sciences Center OCAST Project: HR20-105 Research Area: Cancer Biology

MTA1 is found in vesicles secreted by breast cancer cells

It can then be transferred to other cells surrounding the tumor or in distal organs

By its name, it relates to breast cancer metastasis





Metastasis Associated Protein 1: MTA1

We study how vesicle-associated MTA1 might contribute to breast cancer migration, and whether the secreted MTA1 can serve as a diagnostic tool

Benefit:
It could lead to new therapeutic and diagnostic strategies against metastatic breast cancer - a major cause of breast cancer related death

Recent accomplishment:

- Established cell lines lacking MTA1, which allows us to study MTA1's contribution to breast cancer progression
- Initiated collection of patient plasmas from NIH supported cooperative human tissue network (CHTN) under an approved IRB protocol

Hannafon

Exosome microRNA Contents Are Altered and Contribute to Breast Cancer Progression

The Role of Exosomes in Breast Ductal Carcinoma In Situ

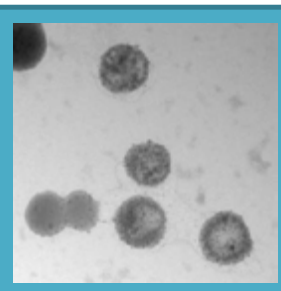
PI: Bethany N. Hannafon, PhD, OUHSC

OCAST Project HR17-052

Research Area: Cancer Biology

Invasive breast cancer often develops from a non-invasive precursor called ductal carcinoma in situ (DCIS)

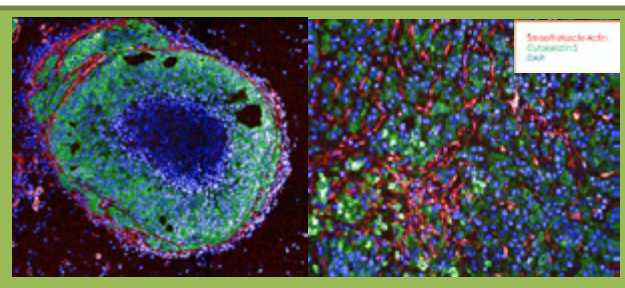
We do not fully understand what drives DCIS progression to invasive breast cancer and we cannot predict when or if it will progress



Electron microscopy images of exosomes isolated from breast cancer cells

Exosomes are small extracellular vesicles secreted from cells that contain and transport small RNAs called microRNAs

Our research is focused on understanding the role of exosomes and their contents in DCIS progression

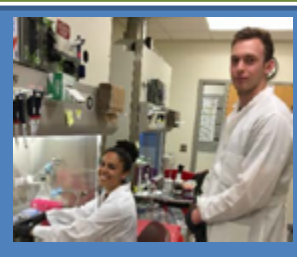


Microscopic images of fluorescently labeled tissue sections of mouse mammary glands with human DCIS (left) or invasive breast cancer (right)

We will also determine whether changes in exosome microRNA contents are altered in patients with DCIS and invasive breast cancer

RECENT ACCOMPLISHMENTS:

DCIS progression is attenuated in a mouse model by blocking exosome secretion resulting in reduced circulating exosome miRNAs



Summer undergraduate student researcher Kiera Vaughn (University of Central OK) and laboratory technician Matthew Bruns (now a 1st year medical student at Oklahoma State University)

THE BENEFITS:

- Understand the biology of early breast cancer
- Identify biomarkers that can predict progression
- Develop ways to prevent progression

PRESENT GOALS:

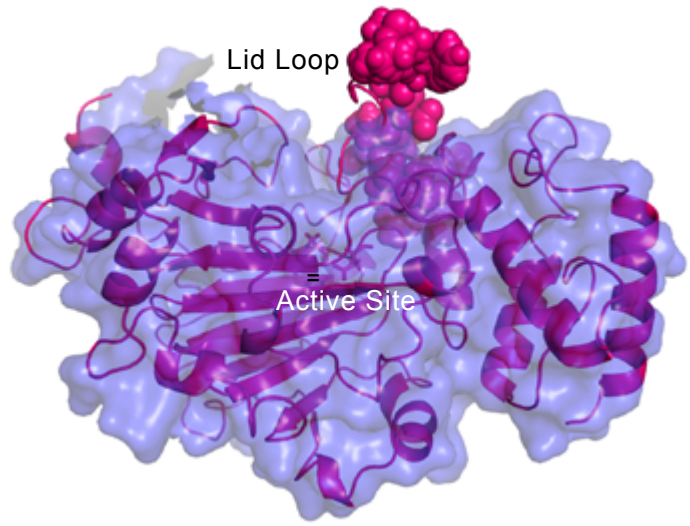
We are continuing to collect blood plasma samples to evaluate the exosome microRNA signatures in patients with DCIS and invasive breast cancer

New drug target for treating breast cancer

Role of a Lysine Hydroxylase in Breast Cancer

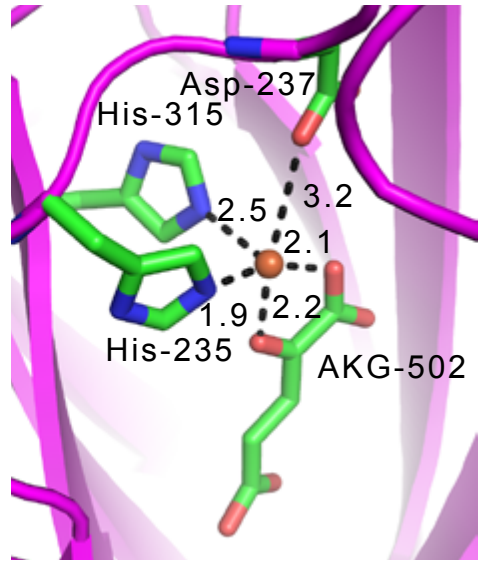
PI: Blaine Mooers, OUHSC OCAST Project: HR20-002 Research Area: Cancer Research

The war on breast cancer is needs new weapons.

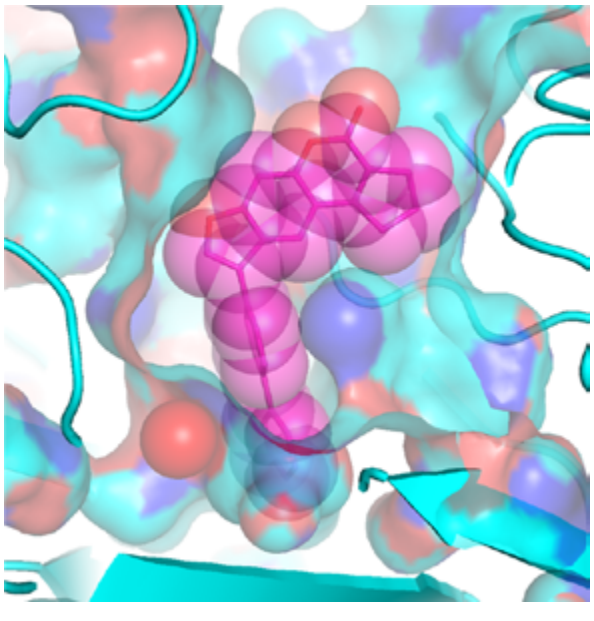


We need to stop enzymes that trigger the growth of tumors.

JMJD4, a lysine hydroylase, is one such bad actor.



A drug could bind to its active site and block further harmful effects.



We found leads with the OU supercomputer. We are checking them in the lab.

Oh

A protein that may be involved in the progression of pancreatic cancer.

Role of JMJD4 in Redox Regulation and Pancreatic Cancer

PI: Sangphil Oh,
University of Oklahoma Health Sciences Center

OCAST Project:
HR17-067

Research Area:
Cancer Research

Pancreatic cancer is VERY AGGRESSIVE

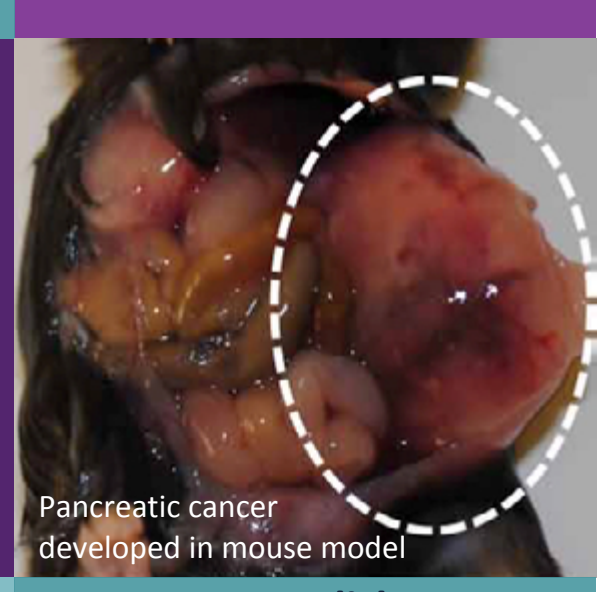
SURVIVAL RATE:

≦ 5% in US

It is RESISTANT to conventional CHEMO-THERAPIES

Ruicai Gu, Ph.D., a postdoctoral fellow in our lab, is culturing pancreatic cancer cells

We found JMJD4 protein is over-expressed in a subset of pancreatic tumors



Pancreatic cancer developed in mouse model

We will focus on understanding how JMJD4 regulates PANCREATIC CANCER PROGRESSION and validating JMJD4 as a NEW TARGET for pancreatic cancer therapy

The benefits:

reduce the mortality rate

reduce costs of health care

Recent accomplishments:

Studying how JMJD4 promotes pancreatic cancer cell survival

Evaluating JMJD4's role in pancreatic tumor development using a mouse model system

New Therapies for Prostate Cancer

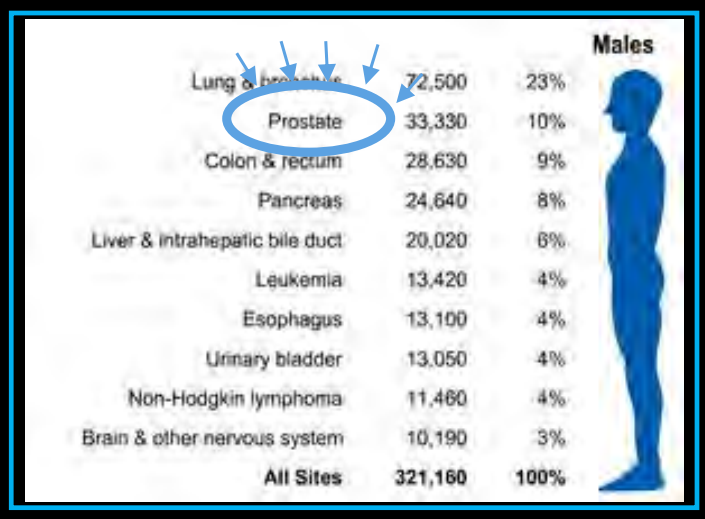
Defining the role of the TMEFF2 transcript in androgen signaling in prostate cancer

OCAST Project: HR18-07

PI: Maria J. Ruiz Echevarria, PhD
Univ. of Oklahoma Health Sciences Center

Research Area: Cancer Research/Cancer Biology

Prostate cancer is the second leading cause of cancer related death in men



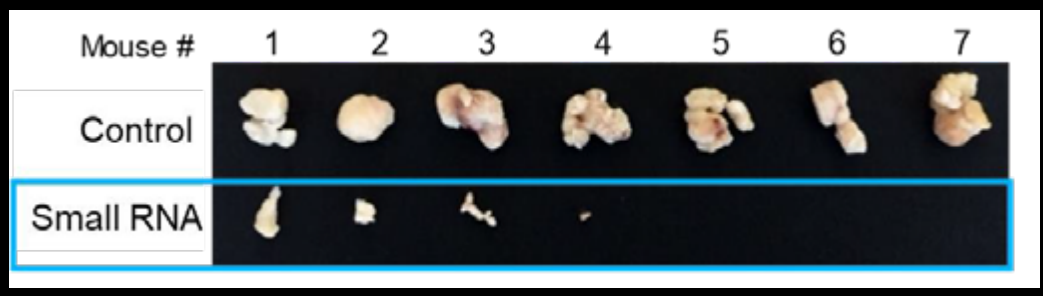
Current therapies for advanced prostate cancer are mainly directed to block the activity of a protein, the *androgen receptor*, which is essential for prostate cancer cell growth

The problem: targeting the androgen receptor leads to *therapeutic resistance* and development of a currently incurable and aggressive form of prostate cancer

OUR SOLUTION: OUR RESEARCH FOCUSSES ON IDENTIFYING NEW WAYS TO INDIRECTLY TARGET THE FUNCTION OF THE ANDROGEN RECEPTOR BY SIMULTANEOUSLY BLOCKING THE ACTIVITY OF MULTIPLE ASSOCIATED PROTEINS (COREGULATORS) THAT ARE NECESSARY FOR ITS FUNCTION.

Methods: Using in vivo, in vitro and bioinformatic approaches, we have identified a series of small RNAs that simultaneously target and inhibit the expression of multiple androgen receptor coregulators, ultimately blocking androgen receptor activity

Results: Expression of these small RNAs prevent prostate cancer cells and tumor xenograft growth and lead to cancer cell death. Because they affect multiple targets, development of therapeutic resistance is unlikely



Expression of specific small RNAs inhibits growth of xenograft tumors in vivo

HIGHLIGHTS

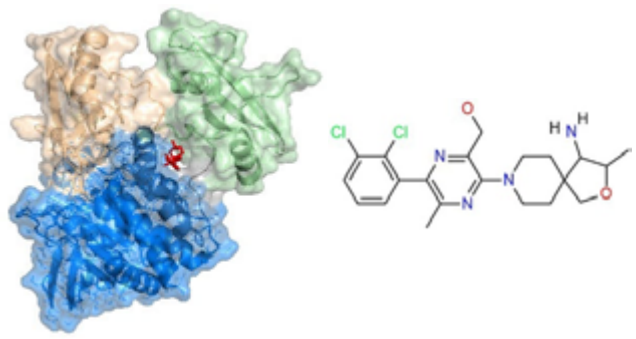
- We have identified small RNAs that target the expression of numerous genes which are significantly enriched for androgen receptor-coregulators. Expression of these small RNAs results in PCa cell death without affecting viability of benign prostate cell lines. These sequences represent novel therapeutics for advanced PCa, with potential for rapid translation into clinical trials.
- These studies are currently under review in the “Molecular Therapeutics– Nucleic Acid” journal

How Cancer Cells Adapt to Anti-Cancer Drugs

Deciphering bypass mechanisms of resistance to SHP2 inhibition

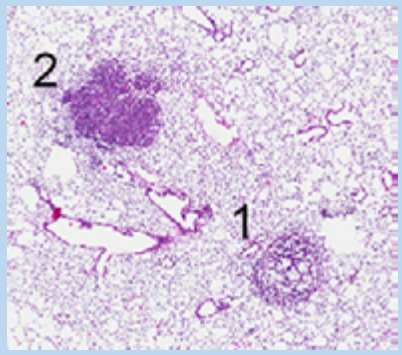
Jie Wu, OU Health Sciences Center OCAST Project: HR19-029 Research Area: Cancer Research

A new target and breakthrough drugs for cancer therapy



Activation of ERBB family kinases

Mechanisms of drug resistance

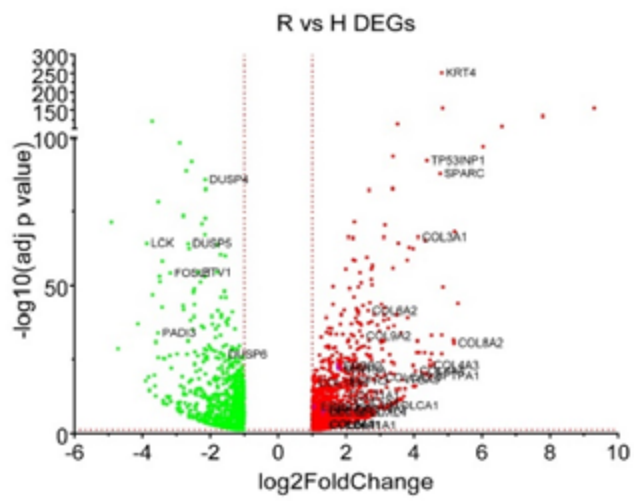


KRAS-driven lung tumors

1.Response,
2.Resistance

Overexpression of extracellular matrix

DEGs of resistant cells



Vulnerability of resistant cells

Combinational treatment

Understand and treat blood cancers

Define the role of Mpl in myelofibrosis

PI:. ZJ Zhao, OUHSC OCAST project: HR18-113 Research Area: Cancer Biology

Myelofibrosis is a type of blood cancer affecting the bone marrow	There is no effective treatment for myelofibrosis	Patients with myelofibrosis have a median survival of 5 years
Animal models of human diseases are very useful	For studying molecular and cellular mechanisms	For identifying and testing therapeutic drugs

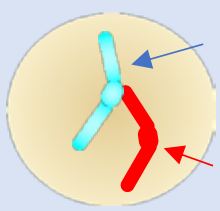
We developed a transgenic mouse model of myelofibrosis and used it to identify potential drugs

Mouse model of myelofibrosis

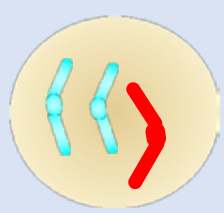
Understanding the machine that distributes chromosomes when cells divide

Orienting Chromosomes on the Meiotic Spindle

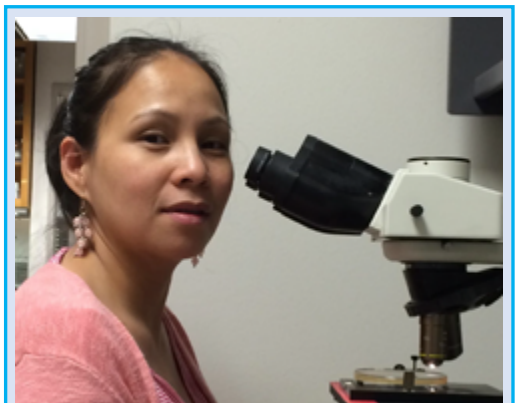
PI: Dean Dawson, OMRF. OCAST Project: HR17-115-1. Research Area: Cell/Molecular Biology



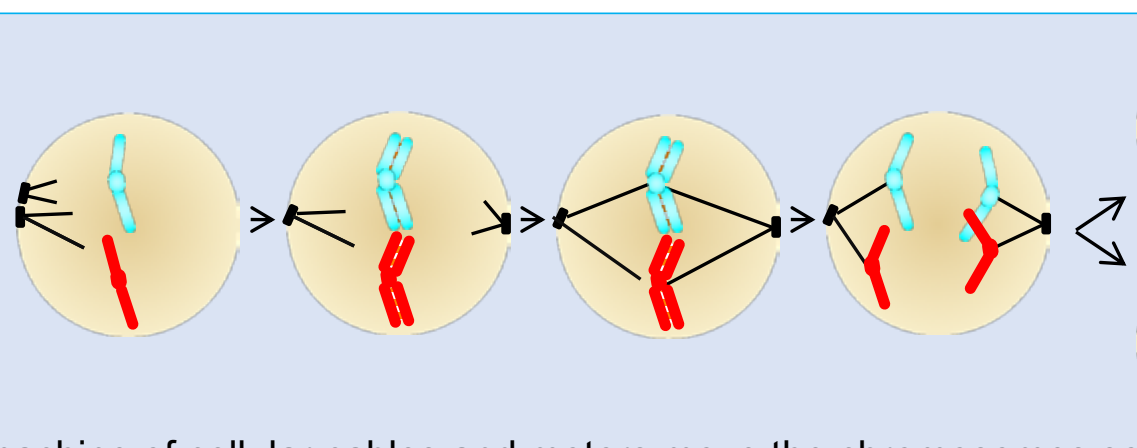
Our genes are arranged on 23 chromosomes. We inherit a copy of each chromosome from each of our parents.



Cells with incorrect numbers of chromosomes are associated with cancer and birth defects.

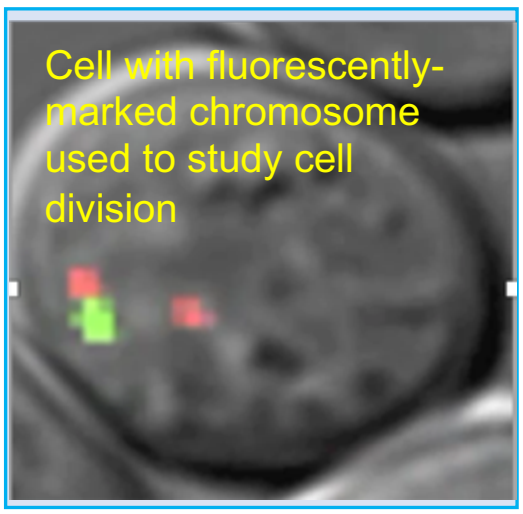


Hoa Chuong a research technician in our lab evaluates cells in the microscope.



A machine of cellular cables and motors move the chromosomes so that when cells divide so that each new daughter cell gets the exact correct chromosome number.

Our research is focus on learning: **how does this machine move chromosomes with such accuracy** and **why does it sometimes makes mistakes?**



Recent accomplishments:

- We developed a new assay to monitor the sliding of chromosomes along cellular cables (called microtubules.
- We found discovered that a controller of cell division affects shortening of the cables as they pull chromosomes.
- Data from our OCAST project were used to procure a grant from the National Science Foundation to continue this project

Understanding the Glue between Cells; Sugar/Protein Connections

Tetherable Glycosaminoglycan Polymers for Insights into Matrix/Cell/Protein Interactions

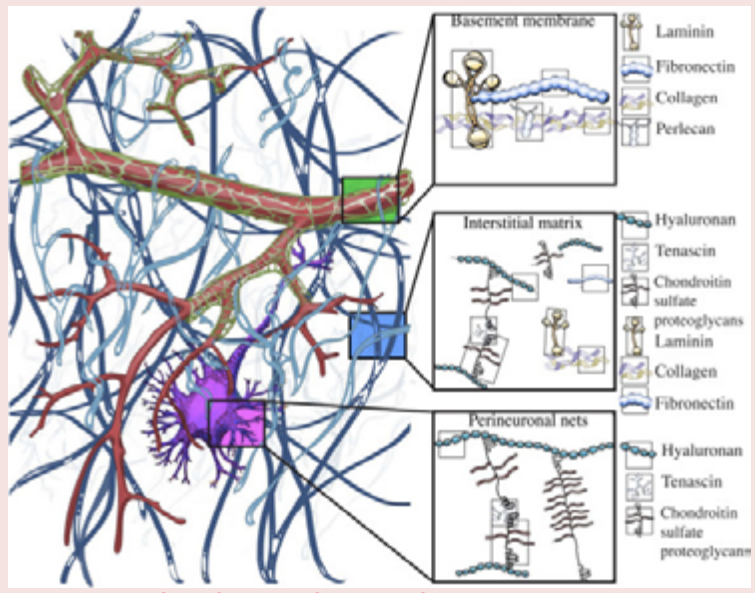
PI: **Paul DeAngelis, OUHSC, Dept. of Biochem. & Mol. Biol.** **OCAST Project HR18-104** Area: **Biochemistry**

Project Highlights

How do you make multicellular life?
Use a 'glue' of sugar polymers and their protein-binding partners to stick various cell types together.

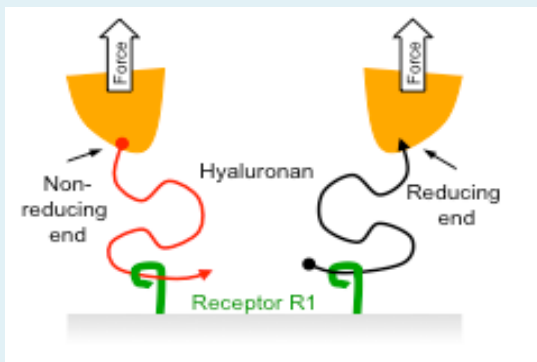
Why study? The 'glue' is critical for health and disease: from normal development of the body's organs, to spreading metastatic cancer cells, or to white cells homing to lymph nodes to fight infections.

How to 'see'? We use custom-made sugar polymers with handles to 'pull' on the sugar while being bound by various proteins. Single molecule atomic force spectroscopy allows us to watch a single interaction so we can obtain an accurate molecular view.



Tissues are glued together with various proteins & sugars.
(schematic: *Matrix Biology* 2018 Vol 71–72 p.432-442)

Measuring the mechanical stability of sugar-protein bonds of the 'glue'.
Customized polymer constructs can be selectively grabbed at either end, and pulled with a probe tip (***orange***). The force and bond breakage are measured for various pairs of sugars (***red*** or ***black***) & proteins (***receptor***).



Recent Accomplishments

- The **directionality** of the sugar chain is important for binding.
- **Sliding** of sugar chains through certain binding protein pockets allows motion.
- **Sugar/protein interactions may behave similarly to some DNA repair and binding proteins, but could use different mechanisms, too.**

Thyroid hormone and cone photoreceptor death

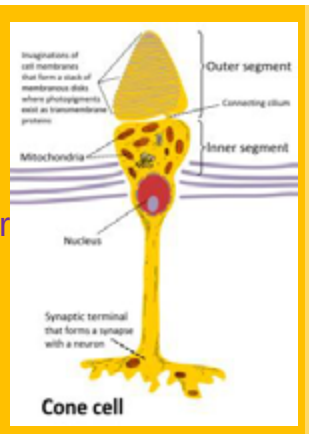
Exploration of the mechanisms underlying thyroid hormone signaling-induced cone photoreceptor degeneration

PI: Xi-Qin Ding, University of Oklahoma Health Sciences Center

OCAST Project: HR20-045

Research Area: Cell/Molecular Biology

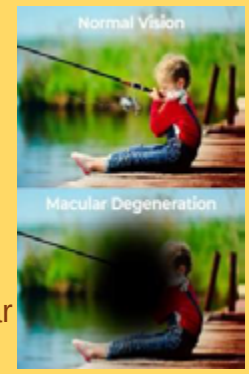
The light-sensing cone photoreceptor cells are responsible for day-light vision, visual acuity, and color vision



https://upload.wikimedia.org

Photoreceptor degeneration affects millions of people around the world

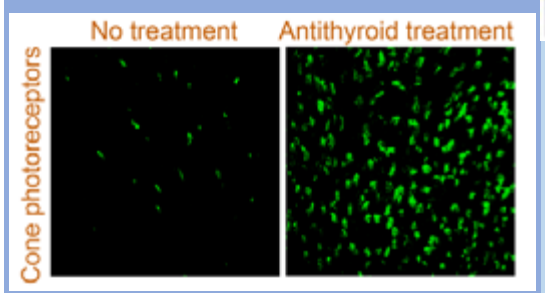
The vision of a patient with macular degeneration

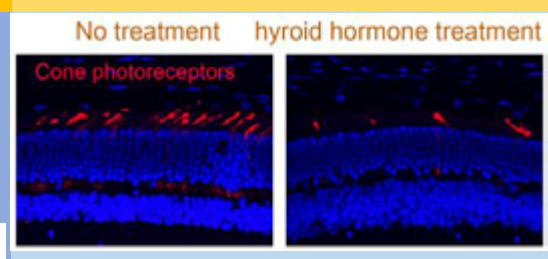


https://www.changeyegroup.com/macular-degeneration/

Thyroid hormone regulates cell growth and metabolism and has been associated with age-related macular degeneration

Inhibition of thyroid hormone production protects cones in a mouse model of retinal degeneration





Excessive thyroid hormone activity induces cone photoreceptor death in a mouse model of retinal degeneration

Our research will focus on understanding how excessive thyroid hormone activity kills cone photoreceptors

- We will determine the cell stress responses to excessive thyroid hormone activity
- We will identify the death pathways contributing to cone death

The benefits:

- Target thyroid hormone to prolong cone photoreceptor survival
- Improve life quality
- Reduce healthcare cost

Recent accomplishments:

- Study retinal/cone photoreceptor structure using light and fluorescent microscopes
- Study retinal and cone photoreceptor function using electrophysiological recordings

How Blood Vessels Regress

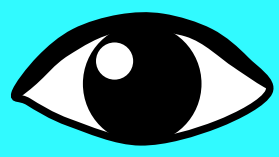
Investigation of the role of hypoxia in initiating hyaloid vessel regression

PI:
Courtney Griffin, OMRF

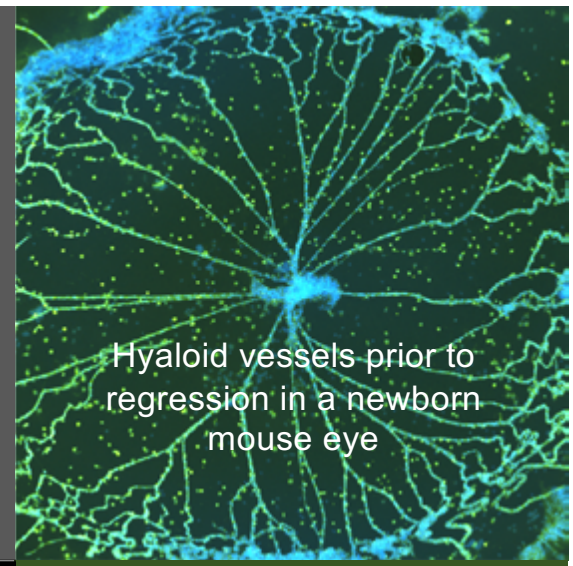
OCAST Project:
HF18-014-1

Research Area:
Cell/Molecular Biology

Blood vessel overgrowth in the eye can cause ***blindness***

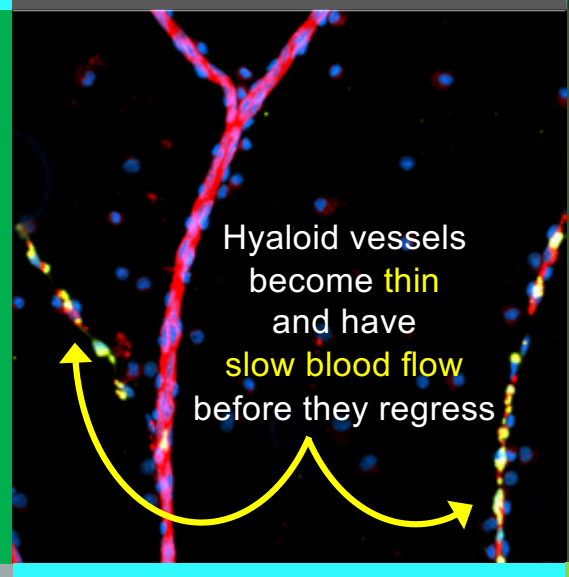


We studied unique vessels called ***hyaloids*** in the mouse eye that naturally regress after birth



Hyaloid vessels prior to regression in a newborn mouse eye

Our ***goal*** was to understand how hyaloids regress so we could trigger regression of overgrown vessels in diseased eyes



We found a family of proteins that **disappeared** in hyaloids immediately before they regressed

This OCAST Postdoctoral Fellowship supported the research of Dr. Chris Schafer

Findings

Using a drug that inhibits the same family of proteins, we caused overgrown vessels with slow blood flow to **regress** in diseased mouse eyes

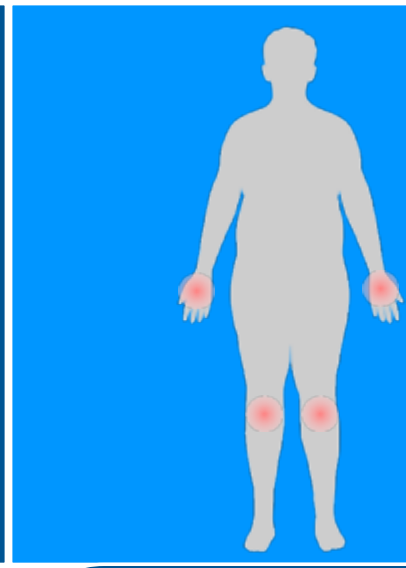
Our research has important ***implications*** for the treatment of patients with *retinopathies*

A new metabolic link between obesity and osteoarthritis (OA)

Role of diabetes-induced lysine malonylation in chondrocyte metabolism and osteoarthritis

PI: Timothy M Griffin, Oklahoma Medical Research Foundation OCAST Project: HF18-022 Physiology/Pharmacology

Obesity increases knee OA *and* hand OA

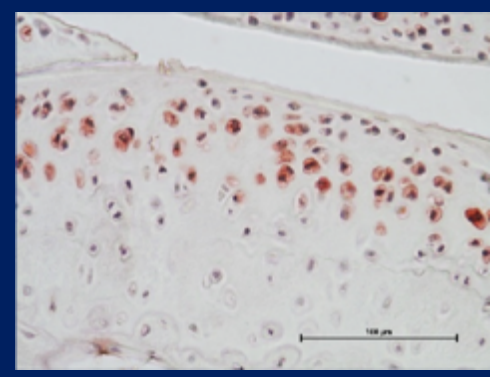


Mechanics alone do not explain the obesity-OA link

2 out of 3 people with OA also have Metabolic Syndrome

Our research tests a new theory of cell metabolic damage called "**carbon stress**", which describes how over-nutrition causes metabolic byproducts to accumulate in cells, bind to proteins, and damage cell function

Image of this byproduct, malonyl-lysine, in cartilage cells of diabetic mice



Post-doctoral awardee: Dr. Shouan Zhu

We discovered that the enzyme that removes the malonyl-lysine byproduct is produced at lower levels in OA cartilage

Accomplishments:

- Dr. Zhu obtained a tenure-track Assistant Professor faculty position in the Ohio University Musculoskeletal and Neurological Institute
- We presented findings at the Annual Meeting of the Orthopaedic Research Society
- Manuscript describing results is currently under review

A mother's adverse nutritional status during pregnancy impacts her child's lifelong risk of metabolic diseases

Fetal epigenetic programming of mitochondrial biogenesis in diabetes during pregnancy: the role of AMPK and microRNA-130b

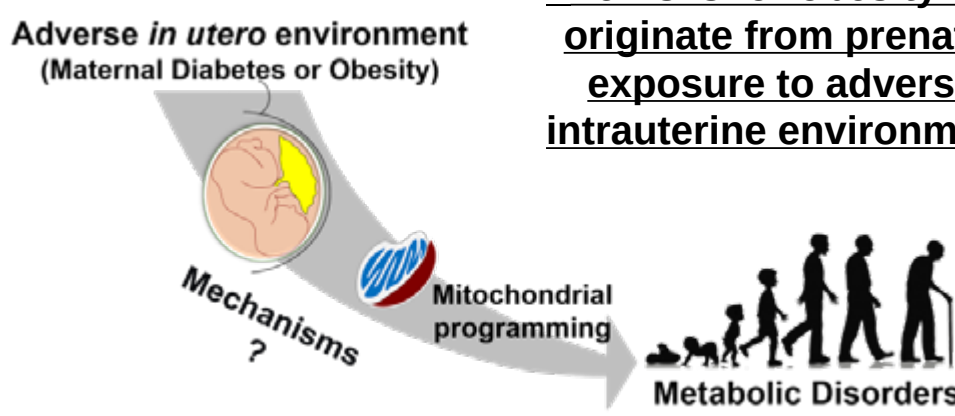
PI: Shaoning Jiang, OUHSC **OCAST Project: HR19-133** **Research Area: Molecular Biology**

Obesity facts

- Obesity is a serious global health problem that increases the risk of diabetes, cardiovascular diseases, non-alcoholic fatty liver diseases, and certain cancer
- More than 35% of adults had obesity in Oklahoma

CDC data 2019

The risks for obesity can originate from prenatal exposure to adverse intrauterine environment



How the environment in the womb "programs" the baby to develop diseases later remain unclear

Goal of current work

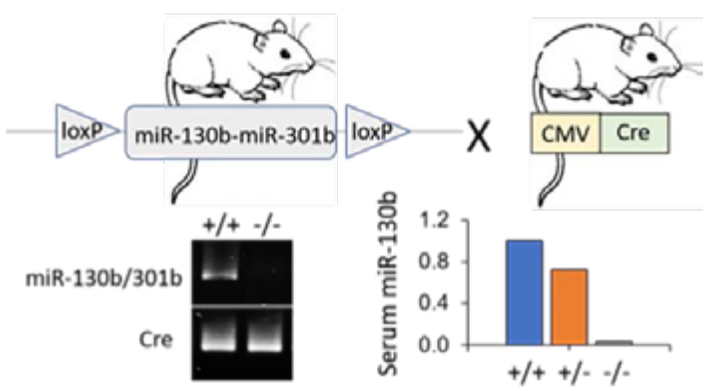
The proposed work will investigate the roles of a particular microRNA family called miR-130b/301b, focusing on the roles in fat development and energy expenditure regulation

miR-130b/301b

- miR-130b/301b was identified by unbiased screening to be linked to human metabolic diseases
- In animal models, miR-130b/301b was increased by feeding pregnant mice with high fat diet
- Can be used as diagnostic marker and therapeutic target

Approaches

- Genetic deletion of miR-130b/301b in mice as animal model
- Human primary cells from pregnant women will be studied



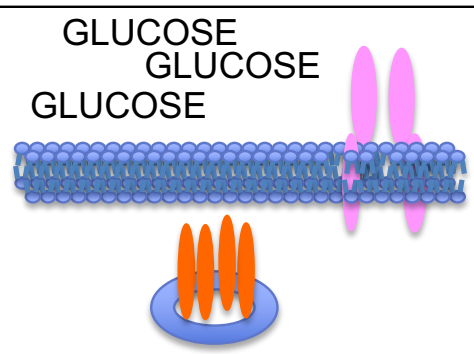
Significance

- Discovered a new role of miR-130b/301b in suppressing brown fat development and energy balance
- miR-130b/301b can be a therapeutic target against obesity
- The studies will lead to better understanding potential molecular mechanisms underlying the long-lasting outcomes in offspring of mothers with obesity or diabetes

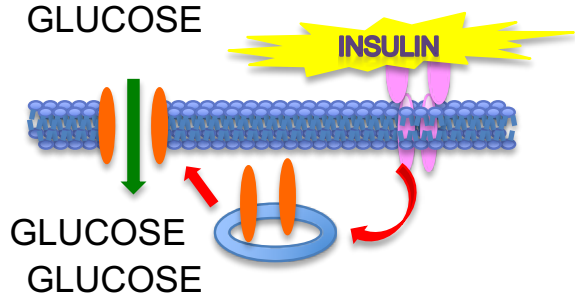
Increasing glucose uptake into skeletal muscle and adipose tissue can prevent type 2 diabetes

Mechanisms regulating GLUT4 expression in obesity

PI: Ann Louise Olson, OUHSC **OCAST Project: HR17-018** **Research Area: Cell/Molecular Biology**



Blood glucose enters cells when GLUT4 proteins (orange) move from inside the cell to the surface.

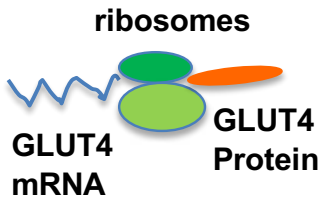


The amount of glucose that enters the cell increases with more GLUT4 proteins.

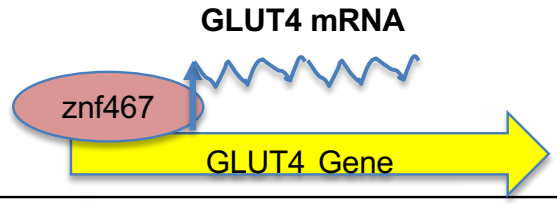
With diabetes, it takes more insulin than normal to move GLUT4 to the surface. If we make more GLUT4 in the cells, we can help insulin do its work.

Our goal is to help cells make more GLUT4

We use a special screening tool to find a protein that will specifically help the cell make more GLUT4 protein by increasing the GLUT4 messenger RNA that is used by ribosomes to synthesize protein.



The protein that we discovered is called znf467. This protein works in the nucleus to help the gene that codes for GLUT4 to be transcribed into GLUT4 mRNA that is then used for the protein synthesis by the ribosome



Ann L Olson, PhD
Professor of Biochemistry & Molecular Biology
College of Medicine

Role of an inflammatory cell death pathway in age-associated inflammation

Testing the Role of Inflammation in Aging and Age-related Diseases

PI: Deepa Sathyaseelan, OUHSC **OCAST Project Number: HR18-053** **Research Area: Physiology/Pharmacology**

Chronic inflammation termed sterile inflammation or inflammaging (inflammation in the absence of detectable pathogens) is a common feature of aging and age-associated diseases.

Our research will focus on understanding whether inflammaging is causing aging and age-associated diseases, and pathway(s) that mediate inflammaging are not known

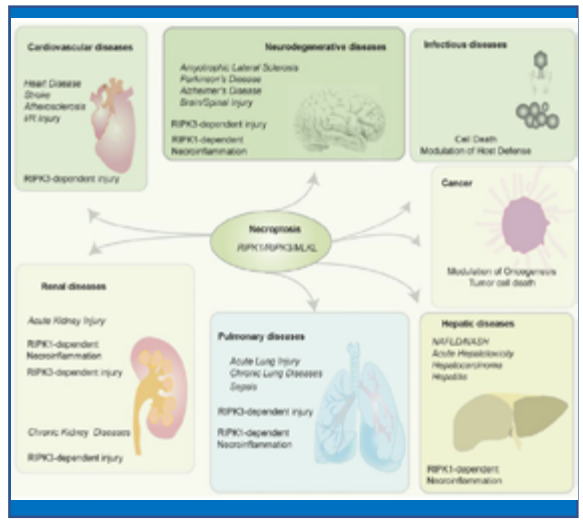
'Necroptosis' is a newly identified form of cell death that causes inflammation, however, role of necroptosis in inflammaging is unexplored.

The study will help us to identify whether necroptosis is a key pathway in inflammaging.

The study could be translationally important because pharmacological agents that inhibit necroptosis are available.

Recent accomplishments:

- Blocking necroptosis in *Sod1 KO* mice using necroptosis inhibitor, Necrostatitin-1s, reduced necroptosis and markers of fibrosis markers in the liver of *Sod1KO* mice.
- Blocking necroptosis reduced liver tumor incidence in a mouse model of diet-induced liver cancer.



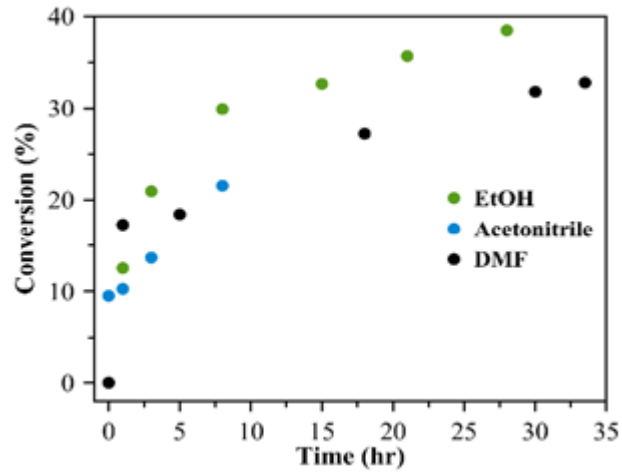
Development of novel nanocatalysts can lead to environmentally friendly and cost-effective processes to produce pharmaceuticals

Copper Nanocatalyst as Efficient Heterogeneous Photocatalyst for Continuous Syntheses of Pharmaceuticals through Cross-Coupling Reactions

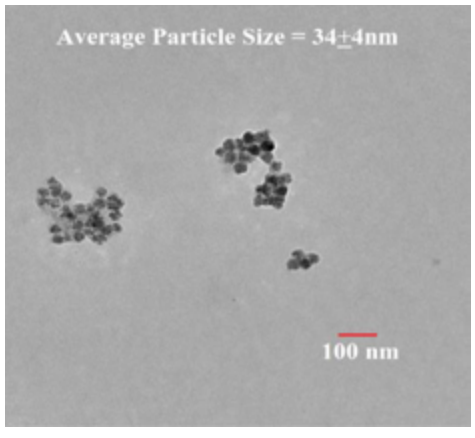
Dr. Marimuthu Andiappan, Oklahoma State University OCAST Project: HR18-093 Research Area: Chemistry & Biochemistry

Highlights

Carbon-Carbon (C-C) coupling reactions are widely used reactions in the pharmaceutical industry. These reactions are conventionally performed using expensive and toxic palladium (Pd) catalysts and hazardous solvents such as dimethylformamide (DMF). The objectives of this project include the development of inexpensive and less-toxic nanocatalysts that can perform C-C couplings in green solvents.



The performance of Cu_2O nanoparticles-catalyst in green solvents (i.e., EtOH and Acetonitrile) compared to the conventional hazardous DMF solvent.



Transmission electron miscroscopic image of Cu_2O nanoparticles.

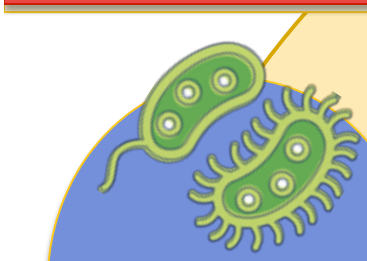
Recent Accomplishments

- We developed inexpensive and comparatively less toxic cuprous oxide (Cu_2O) nanoparticles as a catalyst to perform C-C coupling reactions in green solvents such as ethanol (EtOH) and acetonitrile.
- Inexpensive and less-toxic Cu_2O nanocatalyst and green solvents (EtOH and acetonitrile) can be potentially used as replacements for conventional expensive and toxic Pd catalysts and hazardous DMF solvent.
- The findings can be potentially used to develop new pharmaceuticals manufacturing processes. These new processes can exhibit a number of benefits, including (i) reduced manufacturing cost, (ii) improved drug product quality, and (iii) reduced waste generation compared to the conventional processes using Pd catalyst and DMF solvent.

A new approach to antibacterials: activating bacterial timebombs

Targeting bacterial cell metabolism by manipulating toxin-antitoxin systems

PI: Christina Bourne, OU Dept. of Chem and Biochem OCAST Project: HR17-099 Research Area: Infectious Disease



Annually in the US, AMR causes > 2 mill infections 23,000 deaths (2019, CDC)

Need:

Expanded treatment options to address growing burden of antibacterial resistance

Approach:

Activate endogenous bacterial toxins

Sustained activation will promote "self killing" of bacteria

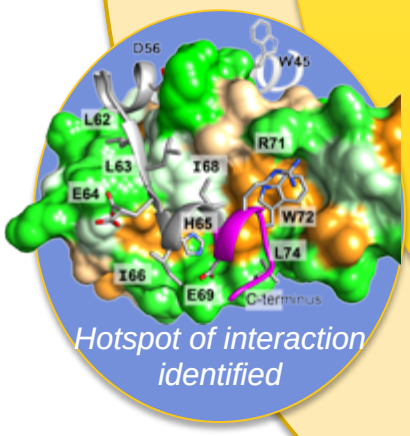
Grad student Kevin Snead working on experiments

Recent Advances

→ Identified where to target to weaken this tight (picomolar) interaction

→ Demonstrated this increases antitoxin removal

→ Highlights how to manipulate this TA system from *P. aeruginosa*



Hotspot of interaction identified

New Knowledge:

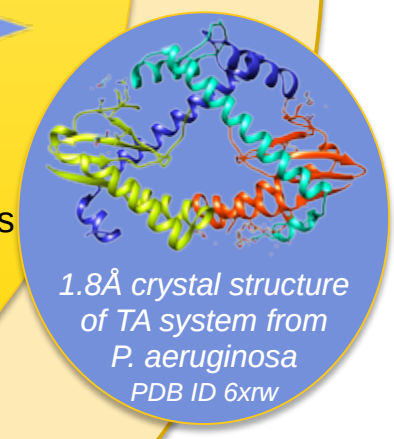
How to manipulate protein interactions

→ promote ParE toxin inhibition of DNA gyrase

Toxin-Antitoxin systems:

Pre-existing in bacterial pathogens

A toxin protein neutralized by binding to an immunity protein

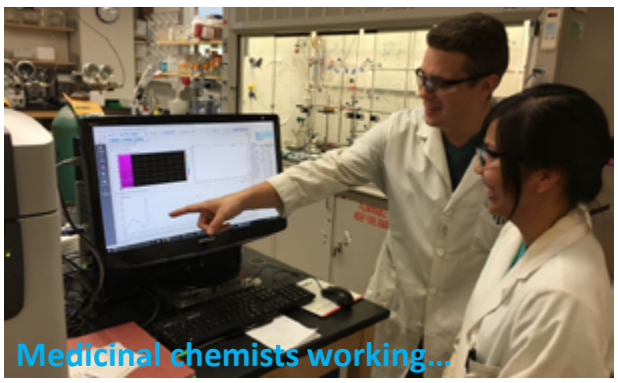


1.8Å crystal structure of TA system from P. aeruginosa
PDB ID 6xrw

Making New Anti-Cancer Drugs That Only Target the Cancer Cells

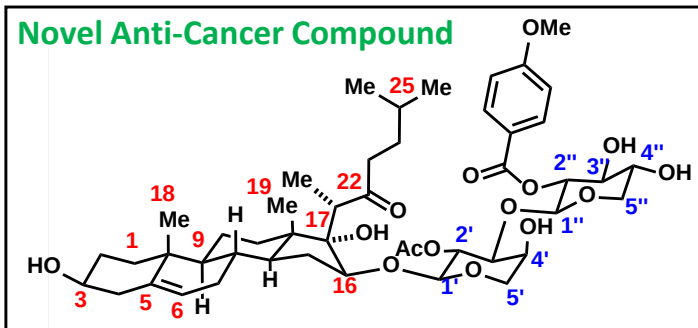
Synthesis and Drug Development of ORP4 Protein Inhibitors: A New Route to Precision Anti-Cancer Therapeutics

PI: Anthony Burgett, University of Oklahoma **OCAST Project: HR17-116** **Research Area: Chemistry and Biochemistry**



Chemical Synthesis

Novel Anti-Cancer Compound

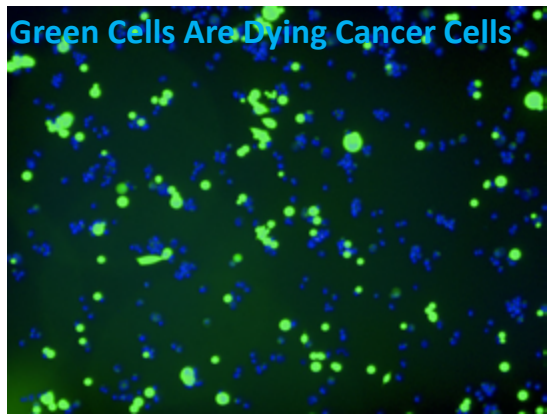


Molecular Drawing of the Anti-Cancer Compound OSW-1

Compound Targets Novel Cancer Specific Protein

ORP4

Cancer Cells Killed by Compound Treatment



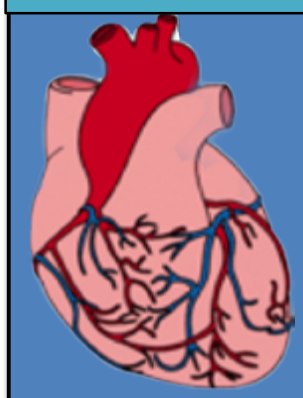
Potential New, Cancer-Specific Therapeutic?

Diabetes causes heart proteins to be abnormally modified

A Novel Mechanism of Diabetic Cardiomyopathy

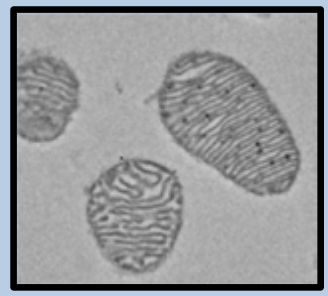
PI: Kenneth Humphries, OMRF ***OCAST Project:*** **HR17-094** **Research Area: Physiology**

Diabetes is a significant health concern in Oklahoma



Diabetes promotes heart disease

We are studying how diabetes affects the heart



Electron microscope image of mitochondria from heart cells

Our research focuses on mitochondria -

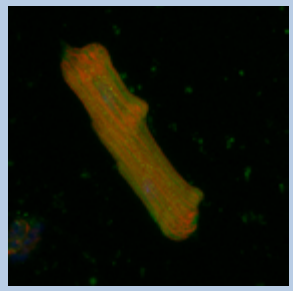
The powerhouse of the cell

We visualize heart cells from

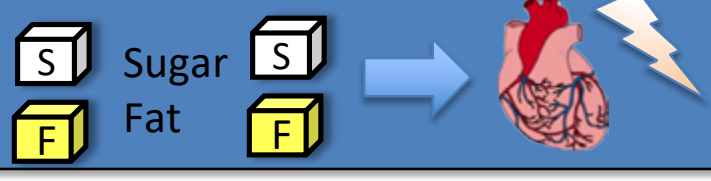
healthy

healthy and diabetic mice

diabetic



…and we determine how diabetes affects the cells ability to produce energy from different nutrients like sugar and fats.



Dr. Kenneth Humphries, head of the research project

RECENT ACCOMPLISHMENTS

Generation of a new mouse model that is helping us understand how diabetes affects mitochondria

Submission of a grant to NIH

New method to determine how diabetes affects mitochondrial proteins

Using Visible-Light Activation to Develop New Tools for Drug Discovery and Production

Late-Stage C-N Incorporation to Bioactive Cores

PI: Angus A. Lamar,
The University of Tulsa

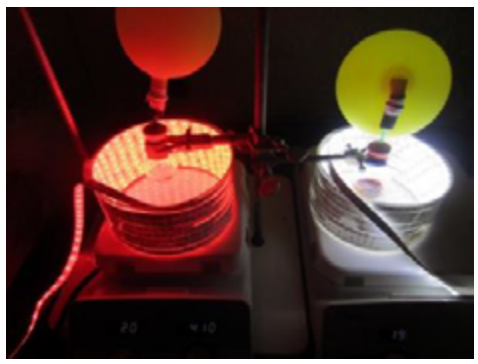
OCAST Project: HR18-013

Research Area: Chemistry and Biochemistry

Nitrogen is an important element found in small-molecule pharmaceuticals.

Most drugs are produced using strategies that install nitrogen functionalities during the **early stages** of the drug synthesis. However, those approaches can add challenges regarding reactions that occur later in the synthetic path.

Product isolation by column chromatography



On the left: A red LED photochamber
On the right: A white LED photochamber

Our research aims to **develop new chemical reactions** to install nitrogen functionality into complex molecules at **late stages** in the synthesis of a drug.

We use non-metal promoted, visible-light activated approaches for nitrogen installation that features a unique reactive species. This unique species has **provided new points of entry for installing nitrogen functionalities at sites that were previously inaccessible.**

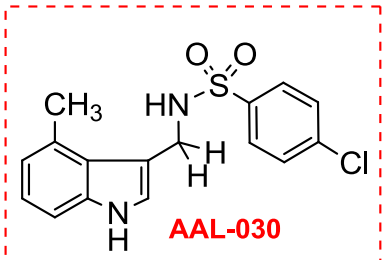
Lamar Research Group - 2018

Benefits

New organic reactions to use in the synthesis of drug molecules

New molecules with anticancer and/or antibacterial properties

New approaches to screen for bioactivity



AAL-030

Two-step (one pot) synthesis from commercially available reagents

Recent Accomplishments:

6 publications since 2018 (plus 1 currently in review)

- Lamar et al., *Molecules* **2018**, *23* (8), 1838.
- Lamar et al., *ACS Omega*, **2018**, *3*, 12868.
- Lamar et al., *Organic Letters*, **2019**, *21*, 4229.
- Lamar et al., *Tetrahedron*, **2019**, *75*, 130498.
- Lamar et al., *Org. & Biomolec. Chem.*, **2019**, *17*, 8391.
- Lamar et al., *ACS Omega*, **2020**, *5*, 7693.

1 patent filed in 2020

- Synthesis and Use of N-Benzyl Sulfonamides

Synthesis of a library of >100 new sulfonamide analogs as potential drug compounds

IC_{50} (μM)

Compound	Cell Type H293	HeLa	NCI-H196
AAL-030	**47.8**	**53.5**	**43.5**
ABT-751	209.1	117.5	139.7
Indisulam	229.1	100.6	155.8

AAL-030 exhibits higher anticancer activity than ABT-751 and Indisulam, which are well-known anticancer agents

A Single, Conserved, Helix Improves Gene Editing Fidelity of Multiple Cas Enzymes

Protein engineering to develop stringent CRISPR-Cas genome tools

PI: Rakhi Rajan, University of Oklahoma

OCAST project: HR20-103

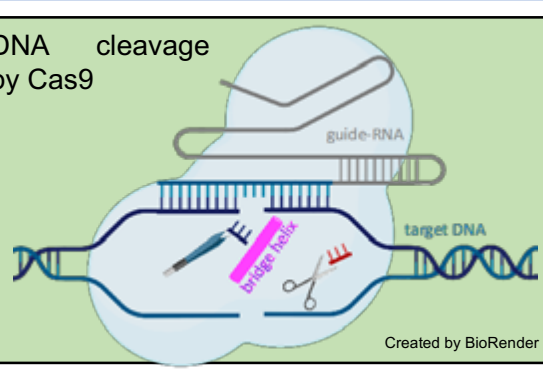
Research area: Chemistry and Biochemistry

CRISPR-Cas system is a bacterial adaptive immune system.

HOW?

It inserts a small piece of the intruder DNA into the bacterial genome, to create memory of past infections. The inserted DNA creates "guide-RNA" that helps Cas proteins to cleave intruder DNA.

DNA cleavage by Cas9



CRISPR-Cas has biomedical relevance.

WHY?

RNA-guided, DNA cleavage mechanism has been repurposed into powerful gene editing tools and is being pursued for gene therapy applications. Cas9 won the Nobel Prize in 2020 due to these potentials.

CRISPR-Cas has undesirable effects.

PROBLEMS

Cas proteins can cleave target DNAs that are not completely matching the guide-RNA, causing debilitating "off target effects" during gene editing applications.

Undesirable effects can be removed.

GOAL

Create stringent Cas protein variants with reduced off-targeting, by modulating the interactions of a highly conserved bridge helix with RNA and DNA

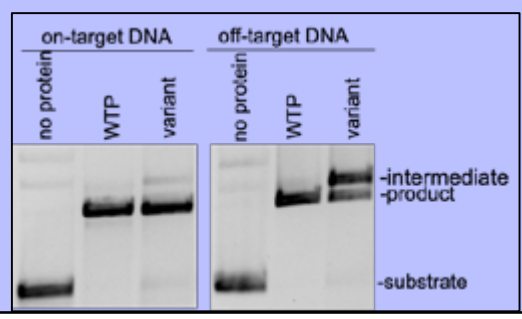
METHODS

- Focused on mutating bridge helices of Cas9 and Cas12a, two proteins commonly used for gene editing applications
- Different positions along the helix will be tested to locate the best protein constructs for gene editing

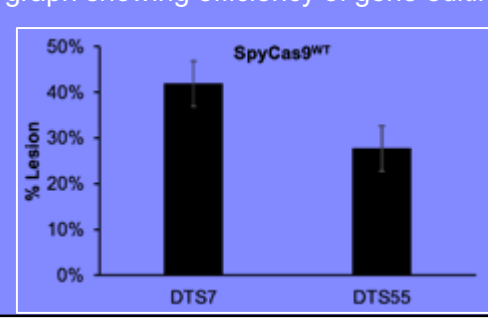
ACCOMPLISHMENTS

- Created protein variants with reduced off-target DNA cleavage, while maintaining comparable on-target DNA cleavage
- Cell-based gene editing experiments were setup to test these variants efficiency in editing diverse genes

A gel showing DNA cleavage selectivity



A graph showing efficiency of gene editing



Towards the Design of New Neuro- and Cardio-Protective Drugs

Rational Development of Selective and Potent Inhibitors to Pro-apoptotic Bax Protein

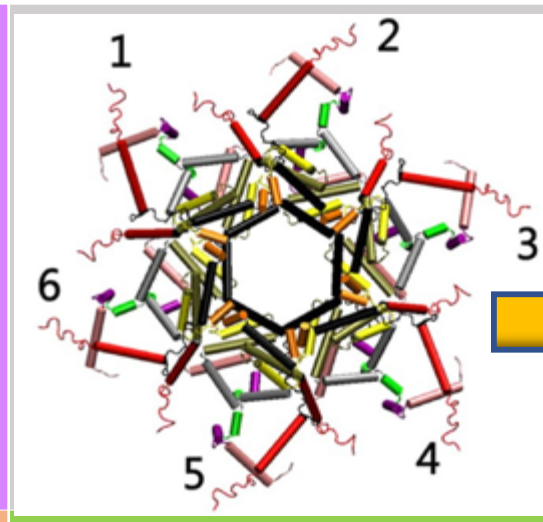
Yihan Shao, University of Oklahoma HR18-130 Chemistry and Biochemistry / Computational Biology

Bax proteins

form holes

on mitochondria

outer membranes



Cell Death

rapid

neuron death

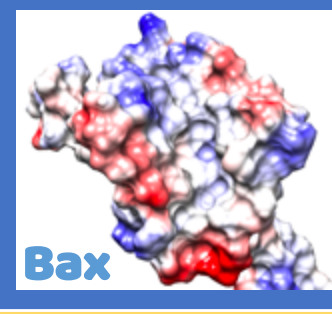
Bax inhibition

promises to slow

down unwanted

cell deaths

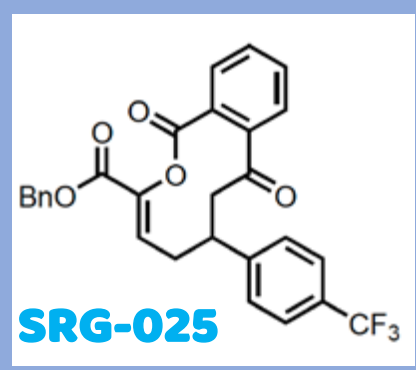
Target Protein Binding Pocket



Design of Potent Ligands

Computer Modeling + Organic Synthesis + Biological Testing

Lead Compounds



SRG-025

Lead Optimization

Analogs of SRG-025 and other lead compounds are being synthesized and tested.

Deadly diarrhea: Identifying the genetic regulatory networks

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

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

C. difficile uses sensor kinase and response regulator proteins to surveil its surroundings and adapt to the host environment

We study these proteins to understand how *C. difficile* responds to nutrient availability, adjusts its lifestyle and initiates spore formation

C. difficile Infection (CDI)

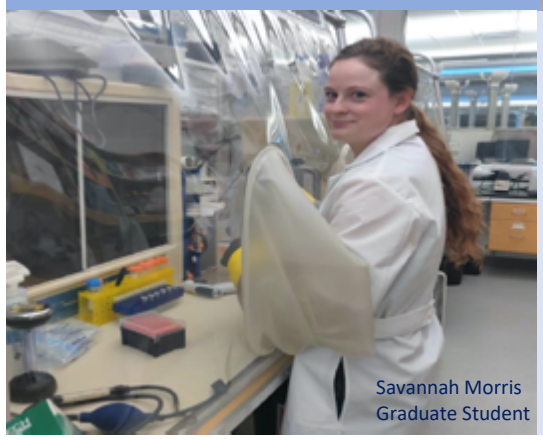
Each year in the US, CDI causes:
500,000 illnesses

1 in 11 adults age 65+ die of CDI within 1 month

~1 in 6 have recurrence in 2-8 weeks

Research Impact:

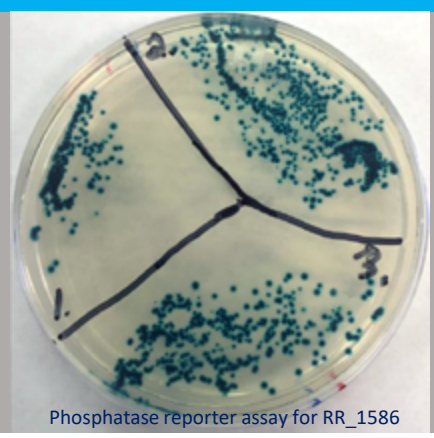
These proteins are potential targets for development of new antibiotics that will decrease the risk of recurrent CDIs



Savannah Morris
Graduate Student

Recent Accomplishments:

- Created a strain of *C. difficile* with an RR_1586 homolog gene deletion
- Obtained quantitative binding data for RR_1586 to target genes
- Examined growth of *C. difficile* under various nutrient limitation conditions
- Determined crystal structure of RR_1586



Phosphatase reporter assay for RR_1586

Decreased food intake can change the genome function that can lead to beneficial effects

Role of DNA methylation in Dietary Restriction mediated Cellular Memory

Archana Unnikrishnan, University of Oklahoma

OCAST Project: HR17-098

Research Area: Genomics & Gene Expression

Project Highlights

- **Food restriction referred as Dietary Restriction (DR) retards aging and extends lifespan.**
- **DR could impart beneficial effects through DNA methylation a genetic modification that regulates gene expression and is critical during development and aging.**
- **The purpose of this project is to determine the effect of dietary restriction on DNA methylation in the intestinal cells.**
- **If we can show that a short period of DR is sufficient to impart life-long beneficial effects, this would be an important discovery because short-term DR would be a more compliant approach translationally than the rigorous life-long regimen.**

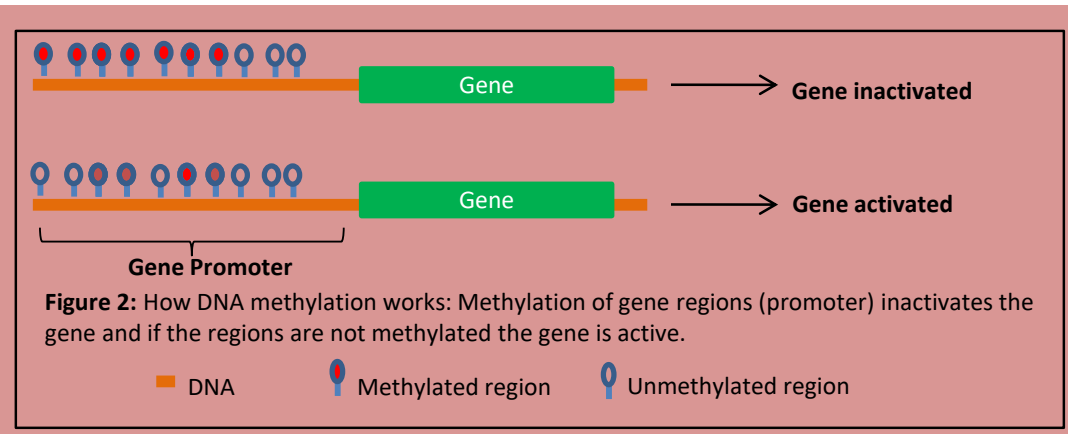
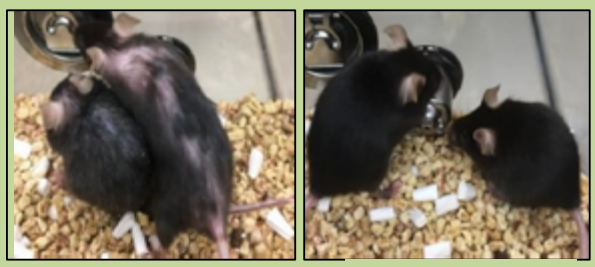


Figure 2: How DNA methylation works: Methylation of gene regions (promoter) inactivates the gene and if the regions are not methylated the gene is active.



Control **Dietary Restricted**

Figure 1: 24 month old C57BL/6 mice fed either *ad libitum* (control) or life-long dietary restricted diet throughout life.

Recent Findings

- **Short-term DR alters DNA methylation levels and gene expression in the intestine.**
- **DR increases intestinal stem cell numbers**
- **Short-term DR enhances intestinal stem cell function.**

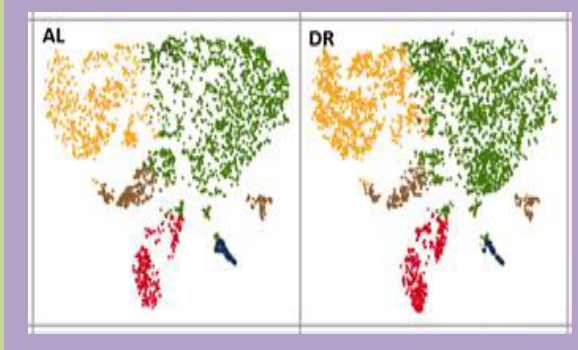


Figure 3: Different Cell types of the intestine from 24 months old mice fed ad libitum or life-long DR diet, analyzed using single cell gene expression analysis. DR increases stem cell numbers. Green- Stem cells, Red-Paneth Cells, Brown-Goblet cells, Orange- Enterocytes, Purple – Fat cells.

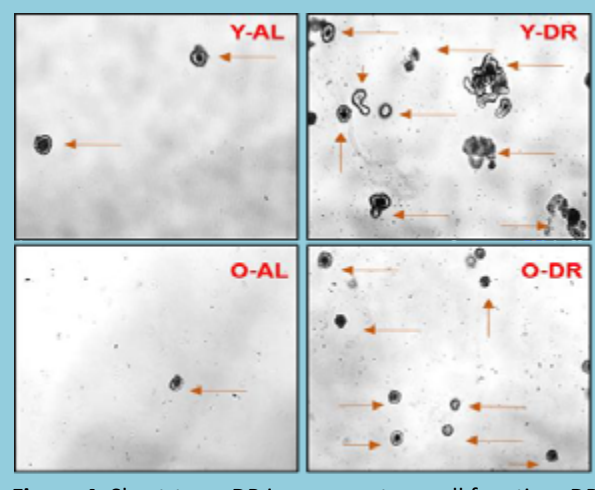


Figure 4: Short-term DR increases stem cell function. DR increased intestine regeneration in culture from stem cells obtained from young (Y) and old (O) AL and DR mice fed DR for 4 months (4X magnification).

An autoimmune pathophysiological and molecular mechanism in Polycystic Ovarian Syndrome

An antibody to a Pituitary Receptor May Induce Ovary Cysts and Infertility 07/01/2017-06/30/2020

PI: Hongliang Li, Department of Medicine, OUHSC OCAST Project: HR17-123

PCOS, a metabolic and reproductive disease, may have a autoimmune etiology

GnRHR-AAb is present as a contributor to the pathophysiology in PCOS subjects

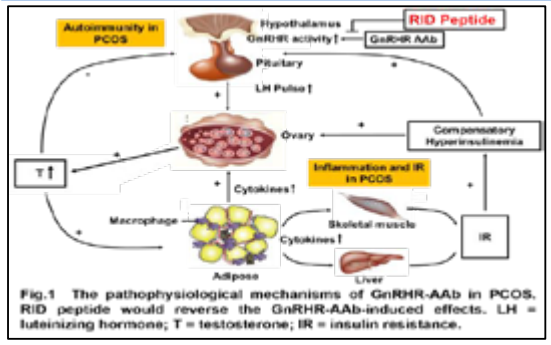


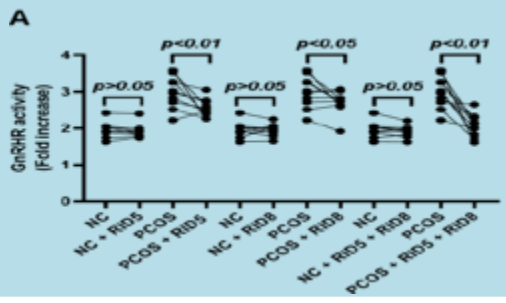
Fig.1 The pathophysiological mechanisms of GnRHR-AAb in PCOS. RID peptide would reverse the GnRHR-AAb-induced effects. LH = luteinizing hormone; T = testosterone; IR = insulin resistance.

GnRHR-AAb enhanced LH pulsatile function, T production, and increased inflammatory cytokines

The RID peptide will prevent the binding of GnRHR-AAb and normalize the HPO axis

Recent accomplishments
Human study
Cell culture
Animal study

Blocking effects of RID peptide



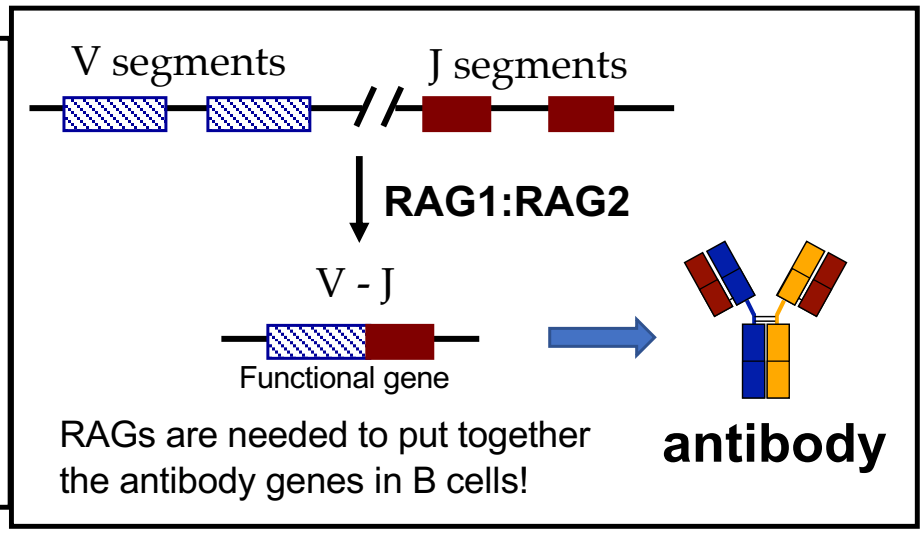
The RID peptide will alleviate several components of the PCOS phenotype

Keeping a check on B and T cell development

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

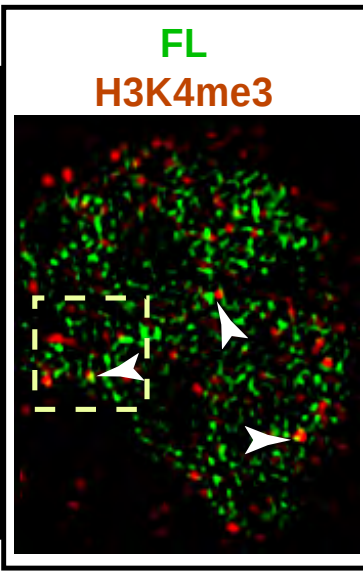
PI: Karla K Rodgers, PhD OCAST Project: HR18-072 Research Area: Immunology

To fight infections our immune system uses a vast repertoire of **antibodies** (made in B cells) and **T cell receptors** (made in T cells). This repertoire is made at the genetic level by the **RAG1** and **RAG2** proteins in a process known as **V(D)J recombination**.



Sometimes mistakes in V(D)J recombination lead to certain types of **leukemias or lymphomas**.

Our research is on how V(D)J recombination is normally regulated, so that mistakes are prevented.

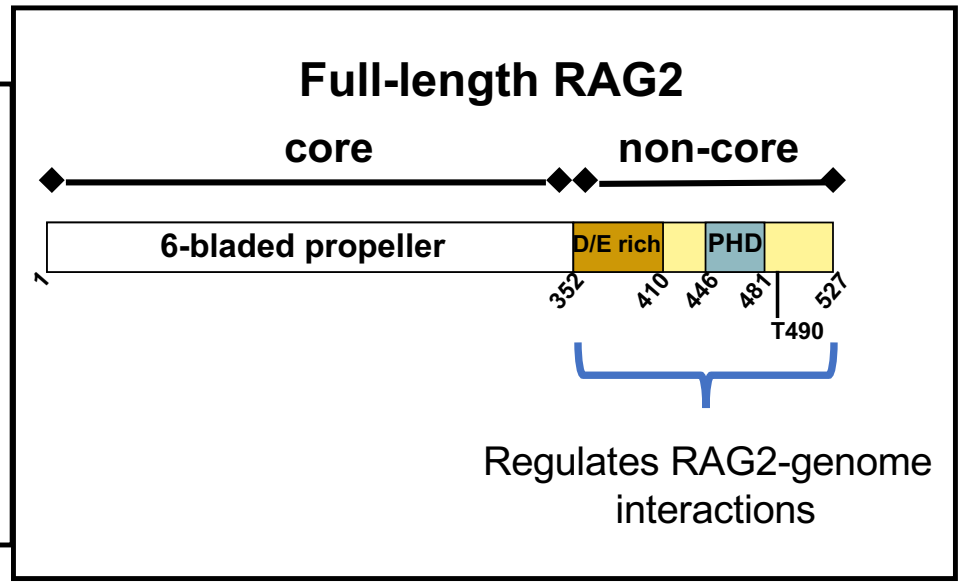


We use **fluorescence microscopy** to visualize RAG2 (FL), labeled with a green probe, in pre-B cells. This image shows one pre-B cell. H3K4me3, labeled with a red probe, is a protein bound to the genome. Arrowheads show examples of co-localization.

Recent Accomplishments:

We have identified specific regions in RAG2 that regulate its interaction with the genome.

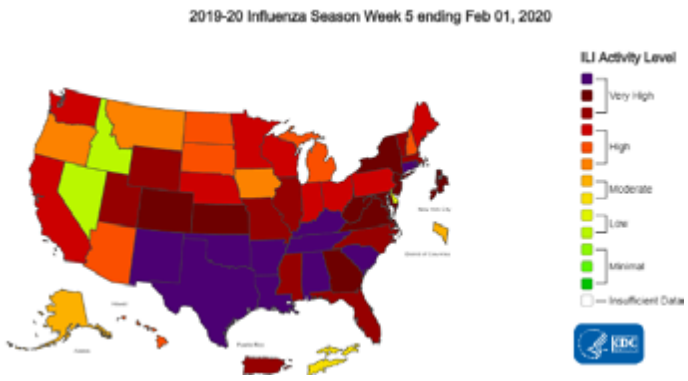
Disruption of this regulatory function results in overactive V(D)J recombination, which can lead to genomic instability.



Suppression of a mitochondrial gene may protect us from seasonal flu

β, β-carotene 9', 10'-oxygenase 2 (BCO2) in acute respiratory distress syndrome

PI: Dingbo Lin, Oklahoma State University **OCAST Project: HR17-114 Research Area: Nutrition**



Seasonal flu

One of the top health concerns worldwide.

People with flu may have a hyperactivation of the immune system.

Lead to fever, chills, shortness of breath, which caused by acute lung inflammation.

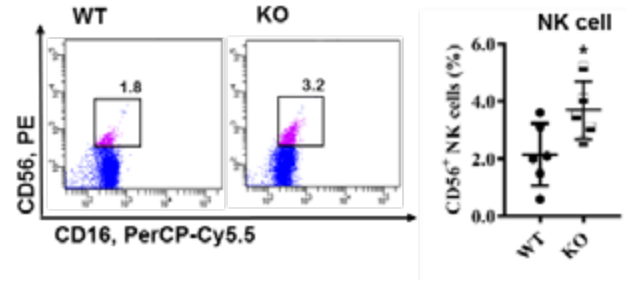
Dietary regulation of the immune responses can be a new way to protect you from the flu.

BCO2

An enzyme that can cleave carotenoids

It is located in the inner membrane of mitochondria.

Lack of this gene led to an accumulation of carotenoids, mitochondrial dysfunction, and low-grade inflammation.



Natural killer cells

Important immune cell that responds to virus infection.

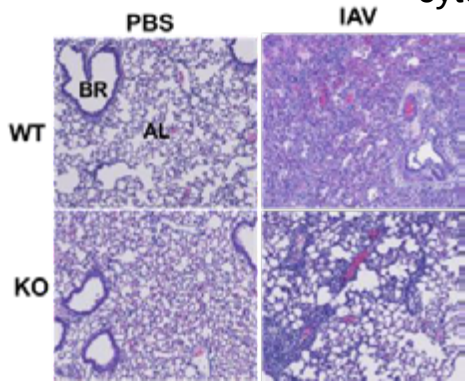
knockout of BCO2 genes leads to natural killer cell population increase.

Inflammatory cytokines

Produced by immune cells during virus infection.

Short time, large quantities of cytokines release will cause organ damage or death.

Knockout of BCO2 genes may weaken the cytokine storm.



Virus replication

Flu virus enter the nucleus and replicate its DNA.

Inhibition of flu virus replication may protect people from flu.

Lack of BCO2 genes may suppress virus replication.

Increases in animal survival rate

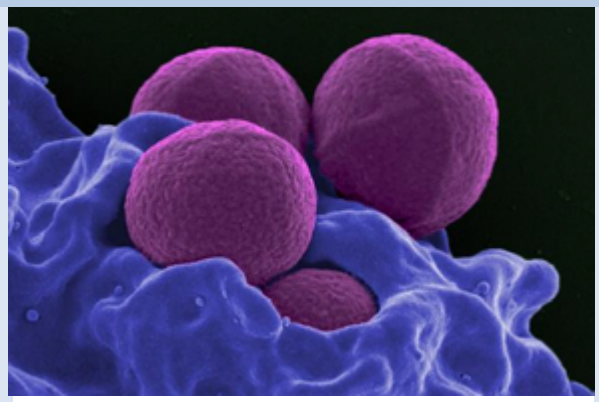
“Superbug” bacteria are growing even stronger, so we are making new drugs to fight back.

The development of daptomycin analogs

PI: Shanteri Singh, University of Oklahoma **OCAST Project: HR19-080** **Research Area: Infectious Disease**

Anyone can get a bacterial infection, but it’s getting harder and harder to cure them.

Resistant bacteria like MRSA and VRSA are becoming *more common*, and they are starting to resist our most powerful drugs.

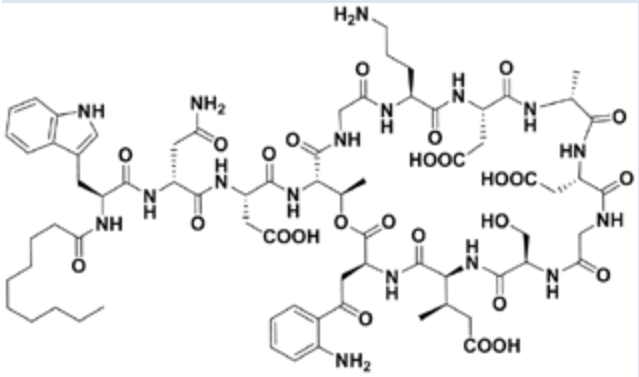


Electron micrograph image of MRSA (courtesy of the National Institute of Allergy and Infectious Diseases.)

Daptomycin (DAP) is one such drug.

We use it as a “drug of last resort”, so it’s saved for only the *nastiest of infections*.

Even so, some bacteria have begun to resist it.



Structure of daptomycin

We want to make DAP more effective against these “superbugs” by *changing its structure*, but we must account for its complex construction.

Using ***enzymes***, we’ve made several versions of DAP with slightly different structures.

We have found that some of these versions can kill the resistant bacteria (almost **80x more effective** than normal daptomycin).

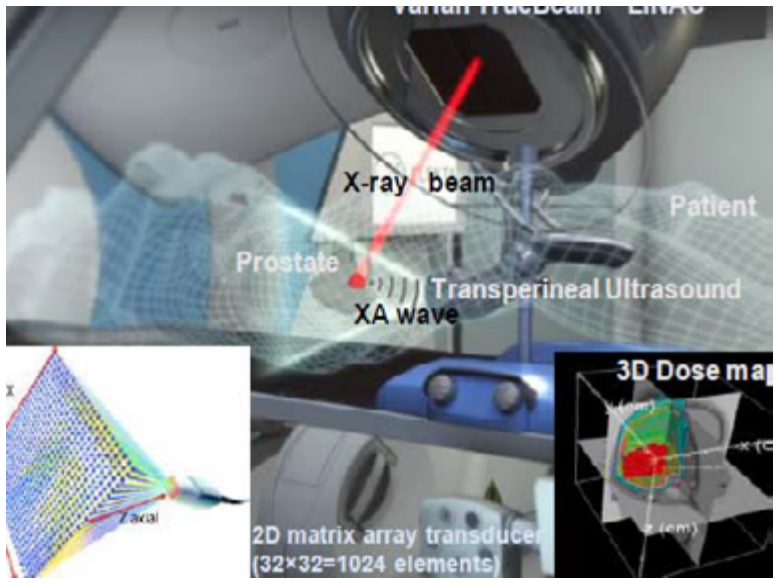
Now, we are trying to make our enzymes *more efficient* at creating the best versions.

With fully optimized enzymes, we can start pushing back against the rising threat of superbugs.

Listening for the Invisible Dose in Cancer Patients X-ray induced ultrasound

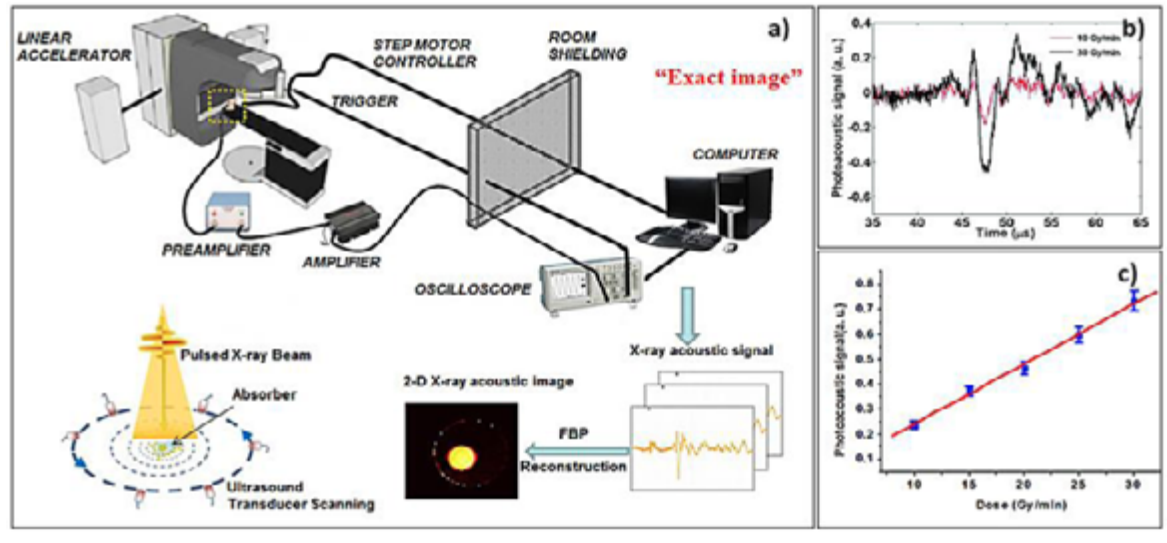
Real-time dosimetry in external beam radiation therapy with X-ray acoustic computed tomography (XACT)

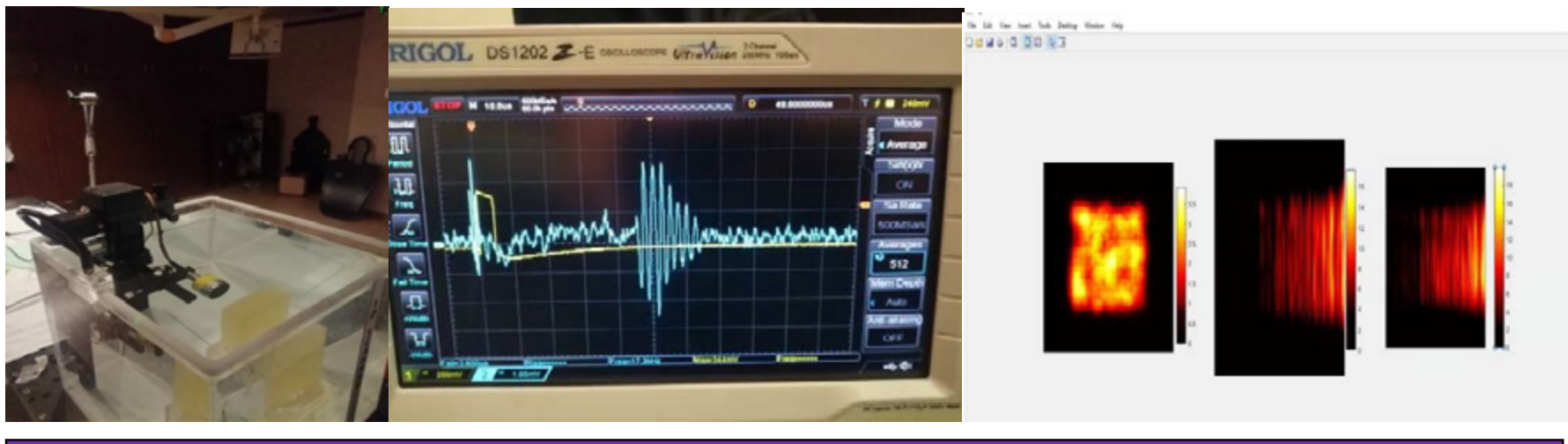
PI: Yong Chen, University of Oklahoma HSC OCAST Project: HR19-313 Research area: Biomedical Engineering



RADIATION DOSIMETRY IS A CRUCIAL PROCESS FOR CANCER PATIENTS UNDER RADIATION THERAPY TO ENSURE THAT THE CORRECT DOSE IS ACCURATELY DELIVERED TO THE DESIRED LOCATION

A schematic of an XACT dosimetry system including in-room detector, signal preamp and amplifier and post data processing software. An example of measured XACT signal vs delivered dose from PI's previous publication





Water phantom measurement shows very promising ultrasound signal and 3D reconstructed dose from 16x16 2D detector array in water for a metal target.

Lead me, follow me and walk with me: analyze your gait motion from a robot

A Mobile Platform for Clinical Gait Analysis

PI: Guoliang Fan, Oklahoma State University (OCAST HR18-069) Research Area: Data Science/Clinical Platform

Can we use low-cost consumer RGB-D (depth) sensor for clinical gait analysis?

Can we analyze a walking person's gait from different perspectives for clinical gait analysis on-the-go?

Our research will focus on advanced computational approaches to improve noisy skeleton data for clinical gait analysis.

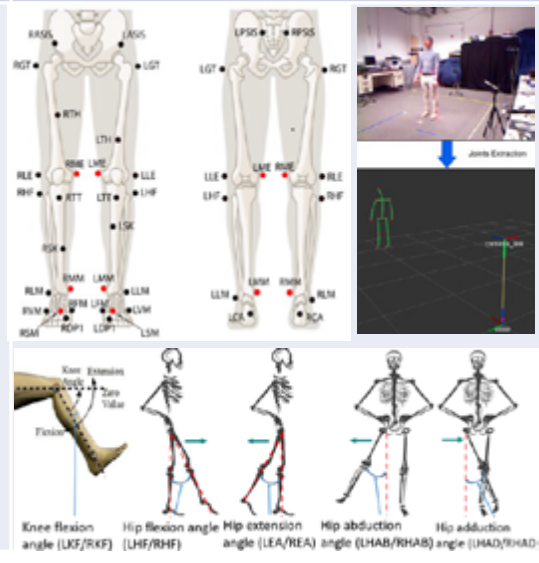
We are developing a mobile platform with motion data capture capability that is able to analyze a person's gait from different perspectives

Recent accomplishments

34% improvement on 3D joint position estimation

25% improvement on bone length estimation

40% improvement on joint angle estimation



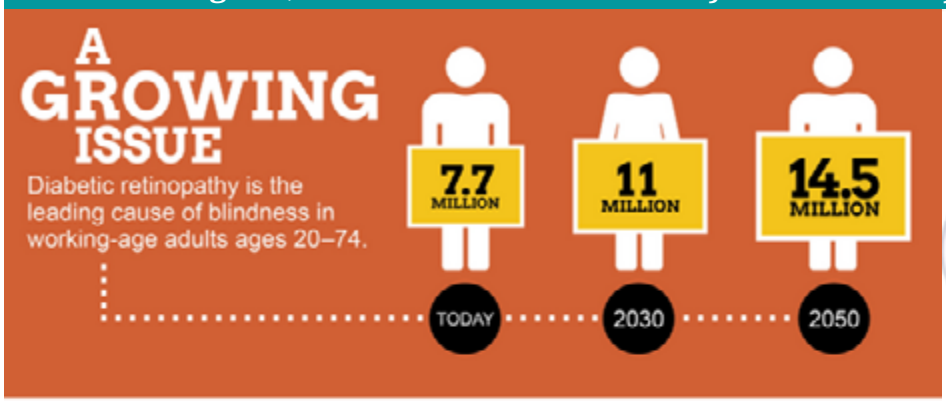
The benefits

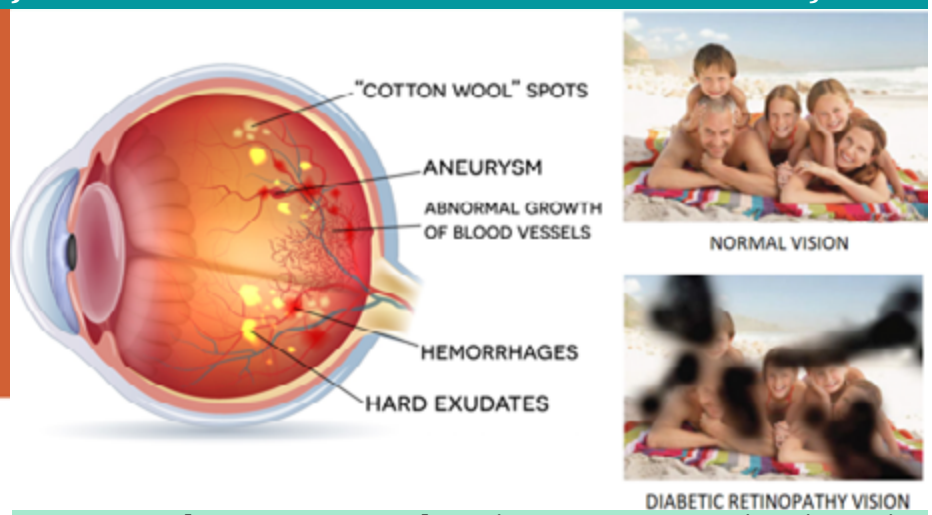
Affordable/portable
Better accuracy
More efficient
Versatility/flexibility
Reduce healthcare cost

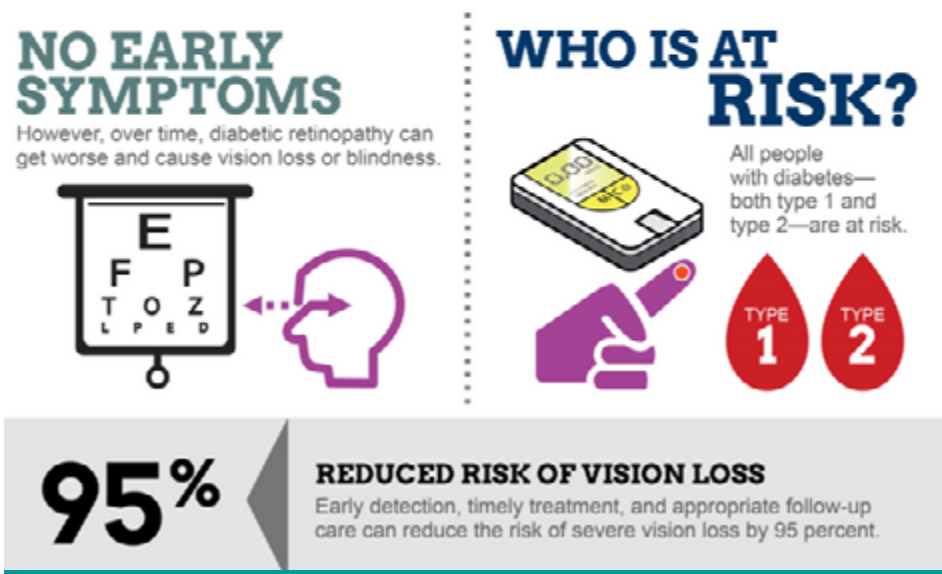
Can diabetic retinopathy be detected in early stage with routine blood tests?

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

PI: Tieming Liu, Oklahoma State University OCAST Project: HR18-087 Research Area: Health Data Analytics



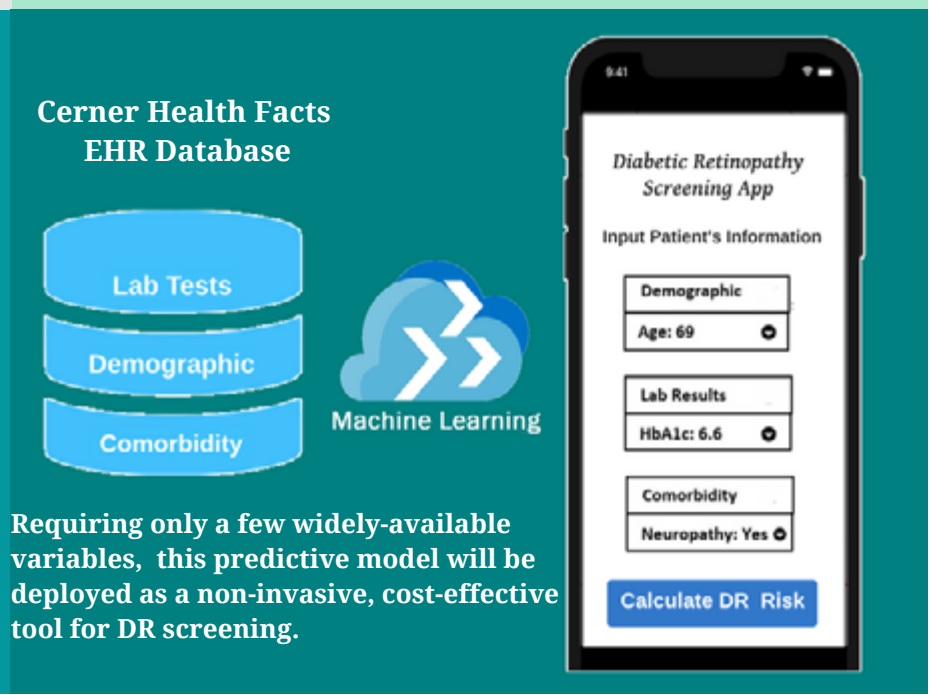




- Currently, a comprehensive eye examination is required for diabetic retinopathy (DR) diagnosis.
- Unfortunately, patient compliance rate with the recommended eye exam is very low, at only 40%.
- As a result, about 25% of diabetic patients with DR remain undiagnosed across the US.
- Unfortunately, the current therapies can only halt DR progression and vision loss cannot reverse it.
- This research is to develop and validate a widely-available and cost-effective tool for DR screening.

Recent Accoplishments:

- We used the Cerner Health Facts EHR Database (Cerner Corporation) to develop a DR predictive model with a few primary-care lab results, demographic and comorbidity data.
- We validated the model using the Healthcare Enterprise Repository for Ontological Narration (HERON) from University of Kansas Medical Center. The model had an accuracy of 78%.
- We presented our research at the 2020 HHDC Research Symposium and won the second place.



Requiring only a few widely-available variables, this predictive model will be deployed as a non-invasive, cost-effective tool for DR screening.

Particles present in urine serve as a source for predicting treatment response in lung cancer patients

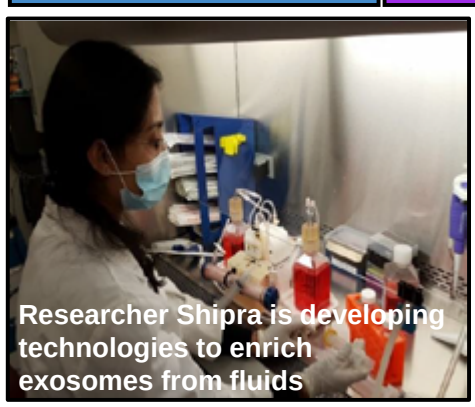
Non-invasive liquid biopsy approach for using exosomes as a surrogate for determining response to immunotherapy in lung cancer patients

PI: Rajagopal Ramesh OCAST Project: HR-18-088 Research Area: Health Sciences

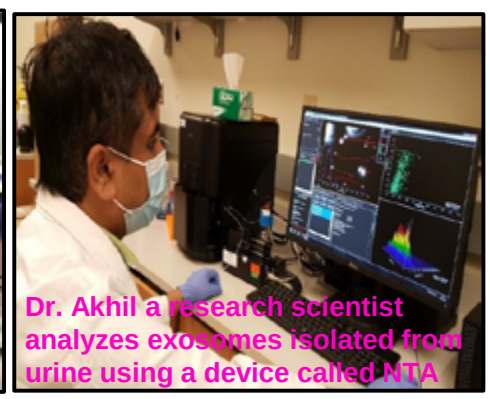
How can a physician quickly know if a cancer patient is responding to treatment?

Exosomes are small particles (<150 nm) that act as messengers transferring information between cells. They are present in bodily fluids including urine.

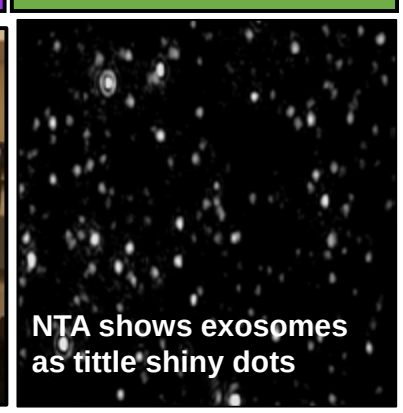
Can we isolate exosomes from urine?



Researcher Shipra is developing technologies to enrich exosomes from fluids



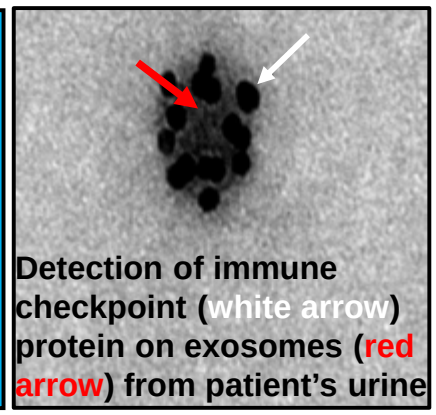
Dr. Akhil a research scientist analyzes exosomes isolated from urine using a device called NTA



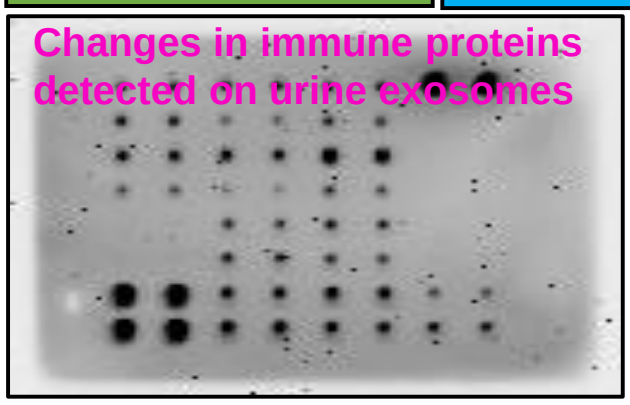
NTA shows exosomes as tittle shiny dots

Can we predict treatment response using exosomes?

We aim to use urine-derived exosomes for predicting response to immunotherapy



Detection of immune checkpoint (white arrow) protein on exosomes (red arrow) from patient's urine



Changes in immune proteins detected on urine exosomes

Potential benefits

- Personalized and precision treatment offered to patients
- Reduce healthcare costs
- Enhanced quality of life (QOL)

Recent Accomplishments

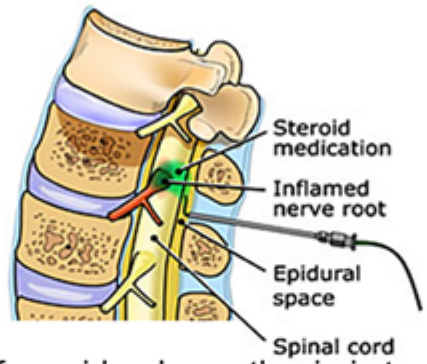
- Successful isolation and characterization of urine-exosomes
- Detection of candidate immune protein on urine-exosomes
- Developed bar-code style reads for immune proteins present on exosomes for predicting treatment outcomes

A new imaging guidance method that can make painless labor safer

Real-time epidural anesthesia guidance using multi-contrast optical coherence tomography needle probe

PI: Qinggong Tang, University of Oklahoma OCAST Project: HR19-062 Research Area: Biomedical Engineering

Epidural anesthesia is one widely used anesthesia methods



The key for epidural anesthesia is to exactly identify and locate the epidural space

Due to **lack of visual feedback** to guide needle navigation, the **failure rate** of epidural anesthesia is up to 20%

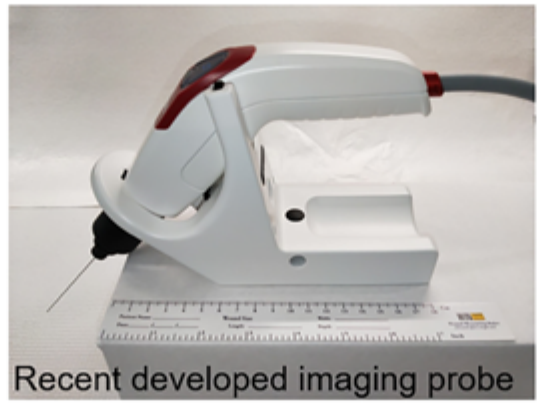
Headache after giving birth to child is one common complication in new mother

Our research is to develop a device for guiding needle insertion

Different from the camera, it can see the tissue before the needle damage it

Impact:

make needle-based interventions safer, easier, and faster



Recent developed imaging probe

Recent accomplishments:

Develop heal-hold probe

Test the system on pigs

Extend it to other applications

A novel wearable vibration therapy device for treating upper limb functional impairment in stoke

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

PI: Hongwu Wang, University of Oklahoma (HSC) **OCAST Project: HR18-034** **Research Area: Biomedical Engineering**

Project Highlights

Functional recovery from neurorehabilitation only lead to 20% of patients' fully resumption of their social life and job activities mainly due to **underdoes**.

Focal vibration (FV) therapy, a non-pharmacological, non-invasive treatment, has had satisfactory outcomes as a useful tool in neurorehabilitation.

We are developing and evaluating a wearable and mHealth technology that delivers **individualized** and **precise** vibration to target muscles.

The device provides patients opportunity to apply the prescribed vibratory stimuli in-home and/or at community settings to **sustain the dosage** needed. It also allows therapists to monitor usage and compliance and to adjust based on progression.

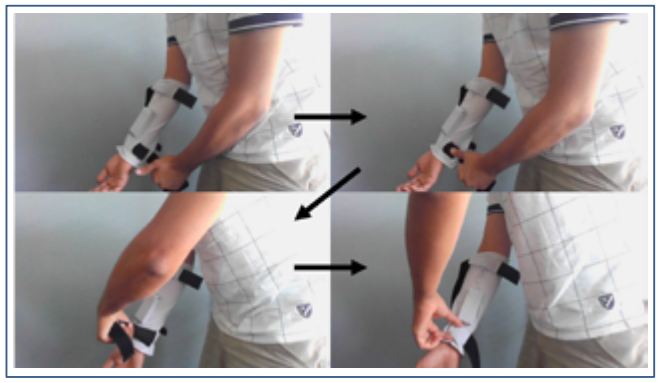
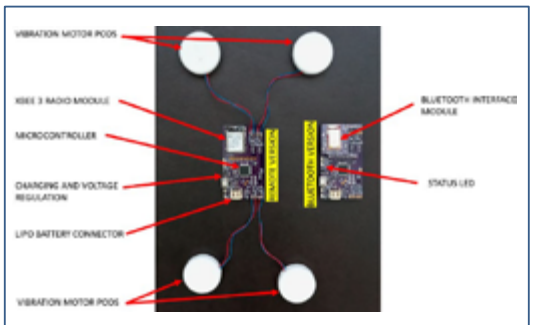


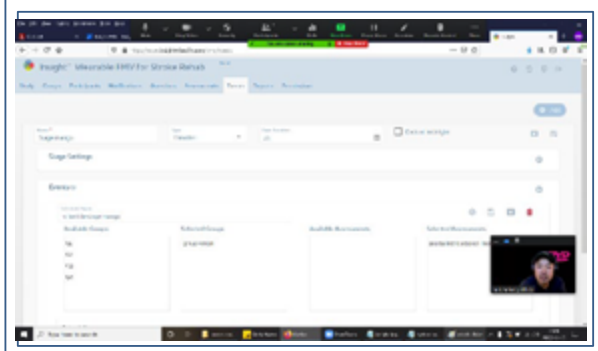
Illustration of wearing the device to right arm by patient him/her self



The final prototype of the wearable vibration device and its hardware components

Recent Accomplishments

- Patients, caregivers and therapists met virtually during COVID-19 pandemic to finalize the design and development.
- A **final prototype** was fabricated and assessed by the patients, caregivers and therapists.
- **An app and web portal** was developed to track the device usage and remotely monitoring and adjusting the vibration
- Wearable Focal Vibration Device and Methods of Use (2020), **Provisional Patent**: 62/991,562.



The web portal that allows therapist to remotely monitor and adjust the vibration regimen

Impaired vascular smooth muscle cells contribute to brain aging

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

Shannon Conley OUHSC HR18-118 Research Area: Cell Biology

In **aging** people develop **cognitive impairment and gait defects**, often progressing to diseases such as Alzheimer's Disease and Related Dementias.

AGING

↓

Decreased IGF-1

↓

Maladaptive VSMCs

- **Decreased proliferation and hypertrophy**
- **Decreased ECM remodeling & secretion of protective factors**
- **Increased apoptosis & senescence**
- **Increased inflammation & oxidative stress**
- **Altered response to mechanical stress**

Mid/Large Vessels

- **Defective autoregulation in response to hypertension**

Microvessels

- **Increased hemodynamic and cellular stress**

Regional vascular instability

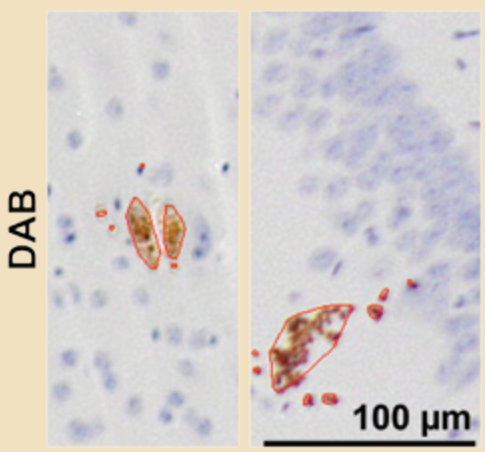
- **CMHs**
- **Blood-brain barrier disruption**
- **Microvascular rarefaction**

Vascular Cognitive Impairment and Dementia
Alzheimer's Disease and Related Dementias
Gait Disorders, Decreased Healthspan

Our research focuses on understanding the role of **decreased hormonal signaling (via IGF-1) on vascular smooth muscle cells (VSMCs)** in the development of age-related cognitive decline.

Recent highlights:

Knocking out the IGF-1 receptor in aged hypertensive mice leads to worsened vascular damage, shown by development of cerebral microhemorrhages (CMH).



brain section showing CMH (brown)

Increased CMH in these mice leads to decline in regularity index (a sign of impaired gait).

Benefits

Our studies are shedding light on the crucial mechanisms that underlie age-related vascular disease in the brain. Understanding the cellular and molecular changes that lead to vascular cognitive impairment is essential to be able to develop targeted therapeutics to retard age-related cognitive decline.

Excess weight gain and changes in brain areas after removal of ovaries

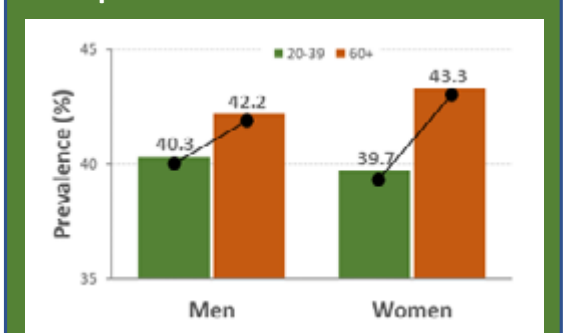
Neuroimmune activation and weight gain in a rat model of postmenopausal obesity

PI: Kathleen S. Curtis, Oklahoma State University – Center for Health Sciences

OCAST Project: HR18-089 **Research Topic: Neurobiology**

Obesity is one of the most common health conditions and leads to serious health issues including diabetes and heart disease.

The prevalence of obesity increases as people age, especially in women after menopause.



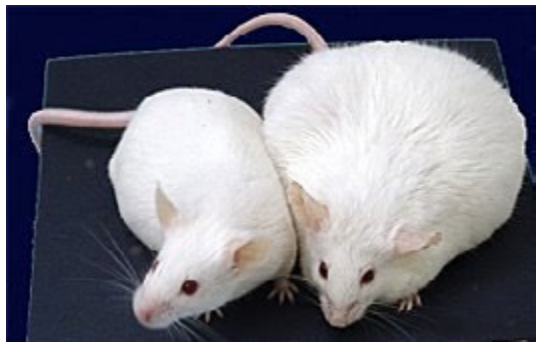
adapted from NCHS Data Brief no. 360

Obesity is poorly understood, but it is known that the brain detects hormones and other signals to 'decide' what, when, and how much we eat…

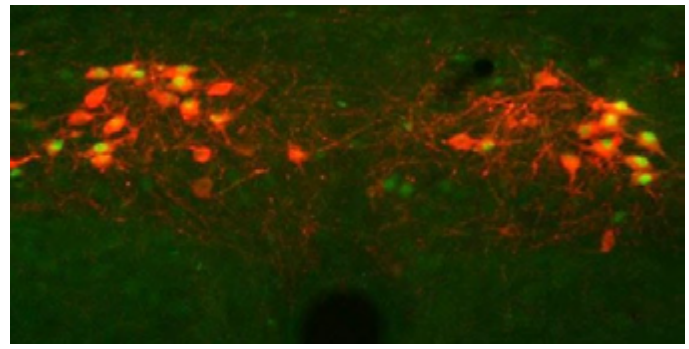
…which affects how much we weigh.

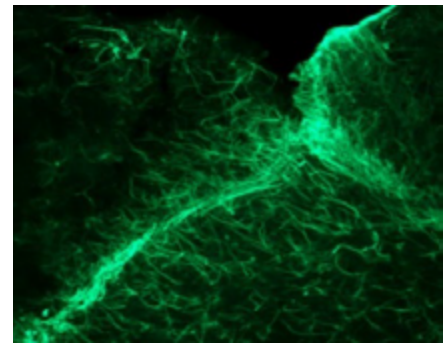
Are there changes in brain areas that control body weight after menopause?

Our team is attempting to answer this question using female laboratory rats that have had their ovaries removed to eliminate their reproductive hormones.

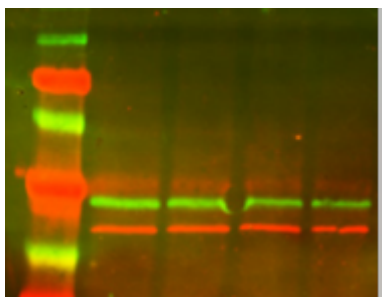


Female rats rapidly gain weight after removal of the ovaries

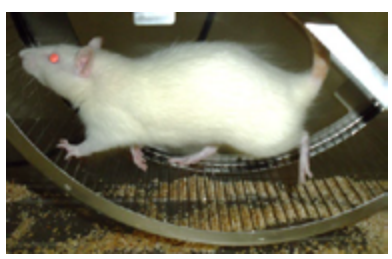




Immunohistochemical methods to examine neural (right) and non-neural (left) cells in brain areas involved in controlling body weight



Western blots of proteins in brain areas involved in controlling body weight



Female rats voluntarily exercise on running wheels

HIGHLIGHTS

Female rats rapidly and reliably gain weight after surgical removal of the ovaries.

Development of this 'postmenopausal' weight gain is associated with changes in brain areas involved in controlling body weight

1) neural and non-neural cells
2) receptors for gut hormones that change during weight gain and eating
3) neuroimmune signals

Importantly, these changes occur in at different times during the weight gain, so may be linked to the *development* of obesity.

Wheel running reduces the weight gain, but the effect is temporary and does not persist when exercise is terminated.

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

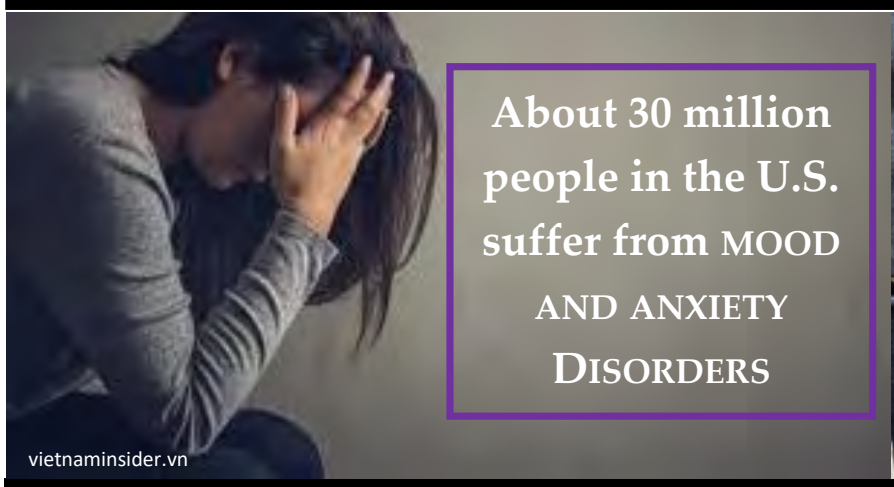
A new medicine to treat mood and anxiety disorders

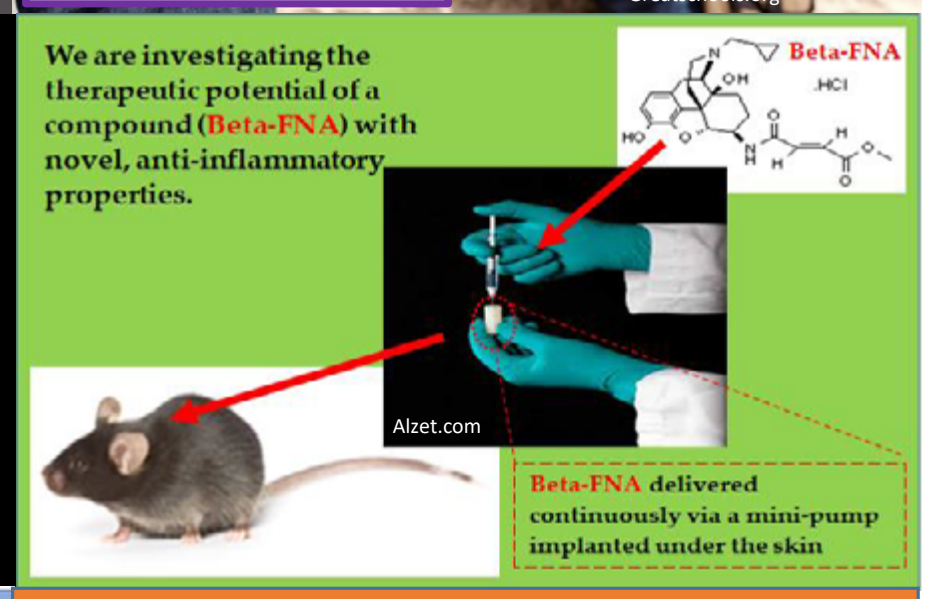
Advancing therapeutic options for treating mood and anxiety disorders using a novel anti-inflammatory agent

PI: Randall L. Davis, Oklahoma State Univ. Center for Health Sciences

OCAST Project: HR18-033

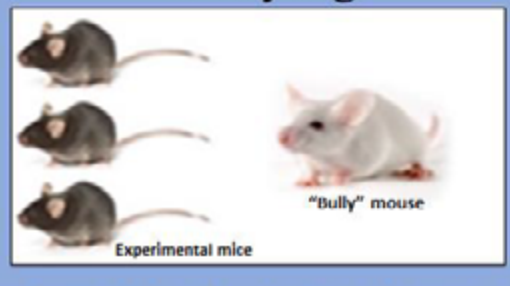
Research Area: Neurobiology





Experimental Model:

Repeated Social Defeat (RSD) or "Bullying"



Three experimental mice have a larger, aggressive mouse (of a different strain) placed in their cage for 2h/day for 6 consecutive days.

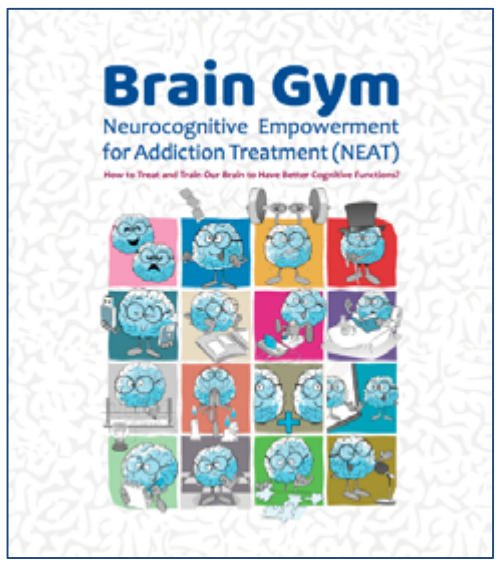
- ❑ RSD ("BULLYING") INCREASED ANXIETY-LIKE BEHAVIOR
- ❑ RSD ("BULLYING") AFFECTED INFLAMMATORY SIGNALING IN THE BRAIN AND OTHER ORGANS
- ❑ BETA-FNA WAS PROTECTIVE IN SOME INSTANCES, MORE STUDIES ARE NEEDED

Brain Rehabilitation for People with Opioid and/or Meth Use Disorder

Neurocognitive Empowerment for Addiction Treatment (NEAT): A Randomized Controlled Trial for Opioid and/or Meth Addiction

Hamed Ekhtiari, MD, PhD (PI), Robin Aupperle, PhD (CI), Laureate Institute for Brain Research HR18-139 Neurobiology

- Addiction to opioids and methamphetamine are associated with **brain deficits**.
- Brain deficits in **memory, attention, decision-making**, and **control** disturb normal daily functioning and attempts for abstinence.
- There has been a relative lack of research focused on **developing interventions targeting brain deficits** in the context of addiction.
- The aim of this study is to develop and test **clinical efficacy** for an intervention targeting these brain deficits.



Brain Gym (NEAT) workbook cover. We use cartoons as a tool to communicate with patients.

Brain Gym (NEAT) cognitive architecture in 16 sessions. Cognitive modules are added gradually to each other from simpler to more complex ones

Accomplishments in 2020

- Completed the RCT intervention for the first four groups of the clinical trial (n=45) and completed 1 year follow up for the first three groups.
- Paused new recruitments for the trial in March 2021 due to the pandemic, but accomplished to do the follow ups with remote assessments.
- Made revisions in the study protocol to adjust for remote assessments and potentials for teleconference intervention and received IRB approval in August 2020.
- Restarted recruiting new participants for the 5th group since November 2020.

Preserving Vision and Preventing Blindness by Better Understanding Immune Responses in the Eye

The Role of TRAF3 in Retinal Function and Inflammation

PI: Michael Elliott, DMEI, OU Health Sciences Center

OCAST Project: HF18-008

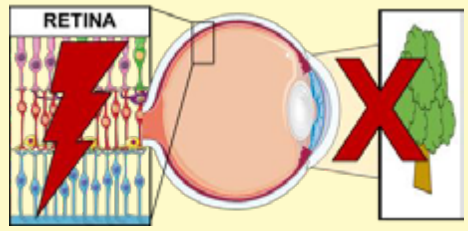
Research Area: Neurobiology

For healthy eyes & vision:

Inflammation in the retina must be **balanced**

Inflammation *can* be **GOOD**

***BUT…* *Too much* INFLAMMATION**

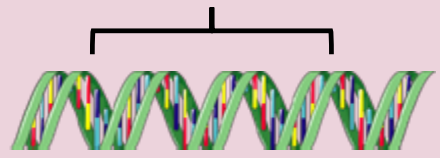


can cause blindness

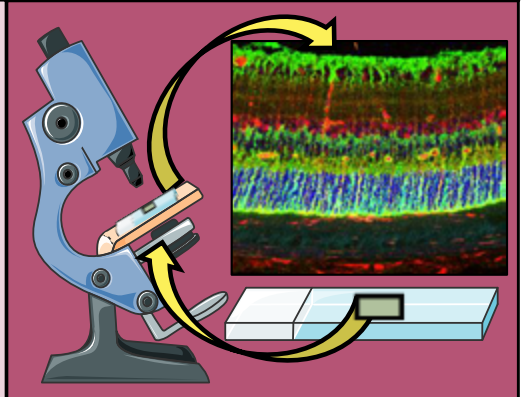
This OCAST Postdoctoral Fellowship supported the research of Dr. Jami Gurley

Mouse models help us mimic inflammatory eye diseases…

Our research focuses on a ***gene*** called **Traf3**

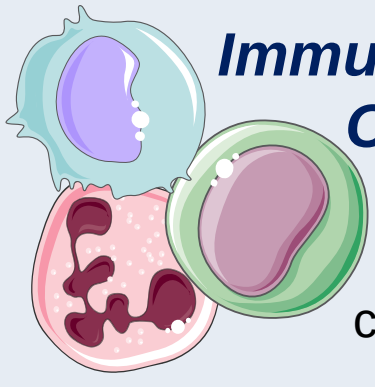


and its role in retinal inflammatory diseases



Microscopes help us visualize the **retina**

…so we can study ***Immune Cells*** that cause damage to the retina



Because our studies suggest that

Traf3

PROMOTES

INFLAMMATION

&

immune responses…

…treatments that

Inhibit

Traf3

ACTIVITY

may help prevent retinal damage & blindness

Understanding Chronic Pain: is it all in your head ?

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

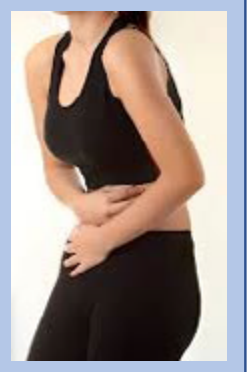
PI: Beverley Greenwood-Van Meerveld, Ph.D., University of Oklahoma Health Sciences Center OCAST PROJECT: HR 18-040 Research Area: Neurobiology

STRESS

Can make you SICK

and can cause

Daily Belly PAIN



Especially in women

Our research focuses on understanding the central molecular mechanisms that contribute to belly pain in females

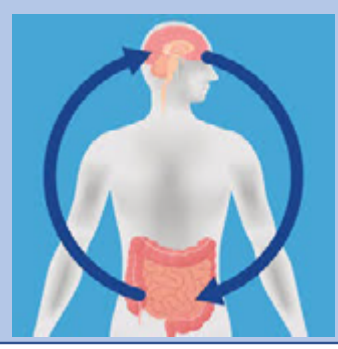
The Benefits:

- Better understanding of belly pain in women
- New behavioral treatments targeted to women
- Improve quality of life of women with daily belly pain
- Fewer lost work days by women

THE

GUT BRAIN

-AXIS-



Recent Accomplishments :

Exposing female rats to stress *increases* belly pain

Showing that stress alters gene expression in the brain

Testing the mechanisms underlying the effectiveness of environmental enrichment to treat belly pain

Changes in clotting cells after concussion may lead to increased risk for stroke many years after the injury

Thrombotic and inflammatory mechanisms in traumatic brain injury

PI: Calin Prodan, MD, OUHSC OCAST Project: HR19-111 Research Area: Neurobiology

Traumatic brain injury (TBI) is common:

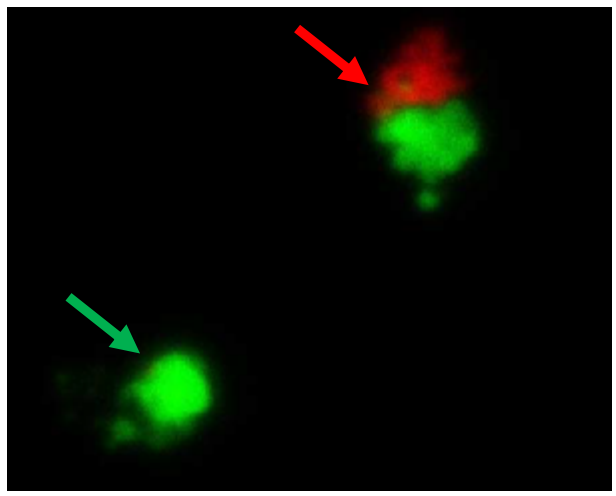
- Occurs in almost 2 million people in the United States each year
- Most cases are mild traumatic brain injuries (concussions)
- Although mild, these injuries are linked to a long-term increase in the risk for stroke later in life.

What we have discovered:

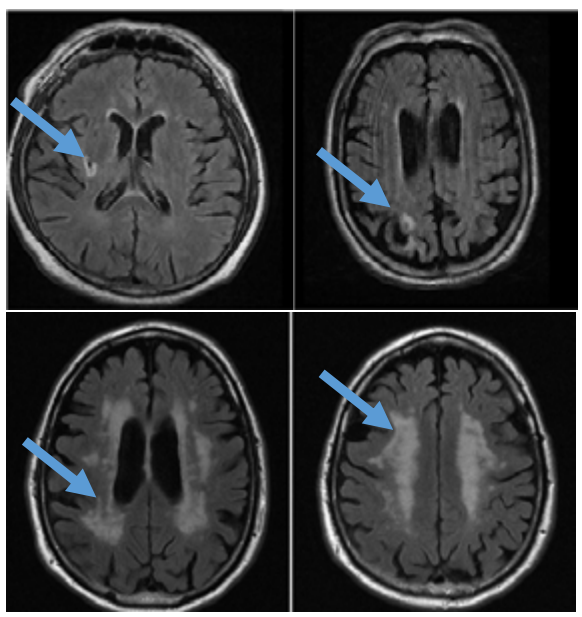
- patients with concussions during military service have increased levels of clotting cells (coated-platelets) years after the last injury
- these levels were linked to inflammation.
- Patients with the highest levels clotting cells were most likely to have silent strokes on MRI

The proposed work:

- investigate how previous concussions lead to increased inflammation, higher levels of clotting cells and silent strokes (long before severe strokes)
- The results of the proposed work may lead to potentially new therapies to prevent stroke and help us understand how best to protect the brain in those at risk for concussion.



Coated-platelets on microscope: green = platelet receptor, red = fibrinogen



Brain scans (MRI) with silent vascular changes (see blue arrows)

What we have done:

- After a delay due to the COVID pandemic, we restarted our project as a collaborative approach that involves the VA Medical Center, OUHSC and OU Norman.
- We finalized a protocol for obtaining repeat brain scans with MRI scans in individuals with concussions and prior scans.
- We have now developed specific research protocols that will allow our research team to access selected patients with documented concussions.
- Active recruitment (with pandemic precautions) is ongoing.

PTSD, Pain and anxiety: Inflammation Initiates Symptoms

Post-traumatic stress disorder and Co-morbid chronic pain: Evidence that TNF initiates a sequelae involving Nociceptin/Orphanin FQ (N/OFQ)

PI: Kelly Standifer, OU College of Pharmacy OCAST Project: HR17-041 Research Area: Neurobiology

PTSD affects 4-8% of people and 35% of them develop persistent pain.

PTSD is difficult to treat in general. Pain is more difficult to treat in PTSD patients.

Females with PTSD often experience more severe and persisting symptoms, including comorbid pain and anxiety

Severity of pain corresponds to severity of PTSD symptoms

What sets in motion pain and anxiety symptoms after a traumatic event? Evidence suggests it is serum TNF…so we blocked its actions with an antibody.

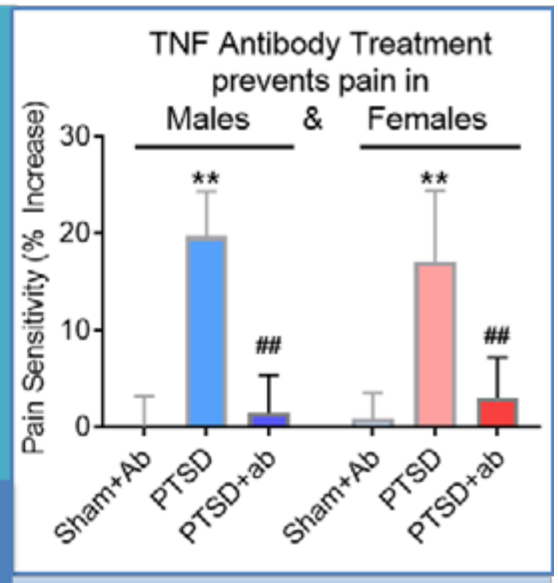


Fig. A single, iv injection of TNF antibody following traumatic event prevented increased pain up to at least 9 days post-trauma.

Accomplishments:

- Single TNF antibody injection after trauma blocks pain, anxiety symptoms and elevated N/OFQ in serum and brain in males, but blocks only pain in females.
- Lack of N/OFQ receptor prevents elevated serum TNF mRNA in circulating white blood cells (WBCs) after trauma in males and females
- TNF increases N/OFQ mRNA in neurons from males, but decreases N/OFQ mRNA in female neurons.
- Identified N/OFQ and TNF changes in brain regions and WBCs between 2 hr and 9 days after trauma
- We found sex differences in expression of N/OFQ and TNF with PTSD-like trauma, as well as differences in their dependence on the presence of the N/OFQ receptor to change.

Our work will focus on understanding sex differences in response to trauma and in response to potential therapeutic options.

Estrogen actions in the male brain may delay disease onset

Role of hypothalamic estrogen receptor-α in 17α-estradiol-mediated metabolic benefits

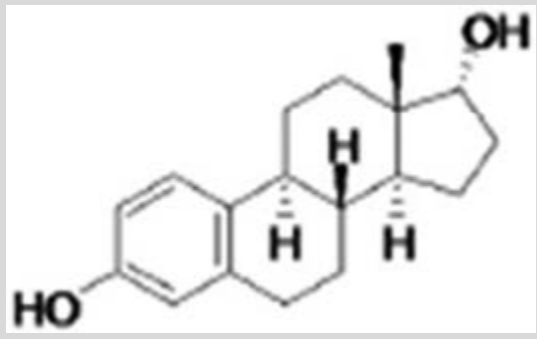
PI: Michael Stout, University of Oklahoma HSC OCAST Project: HR20-024 Research Area: Neurobiology

Estrogens are more abundant in females,

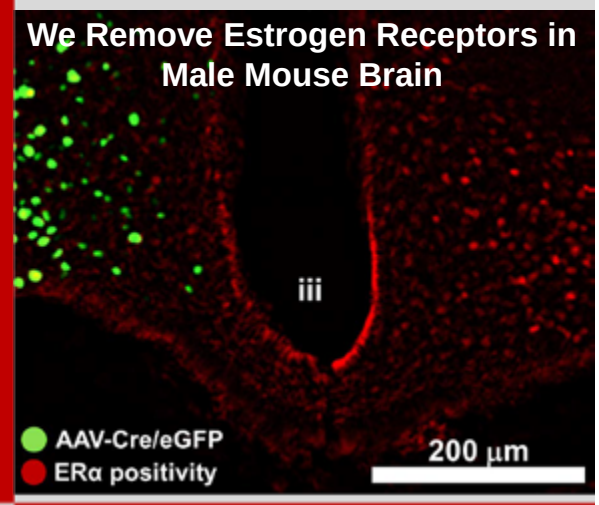
but have also been found to act in males!

We study the hypothalamus in the brain!

17α-estradiol extends lifespan in male mice,



which we hypothesize occurs by signaling In the brain!



We administer 17α-estradiol to the brain of male mice….

…that have had their estrogen receptors removed using genetic tools.

Understanding this biology will…

1. Tell us if males and female develop diseases differently

2. Tell us is estrogen signaling in the male brain can be used as a treatment strategy, potentially in humans

Understanding brain-based causes of attention-deficit/ hyperactivity disorder (ADHD)

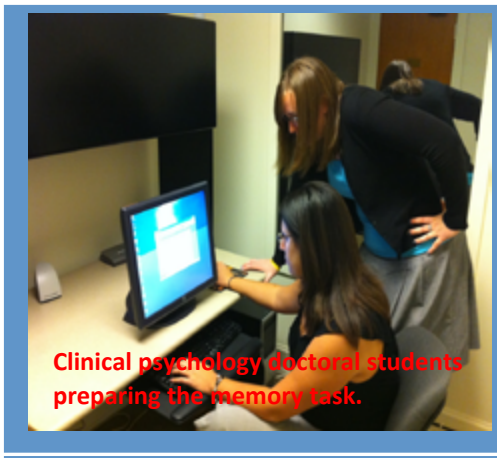
Neurocognitive Deficits Underlie ADHD

PI: R. Matt Alderson, Oklahoma State University OCAST Project: HR17-051 Research Area: Psychology

ADHD is a chronic disorder of childhood and adulthood

ADHD affects 3-5% of school-age children at an annual U.S. cost of illness of over $36 billion

Depiction of neurons firing.



Clinical psychology doctoral students preparing the memory task.

Recent research has sought to identify underlying causal mechanisms of ADHD

This research sought to identify specific, previously unexamined neurocognitive processes that underlie or cause ADHD

The benefits:
Better understanding of ADHD causes

Allows for development of new, non-pharmacological interventions

Allows for improved teaching objectives

Recent Accomplishments:

Identified ADHD-related neurocognitive deficit not previously known to the field

Findings help explain context-specific impairments

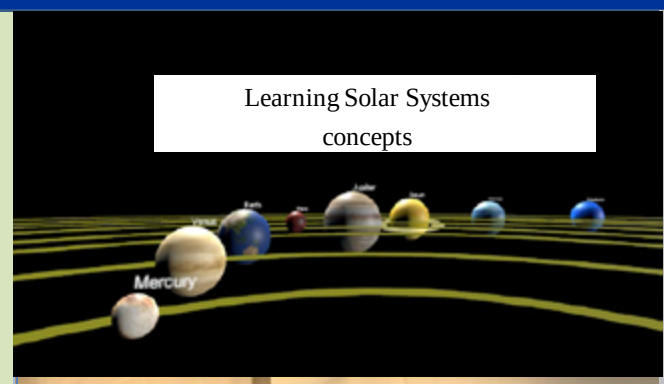
Virtual Learning Environments to support science learning for autistic students

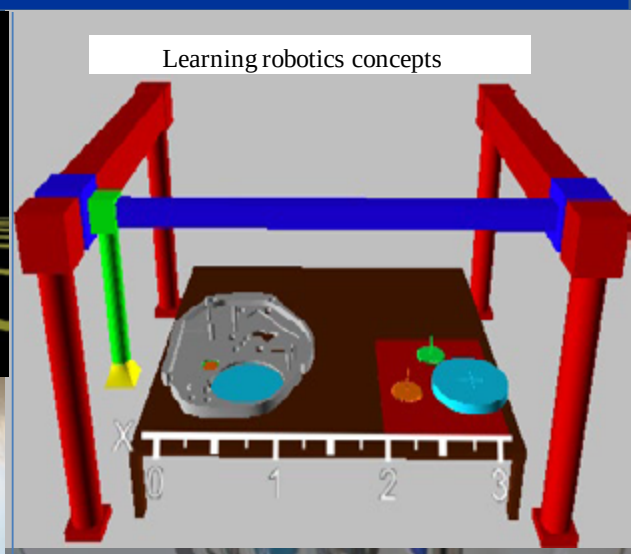
Investigation of Impact of Virtual Reality based cyber learning approaches

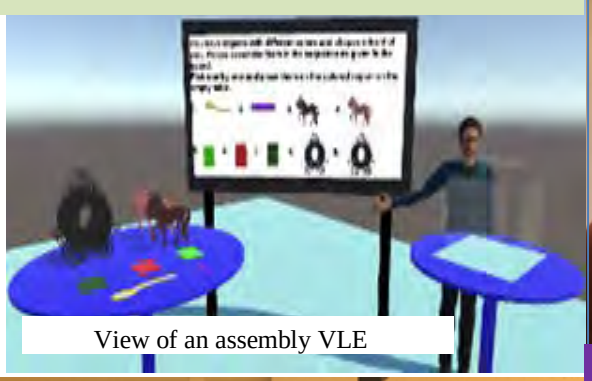
PI: J. Cecil, Oklahoma State University OCAST PROJECT: HR18-077 Research Area: Public Health

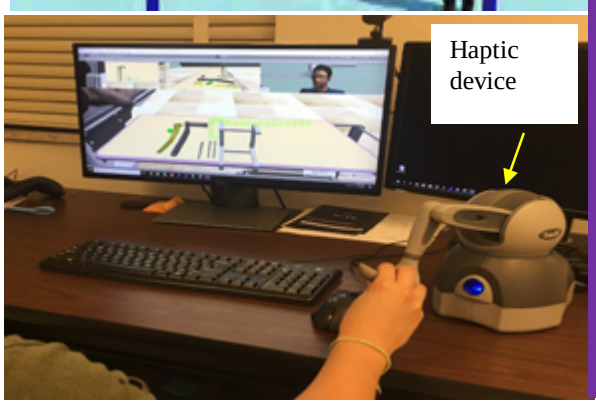
Focus is on Helping autistic children learn science

Creating 3D Virtual Reality Environments to help students learn science and engineering

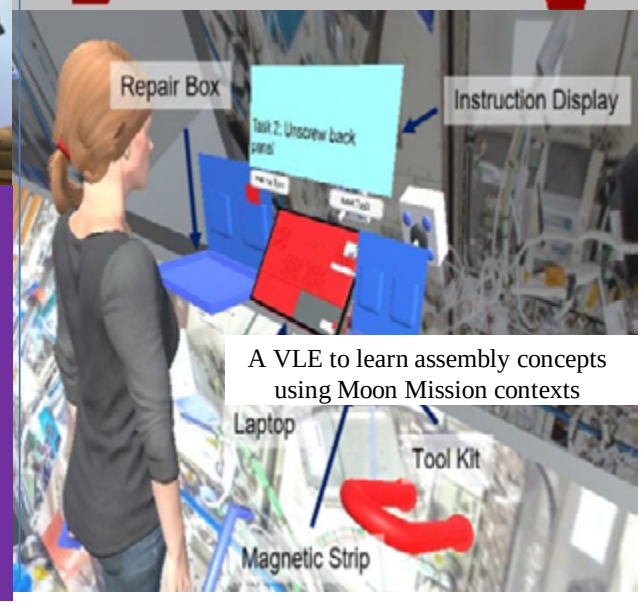








* Learning assembly, robotics, path planning and other topics
* Initial Assessment results have indicated the positive impact of such VLE based approach on helping autistic students learn STEM
- Autistic Elementary, middle, high school students are benefiting



A VLE to learn assembly concepts using Moon Mission contexts

Dads and the Development of Infants in Oklahoma (DADIO)

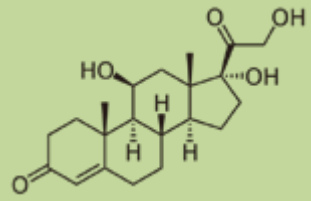
Family Hormonal Profiles of Resilience: Defining Fathers' Roles in Infant Biosocial Development

PI: Jennifer Byrd-Craven, Oklahoma State University

OCAST Project: HR17-003

Research Area: Psychology/Public Health

Fathers play an important role in infant development

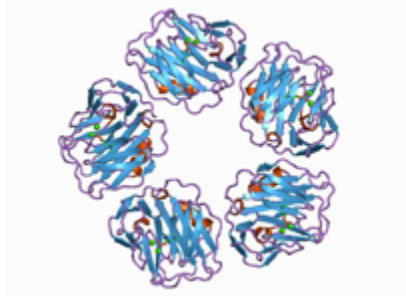


Molecular structure of **cortisol**, released in response to stress, and one of the primary hormones of focus

We know little about how **fathers** impact *stress response system development*

The benefits:
Identification of *protective factors* against stress and disease

This longitudinal study will identify how **fathers** and mothers *contribute to stress system coordination with their* **infants and each other**



Molecular structure of C-Reactive Protein (CRP), a marker of inflammation

Nikki Clauss, former graduate research assistant, processes saliva samples for cortisol, CRP, testosterone and progesterone.

Recent accomplishments:
Salivary assays for *stress hormones* and *inflammation*

Families assessed when infants are ***4, 12, and 18 months old***

Insomnia, Post-Trauma Nightmares, and Suicide Risk

CBT-I versus ERRT: Impact on Sleep, Nightmares, and Suicidal Ideation

PI: Dr. Joanne L. Davis, University of Tulsa **OCAST Project: HR17-087** **Research Area: Nutrition/Psychology/Public Health**

Oklahoma has the 10th highest suicide rate in the country and suicide is the 9th leading cause of death in the state.

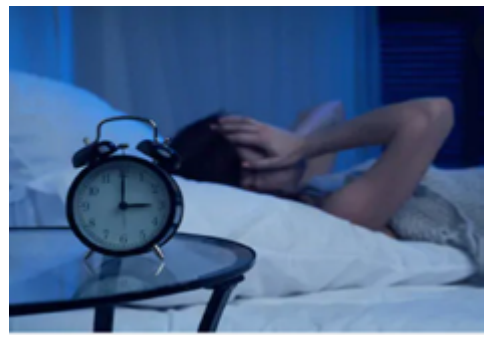
TITAN
THE UNIVERSITY OF TULSA INSTITUTE OF TRAUMA, ADVERSITY, & INJUSTICE

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

We are interested in examining whether treating insomnia and nightmares may lead to a reduction of suicidal ideation.

SLEEP STRONG
The ongoing nightmare research conducted at TU

Research finds an association between suicidality and sleep disturbances and nightmares. While many studies have found that sleep disturbances in general are related to suicidality, there appears to be a unique relationship between the experience of nightmares and suicidality.



Currently there are two evidence based sleep treatments that have shown to be effective in improving nightmares, sleep quantity and quality, and related psychopathology: Cognitive Behavioral Therapy for Insomnia (CBT-I) and Exposure, Relaxation, and Rescripting Therapy (ERRT).

Treatment manual for ERRT

RECENT ACCOMPLISHMENTS

- Extensive recruitment efforts have been made in the Tulsa area.
- 13 participants have been randomized to receive either CBT-I or ERRT treatment. 6 of them have completed treatment.
- Preliminary results have found that both of these treatments reduce the severity of suicidal ideation over 50%.

Can Fat Tolerance Testing Be Adapted for Clinical Use?

Validity and Reproducibility of Clinically Feasible Postprandial Testing

PI: Sam R Emerson, PhD

Oklahoma State University-Stillwater

Award: HR20-027

Research Area: Nutrition/Psychology/Public Health

HIGHLIGHTS:

- Fat tolerance testing – which involves consuming a high-fat shake and measuring the blood fat ("triglyceride") response – may be clinically useful for screening for heart or liver disease risk.
- Fat tolerance testing is not feasible for a clinical setting. We developed an abbreviated fat tolerance test that one day could be used in clinics worldwide as a cardiometabolic risk screening tool.
- This study is determining the validity and reproducibility of our new fat tolerance test in order to ensure the results are trustworthy.
- When utilized in a widespread manner, the abbreviated fat tolerance test may detect cardiometabolic disease risk earlier, leading to better health outcomes and lower healthcare costs.

In this study, blood lipids are measured before and after consumption of a high-fat meal in order to test the validity of a new fat tolerance test. Our fat tolerance test only requires two blood draws: fasting and 4-hours after the meal. We are comparing results against a traditional fat tolerance test that requires 7 blood draws over 6 hours. *Image Credit: MedlinePlus.gov*

RECENT ACCOMPLISHMENTS:

This study was activated October 1, 2020. Since then, 5 participants completed the study. Ten more participants are enrolled to complete the study in early 2021.

Low-priced, entry-level digital hearing aids provide acoustic benefits and enhanced health-related quality of life of older Oklahomans with low incomes

Health-related Quality of Life Benefits from Advanced Digital Technology Hearing Aids

Carole E. Johnson, PhD, AuD, PI **HERO Lab; Dept Communication Sciences and Disorders; College of Allied Health; OUHSC** **HR-16-118**

PROJECT NARRATIVE

Objectives: Untreated sensorineural hearing loss (SNHL) can result in the reduction of health-related quality of life (HRQoL). We conducted a three-year, randomized clinical trial (RCT) and longitudinal study to determine the benefits from low-priced, entry-level digital hearing aids for adults with low incomes (Median income = $13,778; Inter-Quartile Range: $9,645; $19,107). The average price of a hearing aid in the US is $2,500. We hypothesized that these adults would achieve benefits from and satisfaction with these low-priced, entry-level devices.

Design: The RCT randomly assigned 80 adults with mild and moderate SNHL to treatment (N = 42) and waiting list control groups (N = 38) who were administered the World Health Organization Disability Assessment Schedule 2.0 (WHO-DAS 2.0), the Hearing Handicap Inventory for the Elderly (HHIE), and the Abbreviated Profile of Hearing Aid Benefit (APHAB) among other outcome measures before the fitting of hearing aids. Patients in the waiting list control group were fit with hearing aids after the RCT portion of the study. Variables were assessed for normality using Shapiro-Wilks tests. The longitudinal study extended post-fitting follow up to 6-months and 1-year.

Results: Treatment and control groups were equivalent for age (M ~ 67.1 y), mild and moderate SNHL (Four-frequency pure-tone average ~ 43.5 dB HL), and baseline scores on outcome measures. However, the groups varied on sex composition and experience with hearing aids. Analysis of covariance with sex and experience as covariates indicated that those in the treatment group fit with low-priced, entry-level digital hearing aids had significantly greater hearing handicap reduction change scores (HHIE; $p<0.0001$) and greater acoustic benefit change scores (APHAB; $p<0.0001$) compared to the control group. Positive outcomes from hearing aids were maintained at 6-months and 1-year post-fitting of hearing aids. Participants consistently wore their hearing aids between 4 and 8 hours/day.

Conclusions: Low-priced, entry-level digital hearing aids provide a significant increase of HRQoL and acoustic benefits for older Oklahomans with low incomes. Patients were satisfied with their hearing aids. Benefits were maintained at 6-months and 1-year post-fitting of hearing aids.

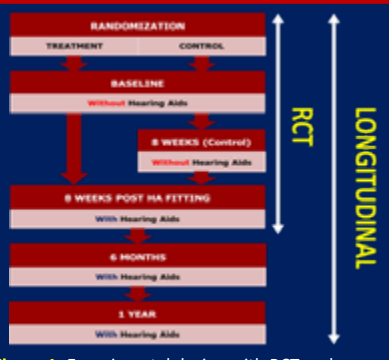


Figure 1. Experimental design with RCT and longitudinal components to the study

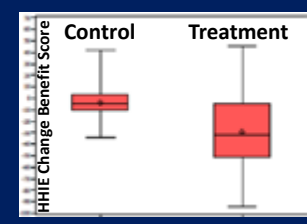
RECENT ACCOMPLISHMENTS

- Results were selected for presentation in the prestigious podium sessions of the 2020 Annual Scientific and Technology Conference of the American Auditory Society, Scottsdale, AZ
- Letter of intent was submitted to with a favorable response from the National Institute of Deafness and Other Communication Disorders of the National Institutes of Health regarding submission of a grant proposal to the NIDCD Hearing Healthcare for Adults: Improving Access and Affordability (R21/R33 Clinical Trials Optional).

Figure 2. Low-priced, entry-level digital hearing aids provide acoustic benefits and enhanced health-related quality of life of older Oklahomans with low incomes

RANDOMIZED CLINICAL TRIAL

Figure 3. Those in the treatment group had a greater mean hearing handicap reduction change score (the lower the change score, the greater the reduction of hearing handicap) on the HHIE after 8-weeks of wearing hearing aids than the control group ($p<0.0001$).



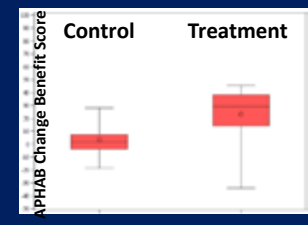
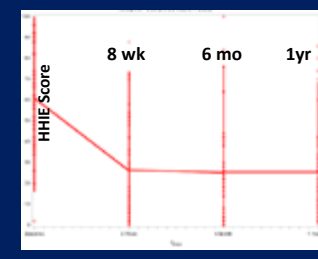


Figure 4. Those in the treatment group had a greater mean acoustic benefit change score (the higher change score, the greater the acoustic benefit) on the APHAB after 8-weeks of wearing hearing aids than the control group ($p<0.0001$).

LONGITUDINAL STUDY

Figure 5. Mean scores for hearing handicap decreased (improved) significantly after baseline. However, both the 6-month and 1-year measures did not differ from the 8-week measure ($p = 0.761$ and $p = .814$, respectively).



REFERENCES

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Ventry I, Weinstein B. The hearing handicap inventory for the elderly: A new tool Ear Hear 1982;3:128–134

World Health Organization. World Health Organization Disability Assessment Schedule 2.0. 1999. Author: Geneva, Switzerland.

Determining if a firefighter is fit-for-duty

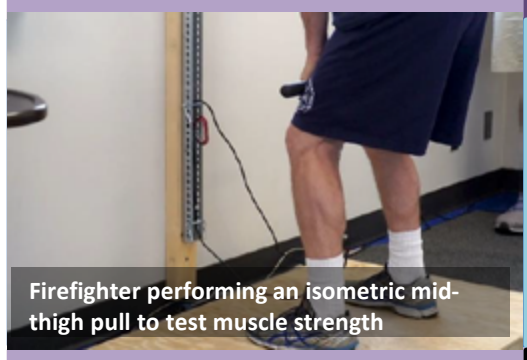
Fit-for-duty: An Examination of the Efficacy of the Physical Abilities Test in Determining Physical Readiness

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

To help minimize the risk of CASUALTIES

firefighters are often required to complete an annual PHYSICAL ABILITIES TEST (PAT)

Firefighter performing a WFI stepmill test of aerobic capacity



Firefighter performing an isometric mid-thigh pull to test muscle strength

The PAT is used to help determine if firefighters are fit-for-duty

Our research explored if the PAT is an indicator of physical readiness

The benefits:

Evidence from this project will help support the ongoing measures to enhance physical readiness evaluation methods

Evaluation of squat mobility and stability

Recent accomplishments:

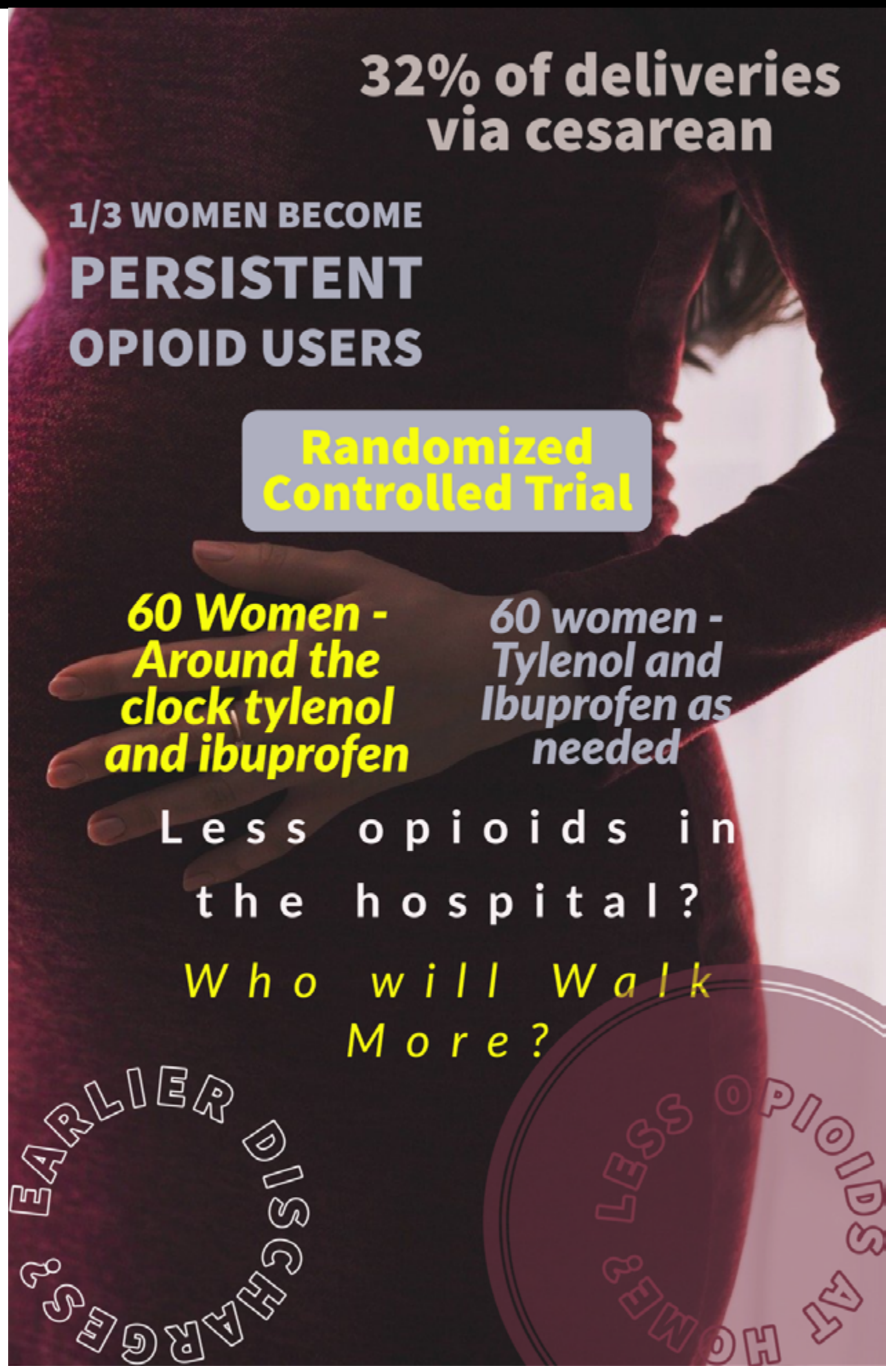
1 manuscript in review

6 scientific abstracts presented at national and regional conferences

Reducing pain and improving movement by using Tylenol and ibuprofen instead of narcotics in mothers who undergo c-sections

Towards Enhanced recovery after Cesarean: Scheduled Post-Operative Medications- a Randomized Controlled Trial

PI: Pavan Parikh, OUHSC OCAST Project: HR20-122 Research Area: Public Health



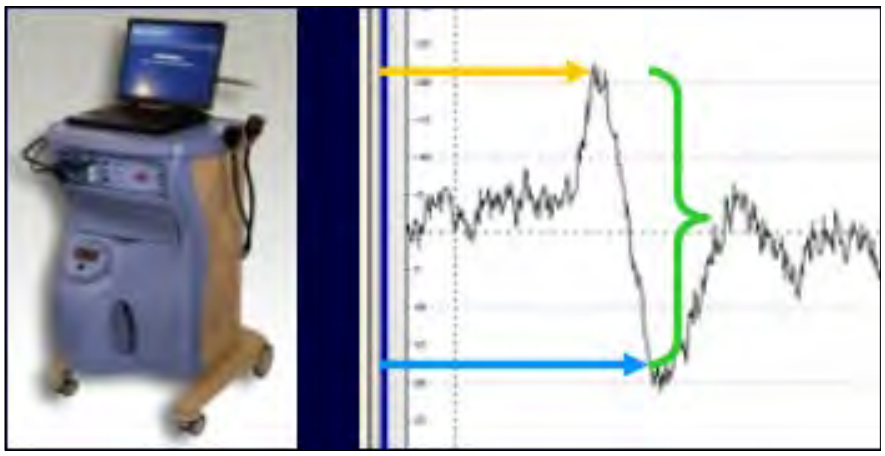
The Oklahoma Study of Native American Pain Risk, Part 2 (OK-SNAP II)

Does Glucose Dysmetabolism Contribute to Native American Pain Disparities?: A Pilot Study

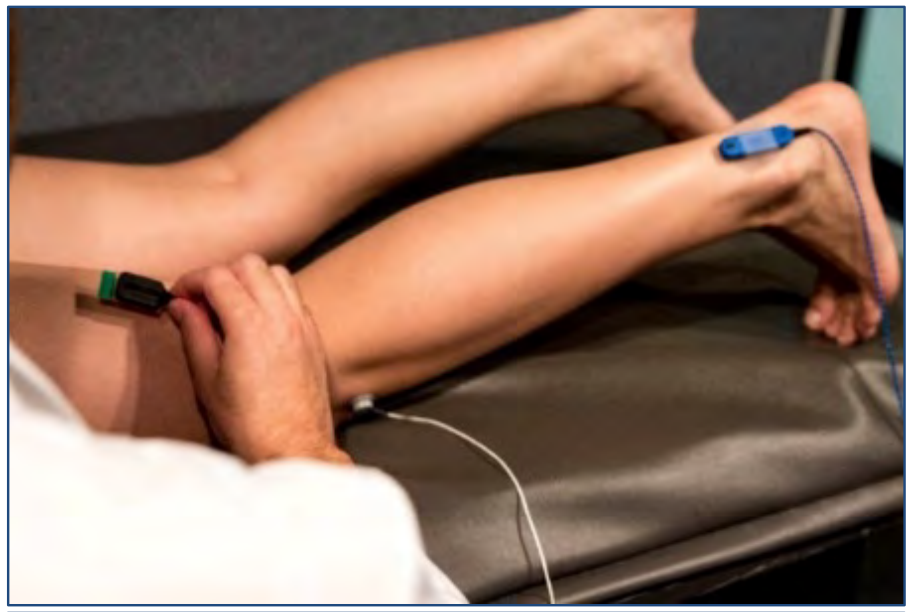
PI: Jamie Rhudy, PhD, The University of Tulsa **OCAST Project: HR18-039** **Research Area: Psychology**

Native Americans (NAs) have a higher prevalence of chronic pain than any other U.S. racial/ethnic group. Diabetes also disproportionately affects this population. This project examines whether glucose dysregulation may contribute to pain risk in Native Americans

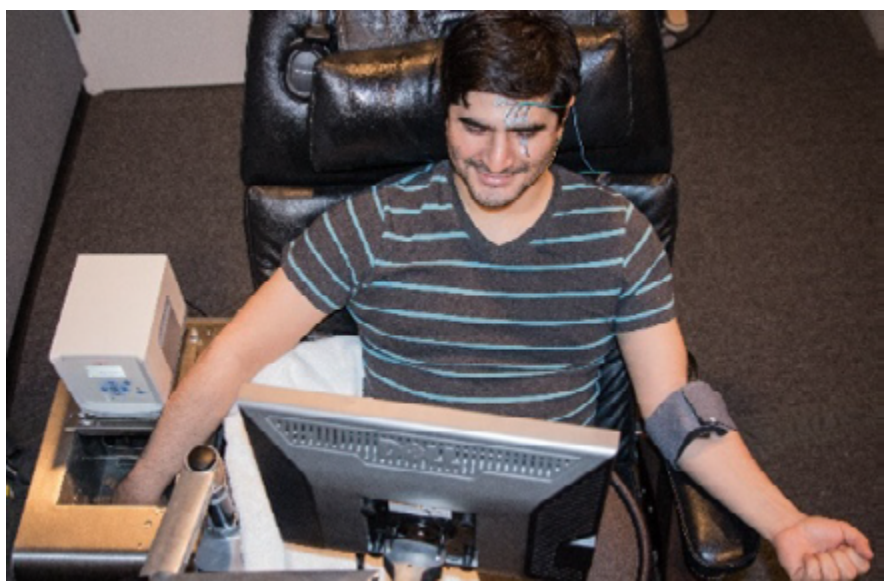
Testing uses state-of-the-art methods to assess the nervous system (peripheral fibers, central sensitization, pain inhibitory processes, pain perception).



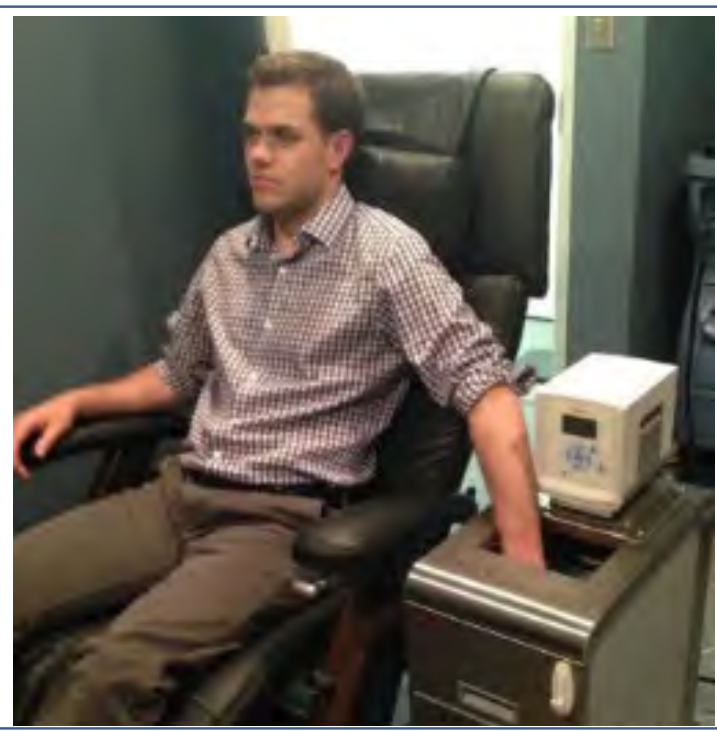
Peripheral A-delta fibers are being assessed from contact heat evoked potentials evoked from the distal leg



A sensor is applied to the back of the leg to record a marker of central sensitization (spinal cord hyperexcitability).



Pain inhibitory processes are tested using a “pain inhibits pain” paradigm



Pain perception is assessed from a painfully cold circulating water bath

Accomplishments:

- Data collection started March 2019
- To date, 26 individuals have completed testing
- Data collection was paused following pandemic onset, but has now resumed

INCREASING MOTHERS' CONNECTION TO THEIR BABIES DURING PREGNANCY HELPS THEM TO BE HEALTHIER

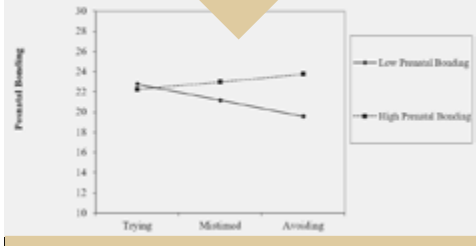
ENHANCING MATERNAL-FETAL BONDING TO PROMOTE HEALTHY PREGNANCIES AND REDUCE ADVERSE PERINATAL OUTCOMES

PI: Karina M. Shreffler, Oklahoma State University
OCAST Project: HR19-129 Research Area: Health Research

Pregnant women who feel more attached to their babies engage in healthier behaviors. Our study tests an intervention designed to enhance maternal prenatal bonding.

Bonding is critical for infants

WOMEN WHO HAVE AN UNINTENDED PREGNANCY ARE AT PARTICULAR RISK FOR LOW POSTPARTUM BONDING WHEN THEY HAVE LOW PRENATAL BONDING.



BLOOM Video 1

INTERVENTION GROUP

PARTICIPANTS IN THE TREATMENT GROUP ENGAGE IN A 2--WEEK INTERVENTION USING EXPLAINER VIDEOS

Preliminary results

THE BLOOM INTERVENTION INCREASED PRENATAL ATTACHMENT OVER A 2-WEEK PERIOD

PI KARINA SHREFFLER TRAINS GRA TARA WYATT ON ENROLLMENT AND STUDY PROCEDURES (PRE-COVID-19)

Recent Accomplishments:

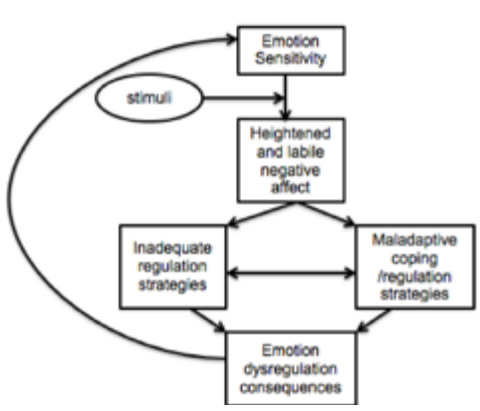
- Survey planning and programming into REDCap is complete; participant payments are set up in the ClinCard system; GRAs are fully trained.
- Due to the COVID-19 pandemic, our study protocol shifted to a fully-virtual study. This change resulted in the development of explainer videos since GRAs could not explain the intervention in person. Video production is expected to be complete by 1/31/21.

Understanding Difficulties with Regulating Emotions

Identifying a Direct Path to Emotion Dysregulation in Borderline Personality

PI: Stephanie N. Mullins-Sweatt, Oklahoma State University **OCAST Project Number: HR-18-079** **Research Area: Psychology**

Emotion dysregulation (ED) is ***directly*** related to ***significant and serious*** negative health outcomes, such as suicide, substance misuse, and risky sexual behavior.



Carpenter & Trull (2012) Model of Emotion Dysregulation

Please select one emotion that most accurately describes this facial expression:

A. Neutral
B. Happy
C. Sad
D. Disgust
E. Fear
F. Anger

Identification of prototypic emotions example

Long-term: Identify the pathways to test the *direct route from emotion sensitivity to heightened negative and unstable affect*.

Facial morphing sensitivity task examples

Broad Impact

This research will **broadly impact** the field of psychopathology by ***gaining a precise understanding of the pathway*** to ED.

Understanding the ***biopsychosocial mechanisms*** by which components of ED interact to produce negative outcomes will inform interventions.

Recent Accomplishments

- ***Successfully recruited*** 18 individuals in **Year 2** prior to disruptions by COVID19, which stalled data collection.
- Participants completed Session 1 and 2, momentary assessment, and emotion discrimination tasks.
- Developed protocol for online administration for Year 3.

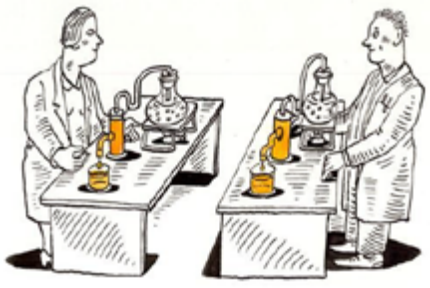
How strong is addiction medicine research?

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

Matt Vassar, Oklahoma State University Center for Health Sciences

Research area: Meta-research, addiction medicine

OCAST Grant No. HR18-119



Reproducible research can be independently performed, replicated, and verified

Transparency with potential conflicts of interest reduces bias and increases reliability of results

Recent Accomplishments & Findings

- Year 1 - 50% of addiction clinical trials sampled (244 of 487) were found to be at high risk of having bias in the study design.
- Year 2 – 50% of systematic reviews sampled (5 of 10) could not have the summary effects approximated by replicating the study methods.
- Year 3 – Evaluate “spin” and financial conflicts of interest in addiction medicine systematic reviews

Investigating the Relationship between Environmental Exposures and Cancer in Oklahoma

Improving Geocoding of Cancer Registry Data and Development of a Spatiotemporal Database of Environmental Exposures

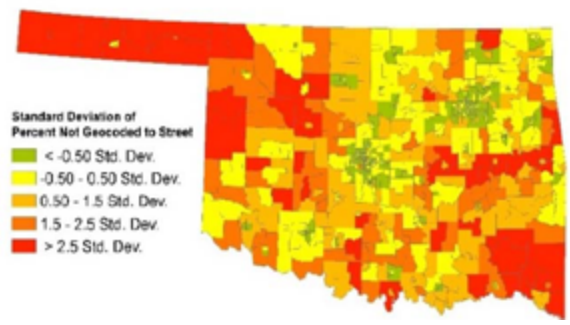
Michael C. Wimberly, U. of Oklahoma

OCAST Project Number: HR16-04

Research Area: Public Health

Project Highlights

- Oklahoma has the 11th highest age-adjusted cancer mortality rate in the US.
- It is important to have accurate address data to understand potential environmental and behavioral risk factors for cancer.
- Development of an environmental database provides a single location for multiple types of environmental contaminants to facilitate health research.
- By better understanding the distribution of cancer in Oklahoma, we can work with policy makers to enhance prevention and screening areas in high-risk locations and populations.



Distribution of Oklahoma Central Cancer Registry cancer cases not geocoded to the street level

Theme	Total
Administrative	4
Air	15
Industrial	3
Land	7
Physical Characteristics	31
Water	53
Total	**113**

Data items by theme in the environmental exposure database[1]

Recent Accomplishments

- Completed an environmental exposure database for Oklahoma[1]
- Completed geocoding Oklahoma Central Cancer Registry and University of Oklahoma Central Cancer Registry Geocoding
- Compiled data on residential history
- Next step: Complete spatial analysis of geocoded cancer data

Why Is This Work Significant?

- We improved geocoding of Oklahoma Central Cancer Registry records by 40%
- These new data will help us to better understand the types of environmental exposures that increase cancer risk

1. Dilekli N, Gopalani SV, Campbell JE, Janitz AE. A geospatial environmental concentrations database of Oklahoma, United States. In Press at Data in Brief, August 2019.

Scar tissue that forms after abdominal surgery may cause costly long-term health problems

The Role of PDGF Signaling Mechanotransduction Nexus in the Development of Peritoneal Adhesions

PI: William L. Berry, OUHSC

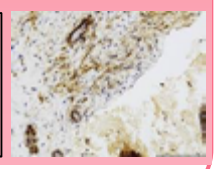
OCAST Project: HR20-131

Research Area: Physiology/Pharmacology

The Problem

- 90% of all patients have internal scar tissue (peritoneal adhesions) that forms following surgery
- Healthcare-associated costs to treat peritoneal adhesions exceed 1 billion annually
- One of the most prevalent cell types found in peritoneal adhesions are called myofibroblasts (brown cells in **Figure 1**)
- Myofibroblasts secrete the material necessary to form peritoneal adhesions

Figure 1. Smooth muscle alpha-actin (SMαA) positive myofibroblasts (brown stain)



The Approach

- Smooth muscle alpha-actin has been shown to be positively regulated by the proteins MRTF-A and MRTF-B which are regulated in part by platelet-derived growth factor (PDGF) signaling
- Myofibroblasts express MRTF-A and MRTF-B (**Figure 2**)
- Targeting these proteins may prevent or reverse myofibroblast formation

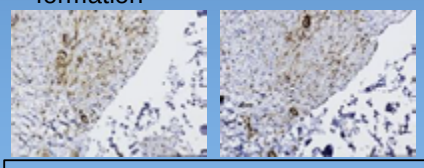
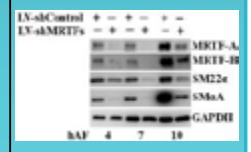


Figure 2. Myofibroblasts in adhesive tissue express the genes responsible for MRTF-A (left) and MRTF-B (right).

The Results

- Hypothesis: Blocking MRTF-A/B will reduce the expression of genes necessary for myofibroblast formation
- We utilized lentiviral vector technology to block MRTF-A/B which reduced the expression of important genes critical to the formation of myofibroblasts (**Figure 3**)
- Therapies to reduce MRTF-A/B expression may be beneficial in patients undergoing abdominal surgery

Figure 3. Blocking MRTF-A/B reduces the expression of SMαA in human patient-derived peritoneal adhesion myofibroblasts (hAF)



Fighting for Brain Health in Aging with "Antiaging" Supplements

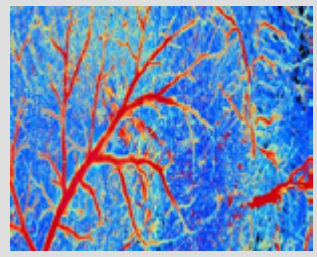
Novel Mechanism of Age-Related Cerebrovascular Dysfunction

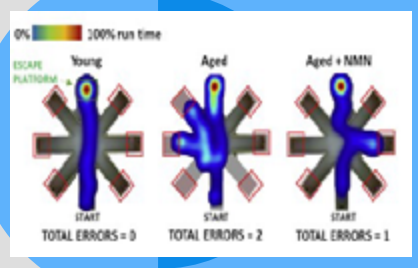
PI: Anna Csiszar, University of Oklahoma Health Sciences Center

OCAST Project: HR-18-092 Research Area: Physiology

Clinical Problem: Cerebral blood flow is essential for the maintenance of normal neuronal function, and becomes progressively impaired during aging, increasing the risk for vascular cognitive impairment. NAD+ is a rate-limiting co-substrate for anti-aging enzyme SIRT1, which is a key regulator of mitochondrial function, cellular redox homeostasis and vascular function. With age cellular NAD+ availability decreases, which is a critical driving force in aging processes. NAD+ biosynthesis by treatment with nicotinamide mononucleotide (NMN) reverses age-related dysfunction in multiple organs.

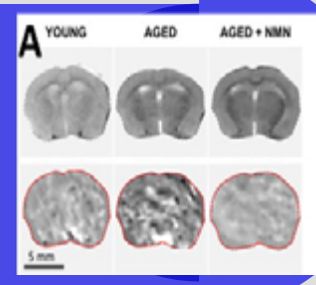
NMN

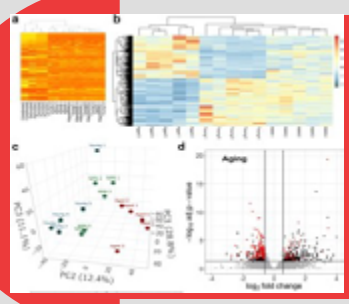




NMN imrpoves learning and memory processes in mice models of aging

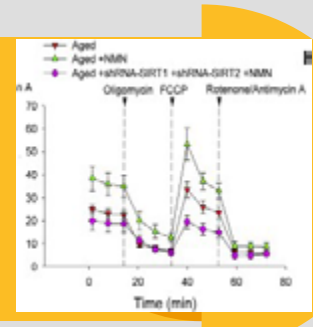
NMN increases blood supply to the brain





NMN rejuvenates the expression of mitochondrial genes improving brain health

NMN treatment is reversing age-related decline in mitochondrial function



Potential Solution: **NMN treatment improves blood supply to the brain cells and restores healthy brain function in aging.**

Chemical probes for developing effective antismoking agents

DISCOVERY OF INDOLIZIDINE (-)-237D ANALOGS AS SELECTIVE α6 NICOTINIC RECEPTOR ANTAGONISTS*

PI: Syed Raziullah Hussaini, The University of Tulsa OCAST Project: HR18-049 Research Area: Physiology/Pharmacology

Cigarette smoking causes 7,500 deaths in Oklahoma each year due to many chemicals present in smoke

Smoking cessation drugs have many side effects as they bind to multiple brain receptors

Smoking transfers nicotine to the brain where it releases a chemical dopamine which causes addiction

We aim to find compounds that bind to only one brain receptor and help people quit smoking without many side effects

Indolizidine (–)-237D is selective toward one receptor and is a potent dopamine inhibitor

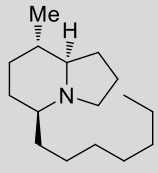
We are preparing and evaluating indolizidine-based compounds that are more potent, selective, and better drug candidates

Utilizing computer-modeling to find best indolizidine-based compounds (OU-HSC (Dr. Blaine Mooers))

Synthesis (TU, Syed Hussaini)

Adama Kuta, a graduate student monitoring the progress of a reaction

Pharmacological testing (OSU-CHS, Dr. David Wallace)



IC_{50} = 0.18 nM
I_{max} = 76%

Indolizidine (–)-237D

Recent Accomplishments:
Optimized a synthetic method and finalized characterization of a few intermediates which resulted in one publication (ACS Omega 2020, 5, 24848)

Heating of antibiotic loaded nanoparticles can clear painful bone infections

Magnetic hyperthermia combined antimicrobial targeting of bone pathogens

PI: Ashish Ranjan, Oklahoma State University OCAST Project# HR17-060 Research area: Osteomyelitis

Bone infection is **dangerous**

and can lead to **amputation**

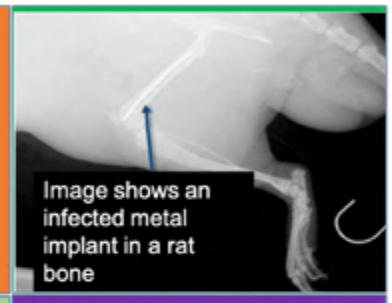


Image shows an infected metal implant in a rat bone

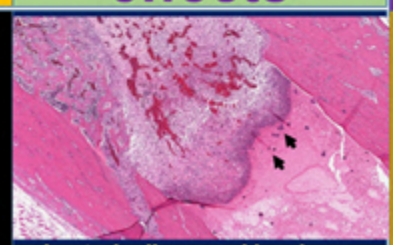
Antibiotic Treatment is **Challenging**

and cause **Toxic side effects**

We will deliver antibiotics with nanoparticles to bones and release them with heating

The benefits

- Minimize surgery
- Eliminate need of amputations
- Reduce antibiotic toxicity



bacteria dispersed in a bone (arrow)

Accomplishments

Increased antibiotic delivery and killing of bone bacteria

Why Do We Develop Alzheimer's Disease In Old Age?

Susceptibility to Amyloid Oligomers in Response to Aging and Insulin/IGF-1 Resistance

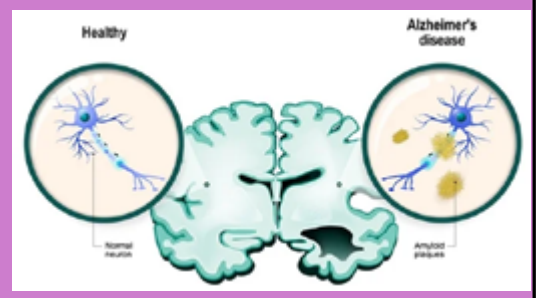
PIs: William Sonntag, PhD Sreemathi Logan, PhD
OCAST Project: HR18-120

University of Oklahoma HSC
Research Area: Cell/Molecular Biology

Alzheimer's Disease only occurs as people get OLDER –

why?

Treatments for Alzheimer's Disease MUST understand mechanisms of aging



Increased amyloid β (1-42) levels are part of the mechanisms of Alzheimer's Disease

Our research finds that

Younger animals are resistant to the effects of amyloid β

AND

Older animals are very sensitive to amyloid β

The 'resilience' of younger animals may be related to levels of IGF-1

Understanding the key interactions of age and disease is critical to human health

Promoting Healthy Aging

Zombie cells cause learning and memory deficits in brain cancer patients who received radiation therapy

Irradiation-induced cognitive decline: role of endothelial senescence

PI: Zoltan Ungvari, OUHSC OCAST Project: HF19-028 Research area: Neurobiology

CLINICAL PROBLEM

Radiation therapy is a common treatment option in brain cancer patients

Long term side effect of radiation therapy - Memory and learning impairments in 40-50% of survivors

HOW WE ADDRESSED IT

Our lab developed a mice model mimicking the clinical doses of radiation to understand why it affects learning and memory

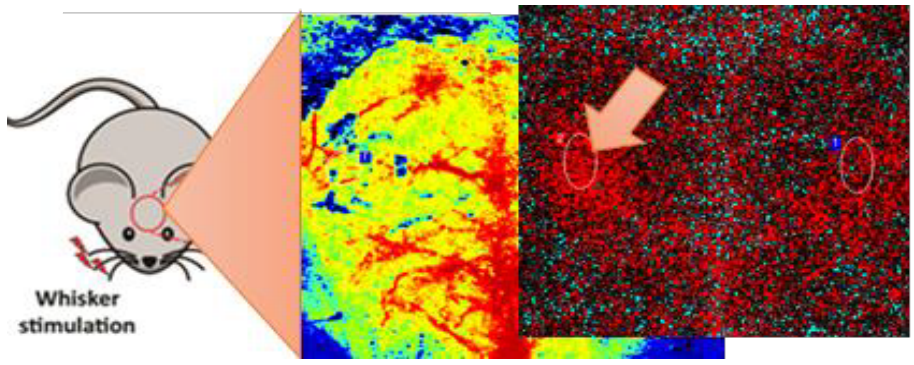
Radiated mice showed poor blood flow responses to the brain

Our research will focus on understanding how radiation affects the cells lining the blood vessels of the brain so we can devise drug targets to prevent this adverse side-effect of radiation

RESEARCH HIGHLIGHTS

Our results showed that radiation causes DNA damage leading to premature aging of the cells (aka Zombie cells) lining the blood vessels in the brain

Eliminating zombie cells using drugs (aka senolytics) improves blood flow responses and memory in radiated mice



Imaging method to assess blood flow responses in mice brain

POTENTIAL SOLUTION

- New treatment to prevent radiation-induced side-effects to the brain
  - Improve the quality of life of cancer survivors
- Potential to apply the current findings for age-related memory decline

Hunt For A New Drug For The Treatment Of Diabetes

Pancreatic beta cell protection of natural product K50 and its mechanism of action

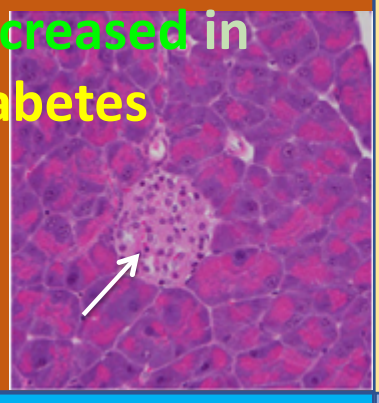
PI: Weidong Wang, OUHSC **OCAST Project: HR17-097** **Research Area: Physiology /Pharmacology**

People with **Diabetes** have **high** blood **glucose** levels

Diabetes affects **400** million people globally

Beta cells in the pancreas produce **insulin** to control blood glucose

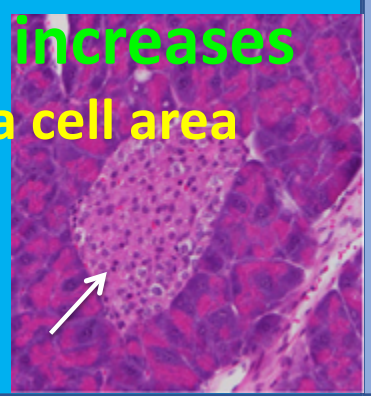
Beta cell area is **decreased** in **diabetes**



More beta cells, **better** blood **glucose** control

Our research aims to discover **new drugs** that **increase** beta cell area

A new chemical K50 increases beta cell area



K50 treatment **lowers** blood **glucose** in diabetic mice

Recent accomplishments:

- **K50** protects against beta cell death
- **K50** suppresses ER stress.

New Targets on Blood Vessels for Metabolic Syndrome

Endothelial regulation of high-fat diet-induced obesity

PI: Jian Xu, OU Health Sciences Center **OCAST Project: HR17-046** **Research Area: Physiology/Pharmacology**

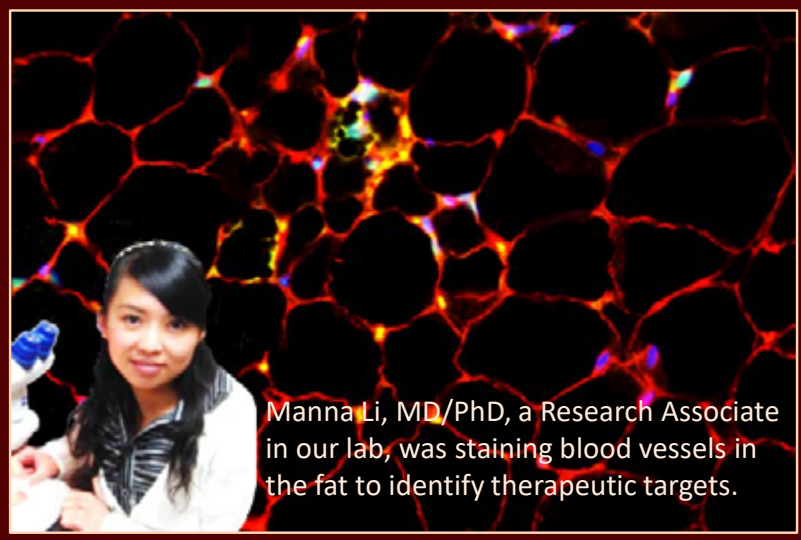
FACTS

Obesity: 3rd major cause of poor health
(1st malnutrition, 2nd infectious diseases)

Functional blood vessels are essential in health.

HYPOTHESIS

Targeting a blood vessel protein improves obesity-associated metabolic diseases.



Manna Li, MD/PhD, a Research Associate in our lab, was staining blood vessels in the fat to identify therapeutic targets.

FINDINGS

Mice fed a high-fat diet loss a blood vessel protein and become obesity.

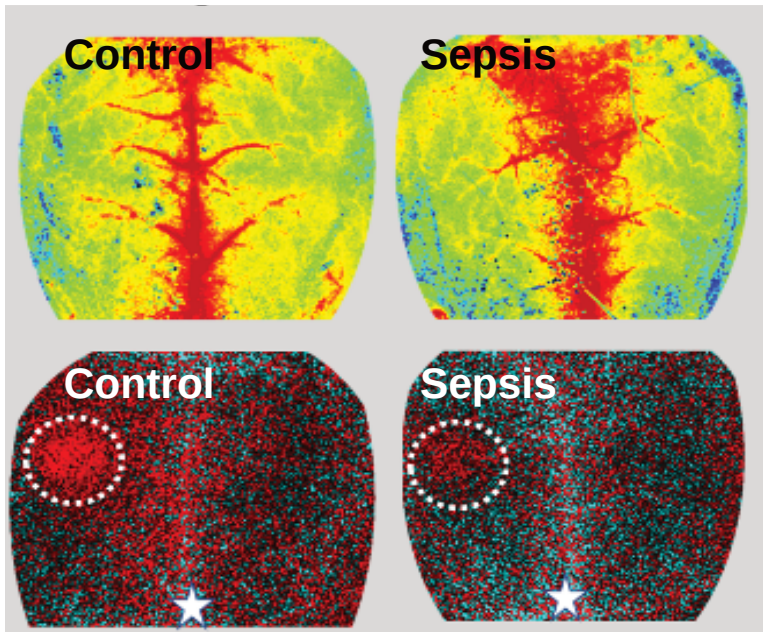
Therapeutic production of this protein improves metabolism in obese mice.

Sepsis is associated with higher risk of death in older adults and higher incidence of memory loss in survivors

Prevention of sepsis-induced multiple organ failure in old age

PI: Andriy Yabluchanskiy, MD, PhD OCAST project: HR17-070-1 Research area: Physiology

- Sepsis develops when bacteria (or other infection organisms) get into the bloodstream and spread throughout the body
- Sepsis is the tenth leading cause of death in patients over the age of 65
- About 50% of sepsis survivors over the age of 60 develop progressive loss of memory
- The mechanisms that underlie this memory loss are currently unknown



- We know that brain requires constant blood supply when neurons are activated
- Our studies show that the coordination between active neurons and blood supply is altered in sepsis (representative image on the left)
- In fact, it appears that sepsis reduces appropriate blood supply during periods of intensive neuronal activity almost by 30% (calculations are on the right)

- We also found that blood vessels are compromised not only in the brain, but in larger vessels such as aorta too
- Image on the right shows that aorta from septic animals does not relax as good as the one from control (non-septic) animal
- Our findings suggest that sepsis leads to generalized impairment of vascular health, which may be the leading mechanism behind development of multiple organ failure