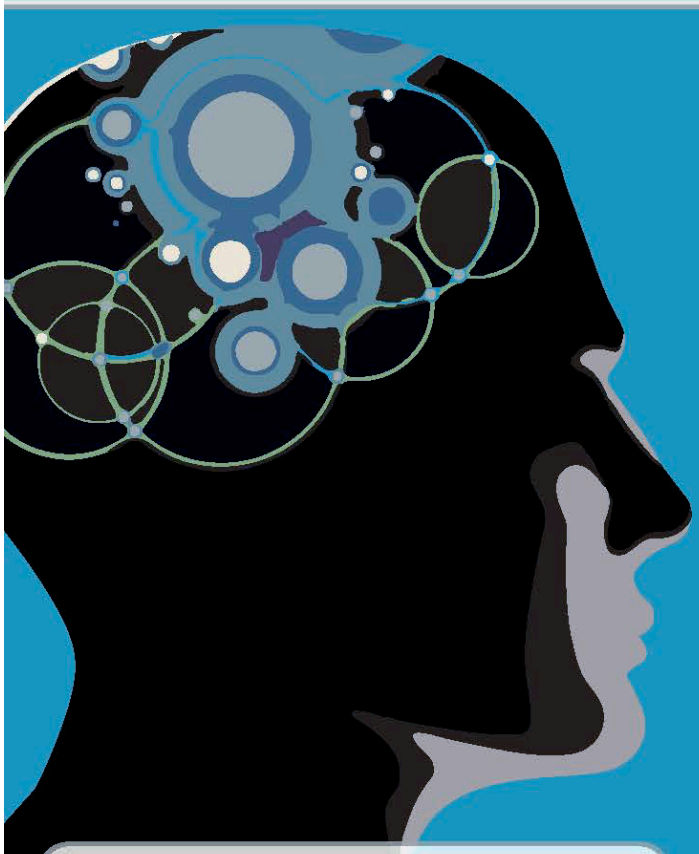
Translational Neuroscience



Annual Symposium

Center of Excellence for Translational Neuroscience and Therapeutics (CTNT) and Garrison Institute on Aging (GIA)

Wednesday, May 10th, 2023
Academic Event Center

11:30 AM **Opening Remarks**

Dr. Lance McMahon, Senior Vice President for Research and Innovation
Dr. Volker Neugebauer, Director, Center of Excellence for Translational Neuroscience and Therapeutics (CTNT)
Dr. Josee Guindon, Translational Neuroscience and Pharmacology Graduate Concentration Advisor

12:00 PM **Keynote Lecture**"Translating Pain Therapeutics: Examples from Preclinical and Clinical Profiles and Implications"

Smriti Iyengar, Ph.D. Program Director, Preclinical Screening Platform for Pain (PSPP), Division of Translational Research | National Institute of Neurological Disorders and Stroke NINDS|NIH

1:00 PM **Q & A Session with Keynote Speaker**

1:30 PM **CTNT Collaborative Research Presentations**

Nadezhda German, Ph.D., Associate Professor, Pharmaceutical Sciences, School of Pharmacy
"Development of urea-based analogs for the treatment of multiple sclerosis"

Leslie Shen, Ph.D., CCRP, Associate Dean for Research and Professor of Pathology, School of Medicine
"Bioactive Compounds for Neuropathic Pain: Gut Brain Axis"

Jonathan Singer, Ph.D., Assistant Professor, Dept. of Psychological Sciences, TTU
"Prevalence, Diagnosis, and Support for Persons with Neurodegenerative Disorders and their Family Members in Urban and Rural Texas"

3:00 PM Poster Session

4:30 PM Refreshments

5:00 PM Awards Ceremony

Distinguished Keynote Speaker and Alexander D. Kenny Lecturer

Smriti Iyengar, Ph.D.
Program Director
Preclinical Screening Platform for Pain (PSPP)
Division of Translational Research | NINDS

Annual Symposium

Center of Excellence for Translational Neuroscience and Therapeutics (CTNT) and Garrison Institute on Aging (GIA)

Lunch will be provided for registered participants

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12:00 PM **Keynote Lecture**

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3:00 PM **Poster Session**

4:30 PM **Refreshments**

5:00 PM **Alexander D Kenny Outstanding Graduate Student Award Speaker and Awards Ceremony**

Valeria Jaramillo-Martinez, Ph.D., Translational Neuroscience and Pharmacology Graduate Concentration, TTUHSC

"Pharmacoperone approach to treat early infantile epileptic encephalopathy associated with NaCT deficiency"

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TEXAS TECH UNIVERSITY
HEALTH SCIENCES CENTER

Center *of* Excellence *for* Translational Neuroscience *and* Therapeutics
Garrison Institute *on* Aging

April 25, 2023

Welcome to the *7th Annual Symposium of the Center of Excellence for Translational Neuroscience and Therapeutics (CTNT)* held jointly with the *Garrison Institute on Aging (GIA)*. The Center continues to bring together basic scientists and clinicians to stimulate scholarly activities, facilitate collaborations, and generate translational research projects. The GIA offers complementary expertise in aging-related disorders and dementias such as Alzheimer's disease and strives to serve as a hub to promote healthy aging and advance knowledge about aging-related health issues and neurodegenerative diseases through collaborations in research, education and community outreach.

At the center of CTNT and GIA is translational research through collaborative and innovative efforts to bridge basic science and clinical entities in the areas of healthy aging, aging-related diseases, nervous system / brain diseases and dysfunctions in conditions such as chronic pain, addiction, neurodegenerative diseases, and comorbid disorders. We are very grateful for the valuable support from Dr. Steven Berk, Dean of the School of Medicine and Executive Vice President for Clinical Affairs, Dr. Leslie Shen, Associate Dean for Research, School of Medicine, Dr. Lance McMahon, Sr. Vice President for Research and Innovation, Dr. Darrin D'Agostino, Provost and Chief Academic Officer, Dr. Lori Rice-Spearman, TTUHSC President, and the Garrison Family Foundation.

It is an immense honor to welcome this year's *Key Note Speaker*, Dr. Smriti Iyengar, Program Director of the Program Director, Division of Translational Research, National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH). Dr. Iyengar has kindly agreed to share with us insights into translational research and funding opportunities through a roundtable meeting and lecture. Additionally, translational research presentations by CTNT-GIA teams and posters by trainees in basic science and clinical disciplines will inform about CTNT and GIA accomplishments and stimulate innovative collaborative efforts

A special thank-you goes to our CTNT Coordinator, Lisa Moran, and to Dr. Josee Guindon, CTNT Steering Committee Member, for creating the program and organizing the event. We are also very grateful to our colleagues who generously agreed to serve as judges for the poster session.

Thank you for your interest and participation in our activities!

Volker Neugebauer, M.D., Ph.D.

Director, Center of Excellence for Translational Neuroscience and Therapeutics
Executive Director and Chief Scientific Officer of the Garrison Institute on Aging

3601 4th Street | Stop 6592 | Lubbock, Texas 79430 | T 806.743.3880| F 806.743.2744

Acknowledgements

Steering Committee

- Josee Guindon, DVM, PhD, Associate Professor, Dept. of Pharmacology & Neuroscience, TTUHSC
- Andrey Karamyshev, PhD, Professor, Dept. of Cell Biology & Biochemistry, TTUHSC
- J. Josh Lawrence, PhD, Associate Professor, Dept. of Pharmacology & Neuroscience, TTUHSC
- Lance McMahon, MS, PhD, Senior Vice President for Research and Innovation, TTUHSC
- Leslie Shen, PhD, Professor, Dept. of Pathology, TTUHSC

We would like to thank Drs. Ganapathy and Henderson for their service on the Steering Committee.

Organizing Committee

- Lisa Moran, CTNT Coordinator
- Josee Guindon, DVM, PhD, Associate Professor, Dept. of Pharmacology & Neuroscience, TTUHSC

Institutional Support

- TTUHSC SOM Dean's Office (Steven L. Berk, MD, and Leslie Shen, PhD)
- TTUHSC Office of Research (Lance McMahon, MS, PhD)
- TTUHSC Provost's Office (Darrin D'Agostino, DO, MPH, MBA)
- TTUHSC President's Office (Lori Rice-Spearman, PhD)
- Garrison Family Foundation

CTNT Factsheet

The Center of Excellence for Translational Neuroscience and Therapeutics (CTNT) strives to bridge preclinical "basic science" research and the clinical setting for innovative collaborative efforts to advance knowledge about mechanisms of nervous system functions and dysfunctions, brain diseases, neuropsychiatric and other clinically relevant disorders for the development of novel and improved diagnostic and therapeutic tools and strategies (https://www.ttuhsc.edu/centers-institutes/translational-neuroscience-therapeutics).

Founded in 2015 and based in the Department of Pharmacology and Neuroscience, School of Medicine, TTUHSC, CTNT has grown to 40 members from 15 different departments or institutes at TTUHSC and TTU, including 23 faculty doing basic preclinical research 15 faculty working with patients or human subjects (https://www.ttuhsc.edu/centers-institutes/translational-neuroscience-therapeutics/leadership-members.aspx). The unique focus of CTNT on translational research rests upon its ability to bring together basic scientists and clinical partners to develop scholarly activities such as research projects and grant applications. The emphasis is on collaborative initiatives that are unlikely to be accomplished by an individual alone. Identifying knowledge gaps and exploring disease mechanisms and potential targets for therapeutic advances are the objectives of translational research. Sharing this information with colleagues and trainees through their participation in this process represents an educational component.

To do so, CTNT provides the expertise and infrastructure for multidisciplinary translational work from molecular to systems levels and to clinical disciplines. Mechanisms of support include the Annual Symposium, CTNT Research Meetings and Grant Development Program (Translational Research Club), the Translational Neuroscience and Pharmacology Distinguished Lecture Series, matching seed funds for collaborative translational research by teams of basic science and clinical faculty, and shared research tools. (https://www.ttuhsc.edu/centers-institutes/translational-neuroscience-therapeutics/research-support.aspx).

GIA Factsheet

Established in 1999 by the Board of Regents, the Institute for Healthy Aging was renamed the Garrison Institute on Aging (GIA) in 2005 in honor of Mildred and Shirley L. Garrison. The GIA is designed to improve the quality of life of the aging population through innovation and collaborative programs in research, community outreach and education, which are well-aligned with the vision of TTUHSC to transform health care through innovation and collaboration. The GIA strives to play a leadership role in initiatives on aging and aging-related disorders and brain diseases across TTUHSC and beyond (https://www.ttuhsc.edu/centers-institutes/garrison-aging/default.aspx).

Our mission is to promote healthy aging and address health issues of the aging population through cutting edge research and innovative educational and community outreach programs. The GIA conducts and facilitates research into investigating the causes of neurodegenerative disease and dementias such as Alzheimer's and related brain dysfunctions. The GIA's educational programs for the community inform on aging-related health issues such as dementias and mental health, on preventative medicine, and on challenges impacting the geriatric population.

Our vision is to serve as the leader and central hub within TTUHSC for collaborative initiatives in research, interdisciplinary education and community outreach related to healthy aging, aging-related disorders, brain diseases and dementias, and mental health through a combination of GIA-based programs and collaborations with

colleagues across TTUHSC and beyond. The GIA plans to continue and grow its more than 40 collaborative projects involving preclinical and clinical studies on aging-related conditions and brain disease.

GIA support and resources for collaborations include research laboratories for molecular biology, electrophysiology, behavioral assessment and imaging, a brain bank, and Project FRONTIER, a longitudinal study to collect epidemiological data on cognitive health and aging in a multiethnic adult sample from rural communities of West Texas. Community outreach and education programs include Healthy Aging Lecture Series, Care Partner Academy, Caregiver Stress-Busting Dementia Program, Mental Health for Caregivers, Dementia Friendly Lubbock (part of Dementia Friendly America and Healthy Lubbock Initiative (with Mayor's Fitness Council), and RSVP (Retired and Senior Volunteer Program established in 1979 under the umbrella of the Corporation for National and Community Service (CNCS), now identified as AmeriCorps Seniors), and a newly implemented mental health telemedicine program for informal caregivers of persons with dementia in rural Texas.

Collaborations

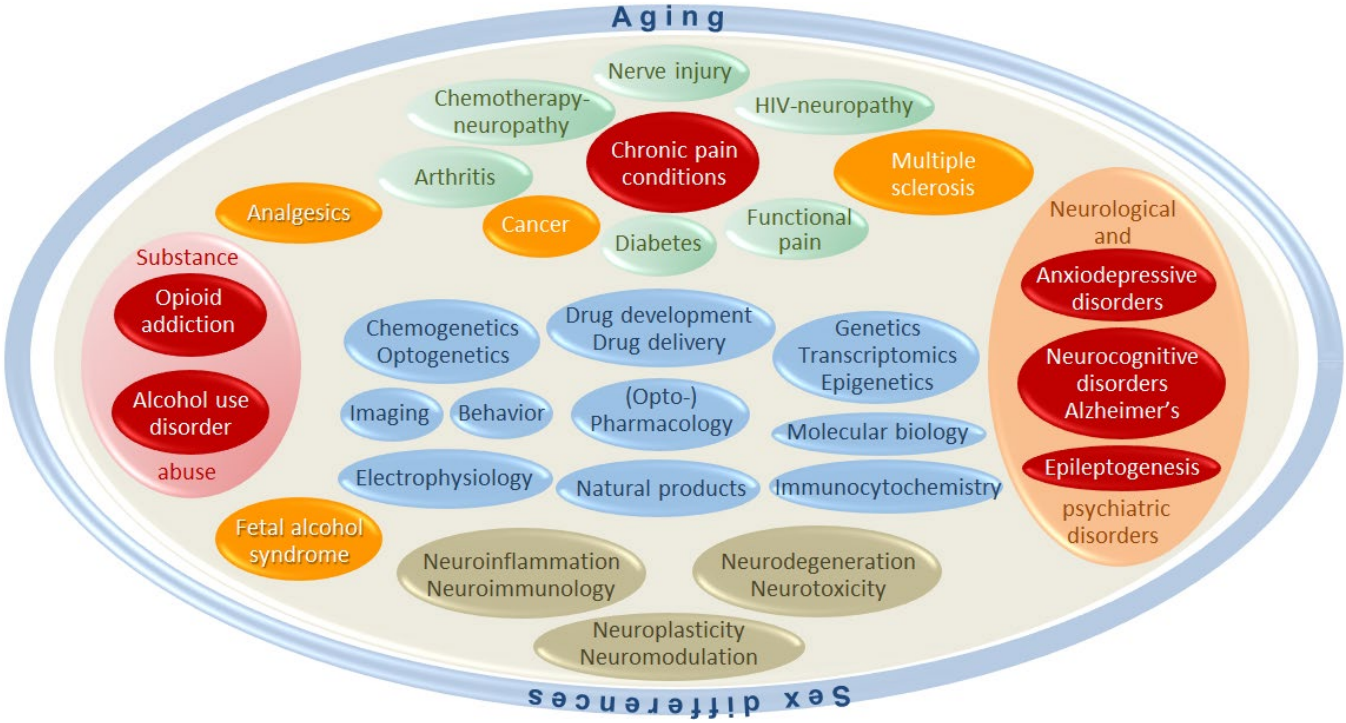
CTNT

CTNT has stimulated collaborations on basic and clinical research projects through seed funds, grant development meetings, and formal and informal networking activities. These resulted in 29 publications 33 scientific meeting abstracts coauthored by more than one CTNT member out of 89 publications and 48 abstracts, and 34 currently funded grants, more than half involving collaborations of CTNT members, for nearly $39 Mio, including more than $37 Mio in federal funding (NIH, USDA). Collaborating departments and institutes at TTUHSC (18) and TTU (7) include Biological Sciences (TTU), Biotechnology and Genomics (TTU), Cell Biology & Biochemistry (SOM), Cell Physiology and Molecular Biophysics and Center for Membrane Protein Research (SOM), Center of Excellence for Integrative Health (SOM), Center for Speech, Language, and Hearing Research (SHP), Center for Tropical Medicine and Infectious Diseases (SOM), Garrison Institute on Aging (TTUHSC), Human Development and Family Sciences (TTU), Immunology and Molecular Microbiology (SOM), Internal Medicine (SOM), Kinesiology and Sport Management (TTU), Laboratory Science and Primary Care (SHP), Mechanical Engineering (TTU), Medical Education (SOM), Neurology (SOM), Nutritional Sciences (TTU), Pathology (SOM), Pharmaceutical Sciences (SOP), Pharmacology and Neuroscience (SOM), Psychiatry (SOM), Psychological Sciences (TTU), Public Health (SPPH), Rehabilitation Sciences (SHP), Surgery (SOM), as well as Baylor College of Medicine, Louisiana State University, Mayo Clinic, Memorial Sloan Kettering Cancer Center, Oregon Health & Science University, North Carolina A&T State University, Ohio State University, Penn State, Scripps Research Institute, Temple University, University of Alabama, University of Arizona, University of Arkansas, University of California Davis, University of Connecticut, University of Nebraska, University of Nevada, University of North Texas, University of Southern Florida, University of Utah, University of Washington, Utah State University, UTHSC Houston, UT San Antonio, UT Southwestern, Washington State University, and Weill Cornell.

GIA

GIA is leading or has generated preclinical (20) and clinical (26) collaborative research projects on aging, Alzheimer's disease and other neurogenerative diseases, and brain disorders. These involve collaborators at various departments and institutes across TTUHSC (13) and TTU (6) and include Biological Sciences (TTU), Cell Biology & Biochemistry (SOM), Electrical & Computer Engineering (TTU), Family Medicine (SOM), Garrison Institute on Aging (TTUHSC), Immunology and Molecular Microbiology (SOM), Internal Medicine (SOM), Kinesiology and Sports Medicine (TTU), Mathematics and Statistics (TTU), Neurology (SOM), Nutritional Sciences and Obesity Research Institute (TTU), Pharmacology and Neuroscience (SOM), Psychological Sciences (TTU), Pathology (SOM), Pediatrics (SOM), Pharmaceutical Sciences (SOP), Psychiatry (SOM), Public Health (SPPH), SON, as well as Creighton University, Louisiana Tech University, South Texas ADRV Brain Bank, TARCC, Texas A&M, UT Health San Antonio.

Collaborative Translational Research Areas – CTNT and GIA



Keynote Lecturer

Smriti Iyengar, Ph.D.

Program Director, Preclinical Screening Platform for Pain (PSPP), Division of Translational Research | National Institute of Neurological Disorders and Stroke (NINDS) |NIH

Smriti Iyengar, Ph.D., is Director Preclinical Screening Platform for Pain (PSPP) program, and Program Director, in the Division of Translational Research, National Institute of Neurological Disorders and Stroke, National Institutes of Health, USA. She is an adjunct Senior Research Professor in the Department of Anesthesia, and in the Department of Clinical Pharmacology, Indiana University School of Medicine. She was formerly at Eli Lilly and Company, and prior to that at G.D. Searle and Company, Schering-Plough Inc. and Ciba Geigy. She is a neuroscientist with extensive research experience focused on neuro-disorders including pain and headache. Her drug discovery expertise includes target, lead and clinical candidate identification and characterization as well as translational and clinical development, regulatory strategy, launch and commercialization. Her postdoctoral training was at Rutgers University as a Charles and Johanna Busch Fellow in the Dept. of Physiology and Neuroscience, with her research focused on central regulation of opioid function and central regulation of neuroendocrine function including the HPA axis and stress. She received her Ph.D. from M.S. University of Baroda, India, where she worked on the neurochemical basis of behavior in the developing brain.

Graduate Student Award Speaker

Valeria Jaramillo-Martinez, Ph.D.

Translational Neuroscience and Pharmacology Graduate Concentration, TTUHSC

Established in 2006, the ADK Outstanding Graduate Student Award is reserved for the exceptional doctoral student that Pharmacology and Neuroscience faculty have determined has truly excelled in every aspect of graduate training- coursework, research, and leadership. In the past 15 years only six doctoral students have received this prestigious award.

Valeria Jaramillo-Martinez received her B.S. in biochemistry from Southeast Missouri State University, Cape Girardeau, MO, USA in 2016. She received her M.S. in chemistry from Eastern New Mexico University, Portales, NM, USA in 2018. She was admitted to the TTUHSC GSBS Ph.D. program in Fall 2018. She worked under Dr. Urbatsch's and Dr. Ganapathy's mentorship for her Ph.D. dissertation project that focuses on characterizing NaCT six most prominent disease-causing mutations, with the long-term goal of developing novel therapies. During her time at TTUHSC she co-authored five research manuscripts, two review articles, one commentary, and one book chapter. In March 2023, she passed her Ph.D. dissertation defense.

Pharmacoperone approach to treat early infantile epileptic encephalopathy associated with NaCT deficiency

Early infantile epileptic encephalopathy type 25 (EIEE25) is a disease that causes epileptic seizures in infants shortly after birth and lasts throughout their lives. EIEE25 symptoms include difficulty speaking and slow and limited motor skills. Currently, there is no treatment for EIEE25. This disease is associated with single-point loss-of-function mutations in the human sodium-coupled citrate transporter (NaCT, Solute Carrier SLC13A5, or mINDY). NaCT is responsible for transporting Na+ and citrate3- into the cell. Importantly, NaCT is the mammalian ortholog of Drosophila INDY (I'm Not Dead Yet, INDY), a lifespan determinant in this organism. In humans, NaCT is primarily expressed in the brain, liver, testes, bone, and teeth. In the brain, NaCT is expressed exclusively in neurons and astrocytes, where citrate plays key roles in the synthesis of neurotransmitters, and energy generation. In contrast, Slc13a5-null mice exhibit minimal evidence of neurological dysfunction, but have a beneficial metabolic phenotype related to the loss of function of the transporter in liver; the beneficial features include resistance to diet-induced obesity, and protection against diabetes, insulin resistance, and metabolic syndrome. The absence of epilepsy in Slc13a5-null mice might be due to the C57BL/6 background because these mice are known to be resistant to epilepsy. To date, 22 missense disease-causing mutations have been identified in human NaCT and eight of them have been studied. The underlying defect varies in these eight mutants that cause loss of function. Some mutations exhibit normal plasma membrane protein expression, but the transport function is diminished while other mutations appear to affect protein folding and proteolytic stability, which may lead to defective trafficking to the cell surface. Published studies, done in cells with heterologous expression, show contradictory results in protein expression of mutant NaCTs, largely due to the lack of NaCT-

specific antibodies that recognize the human protein in immunofluorescence and/or Western blot studies. The results of this research project characterize the six most common missense mutations, which brings us one step closer to understanding the defects of disease-causing mutations at the molecular level, allowing us to begin dissecting NaCT-trafficking pathway(s). Additionally, establishes an in vitro assay for discovery screening of small molecules that can restore the trafficking defects and transport function in Class II mutants of NaCT.

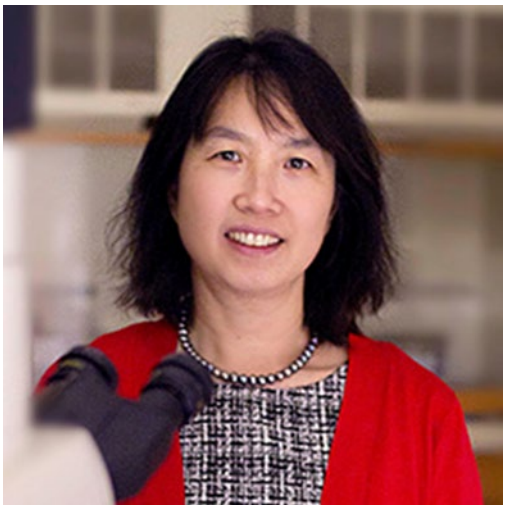
Nadezhda German, Ph.D.

Associate Professor,
Pharmaceutical Sciences, School of Pharmacy, TTUHSC

Dr. Nadia German is a tenured Associate Professor at the Texas Tech University Health Sciences Center (TTUHSC). She received her Ph.D. with an emphasis in Medicinal Chemistry at the University of Iowa, working with Dr. Robert Kerns. Her training continued at Virginia Commonwealth University, where she worked in Dr. Richard Glennon's laboratory, followed by two years at the Research Triangle Institute in the group of Yanan Zhang. Her current research focuses on developing molecules with two different biological activities: the ability to modulate GPCRs and kill cancer cells. Her work is funded by NIH and various foundations' seed grants. She has published over 40 peer-reviewed papers and three book chapters and has 4 patents filed/awarded for the research projects initiated in her laboratory.

Presentation: Development of urea-based analogs for the treatment of multiple sclerosis

The dopaminergic system can regulate the immune response in different conditions. The therapeutic potential of modulation of dopamine activity has been extensively discussed for multiple neurodegenerative diseases. These dopaminergic agents have been proposed to restore dopamine levels and inhibit neuroinflammation. Recently, we have discovered a new class of dopamine transporter inhibitors (DAT inhibitors) highly selective for dopamine transporter over other G protein-coupled receptors. Our research has evaluated the efficacy of these DAT inhibitors and their anti-inflammatory effects. Our findings showed that this class of compounds has statistically significant anti-inflammatory effects and improved motor deficits and pain behaviors in an experimental autoimmune encephalomyelitis model of multiple sclerosis. To our knowledge, this is the first study demonstrating the therapeutic potential of DAT inhibitors in animals with induced autoimmune encephalomyelitis, providing additional evidence for the dopamine-related neuroinflammation model.



Leslie Shen, Ph.D., CCRP

Associate Dean for Research and
Professor of Pathology, School of
Medicine, TTUHSC

Dr. Chwan-Li (Leslie) Shen is an Associate Dean for Research and Professor of Pathology and Physiology, School of Medicine, Texas Tech University Health Sciences Center, Lubbock, Texas, USA. Dr. Shen obtained her B.S. degree from Providence University, Taiwan, her MS degree from Texas Tech University, Texas, and her PhD degree from Purdue University, Indiana, USA. Within her faculty career, she has developed a broad range of expertise in molecular mechanisms, animal models, and clinical trials using bioactive compounds/phytochemicals in the management of chronic diseases including osteoporosis, osteoarthritis, sarcopenia, diabetes, obesity, and neuropathic pain. Dr. Shen has successfully translated her animal study results into human clinical trials and her translational research program has been funded by federal grants (National Institutes of Health and United States Department of Agriculture), industry, and foundations. In addition, Dr. Shen's research and presentations are well received by national scientific societies and public media. Dr. Shen has published 129 journal papers and 3 book chapters, and gave 140+ national and international conference/invited talks. She served as the Associate Editor for "Nutrition Reviews" and "Frontiers in Nutrition" as well as editorial board member of 15 journals in the area of nutrition/exercise and chronic diseases, as reviewer for 140+ journals, and as grant reviewer for private, national, federal, and foreign funding agencies. She became a fellow of United States Bone and Joint Initiative in 2006, and she received a Texas Tech System Chancellor's Council Distinguished Research Award in 2011, and a fellow of NIH Clinical Research Management in 2016, and a fellow of Executive Leadership in Academic Medicine in 2019.

Presentation: Bioactive compounds for neuropathic pain: gut brain axis

Chronic pain is a complex disorder that impacts quality of life and represents a critical health care problem. Among different types of chronic pain, neuropathic pain, arising from damage to the nervous system, including peripheral fibers and central neurons, is notoriously difficult to treat and affects 7-10% of the general population. Currently available treatment options for neuropathic pain are limited and opioid analgesics have severe side effects and can result in opioid use disorder. The goals of treatment are to mitigate pain, restore the function of peripheral fibers and central neurons, and minimize the disabling effects of the disease. Recent studies have shown an association between diet-derived bioactive compounds with anti-inflammatory and anti-oxidant properties and the reduction of neuropathic pain-related inflammation. This presentation will cover the following (i) overview of prevalence and etiology of neuropathic pain, (ii) findings of commonly consumed plant-derived nutrients or bioactive compounds, for example ginger root extract and its bioactive compounds, on neuropathic pain in animal pain models, (iii) possible molecular anti-neuropathic pain mechanisms, and (iv) challenges, limitation, and future direction.

Jonathan Singer, Ph.D.

Assistant Professor, Dept. of Psychological Sciences, TTU

Dr. Jonathan Singer is an Assistant Professor in the Department of Psychological Sciences at Texas Tech University (TTU). He received his Ph.D. in Clinical Psychology from the University of Nevada, Reno. Overall, his interdisciplinary research examines the interconnections of multiple biopsychosocial processes within persons with life limiting illnesses (e.g., AD/ADRD; Advanced Cancer) and their family caregivers. By using various methods (e.g., Ecological Momentary Assessment; Daily Diary), the ultimate goal of his research program is to translate basic and applied research into scalable, evidence-based interventions for persons with life limiting illnesses and their family caregivers. Dr. Singer follows the translational framework and his research has three primary goals: 1) to investigate and identify intervention targets to improve psychological and physical health in persons with life limiting illness and their family caregivers; 2) to identify health disparities in the healthcare system for persons with life limiting illness and their family caregivers; 3) to develop evidence-based pragmatic and highly scalable interventions in persons with life limiting illness and their family caregivers. Dr. Singer is passionate about implementing his research and clinical trials throughout rural Texas and to underserved vulnerable populations.

Presentation: Prevalence, Diagnosis, and Support for Persons with Neurodegenerative Disorders and their Family Members in Urban and Rural Texas

There will be 500,000 people in Texas living with dementia in 2025, and rates will continue to increase over the next 30 years. This increase will not only take a major toll on the healthcare system, but family caregivers—especially those from socioeconomical disadvantaged households—may be forced to provide unpaid 24/7 care for the person with dementia. Recent research has indicated that not only are family caregivers experiencing high rates of caregiver burden and pre-death grief, but they are experiencing higher rates of cognitive decline and mortality, when compared to their age, race, and gender matched controls. In this talk, I will discuss two ongoing clinical trials for family caregivers of persons with dementia (partnering with Garrison Institute on Aging) and how my colleagues and I are utilizing unique methodology to identify robust risk and protective factors for neurocognitive functioning in family caregivers of persons with life limiting illnesses. Also, I will talk about a study we are planning to launch that aims to reduce indirect suicide ideation by adapting group dialectical behavior therapy for family caregivers of persons with dementia. Lastly, I will discuss some of our recent work on identifying the neurobiological underpinnings of pre-death grief in family members of persons with dementia and persons with prolonged grief disorder.

Round Table – Translational Research

Jeremy D. Bailoo, Ph.D.
Assistant Professor, Cell Biology and Biochemistry, Center of Excellence for Translational Neuroscience and Therapeutics

Environmental determinants of disease, animal behavior and cognition, contributions of genetic and environmental factors to individual differences in health and welfare across lifespan

Nadezhda German, Ph.D.
Associate Professor, Pharmaceutical Sciences, Jerry H. Hodge School of Pharmacy, Director, Medicinal Chemistry Program, Center of Excellence for Translational Neuroscience and Therapeutics

Early stage drug development and preclinical development of small molecules for the treatment of CNS disorders and selected types of cancer

Josee Guindon, D.V.M., Ph.D.
Associate Professor, Dept. of Pharmacology and Neuroscience, Center of Excellence for Translational Neuroscience and Therapeutics

Behavioral pharmacology, immuno-histochemistry, molecular biology, animal pain models, modulation of pain pathways, kidney physiological pathways

Michaela Jansen PharmD Ph.D.
Professor, Associate Dean of Curriculum, School of Medicine
Department of Cell Physiology and Molecular Biophysics, Center for Membrane Protein Research
Focus on structure and function studies and pharmacology of membrane transport proteins

Guangchen Ji, Ph.D.
Research Associate Professor, Dept. of Pharmacology and Neuroscience, Center of Excellence for Translational Neuroscience and Therapeutics

Electrophysiological and behavioral analyses of neuroplasticity and brain functions in pain conditions

Andrey Karamyshev, Ph.D.
Associate Professor, Dept. of Cell Biology and Biochemistry, Center of Excellence for Translational Neuroscience and Therapeutics, Center for Membrane Protein Research

Molecular mechanisms of translational regulation, protein interactions in health and disease, protein misfolding in neurodegenerative diseases

J. Josh Lawrence, Ph.D.
Associate Professor, Dept. of Pharmacology and Neuroscience, Center of Excellence for Translational Neuroscience and Therapeutics, Garrison Institute on Aging

Neuromodulation of GABAergic circuits in normal and disease states including Alzheimer's disease

Maria Manczak, Ph.D.
Research Assistant Professor, Department of Neurology, Garrison Institute on Aging, Center of Excellence for Translational Neuroscience and Therapeutics

Mitochondrial dysfunction and autophagy/ mitophagy signaling in aging brain and Alzheimer's disease and other neurodegenerative disorders

Lance McMahon, M.S., Ph.D.
Senior Vice President for Research and Innovation, TTUHSC

Volker Neugebauer, M.D., Ph.D.
Professor and Chair, Dept. of Pharmacology and Neuroscience, Executive Director and Chief Scientific Officer, Garrison Institute on Aging, Director, Center of Excellence for Translational Neuroscience and Therapeutics

Neuroplasticity and brain functions in chronic pain and comorbid disorders, neurogenerative diseases, and other neurological and psychiatric disorders

Jonathan Singer, Ph.D.
Assistant Professor, Psychological Sciences, TTU Center of Excellence for Translational Neuroscience and Therapeutics, Garrison Institute on Aging

Grief and Responses to Illness into Late Life (GRILL), psychological health in aging and illness, interconnection of the biopsychosocial processes within individuals with life limiting illnesses

Igor Ponomarev, Ph.D.
Associate Professor, Dept. of Pharmacology and Neuroscience, Center of Excellence for Translational Neuroscience and Therapeutics

Molecular mechanisms of cellular plasticity in models of Alcohol Use Disorder, neurogenomics, drug repurposing

Leslie Shen, Ph.D., CCPR
Associate Dean for Research and Professor of Pathology, School of Medicine

Women's Health; bioactive compounds, functional food, obesity, bone, pain

Poster Judges

Jeremy D. Bailoo, PhD
Assistant Professor
Cell Biology and Biochemistry
TTUHSC, Lubbock

Nadezhda German, PhD
Associate Professor,
Pharmaceutical Sciences, School of Pharmacy
TTUHSC, Lubbock

Josee Guindon, DVM, PhD
Associate Professor
Pharmacology and Neuroscience
TTUHSC, Lubbock

George Henderson, PhD
Professor
Pharmacology and Neuroscience
TTUHSC, Lubbock

Guangchen Ji, Ph.D.
Research Associate Professor
Pharmacology and Neuroscience
TTUHSC, Lubbock

Andrey Karamyshev, PhD
Associate Professor
Cell Biology and Biochemistry
TTUHSC, Lubbock

J. Josh Lawrence, PhD
Associate Professor
Pharmacology and Neuroscience
TTUHSC, Lubbock

Clint MacDonald, PhD
Professor
Cell Biology and Biochemistry
TTUHSC, Lubbock

Volker Neugebauer, MD, PhD
Professor and Chair
Pharmacology and Neuroscience
TTUHSC, Lubbock

Igor Ponomarev, PhD
Associate Professor
Pharmacology and Neuroscience
TTUHSC, Lubbock

Leslie Shen, Ph.D., CCRP
Associate Dean for Research and Professor of
Pathology, School of Medicine
TTUHSC, Lubbock

Jonathan Singer, Ph.D.
Assistant Professor
Psychological Sciences,
TTU, TTUHSC, Lubbock

Poster Presentation Schedule

1. Basic Science – Undergraduate/Medical Students

Posters	Time	Presenter	Judges
01	3:00-3:10	Annamalai, Aarthi	Dr. Nadezhda German / Dr. Andrey Karamyshev
02	3:15-3:25	Bhattacharjee, Shubhra	Dr. Nadezhda German / Dr. Andrey Karamyshev
03	3:30-3:40	Hernandez, Matthew	Dr. Nadezhda German / Dr. Andrey Karamyshev

2. Basic Science – Graduates

Posters	Time	Presenter	Judges
04	3:45-3:55	Nag, Monica	Dr. Nadezhda German / Dr. Andrey Karamyshev
05	4:00-4:10	Barnes, Robert	Dr. Nadezhda German / Dr. Andrey Karamyshev
06	4:15-4:25	Evans, Lauryn	Dr. Nadezhda German / Dr. Andrey Karamyshev
07	4:30-4:40	Gomez, Alejandra	Dr. Nadezhda German / Dr. Andrey Karamyshev
08	4:40-4:50	Panthagani, Praneetha	Dr. Nadezhda German / Dr. Andrey Karamyshev
09	3:00-3:10	Kisby, Brent	Dr. Guangchen Ji / Dr. Jonathan Singer
10	3:15-3:25	Liu, Xiaobo	Dr. Guangchen Ji / Dr. Jonathan Singer
11	3:30-3:40	McCrea, Grace	Dr. Guangchen Ji / Dr. Jonathan Singer
12	3:45-3:55	Nozohouri, Ehsan	Dr. Guangchen Ji / Dr. Jonathan Singer
13	4:00-4:10	Omy, Tasmin	Dr. Guangchen Ji / Dr. Jonathan Singer
14	4:15-4:25	Orlov, Erika	Dr. Guangchen Ji / Dr. Jonathan Singer
15	4:30-4:40	Orobets, Kseniia	Dr. Guangchen Ji / Dr. Jonathan Singer
16	3:00-3:10	Jaramillo-Martinez, Valeria	Dr. George Henderson / Clint MacDonald
17	3:15-3:25	Pierre, Lauretta	Dr. George Henderson / Clint MacDonald
18	3:30-3:40	Presto, Peyton	Dr. George Henderson / Clint MacDonald
19	3:45-3:55	Sawant, Neha	Dr. George Henderson / Clint MacDonald

3. Basic Science – Postgraduates

Posters	Time	Presenter	Judges
20	4:00-4:10	Antenucci, Nico	Dr. George Henderson / Clint MacDonald
21	4:15-4:25	Baig, Javaria	Dr. George Henderson / Clint MacDonald
22	4:30-4:40	Thompson, Travis	Dr. George Henderson / Clint MacDonald
23	3:00-3:10	Bustamante, Christian	Dr. J. Josh Lawrence / Dr. Leslie Shen
24	3:15-3:25	Castro-Piedras, Isabel	Dr. J. Josh Lawrence / Dr. Leslie Shen
25	3:30-3:40	Do, Hoa Quynh	Dr. J. Josh Lawrence / Dr. Leslie Shen
26	3:45-3:55	Mazzitelli, Mariacristina	Dr. J. Josh Lawrence / Dr. Leslie Shen

27	4:00-4:10	Sarayli Belirgen, Nermina	Dr. J. Josh Lawrence / Dr. Leslie Shen
28	4:15-4:25	Shanmugam, Sambantham	Dr. J. Josh Lawrence / Dr. Leslie Shen

4. Clinical – Undergraduate/Medical Students

Posters	Time	Presenter	Judges
29	4:30-4:40	Agrawal, Manas Yogendra	Dr. J. Josh Lawrence / Dr. Leslie Shen
30	3:00-3:10	Bammel, Alexandra	Dr. Josee Guindon / Dr. Volker Neugebauer
31	3:15-3:25	Hays, Annabelle	Dr. Josee Guindon / Dr. Volker Neugebauer
32	3:30-3:40	McLean, Elisabeth	Dr. Josee Guindon / Dr. Volker Neugebauer
33	3:45-3:55	Sanchez-Villalobos, Cesar	Dr. Josee Guindon / Dr. Volker Neugebauer

5. Clinical – Graduate Students

Posters	Time	Presenter	Judges
34	4:00-4:10	Schneider, Sydnie	Dr. Josee Guindon / Dr. Volker Neugebauer
35	4:15-4:25	Skawrantananond, Shadt	Dr. Josee Guindon / Dr. Volker Neugebauer
36	4:30-4:40	Antwi-Adjei, Philip	Dr. Josee Guindon / Dr. Volker Neugebauer
37	3:00-3:10	Ayika, Chinyere	Dr. Jeremy D. Bailoo / Dr. Igor Ponomarev
38	3:15-3:25	Basu, Tanisha	Dr. Jeremy D. Bailoo / Dr. Igor Ponomarev
39	3:30-3:40	DeSimon, Daniel	Dr. Jeremy D. Bailoo / Dr. Igor Ponomarev
40	3:45-3:55	Elliot, Lauren	Dr. Jeremy D. Bailoo / Dr. Igor Ponomarev
41	4:00-4:10	May, Harry	Dr. Jeremy D. Bailoo / Dr. Igor Ponomarev
42	4:15-4:25	Ugochukwu, Kingsley	Dr. Jeremy D. Bailoo / Dr. Igor Ponomarev

6. Clinical – Postgraduates

Posters	Time	Presenter	Judges
43	4:30-4:40	Fadalla, Carol	Dr. Jeremy D. Bailoo / Dr. Igor Ponomarev
44	4:40-4:50	Sehar, Ujala	Dr. Jeremy D. Bailoo / Dr. Igor Ponomarev

1. Basic Science – Undergraduate / Medical Students

Annamalai, Aarthi

Evaluation of Arsenic content in rice-based infant food: Implications for mental health outcomes

Aarthi Annamalai[1], Shubhra Bhattacharjee[2], Sharon Wanjiru[1], Jeremy D. Bailoo[3], Amrika Deonarine[2]

[1]Department of Biological Science, Texas Tech University, Lubbock, TX, USA, [2]Department of Civil, Environmental and Engineering, Texas Tech University, Lubbock, TX, USA, [3]Department of Cell Biology & Biochemistry, Texas Tech University Health Sciences Center, Lubbock, TX, USA.

Multiple epidemiological studies have found associations between early-life arsenic (As) exposure and childhood mental health-related outcomes such as anxiety, depression, and deficits in executive function. Exposure to As from food is expected to be about three times higher for infants and young children than for adults, in part because their intake per unit body mass is higher and their dietary diversity (i.e., the kinds of foods that they eat) is lower than adults. Rice and cereal products are widely used in infant foods and contributes to dramatic increases in infant As exposure after weaning from breast milk and formula. Here, we studied total As concentrations in commonly consumed rice-based infant products, rice cereals and teething biscuits (teethers), using inductively coupled plasma mass spectrometry (ICPMS). The method for As extraction and quantification from rice-based products was first evaluated using a National Institute of Standards and Technology rice standard reference material (NIST SRM 1568a). The total recovery of As in the SRM was 115.6±21.9%. Following validation of the method, the total amount of As was quantified in two common brand rice cereals for infants, as well as teethers collected from the local supermarkets. Total As concentrations of 97.1±10.9 ppb and 60.7±7.5 ppb were measured in the infant rice cereals from the brands Earth's Best Organic and Gerber, respectively. In addition, total As concentrations of 106.4±19.1 ppb and 51.3±20.8 ppb were measured in baby teethers from the brands Earth's Best Organic and Gerber, respectively. The observed concentrations of total As observed here were significantly higher than the total As regulation for drinking water (10 ppb). Our results therefore highlight that infants may be chronically exposed to As in their food during sensitive periods of development when organ and other systems are "maturing". Such exposure may pre-dispose children to pathological outcomes such as mental illness in adolescence. We plan to further extend the scope of this work to include analyses of food samples from different brands, different supermarkets (which brand their own products) and to include analyses of other kinds of As-containing-foods commonly consumed by infants. Since As toxicity critically depends on its speciation, we additionally plan to perform As speciation analyses using high pressure liquid chromatography (HPLC) hyphenated to ICPMS.

Bhattacharjee, Shubhra

Exposure and bio-accumulation of Arsenic from Diet: Implications for the validity of pre-clinical mouse models

Shubhra Bhattacharjee[1], Praneetha Panthagani[2], Sochi Onubogu[3], Aarthi Annamalai[3], Michael Findlater[4], Scott Trasti[2], Susan E. Bergeson[2], Amrika Deonarine[1], Jeremy D. Bailoo[2]

[1]Department of Civil, Environmental and Construction Engineering, Texas Tech University, Lubbock, TX, USA, [2]Department of Cell Biology & Biochemistry, Texas Tech University Health Sciences Center, Lubbock, TX, USA, [3]Department of Biological Science, Texas Tech University, Lubbock, TX, USA, [4]Department of Chemistry and Biochemistry, University of California Merced, Merced, CA, USA.

Arsenic (As) exposure in food and water has been associated with diagnoses of anxiety, depression, cognitive deficits and delay, and dementias. The toxicity of As depends on its chemical form, so understanding As speciation in food, the primary source of As exposure in humans, is important for estimating risk. The species of As found in foods include inorganic As (iAsIII and iAsv), arsenobetaine (AsB), and dimethylarsinic acid (DMAv), which are all cytotoxic, except AsB. Despite As being prevalent in foods, food safety is a neglected area, and the long-term health effects of low-level As exposure are poorly understood. The study analyzed total As and As speciation in drinking water, corncob bedding material, and two types of chow, LabDiet® 5R58 breeding diet (as pups) or 5R53 maintenance diet (as adults), across a year using inductively coupled plasma mass spectrometry (ICPMS) and anion exchange high-performance liquid chromatography (HPLC) coupled with ICPMS, respectively. The brains of 5-day-old, 14-day-old mice (exposed to 5R58 diet) and >1-year old adult mice (exposed to 5R53 diet) C57BL/6J mice were also examined for total As and As speciation. 5R58 and 5R53 contained 269.2±43.0 ppb and 328.9±51.0 ppb total As, respectively. The predominant As species in 5R58 and 5R53 was AsB, with concentrations of 102±8.0 ppb and 76±6.0 ppb, respectively. The concentration of iAsv was 61.1±15.0 ppb in 5R53 and 64.2±16.9 ppb in 5R58, while the concentration of DMAv was 45.5±11.6 ppb in 5R53 and 48.0±13.1 ppb in 5R58. The corncob bedding contained total As two orders of magnitude lower than the diet (8.0±4.0 ppb), and total As in the water was below detection (<0.0014 ppb). The brains of the 5-day-old mice could not be fully extracted, so the entire heads of these mice were analyzed. The concentration of total As in the heads of the 5-day-old pups was 80.0±40.0 ppb, which was one order of magnitude higher than that of the 14-day-old pups (1.0±0.2 ppb, $p < 0.05$). Adult mice brains contained a total As concentration of 0.8±0.1 ppb, with AsB the only species detected at a concentration of 0.18±0.02 ppb. In contrast, the 5-day-old mice brains contained a higher concentration of AsB, which was the only As species detected, with a range of 7.0 to 23.1 ppb and an average of 14.0±5.0 ppb. These results highlight that laboratory mice are chronically fed high levels of As in their diet which then bioaccumulates in the brain. Since bioaccumulation is observed during early sensitive periods of development, this may explain, in part, why laboratory mice often display high levels of anxiety and abnormal repetitive behaviors. Although AsB is not cytotoxic, it is transported and bioaccumulates in the brain, and thus, may have other potential impacts on normative physiological processes.

Hernandez, Matthew

Retinoic acid signaling in the hippocampal dentate gyrus and its association with learning

Matthew Hernandez[1,2], Ashly Hindle[1,2], Jocelyn Medina[2,3,4], Olga Ponomareva[1], Elizabeth Burroughs[1,2], Jeremy Bailoo[5,6], and J. Josh Lawrence[1,2,3,5]

[1]Department of Pharmacology and Neuroscience and Garrison Institute on Aging, [2]Texas Tech University Health Sciences Center, Lubbock, TX, USA; [3]Honors College and [4]Department of Kinesiology and Sport Management, Texas Tech University, Lubbock, TX, USA; [5]Center for Translational Neuroscience and

Therapeutics, [6]Department of Cell Biology and Biochemistry, Texas Tech University Health Sciences Center, Lubbock, TX, USA.

Approximately 5.8 million Americans are living with Alzheimer's disease (AD). In this study, we propose that all-trans retinoic acid (ATRA), a major bioactive metabolite of Vitamin A, is deficient in the human brains and mouse models of AD. It is widely accepted that amyloid beta (Aβ) accumulation leads to progressive cognitive decline. However, little is known about the mechanisms that disrupt the balance between amyloidogenic and non-amyloidogenic pathways. We propose that antioxidant depletion precedes AD onset and that ATRA is both a major antioxidant and, through activation of the nonamyloidogenic pathway, Aβ production. We further propose that dietary vitamin A modulates brain ATRA levels. Toward this goal, we have obtained transgenic RARE-lacZ mice in which the beta-galactosidase (lacZ) gene is expressed under the control of retinoic-acid receptor elements (RAREs). Crosses of RARE-lacZ mice and AD mouse models will likely provide insight into how AD pathology impacts ATRA brain signaling. However, RARE-lacZ mice have not been validated. First, the site of transgene insertion is unknown. Second, it is unclear whether lacZ expression is maintained when crossed onto the C57BL/6 background. Third, RARE-lacZ mice were initially estimated to have 10-50 copies of the transgene present. Given these caveats, we first sought to validate that the genetics of the RARE-lacZ model is appropriate for our purposes, that lacZ expression and staining display sufficient linearity for use in quantitative applications, and that crosses of RARE-lacZ mice with C57BL/6 background strains do not show substantial basal differences in behavioral/cognitive performance. In preliminary experiments employing both X-Gal staining and immunofluorescent staining for lacZ expression, we validated that a high level of lacZ expression is observed in the dentate gyrus of both the dorsal and ventral hippocampus. To examine the genetics of the model and the consistency of transgene copy number across mice, we performed qPCR for lacZ using genomic DNA from tail snips from homozygous RARE-LacZ$^{+/+}$ and heterozygous RARE-LacZ$^{+/-}$ mice. There was a roughly 2:1 ratio in signal between the RARE-LacZ$^{+/+}$ to RARE-LacZ$^{+/-}$ mice, supporting a genetic model in which the same number of tandem transgene inserts are present at a single locus in all animals. Finally, to test the effect of lacZ copy number and background strain, we used the Water T Maze (9 simple discrimination trials followed by 9 reversal trials and measured latency to the platform, swim speed, and distance traveled, comparing RARE-LacZ$^{+/+}$ and RARE-LacZ$^{+/-}$ crosses (with Swiss, C57BL/6J, and C57BL/6NJ mice). We found that strain significantly affected latency to the platform (Friedman test, $P < 0.05$) and swim speed (ANOVA, $P < 0.05$), while there was no difference in the total distance traveled (Friedman test, ns). When latency to the platform was corrected for the differences in swim speed, there was no significant difference in latency between the strains (Friedman test, ns). Taken together, our interpretation of these observations is that basal learning did not differ between the crosses. Future studies will examine LacZ expression in the RARE-LacZ$^{+/-}$ crosses. In conclusion, this study advances knowledge of retinoic acid signaling and its relationships to learning and lacZ expression.

2. Basic Science – Graduate Students

Barnes, Robert

Exploration of a possible shared serotonergic mechanism of antinociception by Cannabidiol and Amitriptyline in the formalin model of inflammatory pain

Robert C Barnes[1], Melissa McHann[1,2], Isabel Castro-Piedras[1], Daniel J Morgan[3] and Josee Guindon[1,2]

[1]Department of Pharmacology and Neuroscience, and Center of Excellence for Translational Neuroscience and Therapeutics, Texas Tech University Health Sciences Center, Lubbock, TX, USA, [2]Department of Immunology and Molecular Microbiology, Texas Tech University Health Sciences Center, Lubbock, TX, USA, [3]Department of Biomedical Sciences, Marshall University, Huntington, WV, USA.

Cannabidiol (CBD) is a phytocannabinoid with well-established analgesic properties that have contributed to the medicinal use of cannabis for pain over thousands of years. Although sociopolitical changes in the early 1900s decreased interest in its use, recent changes this sphere have restored public interest in cannabis-derived analgesics. Several possible mechanisms of CBD antinociception have previously been proposed, including but not limited to antagonism of cannabinoid receptors CB1 and CB2, positive allosteric modulation of 5-HT1A and α3 glycine receptors, through activation of TRPV1, and through inverse agonism of orphan GPCRs 3, 6, and 12. The tricyclic antidepressant amitriptyline primarily functions through antagonism of serotonin and norepinephrine reuptake but is also known to antagonize H1 histamine receptors, α1 adrenergic receptors, and muscarinic acetylcholine receptors. The analgesic properties of CBD and amitriptyline were evaluated in C57BL/6j mice using the formalin model of inflammatory pain, which is known to produce a characteristic acute and inflammatory phase of pain. In both CBD and amitriptyline, analgesia occurred at lower doses in male mice and in the inflammatory phase of pain. For CBD, antinociception was obtained in the acute phase at 30 mg/kg or higher in male mice and only at 100 mg/kg in female mice. For CBD in the inflammatory phase, antinociception occurred at 2.5 mg/kg or higher in male mice but only at 10 mg/kg or higher in female mice. In amitriptyline, antinociception in the acute phase occurred at 10 mg/kg or higher in both male and female mice while inflammatory phase antinociception occurred in male mice at as low as 0.3 mg/kg while female mice received antinociception at 1 mg/kg or higher. Significant sex differences were only found in the inflammatory phase for both CBD and amitriptyline; significant sex x dose interaction differences were only noted in the inflammatory phase of amitriptyline. Creation of a dose-response curve allowed for the calculation of the ED50 dose and evaluating the effects of combining the ED50 doses of CBD and amitriptyline revealed an additive effect in male mice only. Using the selective 5-HT1A antagonist WAY100635 (0.1 mg/kg) revealed a partial reversal of the antinociception in male mice. The sex differences established in this study supports sex as a key factor in amitriptyline antinociception and the need for more research into its role for CBD antinociception. The effects of WAY100635, meanwhile, support the need for a thorough investigation into the mechanisms required for CBD antinociception in both the formalin model of inflammatory pain and other in vivo pain models.

Evans, Lauryn

Neurological degeneration and Lupus-like phenotypes emerge in mice upon deletion of Dnase1L3

Lauryn Evans[1], Minal Engavale[1], Angelica Infante[1], Josh Lawrence[2], Peter A. Keyel[1]

[1]Department of Biological Sciences, Texas Tech University, Lubbock, TX, USA, [2]Texas Tech University Health Sciences Center, Lubbock, TX, USA.

Systemic lupus erythematosus (SLE) is a chronic autoimmune condition that causes severe inflammation and pain throughout the body. In worst cases, SLE can cause organ failure and be potentially fatal. The only approved FDA therapy for SLE treats downstream symptoms instead of underlying causes and poses a threat of serious side effects. One factor causing SLE is deficiency of the endonuclease Dnase1L3. Dnase1L3 cleaves pro-inflammatory DNA released from dying cells via normal bodily functions such as apoptosis or necrosis. Without Dnase1L3, immune complexes build up in the body, causing the autoimmune symptoms. As seen in mice models, lacking Dnase1L3 causes a mouse to develop lupus-like phenotypes as well as neurological degeneration, so they represent a model for testing Dnase1L3 replacement therapies. In order to distinguish Dnase1L3-/- mice from wild-type mice, genotyping of these mice by PCR is needed. The mice provided by UC Davis were unable to be genotyped with the primers provided. Attempting to optimize the UC Davis PCR protocol with their primers, the reagents were validated, and then varying concentrations of DNA and primers were tested, as well as PCR cycle variation. Following these extensive tests, the genotyping consistently led to inconclusive results. New primers were then designed and tested, and the genotype of the Dnase1L3-/- mice were able to be obtained. After genotype resolution, behavioral analysis, immunophenotyping, brain histology, and serum analyses were performed and showed major differences between biallelic Dnase1L3-/- knockouts and other genotypes. Antinuclear antibody (ANA) and dsDNA tests showed significantly increased levels in Dnase1L3-/- mice. Similarly, a notable increase in immature B cells in Dnase1L3-/- mice was observed during immunophenotyping. Pilot behavioral analyses suggests anxiety-like phenotypes in Dnase1L3-/- mice illustrated in an inability to habituate themselves to a new environmental challenge. Subsequent brain imaging showed a significant increase of GFAP expression indicating CNS injury or consequent neurological degeneration. Identifying these phenotype differences was the first part in being able to validate the effect of eradicating Dnase1L3 in mice. This data suggests Dnase1L3 replacement therapy may represent an effective novel treatment for a diverse collection of symptoms. Treating an underlying cause of autoimmunity phenotypes and neurological degeneration - rather than treating just the symptomatic onset - is expected to sustainably prevent symptoms from occurring.

Gomez, Alejandra

The role of the highly amyloidogenic cystatin-related epididymal spermatogenic (CRES) in sex-specific learning and memory

Alejandra Gomez[1], Petar Grozdanov[1], Aveline Hewetson[1], Jeremy D. Bailoo[1], Gail A. Cornwall[1]

[1]Department of Cell Biology & Biochemistry, Texas Tech University Health Sciences Center, Lubbock, TX, USA.

Amyloids are highly ordered cross β-sheet aggregates that are typically associated with disease states such as neurodegeneration and diabetes. However, work from our laboratory and others have shown that biologically relevant amyloids, termed functional amyloids, carry out a broad range of functions including acting as structural scaffolds, storage depots, protective barriers and signaling complexes. We previously demonstrated an extracellular amyloid matrix with host defense functions surrounds sperm in the normal mouse epididymal lumen. The epididymal amyloid matrix is composed of several members of the highly amyloidogenic

reproductive CRES subgroup of cystatin cysteine protease inhibitors suggesting it is a complex functional amyloid.
We hypothesize CRES and CRES amyloids are also present in the brain and are important participants in learning and memory processes. Preliminary RT-PCR showed CRES and other subgroup members are expressed in the hippocampus, cortex, cerebellum, and other brain regions from adult male and female mice. Western blot analysis of sequentially extracted male mouse hippocampus, cerebellum and cortex showed monomer and higher molecular weight, possibly aggregated, forms of CRES and other subgroup members are enriched in the urea soluble fraction. Further, CRES bound to Protein Aggregation Disease beads, which bind cross-beta sheet structures, suggesting amyloid forms are present in the hippocampus, cerebellum, and cortex.
Immunofluorescence studies of the mouse hippocampus with the neuronal marker NeuN showed that distinct populations of neurons, including the CA3 region and perineuronal net (PNN)-containing neurons, were CRES positive. The CA3 region neurons and PNNs are involved in memory acquisition and consolidation, respectively. Immunofluorescence studies using the astrocyte marker GFAP showed CRES is also expressed by astrocytes. These results suggest CRES is involved in several brain processes. Further, preliminary studies with human hippocampus showed a similar distribution of CRES expression in neurons and possibly other cell populations, including astrocytes.
To investigate CRES involvement in learning and memory, cognitive-behavioral studies were performed using adult wild-type (WT) and a global CRES knockout (KO) mouse model. These studies highlighted that male, but not female, CRES KO mice displayed impairments in learning in a 2-choice water-escape task as well as behavioral inflexibility during reversal. They perseverated on the previously learned escape location when the location of the platform to escape was changed. These findings suggest CRES and CRES amyloids are present in the normal mouse brain and are involved in learning and memory processes.

Jaramillo-Martinez, Valeria

Biochemical and molecular characterization of the most-common SLC13A5-Epilepsy causing missense-mutations

Valeria Jaramillo-Martinez[1], Vadivel Ganapathy[2], Ina L. Urbatsch[2,3]

[1]Translational Neuroscience and Pharmacology, [2]Cell Biology and Biochemistry, and [3]Center for Membrane Protein Research, Texas Tech University Health Sciences Center, Lubbock, TX, USA.

The sodium-coupled citrate transporter (NaCT) is a plasma membrane transporter, which is energized by an inwardly directed electrochemical sodium gradient. It mediates the symport of sodium and the carboxylate citrate into cells. NaCT is expressed in the liver, testis, brain, bone, and teeth, where citrate plays key roles in the synthesis of neurotransmitters, cholesterol, and fatty acids, the generation of energy, and teeth/bone mineralization. In humans, loss-of-function mutations in SLC13A5, the NaCT gene, cause early infantile epileptic encephalopathy type-25 (EIEE25, SLC13A5-Epilepsy), which leads to epilepsy, impaired speech, limited motor skills, developmental delay, and tooth defects. Currently, there is no treatment for EIEE25. Recently, the cryo-electron microscopy structure of the human NaCT was solved in an inward-facing conformation. This was an important advancement in the NaCT field, paving the way for a better understanding of the structure-function relationships for this clinically important transporter. We classified 22 NaCT missense disease-causing mutations based on their localizations in the 3D structure. Class I mutations interfere with the transport function by blocking the elevator-type mechanism for substrate translocation. Class II cause defects in protein folding and protein trafficking to the cell surface, which may be corrected by small molecule therapeutics. As there are not NaCT-specific antibodies, we expressed WT and the mutants

with specific epitopes to facilitate detection, which didn't interfere with the presentation of the mutant phenotypes. The Class I mutations C50R, T142M, and T227M displayed protein and surface expression levels similar to WT. Class II mutants G219R, S427L, and L488P showed significantly decreased protein expression and no plasma membrane expression. Both classes displayed diminished transport activity. These experiments have brought us one step closer to understanding the defects of disease-causing mutations at the molecular level, allowing us to begin dissecting NaCT trafficking pathway(s).

Kisby, Brent

Role of vascular cell types in the neuroimmune mouse model of escalated ethanol consumption: Single nucleus RNA-Seq study

Brent R. Kisby, Michelle McManus, Sambantham Shanmuganum, Igor Ponomarev

Texas Tech University Health Sciences Center; Department of Pharmacology and Neuroscience, Lubbock, TX, USA.

Escalation of alcohol (ethanol) consumption is one of eleven criteria for alcohol use disorder (AUD). Innate immune activation by repeated injections of the TLR3 agonist, Poly(I:C) (PIC), increases alcohol consumption in C57BL/6J (B6) male mice. To investigate the underlying mechanisms of this effect, we used single nucleus RNA-Seq (snRNA-Seq) to identify brain cell types affected by innate immune activation. B6 male mice were given 9 injections of either saline or 10 mg/kg of PIC every 4 days while given access to Every-Other-Day two bottle choice 15% ethanol, resulting in increased alcohol consumption in the PIC group. Twenty-four hours after the final alcohol session, brains were harvested, flash-frozen and subjected to snRNA-Seq analysis. We identified 40 discrete graph-based clusters (49,763 nuclei) corresponding to specific cell types and determined genes differentially expressed (DEGs) between saline and PIC groups within each cell type. Cell types most affected my PIC included endothelial cells (ECs), smooth muscle cells (SMCs), pericytes, and perivascular fibroblasts (PVF), suggesting that vascular cell types play an important role in the neuroimmune signaling. Examples of cell type - specific DEGs include Cldn5 for ECs, Slc7a5 for SMCs, and Slc38a2 for PVF – genes important for cellular functions. These findings are consistent with our preliminary bulk sequencing data showing significant effects of innate immune activation on ECs. Taken together, the data suggest that vascular cell types may contribute to the immune-modulated transition from low to elevated levels of ethanol consumption. These data also provide rationale for development of vasculature-based therapeutics for AUD.

Liu, Xiaobo

A NOVEL DSM-V BASED MODEL OF ALCOHOL USE DISORDER IN MINI PIGS

XB Liu[1], A Gutierrez[2,3], JO Willms[1], M Aguilera[2,3], AA Shaik[2], P Panthagani[1], A Vega[2,4], J Sanchez[2,3], JD Bailoo[2] and SE Bergeson[2]

[1]Department of Translational Neuroscience and Pharmacology; [2]Department of Cell Biology and Biochemistry, Texas Tech University Health Sciences Center, [3]Department of Biological Sciences; [4]Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, TX, USA.

Alcohol Use Disorder (AUD) is a chronic, relapsing condition characterized by lost control over alcohol intake despite adverse social, occupational, or health consequences. Preclinical AUD research has predominantly used

rodent models. A gap in the field is there are no non-primate animal models that satisfy the Diagnostic and Statistical Manual of Mental Disorders V (DSM-V) criteria for diagnosis of AUD. Ideally, safety of therapeutics should be evaluated in multiple mammalian models before FDA approved clinical trials in humans. Given the significant biological and physiological similarities of pigs to humans, including drinking to intoxication, we developed DSM-V based diagnostic tools with good face validity and hypothesized that minipigs would reach criteria for AUD. Using a within-subject design, 11 custom-made DSM-V criteria-based tests of AUD were established. To date, 7 of 11 measures have been evaluated, and all 5 pigs already meet AUD criteria. Every animal drank to intoxication ($p=0.0001$) with a blood alcohol concentration higher than 0.8 mg/ml and showed greater than 80% preference at all concentrations ($p<0.002$). As predicted, as ethanol concentration increased, all pigs showed impaired motor coordination on the agility test ($p=0.0013$). However, only Pig 1 showed craving after deprivation (>130%). Pig 2 and Pig 5 had decreased home pen recreational activity by 66.7% and 68%, respectively. Pig 2 and Pig 4 showed physiological withdrawal symptoms. A full severity assessment will be completed when the remaining 4 criteria are tested. Our results highlight that the minipig may be a highly translationally relevant model species for pre-clinical evaluation of therapeutic strategies for AUD.

McCrea, Grace

The Interplay between All-trans Retinoic Acid, the Gut-Brain Axis, and the Pathogenesis of Alzheimer's Disease: A Potential Mechanism

Grace McCrea[1,2], Matthew Buxton[1,2], Ashly Hindle[1,2], Nicholas Vojtkofsky[1,2], Liane Vásquez-Weber[1,3], Matt Hernandez[1,3], and J. Josh Lawrence[1,2,3,4,5]

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Alzheimer's disease (AD) is a debilitating disease affecting 6.5 million people in the United States (US) presently, anticipating to impact approximately 12.7 million people in the US by 2050. Recent studies demonstrating bacterial lipopolysaccharide (LPS) is present in the hippocampus of AD patients has warranted a closer examination of the role of the gastrointestinal (GI) tract integrity and the gut-brain axis (GBA) in AD. There is growing evidence that microbiota composition of the GI tract influences the cascade of signals sent throughout the complex system of the GBA. In relation to AD, the appearance of LPS in the post-mortem hippocampus could signify a compromised mucosal barrier and tight junction coupling between GI endothelial cells, which subsequently alters the GBA. The breakdown of mucosal and epithelial barrier integrity, combined with immune system activation, results in a pro-pathologic state that creates gut microbial dysbiosis. We propose tight junction deficiencies found in pathologic states arise primarily through preventable environmental causes. A standard literature search including PubMed was used to identify knowledge gaps and molecular interrelationships between VA and AD. There is evidence of Vitamin A (VA) dysregulation in AD pathogenesis and progression. Our currently funded NIH R01 grant addresses how brain transcriptomic, metabolomic and lipidomic profiles are altered by VA deficiency. All-trans retinoic acid (ATRA) is essential for normal expression of the tight junction proteins ZO-1, occludin, and claudin-1. VA deficiency leads to decreased expression of these proteins and subsequently compromises tight junctions. VA is also required for the differentiation of Treg cells. We propose VA deficiency compromises tight junctions, which results in pathologic metabolites like LPS penetrating the epithelium and entering the bloodstream. The loss of Treg cells cannot counteract the proinflammatory response, beginning an escalating cycle of inflammation. In addition, butyrate, a short-chain

fatty acid (SCFA) produced from Firmicutes through fiber fermentation, produces retinoic acid in gut epithelial cells by inhibiting histone deacetylases. In conclusion, the proposed mechanism attempts to explain the complex interrelationship between VA, butyrate, AD, and the GBA. Pharmacologic treatments targeted at such a mechanism could ameliorate and decrease the risk of developing Alzheimer's Disease. Supported by the Medical Student Summer Research Program (MB) and NIH R01 AG071859-01A1 (JJL).

Nag, Monica

Protective Effects of DDQ in Humanized Amyloid Beta Knockin Mice for Late-Onset Alzheimer's Disease

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder often characterized by pathological changes such as accumulation of amyloid beta (Aβ), phosphorylated tau (p-Tau), synaptic damage, and mitochondrial dysfunction in the brain. Recent studies have demonstrated that positive effects of the newly discovered molecule, DDQ (diethyl (3,4-dihydroxyphenethylamino) (quinolin-4-yl) methylphosphonate from our lab have shown to reduce levels of Aβ and p-Tau. Thus, the aim of our study was to examine the protective effects of DDQ in humanized homozygous Aβ knockin (hAbKI) mice that represent late-onset AD. In our ongoing project, we administered DDQ in 15 hAbKI mice at a dose of 20 mg/kg body weight, 3-times per week for 2 months, beginning at the start of 4th month until the end of 5th month. After treatment, we assessed cognitive behavior in DQQ treated hAbKI mice [15], untreated hAbKI mice [15], and Wild Type (WT) mice [15] through Morris Water Maze, Y-maze, open field, and rotarod tests. Protein levels, mitochondrial number and length, and dendritic spine number were analyzed through immunoblotting, immunostaining, transmission electron microscopy, and Golgi-cox staining methods. Our findings revealed significantly increased positive effects in DDQ-treated hAbKI mice for phenotypic behavioral changes, including motor coordination, locomotion/exploratory activity, spatial learning, and working memory. Protein levels of mitochondrial biogenesis, synaptic, and mitophagy genes were upregulated; mitochondrial dysfunction was significantly reduced; and dendritic spines and lengths significantly increased. Our findings suggest that DDQ may have neuroprotective, anti-aging, and anti-Aβ properties, making it a promising candidate for reducing age- and Aβ-induced toxicities in late-onset AD patients.

Nozohouri, Ehsan

Propofol Acutely Increases Blood-Brain Barrier Permeability for Sucrose in Mice

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Background Volatile anesthetic agents, including isoflurane and sevoflurane, increase fluidity of lipid membranes, causing enhanced permeability of the blood-brain barrier (BBB). Propofol is an injectable anesthetic with a main mechanism of action on GABAA receptors. It is highly lipophilic, with a logD7.4 of 4.2.

Recent data show that it increases the permeability of the low molecular weight hydrophilic marker sodium fluorescein in an in vitro model of the BBB (ref. Canfield). Therefore, we hypothesized that propofol will also increase the BBB permeability in vivo. Passive permeability for low molecular weight hydrophilic substances was studied in a mouse model using [13C] sucrose as a highly sensitive and specific marker. Methods C57Bl/6J mice were anesthetized with ketamine:xylazine (100:10 mg/kg) intraperitoneally. Diprivan (propofol 10 mg/mL in lipid emulsion) was infused via tail vein catheteter at a rate of 5 µL/min, corresponding to a dose rate of 120 mg/kg/h in a 25g mouse (n=5). Control groups received no infusion (ketamine/xylazine only, n=6) or an infusion of Intralipid (n=5). The jugular veins on both sides were exposed by skin incision. After 15 min of propofol or Intralipid infusion, we injected the hydrophilic marker [13C12] sucrose (10 mg/kg) by IV bolus into one jugular vein. Blood samples were drawn after 1, 5, 10, 20 and 30 min from the contralateral jugular vein under ongoing infusion. At 29.5 min [13C6] sucrose was injected as a vascular marker, followed by euthanization at 30 min and brain sampling. [13C12] sucrose and [13C6] sucrose were quantified in plasma and brain samples by our established LC-MS/MS technique. Brain uptake clearance, Kin, of [13C12] sucrose was calculated from brain concentrations (corrected for vascular content) and plasma AUC. Statistical comparisons were made by One-Way ANOVA with Tukey posttest. Results Kin values of [13C12] sucrose increased under propofol infusion significantly to 0.119 ± 0.018 µL min- 1g-1 from 0.092 ± 0.007 µL min-1g-1under Intralipid (+29%, $p < 0.05$) and 0.0828 ± 0.013 µL min- 1g-1 under ketamine/xylazine only (+43%, $p < 0.01$). Conclusion Propofol shows similar effects on BBB permeability in vivo as volatile anesthetics, extending observations in vitro. This effect may contribute to toxic effects under long term infusion of this drug.

Omy, Tasmin

Epigenetic-miRNA regulatory circuit confers ovarian cancer chemoresistance through RAD18-mediated DNA damage tolerance and repair signaling

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Ovarian cancer (OC) is the deadliest gynecological malignancy, develops asymptomatically and is typically detected at an advanced stage (stage III–IV) with local or distant metastases. The standard form of treatment for OC entails surgical removal of the total visible tumor, followed by chemotherapy using platinum drugs, either alone or in combination with a taxane. Despite initial responses, more than 70% of OC patients experience recurrent disease. Although a subset of patients benefits from PARP-targeted therapies based on homologous recombination deficiency (HRD) status. Frequently, individuals become resistant to these treatments. This dreadful circumstance highlights the pressing need to identify the molecular mechanisms underlying the disease's aggressive nature upon recurrence and the development of treatment resistance. Several genetic and epigenetic factors have been linked to the reprogramming of tumor cells by controlling the pattern of transcriptional and post-transcriptional gene expression. Particularly, miRNA-mediated regulatory circuit plays a significant role in tumor progression and therapeutic responses. Our analysis of miRNA expression signature in human ovarian cancer cell line panel showed little to no expression of miR221_5p and corresponding increase in DNA damage response and repair gene RAD18 expression. RAD18 plays critical role in cellular DNA damage tolerance and repair activity against chemotherapeutics, including platinum drugs. Similarly, loss of miRNA221_5p is associated with aggressive tumor cell growth, stemness, chemoresistance to platinum drugs, and poor prognosis in several cancers. Based on these information, we have hypothesized that miR221_5p regulates RAD18 mediated DNA damage tolerance and repair, and may offer novel therapeutic intervention to

overcome OC chemoresistance. Our experimental data confers miR221_5p prost-transcriptionally regulates RAD18 by binding to its 3'-UTR region and restores OC cell sensitivity to platinum drugs. Mechanistically, our results demonstrate that miRNA221_5p epigenetically regulates RAD18-mediated DNA damage tolerance and homologous recombination repair, and could be a novel therapeutic to overcome OC chemoresistance. Collectively, our studies identify a novel chemotherapy-induced epigenetic modulator in OC therapeutic resistance and offer novel miRNA 221-5p-mediated therapeutic intervention for the treatment of chemoresistant OC and to prevent disease recurrence.

Orlov, Erika

Mechanisms of Aging: Focus on Cell Type Analysis and the Protective Effects of Partial Drp1 Reduction

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Aging is the time-dependent process that all living organisms experience. It is characterized by declining physiological function due to epigenetic changes, telomere shortening, inflammation, oxidative damage, and mitochondrial and synaptic dysfunction. Recent research has revealed changes in the brain due to aging, particularly increased glia and astrocytes and reduced neurons. Mounting evidence suggests that aging plays a large role in neurodegenerative diseases, including Alzheimer's, Parkinson's, ALS, and Huntington's disease. Further, mitochondrial dynamics abnormalities, specifically mitochondrial fission and fusion imbalance, has been shown in aging and is associated with mitochondrial structural changes. Dynamin-related protein 1 (DRP1) is a GTPase protein that regulates mitochondrial division and distribution and has been shown to be increased with aging and age-related diseases, resulting in excessive mitochondrial fragmentation contributing to pathogenesis. In the current study, we investigated glia, astrocytes, and neurons and the effects of partial reduction of DRP1 in aging. Wild type (WT) and heterozygous knockout dynamin-related protein 1 (DRP1+/-) mice from five different age groups - 2 months, 10 months, 18 months, 25 months, and 31 months were used to analyze microglia, astrocytes, and neurons with age progression. Immunoblotting and immunofluorescence analyses was performed using cortical and hippocampal tissues from all five age groups and compared across age groups. Results revealed increased microglial and astrocytic proteins and decreased neuronal proteins in WT mice as age progressed. Interestingly, age matched DRP1+/- mice showed less changes in protein levels with aging, indication the protective effects of partial DRP reduction on microglia, astrocytes, and neurons.

Orobets, Kseniia

Molecular Mechanism of Frontotemporal Lobar Degeneration Caused by Mutations in Granulin

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Frontotemporal Lobar Degeneration (FTLD) is a neurodegenerative disease characterized by severe dementia. Granulin is one of the proteins associated with FTLD through the haploinsufficiency mechanism. Granulin is a secretory protein, it is synthesized as a precursor containing N-terminal signal sequence. The signal sequences are recognized by Signal Recognition Particle (SRP) for co-translational targeting to the endoplasmic reticulum (ER) and proper biogenesis. Mutations in the signal sequence may prevent the SRP binding activating a protein quality control termed Regulation of Aberrant Protein Production (RAPP). It leads to a loss of mutant protein expression through specific degradation of the mRNA. Indeed, previous studies associated granulin signal peptide mutations W7R and A9D with FTLD through a pathological activation of RAPP. Using bioinformatic analysis on the whole human genome we identified 12 novel granulin mutations which may play a role in FTLD pathology. The mutations were localized to all three signal peptide regions – N-, H- (or a hydrophobic core) and C-region. H-region is important for interaction with SRP. We hypothesize that mutations in this region of the granulin signal sequence activate RAPP and affect granulin mRNA and protein levels. We constructed recombinant mutated granulins and expressed them in the cultured human cells. Utilizing RT-qPCR and Western blotting, we evaluated granulin mRNA and protein levels for the mutants. We found that decrease of hydrophobicity of the H-domain due to mutations S6R, A9T, G13R, G13E leads to reduction of progranulin mRNA and protein levels. Mutations in other domains of the signal sequence either do not affect the expression (A16T, T18A) or trigger mRNA decrease by unknown mechanism (T3S). Our results demonstrate that the molecular mechanism of FTLD associated with mutations in granulin signal peptide may be caused by pathological activation of the RAPP protein quality control.

Panthagani, Praneetha

Medication Development for Alcohol Use Disorder: Evaluation of a Minocycline Analog

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Alcohol use disorder (AUD) has an annual economic burden of >$250 billion dollars in the U.S. with no high efficacy treatment. Minocycline limited alcohol consumption in rodents. Antibiotic activity of minocycline can lead to side effects like dysbiosis and development of antibiotic resistance. Modified minocycline analogs (MMAs) were synthesized to remove antimicrobial activity. Present study focuses on our lead MMA, butyl-ether minocycline (BEM). The aim of this research was to evaluate the following: efficacy (2-bottle choice, chronic intermittent ethanol exposure (CIE)), safety (MTT assay, AMEs test, target/off-target protein binding) pharmacokinetics (in-vitro permeability, phase-I metabolism, *in vivo* single dose pharmacokinetics) to support an FDA application. BEM significantly reduced binge alcohol consumption in a dose responsive manner. At 60 mg/kg i.p. BEM, consumption was also reduced ~80% for both sexes in a chronic/dependent mouse model. BEM did not alter ethanol metabolism in either females or males. BEM had an IC50 of ~125 µM compared to minocycline at ~50 µM in neuroblast cells. Ames test confirmed lack of mutagenic potential. In-vitro Caco-2 studies revealed high permeability of BEM with apparent permeability (Papp) of 27.9 and the Papp increased to 42.6 upon PgP inhibition. In-vitro intestinal and microsomal stability assays indicated the stability of BEM in gastrointestinal environments and with a half-life above 1hr in the Phase-I enzymes. Protein binding assays

suggested that BEM have no off-target binding towards the hERG channel but has affinity for several neurotransmitter receptors that participate in addiction processes and various psychological conditions. BEM also exhibited inhibitory activity towards COX1 and COX2 indicating its anti-inflammatory potential. BEM showed preferred drug-like characteristics in terms of efficacy, solubility, permeability, stability, and half-life. High hydrophilicity and permeability of BEM makes it a class 1 drug according to Biopharmaceutical Classification System, the most desirable class of pharmaceuticals. Further studies on MMAs are warranted to evaluate the mechanism of its action and its side-effects to submit an IND application to FDA. Present studies confirmed that BEM is an excellent lead candidate for AUD treatment.

Pierre, Lauretta

5HT3A interaction with RIC3 chaperone in mouse brain and SH-SY5Y cell lysates

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Pentameric ligand-gated ion channels (pLGICs) are cys-loop receptors important in transduction of electrical signals between neurons in the peripheral and central nervous system. Their significant role in neurotransmission has increased the research in neuropharmacology. Members of this protein family are found in mammals, but also in prokaryotes that can often incorporate additional domains whose roles are largely uncharacterized. pLGICs include nicotinic acetylcholine receptors, y-amino butyric acid A receptors, glycine receptors and type 3 serotonin receptors (5HT3). These receptors are integral membrane protein complexes composed of five subunits that surround the central pore. Each subunit incorporates a large extracellular domain which contains the agonist-binding site, four transmembrane segments (TM1-4) which form the ion pore, a large intracellular domain (ICD) between TM3 and TM4, and a short extracellular C-terminal region. The ionotropic serotonin subtype-3 (5-HT3) receptor is of current interest as a therapeutic target in the treatment of alcohol abuse. Selective pharmacological antagonists reduce alcohol consumption in preclinical and clinical models. To date only two applications have been fully realized in the clinic: the treatment of emesis and irritable-bowel syndrome. Competitive antagonists, called setrons, target 5HT3R, are used in the management of nausea and vomiting associated with radiation and chemotherapies in cancer patients. These drugs interact with off-target subunits of the receptor and consequently lead to many undesired effects including headache and drowsiness. In order to understand and characterize effective control of neurotransmitter-gated pLGICs, we have explored the interaction of 5HT3R with RIC-3 chaperone which mediates functional expression of the channels. In the present study, synthetic pLGIC peptides were used to probe and characterize the interaction with RIC-3 in native sources such as mouse brains and neuronal cell lines.

Presto, Peyton

Characterizing the transcriptomic profile of the central and basolateral amygdala in a rat model of chronic neuropathic pain

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Chronic pain is a pervasive healthcare issue comprised of complex interactions between sensory, cognitive, and emotional-affective dimensions. Together, this intricate interplay presents a challenge to the identification of effective therapeutic strategies. One obstacle to the discovery of successful treatment options arises from a lack of full understanding of the mechanisms and targets involved in the transition to a chronic pain state. Therefore, mechanistic insights into pain-related signaling processes are critical to identify new molecular targets for translational research and evidence-based medicine. Gene expression analysis provides a sensitive measure of cellular function, and abnormal changes in gene expression may ultimately impact behavior and disease states. Transcriptomic analysis provides crucial insight into actively expressed genes and transcripts from cells in various conditions, rendering this method an appealing approach to the discovery of novel molecular targets. Transcriptomic profiling in the periphery and spinal cord has revealed an upregulation of many transcription factors and cytokines in neuropathic pain, though pain-related gene expression profiles within the brain are overwhelmingly understudied. A limbic brain region, the amygdala has emerged as a key player in the emotional-affective aspects of pain and pain modulation. Changes in amygdala activity have been observed in pain models and neuroplasticity within the amygdala has been linked to pain-related behaviors. However, the molecular signatures of pain-related amygdala plasticity that may drive these behaviors remain to be determined. Here we characterize the amygdala transcriptional profile of adult male rats at the chronic stage of neuropathic pain. Tissues containing either the basolateral (BLA) or central (CeA) nucleus of the amygdala were collected for RNA sequencing 4 weeks after spinal nerve ligation (SNL) or sham surgery. Within the BLA, pathway and biological function enrichment analysis revealed differential expression in genes coding for GABAergic receptor signaling, calcium regulation, and long-term potentiation. In the CeA, differentially expressed genes included those related to opioid prodynorphin and proopiomelanocortin pathways, corticotropin releasing factor receptor signaling, and vasopressin synthesis. SNL surgery also promoted an upregulation in the CeA of genes related to neuroimmune signaling, such as Hmgb1, Gfap, and Tnfr1. Together these findings provide mechanistic insight into pain-related amygdala function that may guide the development of novel therapeutic strategies for neuropathic pain relief.

Sawant, Neha

Protective effects of Citalopram against phosphorylated Tau induced neurotoxicities in the dorsal raphe nucleus

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Background: Depression is among the most common neuropsychiatric comorbidities in many Tauopathies including Alzheimer's disease (AD). Apart from its anti-depressive and anxiolytic effects, selective serotonin reuptake inhibitor (SSRI) treatment also offers intracellular modifications that may help to improve neurogenesis, amyloid burden, Tau pathology, and neuroinflammation. Despite its multifaceted impact in the brain, the exact physiological and molecular mechanism by which SSRIs such as Citalopram improve neurogenesis and synaptogenesis in dementia is poorly understood. Purpose: In the present study we explored phosphorylated Tau (pTau) related cellular changes as well as protective effects of Citalopram on the dorsal raphe nucleus (DRN), which is the largest serotonergic nucleus in the brain. Methods: We investigated pTau, TPH2, SERT, 5HTR1a, Synaptophysin and PSD95, mRNA and protein levels by RT-qPCR, immunoblotting and immunofluorescence staining in Citalopram treated and untreated Tau mouse models as well as in serotonergic

RN46A-B14 neurons, transfected with wild-type and mutant Tau cDNA. Additionally, we also conducted cell survival analysis and Seahorse analysis on the RN46A-B14 neurons, behavioral studies on mice and Golgi-cox staining on postmortem mouse brains. Results: Citalopram treatment reduced pTau, SERT, and 5HTR1a levels, while up-regulating synaptophysin and PSD95 levels in both mouse and cell models of mutant Tau. These findings were endorsed by the increased dendritic spine density and improved cognitive behavior of the treated mice compared to that of the untreated ones. Further, Citalopram also increased survival and maximal OCR of pTau transfected RN46A-B14 neurons. Statistical significance was determined, using one-way ANOVA. Conclusions: Taken together these findings suggest Citalopram could not only be a promising therapeutic drug for treating depression in AD, but also for delaying the progression of AD.

3. Basic Science – Postgraduates

Antenucci, Nico

Chemogenetic manipulation of amygdala kappa opioid receptor neurons modulates neuropathic pain behaviors

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This study investigates the role of the dynorphin/kappa opioid receptor (KOR) system in the amygdala's central nucleus (CeA) in averse-affective behaviors associated with stress- or injury-induced pain conditions. The CeA is a crucial neural substrate for the emotional-affective dimension of pain, receiving highly processed nociceptive and affect-related information from the lateral-basolateral network. The CeA primarily consists of gamma-aminobutyric acid neurons, some of which co-express neuropeptides such as corticotropin-releasing factor (CRF) and dynorphin. Using chemogenetic manipulation of CeA-KOR neurons, the study examines their contribution to pain behaviors in control conditions and a neuropathic pain model. The study sheds light on the synaptic and cellular mechanisms underlying the role of the dynorphin/KOR system in averse-affective behaviors in pain conditions.

Baig, Javaria

Increased Lifespan of MicroRNA-455-3p Mouse Models of Alzheimer's Disease: Possible Protective Role of Mitophagy

J. Baig, P. Hemachandra Reddy

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MicroRNA (miRs) are small, single-stranded, non-coding RNA molecules reported to be involved in RNA silencing and post-transcriptional regulation of gene expression in cells. Multiple miRs have been studied in our lab, but overexpressed miR-455-3p in mice (miR-455-3p Tg mice) was observed to increase cognitive and memory functions and increase lifespan five months longer than the wild-type (WT) mice, whereas miR-455-3p knockout (KO) mice lived four months shorter than WT mice, but the exact mechanism of increased lifespan in miR-455-3p Tg mice is unknown. In Alzheimer's disease (AD), defective mitophagy, selective removal of dead/damaged mitochondria, was observed in AD cells, AD mice, and AD brains. We hypothesize that mitophagy may play a key role in the enhanced lifespan of miR-455-3p Tg mice compared to its WT counterparts. Messenger RNA and protein levels of 17 genes that are associated with mitophagy, were studied using the cortical brain tissues of miR-455-3p Tg, miR 455-3p KO, and WT mice at two timepoints: 2 months and 12 months. The overall, early preliminary data revealed mitophagy genes and proteins had an increase in expression in MiR-455-3p Tg mice and a decrease in expression in MiR-455-3p KO mice compared to their WT counterparts, indicating an increase in mitophagy in the cells in MiR-455-3p Tg mice compared to WT mice. These results suggest that enhancement of mitophagy in MiR-455-3p Tg mice compared to their WT

counterparts may be contributing to the increased lifespan in mice, and thus may have a protective role in AD and other age-related diseases.

Bustamante, Christian

Innate Immune Activation by TLR3, Poly(I:C), In Mice Results In Escalation Of Ethanol Intake and Changes in Gene Expression In Brain Reward Regions

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Chronic high alcohol (ethanol) drinking is one of the characteristics of Alcohol Use Disorder (AUD). Innate immune activation by TLR receptor agonists has been shown to be associated with excessive alcohol consumption in mice. We hypothesize that innate immune activation causes cell type-specific changes in gene expression in brain reward regions and some of these changes may drive excessive drinking. The goal of this project was to identify genes associated with the activation of the innate immune system and which are associated with excessive drinking in mice. We used C57BL/6J (B6J) male mice that drink high amounts of ethanol as a model of AUD. Animals were randomly assigned to receive repeated injections of Poly(I:C) (PIC), a TLR3 agonist, or repeated saline injections. Animals were allowed to choose between alcohol or water every other day (18 dinking sessions). To control for all variables, animals were assigned to one of four groups: saline/water (SW), saline/ethanol (SE), PIC/water (PW), and PIC/ethanol (PE). Brains were harvested at three different timepoints, and bulk RNA-seq was performed within six brain regions associated with drug reward. A principal component analysis (PCA) was performed to identify potential outliers and visualize the effect of the PIC. Subsequently, FastQ files were quantified using Salmon and differentially expressed genes (DEGs) were identified using edgeR. Deconvolution of cell types based on normalized mRNA abundance was performed using a scRNA database of the Allen Brain Atlas. Repeated PIC injections resulted in escalation of ethanol consumption in the PE group compared with SE animals. None of the samples were identified as outliers by PCA, and it was possible to associate the PIC effect with at least one PCA component, suggesting drastic effects of immune activation on gene expression. At least 900 DEGs were found for each of the six regions when PE and SE groups were compared after chronic exposure. In all brain regions, upregulated DEGs were significantly associated with endothelial cells and microglia. On the other hand, downregulated DEGs were associated with neurons. These findings suggest that neuroimmune activation, triggered by PIC, leads to the excessive alcohol consumption in B6J male mice, and the DEGs identified are mechanistic targets for this intake increase.

Castro-Piedras, Isabel

Effects Of Innate Immune Activation By LPS Or Poly(I:C) On Ethanol Drinking In The F1 Crosses Between FVB/NJ and C57BL/6J Mouse Strains

Castro-Piedras, Isabel[1]; Kisby, Brent[1], Shanmuganum, Sambantham[1], Ponomarev, Igor[1]

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Alcohol (ethanol) consumption is one of the characteristic hallmarks of Alcohol Use Disorder (AUD). Innate immune activation by toll-like receptor (TLR) agonists is associated with changes in alcohol consumption in mice, and these effects are genotype- and sex-dependent. In order to better understand the role of interactions between neuroimmune signaling, genotype, and sex on ethanol drinking, males and females of more genotypes need to be tested. The goal of this study was to test the effects of innate immune activation via lipopolysaccharide (LPS), a TLR4 agonist, or Poly(I:C) (PIC), a TLR3 agonist, on ethanol consumption in the F1 crosses between C57BL/6J (B6J) and FVB/NJ (FVB) mouse strains, which are animals with high levels of ethanol drinking. We bred ethanol-naïve B6J and FVB mice to generate intercrossed F1 hybrid male and female offspring. All animals were put through the 2-bottle choice every-other-day ethanol paradigm, which generates high levels of voluntary ethanol drinking, and were randomly assigned to a total of 10 repeated injections of either saline, LPS (0.1 mg/kg), or PIC (10mg/kg). Six and 24 hours after the last injection brains were removed, frontal cortex dissected, and levels of 9 immune-related genes were measured using qPCR: *Tnfa*, *Il1b*, *Il6, Ccl2*, *Ccl5*, *Tlr3*, *Tlr4*, *Myd88*, *Ticam1*. Immune activation by PIC produced escalation of ethanol drinking in males but not females of both FVB/B6J and B6J/FVB crosses, while LPS resulted in a reduction of ethanol consumption or a trend to reduce drinking in males but not females of both crosses. Levels of *Ccl2, Ccl5,* and *Tnfa* were statistically different between males and females after PIC treatment, which may, at least in part, explain behavioral differences. Taken together, these results further confirm that effects of immune activation on ethanol consumption depend on genotype, sex, and mode of activation TLR3 vs TLR4) and suggest that FVB/B6J and B6J/FVB F1 males are a good model for TLR3-dependent escalation of alcohol drinking. Supported by AA027096 and AA028370.

Do, Hoa Quynh

Binding motif for RIC-3 chaperon protein in serotonin type 3A receptors

Hoa Quynh Do, Michaela Jansen

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Serotonin or 5-hydroxytryptamine type 3A receptors (5-HT_{3A}) belong to the pentameric ligand-gated ion channel super-family, which have been long-standing therapeutic targets for psychiatric disorders and neurological diseases. Due to structural conservation and significant sequence similarities in the extracellular and transmembrane domains of this family, clinical trials for drug candidates targeting these two domains have been hampered by off-subunit modulation. The intracellular domain of this family, in contrast, exhibits significant diversity in length, amino acid composition, and function, and hence positions itself as a potential drug target. We, therefore, explored the interaction interface of the 5-HT_{3A} intracellular domain (ICD) with its regulator, the resistance to inhibitors of choline esterase (RIC-3) protein. We have previously shown that RIC-3 interacts with the L1-MX segment of the ICD fused to maltose-binding protein. In this study, using synthetic L1-MX-based peptides, Ala-scanning, and a pull-down assay, we identified motif DWLRXX(X)VLDR, as a critical motif for interaction with RIC-3. This motif is repeated twice within the ICD. One site is within the MX-helix, another site is at the MAM4-helix transition. For both sites, triple-Ala substitutions (MX: W347, R349, and L353; MAM4: W447, R449, and L454) disrupt the interactions between 5-HT_{3A}-ICD-peptide and RIC-3. Complementary studies using full-length 5-HT_{3A} subunits confirmed that the Ala substitutions reduced the RIC-3 mediated modulation of 5-HT_{3A} functional surface expression. We thus identified two binding sites for RIC-3 with a shared duplicated motif in 5-HT_{3A} subunits, one in the MX-helix and one at the MAM4-helix transition.

Grozdanov, Petar

The role of alternative polyadenylation in a TLR3-mediated mouse model of escalated alcohol consumption

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Alternative polyadenylation (APA) produces mRNAs with different lengths of their 3' untranslated regions (UTR). APA is a widespread, but often overlooked mechanism to regulate gene expression at the posttranscriptional level. Longer APA transcripts have been shown to be enriched in neuronal processes, while shorter APA transcripts are often confined to the neuronal bodies. This differential localization of the transcripts may affect neuronal functions including neurogenesis and synaptic plasticity, key processes associated with the development of alcohol use disorder (AUD). The purpose of this study was to investigate the role of APA in AUD using a well-established neuroimmune mouse model of excessive ethanol consumption, in which repeated injection of a TLR3 agonist, Poly(I:C) (PIC) produces escalation of ethanol drinking in C57BL/6J male mice. We used RNA-Seq to determine the effects of chronic ethanol drinking or/and innate immune activation by PIC on gene expression and APA in frontal cortex. Our analysis identified hundreds of genes undergoing APA (e.g., Camk2a, Psd3, Ctnnd2, Grm5, Homer1) or differential expression (DE, e.g., B2m, C1qa, C1qb, Flt1, Sparc) after immune activation by PIC, suggesting that these genes may contribute to the PIC-induced escalation of ethanol drinking. Strikingly, the APA and DE genes did not overlap. Moreover, using previously published cell type-specific single nucleus RNA-Seq datasets, we were able to determine that the APA genes were primarily expressed in neurons, while the DE genes were expressed in microglia, endothelial and mural cells. Gene ontology functional group analyses revealed that the pathways associated with APA and DE genes were different: APA genes were involved in glutamate receptor signaling, cognition, and locomotor behavior, whereas the DE genes were involved in activation of the innate immune system and interferon alpha, beta, and gamma pathways. In summary, our study suggests that APA is an important molecular mechanism invoked in AUD that has the potential to regulate localized neuronal protein expression during AUD development. In addition, our study highlights new molecular targets for pharmacological interventions of AUD and other substance use disorders. Supported by AA027096 and AA028370.

Mazzitelli, Mariacristina

Amygdala mGluR2 and mGluR3 modulate different aspects of arthritis pain-related behaviors

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Pain is a multidimensional experience with an important averse-affective dimension. The amygdala, a limbic brain area, is critically involved in the emotional-affective aspects of behaviors and in pain modulation. The

central nucleus of amygdala (CeA) serves major output functions, and neuroplasticity in the CeA is mechanistically linked to pain-related behaviors in different pain conditions. The activation of Gi/o-coupled group II metabotropic glutamate receptors (mGluRs), which include mGluR2 and mGluR3, can decrease neurotransmitter release and regulate synaptic plasticity. mGluR2/3 have emerged as potential targets for neuropsychiatric disorders and they can inhibit pain-related processing and behaviors, but the contribution of mGluR2 and 3 in the amygdala to pain-related behaviors remains to be determined. This knowledge gap was addressed here in a rodent model of arthritis pain. Audible (nocifensive response) and ultrasonic (averse-affective response), mechanical withdrawal thresholds and anxiety-like behaviors were measured in adult rats 5-6 h after the induction of a kaolin/carrageenan-mono-arthritis in the left knee joint. The following drugs were stereotaxically administered by microdialysis into the CeA of arthritic rats: a group II agonist (LY379268), a PAM selective for mGluR2 (LY487379) or a combination of a group II mGluR agonist (LY379268) with a NAM selective for mGluR2 (VU6001966). Selective activation of mGluR2 decreased vocalizations and increased mechanical withdrawal thresholds, while selective activation of mGluR3 had similar inhibitory effects on emotional-affective responses but not mechanosensitivity in the arthritis pain condition. Group II mGluR activation improved the open-arm choice in the elevated plus maze in arthritic rats, suggesting anxiolytic effects, which were mimicked by selective activation of mGluR3, but not mGluR2. Our data suggests that mGluR3 mediates the anxiolytic effects of group mGluR function whereas mGluR2 plays a critical role in the modulation of mechanosensory aspects (antinociceptive properties) of arthritic pain. Both subtypes are involved in the beneficial effects of group II mGluRs on emotional-affective responses (vocalizations) in arthritis pain. The data identify distinct roles of mGluR2 and mGluR3 in amygdala (CeA) in different aspects of pain modulation, which may guide subtype-selective therapeutic strategies.

Sarayli Belirgen, Nermina

5HT3A interaction with RIC3 chaperone in mouse brain and SH-SY5Y cell lysates

Nermina Sarayli Belirgen MD PhD, Hoa Quynh Do PhD, Michaela Jansen PharmD PhD

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Pentameric ligand-gated ion channels (pLGICs) are cys-loop receptors important in transduction of electrical signals between neurons in the peripheral and central nervous system. Their significant role in neurotransmission has increased the research in neuropharmacology. Members of this protein family are found in mammals, but also in prokaryotes that can often incorporate additional domains whose roles are largely uncharacterized. pLGICs include nicotinic acetylcholine receptors, y-amino butyric acid A receptors, glycine receptors and type 3 serotonin receptors (5HT3). These receptors are integral membrane protein complexes composed of five subunits that surround the central pore. Each subunit incorporates a large extracellular domain which contains the agonist-binding site, four transmembrane segments (TM1-4) which form the ion pore, a large intracellular domain (ICD) between TM3 and TM4, and a short extracellular C-terminal region. The ionotropic serotonin subtype-3 (5-HT3) receptor is of current interest as a therapeutic target in the treatment of alcohol abuse.Selective pharmacological antagonists reduce alcohol consumption in preclinical and clinical models. To date only two applications have been fully realized in the clinic: the treatment of emesis and irritable-bowel syndrome. Competitive antagonists, called setrons, target 5HT3R, are used in the management of nausea and vomiting associated with radiation and chemotherapies in cancer patients. These drugs interact with off-target subunits of the receptor and consequently lead to many undesired effects including headache and drowsiness. In order to understand and characterize effective

control of neurotransmitter-gated pLGICs, we have explored the interaction of 5HT3R with RIC-3 chaperone which mediates functional expression of the channels. In the present study, synthetic pLGIC peptides were used to probe and characterize the interaction with RIC-3 in native sources such as mouse brains and neuronal cell lines.

Shanmugam, Sambantham

Placental oxidative stress by alcohol suppresses cellular cysteine/cystine transporters by impairing NRF2-related control of GSH redox protection

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Background: Placenta mediate transfer of nutrients from the maternal blood to the fetus and provide support to fetal growth and survival. An exposure to some xenobiotics and/or recreational compounds, including ethanol (E) during pregnancy has been shown to affect placental functions possibly contributing to impaired brain development. Increased placental oxidative stress and apoptotic cell death have been evidenced on chronic gestational E exposure in rats. NFE2L2 (NRF2) a redox sensitive transcriptional regulator, serves as sensors of chemical- and radiation-induced oxidative/electrophilic stresses and plays a central role in the induction of antioxidant genes in response to oxidative stress. Glutathione (GSH-an intracellular antioxidant) synthesis is controlled by the availability of Cysteine/Cystine which are transported by SLC family of genes (*SLC1A1/EAAC1* and *SLC7A11/xCT*). *In-utero* ethanol (E) exposure impaired the NRF2 mediated GSH/Redox homeostasis. Thus, the objective of the present study is to elucidate the ability of activation of NRF2 to counteract the E-induced dysregulation of NRF2/ARE dependent GSH synthesis and the two transport systems in the placenta. Methods: *In-utero* E-exposure of pregnant Sprague-Dawley rats to intermittent ethanol vapor (IEV) daily from GD11 to GD20 with a 6 h ON/18 h OFF in E-vapor chamber and *in-vitro* HTR8 cells were used. Transient transfection with NRF2 cDNA or activation by KI696/dimethyl fumarate/resveratrol in HTR8 cells were used to elicit gain of function of NRF2. The samples were then processed for ROS assay, MDA assay, NRF2-transactivation reporter assay, transporter activity, GSH/GSSG assay, qRT-PCR and Western blotting for NRF2, EAAC1, xCT and proteins involved in GSH synthesis. Results: *In-utero* (GD11-GD20 E exposure) and *in-vitro* E elicited an increase of MDA suggesting oxidative damage in placenta and increase in ROS levels in HTR8 cells. Similarly, the expression of EAAC1 and xCT was significantly decreased in E-treated placenta tissue and HTR8 cells, respectively. Genetic and Pharmacological activation of NRF2 using cDNA or KI696/DMF/Resveratrol prevented the E induced oxidative stress, increased the expression of EAAC1 and xCT. KI696 increased the Xc^- transporter activity by ~2.5 fold. KI696 treatment increased total GSH levels ~ by 40% in the HTR8 cells. Conclusion: These results indicate that E-mediated NRF2 dysregulation, induced oxidative damage and impairment of GSH homeostasis. Thus, interventions using cysteine/cystine transporters could be a potential target for restoring redox homeostasis in E-exposed placenta.

Thompson, Travis

Proteopathy in Alzheimer's disease: translational insights from a mathematical perspective

Travis B. Thompson[1]

Alzheimer's disease (AD) is the most common form of dementia. The primary risk factor for developing AD is age and, with populations skewing more rapidly towards the elderly, AD is now a significant health concern around the world. The classical biological hallmarks of AD progression are aggregates of misfolded amyloid-$\beta$and tau neurofibrillary tangles (NFT) alongside gray matter atrophy; in turn, tau NFT prevalence correlates with both gray matter atrophy and with cognitive decline. Advances in imaging technology, such as enhanced MRI sequences and PET, alongside new radiotracers, such as florbetapir and flortaucipir, now allow us to collect an unprecedented amount of data regarding the cohort-level and longitudinal progression of A$\beta$and tau NFT pathology in AD. In addition, recent in-vitro evidence surrounding the prion-like hypothesis and strong axonally-anisotropic propagation of misfolded seed proteins has shed important light on fundamental mechanisms underlying the progression of protein pathology in AD. The mathematical modeling of neurodegenerative diseases, such as AD, has gained a significant amount of traction over the last five years. Diffusion tensor images (DTI) can be used to assemble structural human brain connectomes and **network dynamical systems**, expressing terms that represent the disease mechanisms from animal models and in-vitro experiments, can be defined on these structural graphs. Using these models, we can make predictions about patient progression or ask important translational questions such as: What model factors play a significant role in AD etiology and progression? In this poster, we present several mathematical models that suggest that *clearance mechanisms* (vascular, proteasomal, lysosomal, autophagic and glymphatic) play a pivotal role in AD progression, may help us to understand AD as a secondary tauopathy and may explain the emergence of different AD subtypes. Translationally, these models suggest that clinical interventions bolstering the brain's clearance systems may offer effective treatments while encouraging lifestyle factors that promote healthy brain clearance may delay the onset and progression of AD.

4. Clinical – Undergraduate / Medical Students

Agrawal, Manas Yogendra

Elucidating the anticancer mechanism of an antipsychotic agent for the treatment of Glioblastoma

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Glioblastoma (GBM) treatment has a myriad of challenges, such as the impermeability of chemotherapeutics through the blood-brain barrier (BBB), drug resistance to standard care therapy such as temozolomide (TMZ), including severe toxicity due to high doses necessary for the action. With the current therapies proving inadequate to elicit the desired response, we aimed at rechanneling an FDA-approved antipsychotic agent, Pimavanserin tartrate (PVT), for GBM and attempted to elucidate its mechanism of action. The antineoplastic property of PVT was unraveled by performing a Sulfarhodamine-B cytotoxicity assay on human and murine GBM cell lines. PVT inhibited the growth of GBM cells at an IC_{50} in the range of 5 – 8µM, whereas the IC_{50} of TMZ was around 1000µM, 200 times higher than PVT. PVT also enhanced the efficacy of TMZ by reducing its IC_{50} when given in combination. The mode of cell death caused due to PVT was found to be apoptosis. This finding was concluded based on immunoblotting of several pro-apoptotic proteins, such as cleaved caspase-3 and Bim, which were upregulated due to PVT. Moreover, the annexin-V assay was performed using flow cytometry to confirm the mode of cell death to be apoptosis. 10µM PVT treatment of GBM cells lead to a 70% increase in the apoptotic cell population. We further screened several oncoproteins to discover the modulation caused by PVT in GBM cells. It was found by western blotting that PVT downregulated Akt phosphorylation. Further, it was seen that there was an increase in the expression of FOXO proteins, negative downstream regulators of Akt, which get translocated to the nucleus leading to increased transcription of Bim. Thus, we found that PVT regulates the PI3K/Akt signaling in GBM cells leading to their apoptosis. To corroborate our findings and confirm if the PVT crosses the BBB, we performed an orthotopic *in vivo* study of PVT. Luciferin-transfected GBM cells (CT2A-Luc) were intracranially injected in the bregma of immunocompetent C57BL/6 mice, and PVT (10mg/kg-the human equivalent dose) was administered orally every day. Tumor growth was monitored by checking the luminescence of the cells using an IVIS imager. We observed a significant decrease in the tumor growth of PVT-treated mice with no organ toxicity. All the pre-clinical investigations involving animals were carried out in line with the ethical standards laid out by the Institutional Animal Care and Use Committee (IACUC). Thus, we conclude that PVT suppresses the GBM progression by modulating the PI3K/Akt/Bim signaling axis with minimal toxicity profile.

Bammel, Alexandra

Elucidating Clinical and Juvenile Justice Implications for Youth with Neuropsychological Differences

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Traumatic brain injury (TBI) refers to brain damage from a blow to the head whereas an orthopedic injury (OI) refers to a noncranial physical injury. TBI is associated with long-term sequalae, largely attributed to damage to the frontal lobe, which controls higher-level executive functions such as problem-solving, judgment, impulsivity, and interpersonal behavior (Scott & Schoenberg, 2011; Stuss, 2011). Youth who sustain an OI also appear to be a discrete neuropsychological group and exhibit greater hyperactivity than uninjured youth, consistent with hyperactivity being a common factor precipitating orthopedic injuries (Karayagmurlu et al., 2019). Further, youth with a TBI exhibit more inattention (Yeates et al., 2005), fatigue (Bogdanov et al., 2021), and different post-injury trajectories in corpus collosum qualities (Wu et al., 2010) compared to youth with OI. Youth who sustain a TBI and youth who sustain an OI represent distinct neuropsychological groups relative to each other and to normative samples. Yet, having either a TBI or OI is associated with greater psychological distress, substance use, criminal offending, and worse adaptive functioning (Chaitanya & Kumar, 2015; Schachar et al., 2015; Schofield et al., 2018). Thus, it is worth clarifying whether there are unique pathways leading to juvenile justice system involvement for youth with a prior TBI compared to youth with a prior OI. We analyzed health risk behaviors of 62 adolescents (20 mild TBI, 16 moderate-to-severe TBI, 26 OI) treated at two metropolitan area hospitals in a large Southern state at the time of injury and at one-year follow-up. Youth were aged 11- to 19-years-old (M=14.03; SD=2.5), mostly male (66%), and of diverse race (77% White, 15% Black, 6% Asian) and ethnicity (32% Hispanic). TBI severity was assessed using the Glasgow Coma Scale (GCS) and neuroimaging evidence of intracranial anomalies (Teasdale & Jennett, 1974; Teasdale et al., 2014). OIs were defined as extracranial physical injury requiring overnight hospitalization. Health risk behaviors were measured using the Centers for Disease Control and Prevention's Youth Risk Behavior Survey (YRBS; CDC, 2007). To control for individual differences, pre- to post-injury difference scores were calculated for each participant. Resulting change scores were mean-centered and statistical assumptions for ANCOVAs were checked. One-way ANCOVAs were conducted to determine whether TBI status is associated with changes in health risk behaviors. Two distinct pathways emerged wherein youth with an OI exhibited a greater increase in violence and aggression relative to youth with a mild TBI while controlling for age (by 0.93 standard deviations; p=0.009). Youth with a severe TBI displayed greater increases in marijuana use than those with an OI while controlling for age (by 0.81 standard deviations; p=0.022). Results indicate separate trajectories into the juvenile justice system for youth with a TBI compared to an OI. Youth with an OI may be at greater risk for juvenile justice system involvement due to aggressive behavior where youth with a TBI may be at risk due to substance use. Findings suggest a need for more specialized criminogenic and clinical foci for these two groups. To improve overall functioning and reduce criminal risk, problem-solving skills and coping mechanisms may constitute relevant targets for youth with a TBI (Wade et al., 2017). Anger management interventions may be more helpful for youth with an OI. Additionally, past research has speculated that individuals with a TBI may use cannabis to cope with anger or agitation (Hawley et al., 2018). Future research should explore the possibility that youth with a TBI exhibit lesser violent behaviors due to a tendency to "self-medicate" post-concussive symptoms using cannabis.

Hays, Annabelle

Resiliency among adolescents with varying TBI status

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Texas Tech University, Department of Psychological Sciences

Resiliency, or one's ability to adapt following hardship, is increasingly being applied to understand recovery following a TBI. Several studies examine resiliency factors which protect against specific negative outcomes

related to TBI. Yet, few studies have used a formal measure to investigate the direct relationship between head injury status and resiliency, and none use adolescent samples. Thus, we examined whether an adolescent's level of resiliency differs depending on head injury status (i.e., mild TBI, moderate TBI, severe TBI, or Orthopedic Injury [OI]). Analyses were conducted using 58 adolescents aged 10-19 treated for a TBI (n=8 for mild; n=2 for moderate; n=19 for severe) or an orthopedic injury (OI; n=29) in Southern U.S hospitals from 2010-2013. TBI was defined as having a Coma Scale score between 3 and 15 and evidence of intracranial anomalies. Inclusion in the OI group was contingent upon non-cranial injuries and an overnight hospitalization. Resiliency was measured using the Child and Youth Resiliency Measure (CYRM), which assesses factors including social support and problem-solving ability.A one-way ANOVA indicated a child's resiliency significantly differs depending on head injury status ($F = 5.76$, $p = .002$). Specifically, youth with a severe or moderate TBI self-reported significantly lesser resiliency than youth with an OI (by about 14 and 30 points, respectively, on our resiliency scale with a total possible score of 140; $p = .012$, 95% CI [-26.16, -2.43] for severe TBI; $p = .046$, 95% CI [-59.12, -0.35] for moderate TBI). Our findings suggest adolescents with a TBI exhibit poor resiliency compared to adolescents with OI's. Moreover, youth with more severe TBI may be particularly at risk for poor resiliency and, consequently, a range of additional poor outcomes. Future research should examine how TBI severity impacts resiliency using a larger sample.

McLean, Elisabeth

Understanding the Interplay between Marital Status and Ethnicity on Neurocognitive Functioning in Rural-Dwelling Older Adults

Elisabeth McLean[1], BA, Jonathan Singer, PhD[1], Peter Rerick, PhD[2], Lauren Elliott, BA[1], Carol Fadalla, BS[1], Alayna Jump[1], Veronica Molinar-Lopez, BA[3,4], & Volker Neugebauer, MD, PhD[3,4]

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Objective: Research indicates being married is related to better physical and psychological health. Little is known regarding the relationship between marital status and neurocognitive functioning and whether it differs based on ethnicity (Hispanic vs. non-Hispanic). This is the first study to examine this relationship in a sample of aging adults in rural Texas.
Method: Data from 1864 participants (Mage=59.68, SDage=12.21), who were mostly Hispanic (n=1053), women (n=1295), and married (n=1,125) from Project FRONTIER were analyzed. Neuropsychological testing comprised RBANS, Trails Making Test, and Clock Drawing. Participants were dichotomized, married and unmarried.
Results: There was a significant interaction between Hispanic identity and marital status on overall neurocognitive functioning ($F(1,1480) = 4.79$, $p < .05$, $\eta p\ 2 = .003$). For non-Hispanic individuals, married individuals had higher overall neurocognitive functioning compared to unmarried individuals, whereas neurocognitive functioning for Hispanic individuals did not significantly differ between married and unmarried individuals. There were significant main effects as married individuals (M=84.95, SD=15.56) had greater overall neurocognitive functioning than unmarried individuals (M=83.47, SD=15.86; $F(1,1480) = 14.67$, $p < .001$, $\eta p2 = .01$), Hispanic individuals (M=78.02, SD=14.25) had lower overall neurocognitive functioning than non-Hispanic individuals (M=91.43, SD=15.07; $F(1,1480) = 284.99$, $p < .001$, $\eta p2 = .16$).

Discussion: Hispanics living in rural areas experience additional stressors that could lead to worse neurocognitive functioning, which is supported by the Lifespan Biopsychosocial Model of Cumulative Vulnerability and Minority Health, which postulates that race/ethnicity/SES-related stressors exacerbate the impact of other life stressors. Reduction of stress on rural Hispanics should be a priority as it could positively affect their neurocognitive functioning.

Sanchez-Villalobos, Cesar

Ranking gene expressions on hippocampal transcriptomes elucidate differentiating genes in Alzheimer's Disease

Cesar Sanchez-Villalobos, Ranadip Pal, J. Josh Lawrence

Alzheimer's Disease (AD) is the most common type of dementia, leading to cognitive impairment and memory loss. It is also one of the leading causes of death in the United States. Although neuroscientists have spent considerable effort trying to understand and treat this disease, the molecular mechanisms underlying this disorder remain unclear, which is an obstacle in developing effective treatment strategies. In this work, we apply Relief Based Algorithms (RBA) to the dataset from van Rooij et al. (2018). The data consists of the RNAseq expression of 14564 genes from the hippocampus of 28 brains (18 AD and 10 age-matched controls). After applying RBA and computing the feature importance aided with a Random Forest (RF) classifier, we reduced the number of predictors to only 14 genes. Most genes in the selections have not been reported in the AD-related literature. One of the genes is KCNIP1, a potassium voltage-gated channel interacting with channels linked to epilepsies and heart disorders but not yet to AD. From our exploratory analysis, we concluded that the multivariate interaction of these genes gives us a high accuracy when we try to discriminate between the two groups. Therefore, we are validating our results by using other datasets of post-mortem Hippocampus transcriptomes.

Schneider, Sydnie

Potential Neurocognitive Disparities between Foreign and Native-Born Rural Hispanic Communities: A Project Frontier Study

Sydnie Schneider[1], Jonathan Singer [1], Carol Fadalla [1], Lauren Elliott [1], Peter Rerick [4], Elisabeth McLean [1], Miranda Tello [1], Veronica Molinar-Lopez [2,3], & Volker Neugebauer [2,3]

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Background: Research has highlighted Hispanic individuals residing in the U.S. are at an increased risk for neurocognitive decline compared to other racial-ethnic minorities. Neurocognitive decline among Hispanics may be the result of medical co-morbidity, lower socioeconomic status, or stress due to acculturation. Yet, studies have also found that newly immigrated populations, who have spent less time in the U.S., have better health outcomes—a phenomenon coined the immigrant paradox. Few studies have examined this relationship in Hispanics living in rural West Texas. Therefore, this study explored whether there are neurocognitive disparities between foreign and native-born Hispanics and how time spent in the U.S. impacts those disparities.

Methods: Data from Project FRONTIER (Facing Rural Obstacles to Healthcare Now Through Intervention, Education, & Research) was used for this study, which includes 441 Mexican born Hispanics and 565 U.S. born from rural counties in West Texas. We also examined time spend in the U.S. and if the person was born in the U.S. or not. Current neuropsychological assessment of participants was conducted using five measures: The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; overall cognitive functioning), The Trails Making Test A and B (rote memory; executive functioning), and Clock Drawing 1 and 2 (long-term processing and memory; visuospatial/visuoconstructive ability).Results: The MANOVA analysis identified a significant interaction between birthplace and neurocognitive functioning (F=8.08, η2p =.039). More specifically, Hispanics born in the U.S. had worse neurocognitive functioning than Hispanics born in Mexico. Post-hoc ANOVAs revealed a significant main effect for overall cognitive functioning (F=5.64; η2p =0.006) rote memory (F=10.88; η2p =0.011); executive function (F=19.62; η2p =0.019), long-term processing and memory (F=30.53; η2p =0.030), and executive functioning (F=8.30; η2p =0.008) for birthplace, as participants who were born in the U.S. had lower neurocognitive functioning, in all domains, than participants who were born in Mexico.Conclusion: Results found that, contrary to hypothesis, U.S.-born Hispanics has significantly greater levels of neurocognitive impairment than Hispanics born in Mexico. Therefore, the results of this study support the notion that Hispanics born in Mexico may have better neurocognitive outcomes than Hispanics born in Mexico (i.e., the Immigrant Health Paradox). Previous studies have hypothesized that do to the domains of migrating and working in the U.S., better health status for these individuals is vital; whereas, U.S. born Hispanics might experience more psychological and environmental stressors to assimilate and acculturate, which has been found to negatively affect neurocognitive functioning.

Skawratananond, Shadt

Mitochondria division inhibitor 1: a promising therapeutic strategy for Huntington's Disease

Shadt Skawratananond, Neha Sawant, P. Hemachandra Reddy

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Huntington's disease (HD), first detailed in 1872 by George Huntington, is an inherited neurological disease characterized by an abnormal expansion of the CAG trinucleotide repeat on the huntingtin (HTT) gene resulting in the production of mutant huntingtin protein (mHTT). The presence of mHTT has deleterious implications on the neuronal pathways in the basal ganglia and striatum, primarily due to imbalanced calcium signaling. HD is manifested through motor symptoms such as a chorea, resting tremor, and unsteady gait, as well as non-motor symptoms such as dementia, cognitive impairment, and depression. Despite extensive research, there is currently no cure for HD. However, various therapeutic strategies have been explored, especially including targeting the mitochondria, as it is known that mHTT directly interacts with the mitochondrial dynamin related protein 1 (Drp1), leading to increased levels of fission, oxidative stress, and mitochondrial bioenergetics. Mitochondria also associate with other cell organelles such as the endoplasmic reticulum (ER) at specialized contact sites where the ER releases calcium ions into mitochondria thus maintaining mitochondrial dynamics and bioenergetics. Mitochondrial division inhibitor 1 (Mdivi-1) is a promising cell-permeable, selective mitochondrial fission inhibitor that has been shown to slow the onset and progression of HD by maintaining mitochondrial dynamics and fragmentation. The restorative effects of Mdivi-1 on ER-mitochondrial contacts and an enhanced expression of proteins were analyzed by immunoblotting, cell culture, and confocal microscopy of mutant HD STHdhQ111 and wild type STHdhQ7 cells. Additionally, a significant reduction of mitochondrial fission activity was analyzed by measuring both mRNA and protein levels of Drp1. These analyses thereby

suggest a new pathway by which Mdivi-1 plays a protective role in HD cells and thus corroborate with earlier research that Mdivi1 could be a promising therapeutic molecule for treatment of HD.

5. Clinical – Graduate Students

Antwi-Adjei, Philip

Associations between Vitamin D Deficiency/Insufficiency and Diabetes in Older Rural West Texans: A Project FRONTIER Study

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BACKGROUND: Bioactive vitamin D (calcitriol) is a hormone essential for many metabolic processes in the body. Vitamin D (VD) deficiency and insufficiency have been associated with a risk of metabolic disorders like diabetes. The prevalence of diabetes is known to be high amongst Hispanics in Texas. Understanding the connection between levels of Vitamin D and the prevalence of diabetes in Hispanics may be a useful clinical tool in combating the disease in Western Texas.
HYPOTHESIS: Does low levels of Vitamin D predispose Hispanics in Western Texas to diabetes?
METHODS: Data was obtained from a cohort of 299 rural West Texans (mean age 62.6 ±11.7, 70.9% female, and 40.5% Hispanic/Latino ethnicity (HLE) recruited into Project FRONTIER (Facing Rural Obstacles to Health Care Now Through Intervention, Education, and Research). Relationships between self-reported measures of general health, history of disease, vitamin supplementation and diabetes-related blood-based biomarkers were investigated. Descriptive statistics and regression analyses were used to determine correlations between serum VD levels and diabetic biomarkers and other parameters.
RESULTS: A significant negative correlation was seen for VD level and diabetes ($p=0.0018$), and the risk factors for diabetes i.e. obesity ($p=0.020$), body-mass index ($p=0.0001$) and abdominal circumference ($p<0.0001$).Simple linear regression found significant negative associations between VD level and fasting blood glucose level ($p=0.0004$) and HbA1c level ($p = 0.0005$). Also VD level negatively associated with the probability of having diabetes ($p=0.0003$) and pre-diabetes status (>110 mg/dL) ($p<0.0001$). Hispanic ethnicity associated with significantly higher HbA1c levels ($p = 0.0006$) and higher fasting glucose levels than non-Hispanic populations ($p = 0.0034$).
CONCLUSION: Low VD levels is associated with an increased probability of diabetes in Hispanics in West Texas

Ayika, Chinyere

Investigating Adolescent TBI Severity as a Predictor of Loneliness

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Traumatic brain injury (TBI) is associated with increased deficits in psychosocial functioning. However, findings on the relationship between childhood TBI and social outcomes are mixed. While studies find children with a TBI exhibit poorer social, emotional, and behavioral functioning compared to non-injured children, one study from Ross and colleagues (2011) failed to find any significant association between head injury status and outcomes of loneliness. Further research is needed to clarify a TBI's impact on loneliness during childhood and adolescence. We use data from 88 youth ages 10-19 treated in metropolitan-area hospitals of the Southern U.S. for either a TBI (N=33) or an orthopedic injury (OI; N=55). Children with a Glasgow Coma Scale score between 3 and 15 and evidence of intracranial anomalies were defined as having a TBI. Children with non-cranial physical injuries and at least one night hospitalized comprised our OI group. Loneliness was measured using the 24-item Children's Loneliness and Social Dissatisfaction Scale. A one-way ANOVA indicated that a child's head injury status (i.e., mild TBI, moderate TBI, severe TBI, or an OI) was significantly associated with the child's self-reported loneliness ($F = 3.718$, $p = .017$). Post-hoc Tukey tests revealed that youth with a moderate TBI reported significantly more loneliness compared to youth with a mild TBI, scoring an average of 15 points higher on our loneliness scale with a total possible score of 120 ($p < .05$, 95% CI [2.05, 27.70]). Our findings help clarify prior conflicting results and suggest that head injury severity is an important predictor of loneliness and thus may be useful for predicting outcomes and making treatment recommendations for youth who have suffered a TBI. Still, future studies should clarify the effects of TBI on loneliness, given there are still some conflicting results and a general lack of research in this area.

Basu, Tanisha

Lifestyle and Biological Factors in Cognitively Healthy Superior Agers in Rural West Texas

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Background and Purpose: Alzheimer's disease (AD) is a global pandemic among the elderly with devastating consequences with no cure. The conditions that lead to dementia are varied with regard to lifestyle, genetic profile, and socio-economic conditions. Within the rural West Texas community, it is seen that some of the elderly population in their 60-90s age without any cognitive impairments, while others begin to experience cognitive decline and chronic conditions. The purpose of our current study is to understand the factors associated with cognitively healthy brain in superior agers in rural West Texas. Methods: We designed a longitudinal prospective cohort study with a purpose of understanding the factors that affect cognitive status in individuals at the age of 60–90. Our ongoing study hopes to recruit 4000 cognitively healthy and 500 AD/ADRD patients to determine the factors that delay aging in some individuals by investigating various aspects including genetics, epigenetics, ethnicity, biology, culture and lifestyle. This is done by gathering information about participants' cognitive assessments (Montreal Cognitive Assessment), anthropometric measurements, blood profiles, brain scans, and health and wellness questionnaires. Results and Discussion: Currently our study is in year one and has recruited 22 healthy and 2 AD patients. Our preliminary data strongly indicates that poor scores on the MOCA test are directly associated with the incidence of brain atrophy as seen through MRIs. Physical and mental wellbeing assessed using bloodwork and questionnaires is greater among the cognitively healthy population. We observed that healthy lifestyle such as diet and exercise was associated with the healthy aging population.

Conclusion: Based on our current data, it is evident that there is an association among the scores on the MOCA test, brain atrophy, biomarkers and psychosocial parameters. The outcomes of our study will provide novel insights into healthy aging in rural West Texas. These data indicate that hospitalization is a rare aspect of pediatric COVID-19 disease, but both acute COVID and MIS-C played a significant role in the burden of inpatient disease for pediatric patients in our region during the first year of the pandemic. Further investigations should explore the role of newer variants (Delta, Omicron) in the epidemiology of pediatric patients requiring hospital care for COVID-19 related conditions.

DeSimon, Daniel

Tibial "Bingo" Neuropathy - A Case Report

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Case Description: The patient presented with left calf and plantar foot pain and numbness for three months, around the same time when she received a computer as a gift. She bought an office chair and started to enjoy playing online bingo on a daily basis, for about 3 hours a day. The pain is worse when she is seated with her left leg bent and improves when she walks around. The pain has subsided since the patient started taking cyclobenzaprine one month ago, and the patient's current complaint is numbness.
Setting: Outpatient physiatry clinic
Patient: 60-year-old female with a past medical history of type two diabetes mellitus diagnosed three years ago.
Results: On physical exam, there was no bony deformity, tenderness, rash, or inflammation of the feet or legs. The patient had full ankle range of motion for dorsiflexion and plantarflexion, as well as inversion and eversion. The patient demonstrated lower extremity 5/5 strength bilaterally and pulses were palpable. Sensation to light touch was intact throughout the lower extremity bilaterally. Steady gait was noted and the patient did not complain of pain during the physical exam. EMG evaluation was completed and demonstrated 1+ polyphagia of the left flexor digitorum longus. Left superficial fibular, sural, fibular, and tibial responses were within normal range during the nerve conduction study. Point of care ultrasound did not reveal focal areas of nerve damage, as it was not possible to visualize the nerve in the posterior compartment of the leg. These findings were consistent with left tibial neuropathy secondary to ischemia.
Discussion: This patient presented with left lower leg pain with an associated numbness on the bottom of her foot. The patient reported her symptoms began three months ago shortly after she started playing bingo for several hours a day in an office chair. Overall clinical history, physical exam, electrodiagnostic, and sonographic findings indicated a diagnosis of left tibial neuropathy with no apparent localization into the tarsal tunnel. Due to the anatomy of the tibial nerve, providing innervation to muscles below the popliteal fossa and foot, ischemia related to sitting in an office chair daily for prolonged periods playing bingo most likely contributed to the patient's symptoms.
Conclusion: This case demonstrates the possible risk of tibial neuropathy secondary to ischemia due to sitting for a prolonged period of time in an ergonomically incorrect position.
Disclosures: No financial relationships or conflicts of interest

Elliot, Lauren

Neurocognitive Functioning in Hispanic and Non-Hispanic Individuals in Rural West Texas: Understanding the Influence of Age and Education

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Background: Research indicates education and age influence neurocognitive functioning; however, little is known about education and age affecting Hispanic and non-Hispanic populations, specifically, within underserved rural individuals in West Texas. Methods: 1864 participants (752 non-Hispanic, 1053 Hispanic; Mage = 59.68 years, SDage = 12.21) in Project FRONTIER (Facing Rural Obstacles to Healthcare Now Through Intervention, Education, & Research) completed five neuropsychological tests: The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Trails Making Test A and B, and Clock Drawing 1 and 2. Age was dichotomized at 65 to assess older (65+) vs younger adults (< .001, η2p = 0.184) on indicators of neurocognitive functioning. Post-hoc analysis revealed older participants had lower overall neurocognitive functioning on RBANS (M = 82.52, SD = 16.75) than younger participants (M = 85.24, SD = 14.95). Post-hoc analysis revealed Hispanic participants had lower overall neurocognitive functioning (M = 78.49, SD = 14.26) than non-Hispanic participants (M = 92.11, SD = 15.07). The second MANOVA identified a significant interaction between ethnicity and education on neurocognitive functioning (Roy's Largest Root = 5.11, F (5, 1,548), p < 0.001, η2p = 0.016). Non-Hispanic individuals who reported less education had worse neurocognitive functioning compared to participants with more education. However, Hispanic participants did not have as significant increase between low education compared to higher education. Conclusions: Lower age and higher education were linked to greater neurocognitive functioning. However, educational attainment had a disproportionate lower impact on neurocognitive functioning for Hispanic individuals compared to non-Hispanic individuals. These results are consistent with the theory of Minorities' Diminished Returns, which posits educational attainment has weaker protective effects for ethnic minority groups. It could be hypothesized the education system is structured to provide greater benefits for non-Hispanic individuals, compared to Hispanic individuals. Due to potential systematic biases, education status may only serve as a protective factor for those it was developed: non-Hispanic, white individuals.

May, Harry

Differentially expressed genes in Neuroblastoma PDXs in response to topotecan and cyclophosphamide

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Neuroblastoma (NBL) is the most common extra-cranial solid tumor that arises in the sympathetic nervous

system among children. NBL accounts for about 6% of childhood cancers and approximately 15% of all pediatric cancer deaths. While the survival rate for patients with low- and intermediate risk disease approaches 100%, the 5 years survival rate for high-risk NB patients is less than 60%. Approximately 15% of high-risk neuroblastoma patients develop progressive disease (PD) during induction chemotherapy. Laboratory models are needed to understand mechanisms of early neuroblastoma PD. We evaluated 31 subcutaneous patient-derived neuroblastoma xenografts (PDX) established at diagnosis (Dx, n=15) and PD (n=16) from the Children's Oncology Group/ALSF repository (www.CCcells.org). Response over 175 days was assessed to 3 cycles of cyclophosphamide (cyclo, 30 mg/kg) + topotecan (topo,0.6 mg/kg) daily x 5 days every 21 days. RNA sequencing of PDXs prior to therapy in three batches was corrected for batch effect using Combat. Differentially expressed genes were identified using DESeq2 and limma. Of the 31 PDXs, six PDXs were non-responders (NR), two stable disease (SD), eleven partial responders (PR), four complete responders (CR), and eight maintained CRs (MCR). SD models were classed in the NR group along with six NRs, and 23 PR/CR/MCR were classed in the response group (R) to identify differentially expressed genes between the NR group and the R group. DESeq2 identified over 20 genes that are differentially expressed. Gene Set Enrichment Analysis found pathways that are statistically significant, including Hallmark E2F targets, Hallmark G2M checkpoints, and Hallmark MYC targets V1 and V2. To confirm the genes that are differentially expressed, we conducted real-time RT-PCR in PDX samples as well as matching cell lines. Next, for further verification, we'll perform in vitro cytotoxicity assays with various expressions of the selected gene candidates. The utilization of PDX models is crucial in understanding the role of differentially expressed genes in the NR group since biopsies are not routinely done in clinical settings. Our data will provide guidance in identifying specific genes that are associated with poor response to chemotherapy in neuroblastoma patients.

Ugochukwu, Kingsley

The Use of Topical Capsaicin Cream as A Preferred Antiemetic in Cannabis Hyperemesis Syndrome - A Form of Functional Gut-Brain Axis Disorder

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Background: Cannabis is one of the most widely used recreational drug in the United States. With the increase in legalization across states, have resulted in the high ingestion amounts of cannabis resulting in Cannabinoid hyperemesis syndrome (CHS). CHS is a form of functional gut-brain axis disorder that consist of cyclical bouts of nausea, vomiting, and abdominal pain, that is classically relieved with hot showers. Patients with CHS, tend to be long-term cannabis smokers whose symptoms are seldom relieved by traditional antiemetics1,2. CHS treatment is focused on symptom relief and cannabis cessation education. Capsaicin is a topical agent that have been reported to mimic the effects of hot showers and have been shown to be efficacious in abating the symptoms of CHS. Capsaicin exerts its action via Transient receptor potential vanilloid 1 (TRPV1) which can be found in the nociceptive neurons in the central and peripheral nervous system1,5. Capsaicin can be purchased as an over the counter (OTC) preparation, therefore, should be a reasonable and preferred first-line treatment for CHS patients. While this recommendation is made based on limited data, it can be argued that capsaicin is cheap, well tolerated, and has a low-risk side-effect profile when compared to other traditional anti-emetics3. This would in-turn reduce the burden/distress for the patient, frequent hospital admissions, and overall cost impacts of healthcare4. Methods: The keywords "Cannabis hyperemesis syndrome", "Cannabinoids hyperemesis syndrome", "Capsaicin", were used to review literature from 3 electronic databases (PubMed, Cochrane, and Embase). These literatures were filtered with publication date of the last 10 years till date (March

2023) which generated a total of 38 results from the databases. After applying exclusion criteria, 31 citations were excluded. A total of 7 literature were reviewed for this abstract. Inclusion Criteria: Articles, clinical trials, case report, and case series which were written in English Language. Exclusion Criteria: Conference papers, editorials, and non-English articles. Results: The literature review showed a shorter length of stay (LOS) in the emergency department if capsaicin is applied (on the anterior abdomen/peri-umbilical region) earlier upon admission. It was concluded that the antiemetic effect of capsaicin was more efficacious at 60 min compared to 30 min measured from the initial administration of capsaicin4,6-7. Conclusion: Due to the cyclical and unpredictable nature of CHS, a standardized treatment protocol can be formulated to incorporate capsaicin as a first line prophylactic antiemetic as well as the preferred first line antiemetic for patients with CHS. This is of importance in patients with congenital or acquired QT prolongation syndrome who cannot be given most traditional anti-emetic such as ondansetron. Future prospective, placebo-controlled studies are needed to address the dosage, safety, and tolerability of capsaicin for treatment of CHS.

6. Clinical – Postgraduates

Fadalla, Carol

Examining the Impact of Depression on Neurocognitive Disparities in Hispanic and Non-Hispanic Rural Aging Adults: A Project Frontier Study

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Background: Hispanic adults are at an increased risk for neurocognitive decline compared to other racial-ethnic minorities. Few studies have examined the prevalence of neurocognitive decline among Hispanics living in rural West Texas—a population deeply underserved. Therefore, this study explored whether depression moderated the relationship between neurocognitive functioning and ethnicity, utilizing data from Project FRONTIER (Facing Rural Obstacles to Healthcare Now Through Intervention, Education, & Research).Methods: 1,842 participants (Mage = 59.68 years, SDage = 12.21) 1,053 Hispanics and 752 non-Hispanics, from multiple rural counties in West Texas were included between June 2006 and January 2022. We evaluated neuropsychological testing using five measures: the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), the Trails Making Test A and B, and Clock Drawing 1 and 2. The Geriatric Depression Scale (GDS) was used to assess depression, and we dichotomized depression scores using a validated cutoff of “no depression” (0-10) and “mild/severe depression” (11-30). Results: The MANOVA identified a significant interaction between ethnicity and depression on neurocognitive functioning (Roy’s Largest Root = 3.56, F(5, 1,548), p= 0.003, η2p = 0.01). More specifically, non-Hispanic individuals who reported mild/severe depression had worse neurocognitive functioning compared to participants with no depression. However, there was no difference for Hispanic participants who reported mild/severe depression compared to those with no depression. A post-hoc ANOVA revealed a significant main effect on neurocognitive functioning (RBANDS) for ethnicity (F(5, 1,549), p < .001, η2p = 0.06), as participants who identified as Hispanic (M= 79.41 and SD= 0.57) had lower overall neurocognitive functioning than non-Hispanic (M= 88.38; SD= 0.78) participants. On indicators of neurocognitive functioning, a significant main effect for depression was found (F(5, 1,549) = 13.62, p < 0.001, η2p = 0.04). Conclusion: Results are consistent with the minority stress model, which states racial-ethnic minorities are exposed to chronic stressors that negatively influences functioning. Non-Hispanic individuals encounter fewer chronic stressors than minorities and, the introduction of stressors, like depression, may impact neurocognitive functioning—unlike Hispanic individuals. Previous studies suggest chronic life stressors are equally detrimental to cognitive functioning in individuals with and without depression. Results support the need for culturally tailored interventions because underlying factors related to cognitive function differ, such as depression in non-minority individuals.

Sehar, Ujala

Caregiving Practices in the Hispanic population and Urgent Need for Developing Interventions for Hispanic Family Caregivers

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Background and purpose: Alzheimer's disease (AD) and Alzheimer's disease-related dementias (ADRD) are the primary public health concerns in the United States and around the globe. Increasing evidence suggests that Hispanics are the fastest-growing ethnic population in the USA. Further, Hispanics develop clinical symptoms of AD/ADRD and other comorbidities, at least seven years earlier than non-Hispanic whites. Currently, AD/ADRD individuals are taken care of by family caregivers, which puts a tremendous burden on caregivers who are usually older themselves. Family caregivers provide all-day care for individuals with long-term illnesses, such as AD/ADRD, while managing their health. Our study aims to assess the status of Hispanic caregivers and their burden. Methods:The current study collected information about family caregivers of AD/ADRD patients and assessed caregivers' essential activities of daily-living and their physiological, mental, behavioral, and social health. Our study also focused on effective interventions for family caregivers that includes educational and psychotherapeutic components. It critically assessed the innovative methods and validations to support Hispanic family caregivers in rural West Texas. Results and discussion: Our initial findings showed that family–centred caregiving is very common in the Hispanic culture due to their ethnocentric beliefs that also tend to delay seeking diagnosis and treatment. The demands of caregiving can harm the caregiver's health and result in poor mental health that might harm the patients as well as long-term outcomes. Many ties that distinguish Hispanic families are beyond the scope of the present surveys/metrics, and techniques. It is critical for AD/ADRD patients and their families to find prospective sources of unpaid care, comprehensive metrics, and procedures to assess these families' needs, including the kinds of links that make up these families.Conclusion: To address the unmet needs of Hispanic family caregivers, we propose to develop culturally appropriate innovative methods involving educational and psychotherapeutic components and validation tools. Acknowledgements (for the poster): The study was conducted using data collected as part of Texas Youth Depression and Suicide Research Network with the help of clinical research coordinators from the TTUHSC Clinical Research Institute. The study was funded by the Texas Child Mental Health Care Consortium.