Neuroplasticity in Clinical Disorders

From Chronic Pain to Neurodegenerative Diseases

Distinguished Keynote Speaker and Alexander D. Kenny Lecturer

"NINDS and the Taxpa yer's Investment in Neuroscience"

Walter Koroshetz, M.D.,

Director, National Institute of Neurological Disorders andStroke (NINDS) | National Institutes of Health (NIH)

Annual Symposium

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

Tuesday, April 19, 2022
ACB Lobby and ACB 100

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. Tom Tenner, Professor, Department of Medical Education

12:00 PM **Keynote Lecture**, "NINDS and the Taxpayer's Investment in Neuroscience"
Walter Koroshetz, M.D., Director, National Institute of Neurological Disorders and Stroke (NINDS) | National Institutes of Health (NIH)

1:00 PM Q & A Session with Keynote Speaker

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

- **Volker Neugebauer**, M.D./Ph.D.,
  Igor Ponomarev, Ph.D.,
  Peyton Presto, MD/Ph.D. Student
  "Pain mechanisms-neuroimmune signaling in the brain"

- **Michaela Jansen**, PharmD., Ph.D.
  "Molecular Determinants for the Interaction between the Chaperone RIC-3 and Pentameric Channels"

- **Josh Lawrence**, Ph.D.
  "Hippocampal function in Alzheimer's disease"

3:00 PM **Poster Session**

5:00 PM **ADK Outstanding Student Award and Awards Ceremony**

5:45 PM **Refreshments**

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Lunch will be provided for registered participants

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TEXAS TECH UNIVERSITY
HEALTH SCIENCES CENTER

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

April 5, 2022

Welcome to the *6th 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.

Our collaborative and innovative efforts to bridge basic science and clinical entities in nervous system disorders from chronic pain to neurodegenerative diseases could not have been accomplished without the support from Dr. Steven Berk, Dean of the School of Medicine and Executive Vice President for Clinical Affairs and Dr. Leslie Shen, Associate Dean for Research, School of Medicine. A special thank-you goes to Dr. Lance McMahon, Sr. Vice President for Research and Innovation, for his support of research through matching seed funds and research infrastructure. We would like to thank Dr. Lori Rice-Spearman, President, and Dr. Darrin D'Agostino, Provost and Chief Academic officer, for their support of the GIA.

It is an immense honor to welcome this year's *Key Note Speaker*, Dr. Walter Koroshetz, Director of the National Institute of Neurological Disorders and Stroke (NINDS). Dr. Koroshetz has kindly agreed to share with us research and training advances, goals, and strategies of NINDS in his lecture and in meetings with basic science and clinical CTNT and GIA team members. Additionally, translational research presentations by CTNT-GIA teams and posters by trainees in basic science and clinical disciplines are intended to inform about CTNT and GIA 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. Tiffany Denton, previous CTNT Coordinator, shared valuable insights on the logistics of this meeting. And we are 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

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

Acknowledgements

Steering Committee

- Vadivel Ganapathy, PhD, Professor and Chair, Dept. of Cell Biology and Biochemistry, TTUHSC
- Josee Guindon, DVM, PhD, Associate Professor, Dept. of Pharmacology & Neuroscience, TTUHSC
- George Henderson, PhD, 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

Organizing Committee

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

Institutional Support

- Steven L. Berk, MD, Dean, School of Medicine, TTUHSC
- Leslie Shen, PhD, Associate Dean for Research, School of Medicine, TTUHSC
- Lance McMahon, MS, PhD, Senior Vice President for Research and Innovation, TTUHSC
- 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) serves 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 and neuropsychiatric 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, our Center has grown to 40 members from 15 different departments or institutes at TTUHSC and TTU, including 22 faculty doing basic preclinical research 18 faculty working with patients or human subjects (https://www.ttuhsc.edu/centers-institutes/translational-neuroscience-therapeutics/leadership-members.aspx).

CTNT provides the expertise and infrastructure for multidisciplinary translational research for translational research 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 Lecture Series, Seed Funds for collaborative translational research and scholarly activity by teams of basic science and clinical faculty, and shared research tools. (https://www.ttuhsc.edu/centers-institutes/translational-neuroscience-therapeutics/research-support.aspx).

CTNT support and core facilities are available for innovative collaborative research projects by teams of basic scientists and clinicians to generate translational scholarly activities and external funding to support the mission of the Center and TTUHSC.

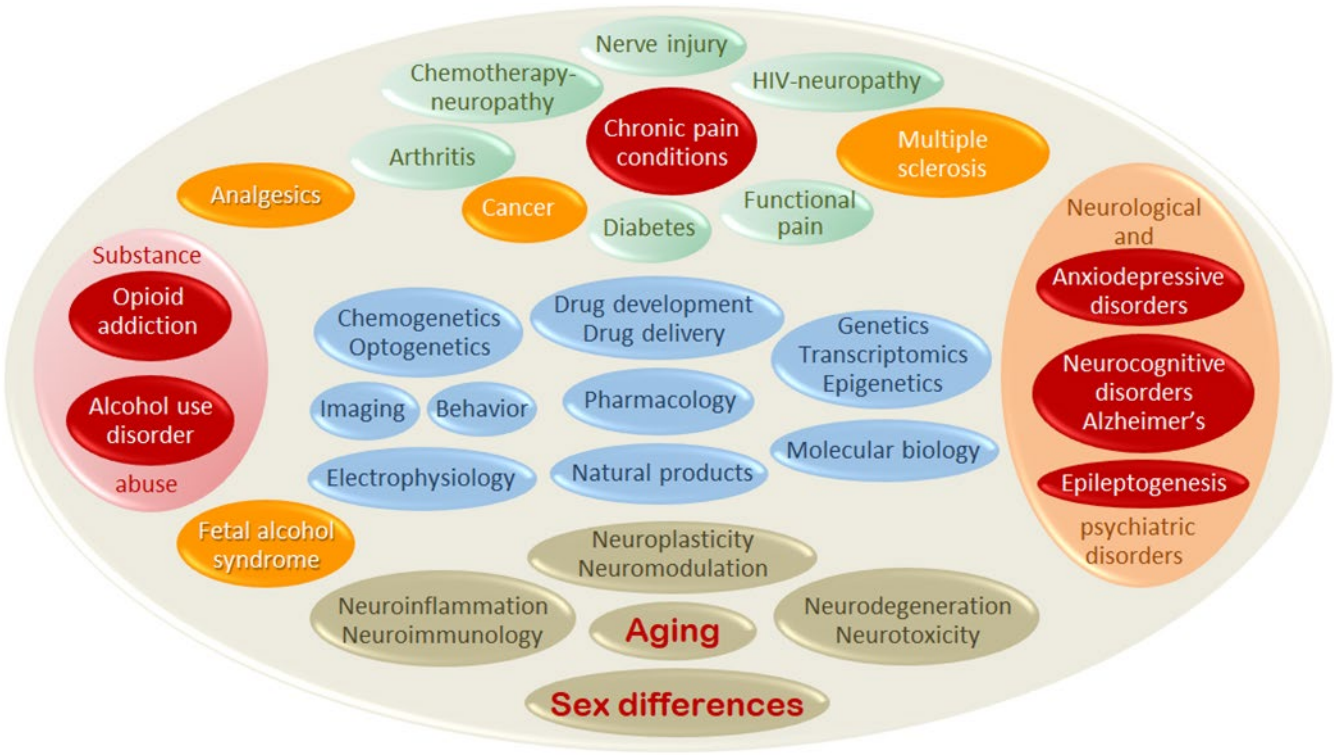
GIA Factsheet

Established in 1999 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 promotes healthy aging through cutting-edge research in aging-related health issues, such as Alzheimer's disease, and through innovative educational and community outreach programs. The GIA team investigates causes of neurodegenerative diseases and educates the community on preventative medicine and challenges impacting the geriatric population.

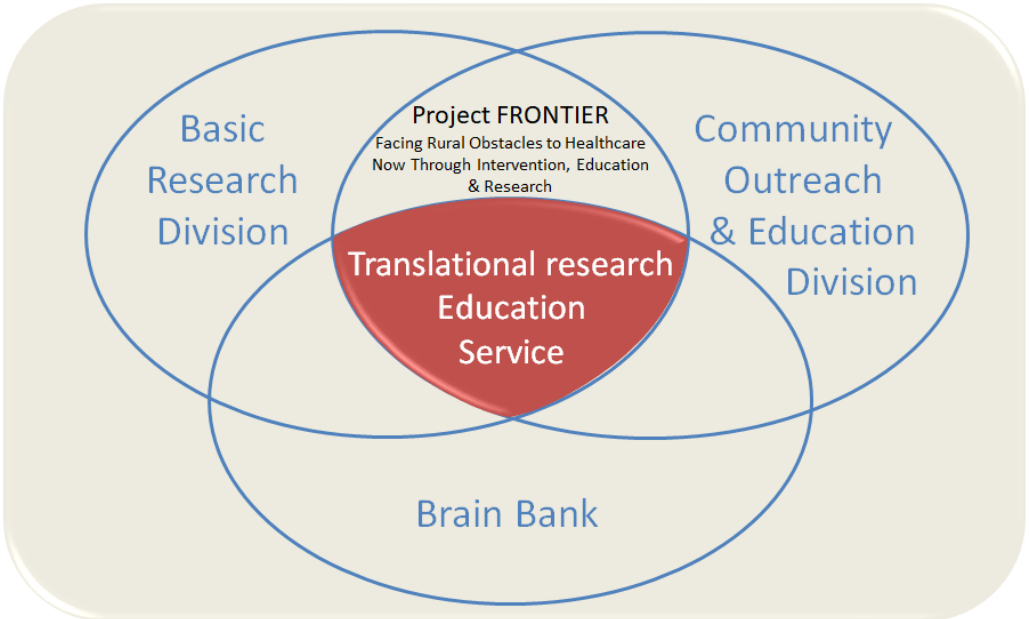
The GIA vision is to serve as the central hub within TTUHSC to stimulate and accomplish collaborative initiatives in research, interdisciplinary education and community outreach related to healthy aging and aging-related disorders. https://www.ttuhsc.edu/centers-institutes/garrison-aging/default.aspx

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, RSVP (Retired and Senior Volunteer Program established in 1979 under the umbrella of the Corporation for National and Community Service, CNCS, now AmeriCorps Seniors).

Collaborative Translational Research Areas – CTNT and GIA



GIA Organization and Activities



Keynote Lecturer

Walter Koroshetz, MD

Director, National Institute of Neurological Disorders and Stroke (NINDS)

National Institutes of Health (NIH)

Dr. Koroshetz serves as Director of the National Institute of Neurological Disorders and Stroke. He joined NINDS in 2007 as Deputy Director and has held leadership roles in a number of NIH and NINDS programs including co-leading the NIH's BRAIN Initiative, the NIH RECOVER Initiative in the study of Post Acute Sequelae of COVID-19, NIH Blueprint for Neuroscience, the NIH Post Acute Sequelae of Covid-19 Initiative, the Traumatic Brain Injury Center collaboration between the NIH intramural and the Uniformed Health Services University, the Helping to End Addiction Long Term (HEAL) Initiative. He co-leads a number of NIH Common Fund's programs including the Undiagnosed Disease Network, the Acute to Chronic Pain Transition programs, Somatic Gene Editing program, Transformational ALS research program, and he was instrumental in founding the NIH Office of Emergency Care Research.

Before joining NINDS, Dr. Koroshetz served as Vice Chair of the neurology service and Director of stroke and neurointensive care services at Massachusetts General Hospital (MGH). He was a professor of Neurology at Harvard Medical School (HMS) and led neurology resident training at MGH between 1990 and 2007. Over that same period, he co-directed the HMS Neurobiology of Disease Course with Drs. Edward Kravitz and Robert H Brown.

A native of Brooklyn, New York, Dr. Koroshetz graduated from Georgetown University and received his medical degree from the University of Chicago. He trained in internal medicine at the University of Chicago and Massachusetts General Hospital. He then trained in Neurology and Neuroscience at MGH and Harvard Neurobiology focusing on how synaptic mechanisms might contribute to neuronal death. His early research in the lab and clinic focused on Huntington's disease and with the team at MGH performed the first study of pre-symptomatic testing based on linkage analysis. A major focus of his clinical research career was the development of measures in patients that reflect the underlying biology of their conditions. This led to brain the development and validation of imaging techniques including Magnetic Resonance (MR) spectroscopy in Huntington's disease; diffusion/perfusion MR and CT X-ray angiography and perfusion imaging in stroke. These stroke imaging tools are now commonplace in stroke care. Guided by these tools he pioneered acute clot removal for acute stroke patients with large artery occlusion which is now practiced at Comprehensive stroke centers around the country. Through his work with the American Academy of Neurology, American Stroke Association and ACGME, he played a significant role in the revolution in acute stroke care in the US and the growth of the neurointensive care field.

Alexander D Kenny Outstanding Graduate Student Award Speaker

Mariacristina Mazzitelli

PhD Candidate,
GSBS Translational Neuroscience and Pharmacology Graduate Concentration
Texas Tech University Health Sciences Center

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 five doctoral students have received this prestigious award.

Mariacristina Mazzitelli received her B.S./M.S. in Pharmaceutical Chemistry and Technologies from the University of Naples "Federico II" in Italy. After research training through the Erasmus Program of the European Union and at the University of Campania "Luigi Vanvitelli", Italy, she moved to Lubbock to join Dr. Neugebauer's group at TTUHSC in 2016. She was admitted to the TTUHSC GSBS Ph.D. program in the Spring of 2018, and continued to work under Dr. Neugebauer's mentorship for her Ph.D. dissertation project that focused on the role of amygdala neurons in the modulation of pain. In March 2022, she passed her Ph.D. dissertation defense.

Optogenetic and pharmacological manipulations of amygdala in pain

The amygdala, a limbic brain region, plays a key role in emotional behaviors and in averse-affective aspects of pain and pain modulation. Abnormally increased amygdala output activity correlates with pain states. Therefore, reducing uncontrolled amygdala activity is a desirable strategy to mitigate pain. The corticotropin releasing factor (CRF) system in the amygdala has been linked to pain behaviors and pain-related amygdala plasticity, but little is known about the role of amygdala CRF neurons in pain. One way to modulate neuronal activity selectively is optogenetics, which is based on the expression of excitatory or inhibitory light sensitive molecules in specific cell types and their activation by light of appropriate wavelengths. Optogenetic modulation of amygdala neurons could mitigate pain. Pharmacological modulation of neurotransmitter function is also a promising strategy to mitigate pain. Group II metabotropic glutamate receptors (mGluRs), which consists of mGluR2 and mGluR3 subtypes, couple to Gi/o to decrease neurotransmitter release, are expressed throughout the nervous system, and they have emerged as potential therapeutic targets in several diseases, including pain. Amygdala group II mGluRs have been linked to pain modulation, but the roles of individual subtypes and their contributions to systemically acting group II mGluR activators are not yet known. This research project showed that optogenetic activation of amygdala CRF neurons generated sensory and emotional-affective pain-like behaviors and spinal nociceptive processing under normal conditions in the absence of tissue injury, whereas optogenetic inhibition of CRF neurons in an arthritis pain model mitigated affective, but not sensory, pain behaviors and inhibited spinal nociceptive processing. While activation of either mGluR2 or mGluR3 subtype inhibited emotional responses in an arthritis pain model, mGluR2 also inhibited sensory pain behaviors and mGluR3 also anxiety-like behaviors. This work identified amygdala CRF neurons as an important target for optogenetic and pharmacological interventions to mitigate pain.

CTNT Collaborative Research Presenters

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

Igor Ponomarev, Ph.D.
Associate Professor, Dept. of Pharmacology and Neuroscience, TTUHSC

Peyton Presto, M.S.
M.D. /Ph.D. Candidate
GSBS Translational Neuroscience and Pharmacology Graduate Concentration, TTUHSC

Dr. Neugebauer obtained his M.D. and Ph.D. degrees from the University of Würzburg, Germany. He received broad training in physiology, pharmacology, neuroscience and neurology at the University of Würzburg and the University of Texas Medical Branch (UTMB) at Galveston, TX. Dr. Neugebauer has been studying synaptic and cellular mechanisms of neuroplasticity and brain functions in pain, comorbid conditions, and various neurological and psychiatric disorders for more than 30 years. His work has been published in 150 articles and has been funded continuously by NIH for nearly 25 years and is currently supported by 6 NIH R01 grants and a USDA grant (5 of these as PI/MPI). Dr. Neugebauer discovered neuroplastic changes in the amygdala as a critical pain mechanism. The analysis of emotional-affective and cognitive brain mechanisms of pain centered on amygdala plasticity and interactions with cortical regions is a key contribution of his work to the field of pain research and neuroscience. A recent focus is on neuroimmune signaling and sex differences. Collaborative preclinical research projects explore brain mechanisms of neurological and psychiatric disorders, alcohol use and addiction disorders, comorbidities with depression and anxiety disorders, neurodegenerative disorders such as Alzheimer's disease, and epileptogenesis. Collaborative studies in humans include epidemiological studies and interventions in chronic pain and dementias such as Alzheimer's disease.

Dr. Ponomarev received his Ph.D. degree in behavioral neuroscience from Oregon Health & Science University and postdoctoral training in molecular biology, genomics and bioinformatics from the University of Texas at Austin. His research focuses on the interplay between genetic, epigenetic, neuroimmune, and environmental factors in controlling brain gene expression and behavior in models of alcohol use disorder (AUD). He studies molecular mechanisms of AUD using genome-wide transcriptomic and epigenomic profiling and applies the tools of systems biology, such as gene network approaches, to provide an integrated view of brain responses to alcohol. His lab has recently employed the single cell transcriptomics technology, which allows for single cell and cell population resolution of molecular changes associated with disease and treatments. An important

component of this effort is discovering and prioritizing molecular targets for medication development to treat AUD and comorbid CNS disorders. Dr. Ponomarev has been continuously funded by NIH since 2008 and is currently the PI or MPI on three and a Co-I on one NIH grants. He is currently funded by NIAAA to study the role of neuroimmune signaling in AUD and also contributes his expertise in neuroscience, transcriptomics, bioinformatics, and neuroimmune signaling to several collaborative projects including central mechanisms of chronic pain (with Dr. Neugebauer) and Alzheimer's disease (with Dr. Lawrence).

Peyton Presto is an MD/PhD candidate in her third year of graduate studies in the Translational Neuroscience and Pharmacology graduate concentration based in the Department of Pharmacology and Neuroscience. She works in Dr. Neugebauer's lab and is studying neuroimmune signaling mechanisms of pain within the amygdala, particularly with regard to the transition from the acute to chronic phase and to potential sex differences, through a collaborative project with Dr. Ponomarev's lab. Peyton is from Cullman, Alabama, and attended The University of Alabama, where she received a master's degree in finance and bachelor's degrees in chemical engineering and finance. Peyton is excited to pursue a career as a physician-scientist within the pain field after her completion of the medical curriculum.

Pain mechanisms – Neuroimmune signaling in the brain

Chronic pain is a complex disorder affecting more than 20 percent of adults in the United States (Jason et al 2022 Pain 163 e328-e332). The different sensory, affective and cognitive dimensions of chronic pain reside with different neural subsystems and brain regions. The amygdala, specifically, its central nucleus (CeA), is a brain region that has emerged as an important player in the emotional-affective dimension of pain and in comorbid anxio-depressive disorders. Preclinical studies found that neuroplasticity in the amygdala develops in pain conditions and drives pain behaviors. Underlying mechanisms, especially at the chronic pain stage, are not fully understood. Here we discuss evidence for a critical role of neuro-immune signaling in the chronification of neuroplasticity and pain. Our electrophysiological studies in brain slices show that amygdala neuroplasticity at the acute pain stages is due to plastic changes at synapses that carry nociceptive (i.e., pain-related) information to the amygdala. At the chronic stage, however, synaptic plasticity is no longer detected but neuronal hyperactivity persists. This led us to hypothesize that mechanisms other than synaptic plasticity are involved. Specifically, we are exploring the novel concept that non-neuronal factors (glia cells) are activated by synaptically-driven increased neuronal activity at the acute stage and then maintain neuronal hyperexcitability through glia-to-neuron signaling. To test our hypothesis, we are using transcriptomic analyses to identify different cell types and molecular factors involved in neuro-immune signaling at different stages of pain and in the transition from acute to chronic pain. We then select molecular factors as targets to modulate neuro-immune signaling for validation in behavioral assays of sensory and affective aspects of pain. Cellular and synaptic mechanisms of action are determined in electrophysiological and imaging studies. Our preliminary transcriptomic study in the CeA tissue identified several molecules implicated in neuro-immune signaling after the induction of pain. One molecular target is high mobility group box protein 1 (Hmgb1), a common marker for many pro-inflammatory conditions in the brain, and we selected it for functional validation experiments. Subacute knockdown of Hmgb1 via stereotaxic injection of Hmgb1 siRNA (pooled AAV vector) into the right CeA of adult neuropathic rats ameliorated anxiety-like behaviors (open field test and elevated plus maze), inhibited emotional-affective responses (audible and ultrasonic vocalizations), and decreased mechanical hypersensitivity (von Frey test and paw compression assay) at the chronic phase in a sex-dependent manner. In behavioral assays we also found that chemogenetic silencing of microglia inhibited pain behaviors (mechanical sensitivity and emotional-affective responses) at the chronic stage of the neuropathic pain condition. Together these findings suggest that neuro-immune signaling mechanisms, such as communication between glial cells and neurons via molecular factors like Hmgb1, contribute to the

transition from acute to chronic pain and to the maintenance of a chronic pain state. Inhibition of these mechanisms may serve as a potential therapeutic strategy for chronic neuropathic pain relief.

Supported by NIH grants R01 NS038261, R01 NS106902, R01NS118731, R01 NS120395, and R01 AA027096

Michaela Jansen, PharmD., Ph.D.
Associate Professor, Dept. of Cell Physiology and Molecular Biophysics
Assistant Dean, Pre-Clerkship Curriculum
Center for Membrane Protein Research
Texas Tech University Health Sciences Center

Dr. Michaela Jansen holds a Pharm.D. and Ph.D., both from the Johannes Gutenberg-University in Mainz, Germany. Current research projects encompass the disciplines of biophysics and neuroscience with a focus on the structure and function of specific membrane transport proteins that are relevant for human health and disease. Specifically, studies in her laboratory aim to identify and characterize drug binding sites, to develop and experimentally probe 3D models of membrane transport proteins, to determine functional conformational changes of membrane proteins, to study molecular mechanisms of drugs interacting with such proteins, and to characterize protein-protein interactions for the identification of highly selective drug targets. Dr. Jansen's has been the principal investigator on federal grants, mostly from the National Institute for Neurological Disorders and Stroke (NINDS) at the National Institutes of Health (NIH), for projects related to the large superfamily of eukaryotic pentameric ligand-gated ion channels since 2003. Dr. Jansen has mentored more than 60 undergraduates, graduate students, medical students, and postdoctoral researchers for their research projects. Lastly, she is a member of two centers of excellence at Texas Tech University Health Sciences Center, the Center for Membrane Protein Research and the Center for Translational Neuroscience and Therapeutics.

Molecular Determinants for the Interaction between the Chaperone RIC-3 and Pentameric Channels

Serotonin or 5-hydroxytryptamine type 3 (5-HT_3) receptors belong to the family of pentameric ligand-gated ion channels (pLGICs), which also includes nicotinic acetylcholine, γ-amino butyric acid A, and glycine receptors. These receptors have been long-standing targets for the development of pharmacotherapies for anxiety, epilepsy, schizophrenia, addiction, and neurological diseases like Alzheimer's and Parkinson's disease. Within the family of more than 40 subunits found in humans both the extracellular and transmembrane domains share significant sequence similarity and identity, respectively. Clinical trials for drug candidates targeting these domains have been largely hampered by undesired effects mediated by off-target subunit modulation. With the present study, we explore the interaction interface of the 5-HT_{3A}R intracellular domain (ICD) with the resistance to inhibitors of choline esterase (RIC-3) protein. Protein-protein interactions represent attractive and successful targets for contemporary drug development. The ICD is the most diverse

domain of pLGICs, and is composed of a short linker L1, a short α-helix MX, and a long linker L2 followed by an α-helical segment (MA) that is continuous with the last transmembrane segment M4. Here, we demonstrate that within the 5-HT_{3A}-subunit, the MX segment contains the RIC-3 interaction interface, and that the same motif is duplicated such that a second binding site is located to the intersection between the MA and M4-helices. The identified interaction interfaces provide insights for the design of compounds to mimic or interfere with the RIC-3 5-HT_{3A} interaction.

J. Josh Lawrence, Ph.D.

Associate Professor, Dept. of Pharmacology and Neuroscience
Center of Excellence for Translational Neuroscience and Therapeutics
Garrison Institute on Aging
Texas Tech University Health Sciences Center

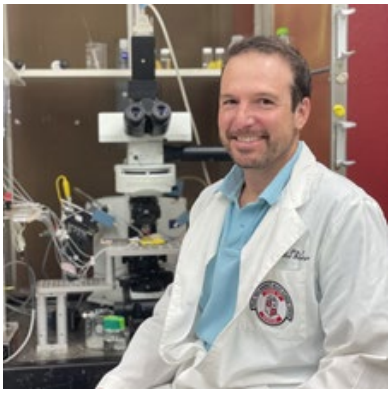
Dr. Lawrence is a newly tenured Associate Professor in the Department of Pharmacology and Neuroscience at the TTUHSC School of Medicine. He received his BS from Allegheny College in 1992 and PhD in Neuroscience in 1999 from the University of Wisconsin-Madison. His laboratory has historically focused on determining how specific neuronal cell types, circuits, and synapse types within the hippocampus contribute to learning and memory operations. As a postdoctoral fellow and staff scientist at the NIH, his interest in cell-type specific specializations brought him to the dentate gyrus (DG) and CA3 regions of the hippocampus. As an Assistant Professor at the University of Montana, he established an NIH/NINDS-funded laboratory focused on understanding how extrinsic GABAergic and cholinergic input from the medial septum-diagonal band of Broca (MS-DBB) impacts the excitability of specific cell types in the hippocampus. Before coming to TTUHSC, he gained exposure to the Alzheimer's disease (AD) field through an NIH/NIA-funded small business grant. Since joining TTUHSC, he has become affiliated with the Center of Excellence in Translational Neuroscience and Therapeutics, TTUHSC's Garrison Institute on Aging, and the Center of Excellence in Integrative Health, which gained him an integrative understanding of age- and AD-related cognitive impairments. His currently funded NIH/NIA R01 grant ventures into nutrigenomics by investigating the relationship between vitamin A depletion and AD pathogenesis.

Hippocampal function in Alzheimer's disease: the importance of vitamin A in circuit function

In the hippocampus, maintaining balance between excitatory and inhibitory circuits is critical for normal learning and memory operations. In the earliest stages of Alzheimer's Disease (AD), performance during novelty detection tasks is impaired, which is accompanied by enhanced activity in the hippocampus. Failure of one or more inhibitory circuits could disrupt excitatory-inhibitory circuit balance and impairment in hippocampal brain rhythms, thereby accounting for these observations. Although there are genetic and environmental contributions to AD, the environmental components are poorly understood. There is accumulating evidence for diet being a major driver of AD risk, involving nutritional deficiencies. There is

growing evidence for a role of Vitamin A (VA) deficiency in Alzheimer's disease (AD) pathogenesis and progression. All-trans retinoic acid (ATRA), the bioactive metabolite of VA in the brain, serves diverse roles in the human hippocampus: an exogenous antioxidant (AO), a receptor ligand mediating cytosolic signaling, and a hormone-like nuclear transcription factor. Several studies provide evidence that ATRA itself and agonists of retinoic acid receptors (RAR) promote activation of the non-amyloidogenic pathway by enhancing expression of α-secretase, thereby providing a mechanistic basis for preventing amyloid beta (Aβ) toxicity. While there is a substantial body of evidence of VA deficiency in preclinical AD models and in serum samples of AD patients, it is not known whether ATRA is deficient in AD in the human hippocampus. Here, using a publicly available human transcriptomics dataset, we evaluated the extent that ATRA-sensitive genes are dysregulated in the human hippocampus from post-mortem AD tissue compared to age-matched controls. Consistent with ATRA deficiency, we found that the many ATRA-sensitive genes were significantly dysregulated. Overall, an investigation of ATRA-sensitive genes in the human hippocampus bolsters the scientific premise that ATRA is depleted from the human hippocampus in AD. Using preclinical AD models, future studies will examine how transcriptional regulation of ATRA-sensitive genes in specific hippocampal cell types sustains hippocampal learning and memory operations in the aging brain.

Round Table – Research Training Opportunities



Pablo Artigas, Ph.D.
Associate Professor, Dept. of Cell Physiology and Molecular Biophysics, Center for Membrane Protein Research

Structure-based functional studies of P-type ATPases and their regulation

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

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

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 neurological and psychiatric disorders

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

Brandt L. Schneider, Ph.D.
Dean, Graduate School of Biomedical Sciences, Director, Institute of Anatomical Sciences

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

Round Table – Collaborative Research Projects

Jeremy D. Bailoo, Ph.D.
Research Assistant Professor, Civil, Environmental and Construction Engineering, Cell Biology and Biochemistry, Center of Excellence for Translational Neuroscience and Therapeutics

Developmental psychobiology, contribution of genetic and environmental factors to individual differences in health and welfare across lifespan

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

Pharmacology of the analgesic and abuse-related effects of opioids. Neurobehavioral effects of drugs of abuse, especially in the context of human immunodeficiency virus (HIV)

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

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, 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 neurological and psychiatric disorders

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

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

Jenny Wilkerson, Ph.D.
Research Assistant Professor, Dept. of Pharmaceutical Sciences, Center of Excellence for Translational Neuroscience and Therapeutics

Pain research and neurodegeneration, role of the immune system in preclinical models of pain and neurodegeneration, natural product pharmacology, and CNS therapeutics with diminished drug abuse liability

Poster Judges

Petar Grozdanov, PhD
Director, Molecular Biology and Image Analysis
Core Laboratories, Research Assistant Professor
Cell Biology and Biochemistry
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

Chanaka N. Kahathuduwa, M.B.B.S., M.Phil., PhD
Assistant Professor/Clinical Assistant Professor
Laboratory Sciences and Primary Care / Psychiatry
TTUHSC, Lubbock

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

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

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

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

Jenny Wilkerson, PhD
Research Assistant Professor
Pharmaceutical Sciences
TTUHSC, Amarillo

Poster Presentation Schedule

1. Basic Science – Undergraduate/Medical Students

Posters	Time	Presenter	Judges
1	3:00-3:10	Halbgewachs, Karsyn	Dr. Guangchen Ji/ Dr. Igor Ponomarev
2	3:15-3:25	Loewen, Jocelin	Dr. Guangchen Ji/ Dr. Igor Ponomarev
3	3:30-3:40	May, Harry	Dr. Guangchen Ji/ Dr. Igor Ponomarev
4	3:45-3:55	Ortiz, Yuma	Dr. Guangchen Ji/ Dr. Igor Ponomarev
5	4:00-4:10	Uppala, Shreya	Dr. Guangchen Ji/ Dr. Igor Ponomarev

2. Basic Science – Graduates

Posters	Time	Presenter	Judges
6	3:00-3:10	Gomez, Alejandra	Dr. George Henderson/Dr. Petar Grozdanov
7	3:15-3:25	Hernandez, Sarah	Dr. George Henderson/Dr. Petar Grozdanov
8	3:30-3:40	Jaramillo-Martinez, Valeria	Dr. George Henderson/Dr. Petar Grozdanov
9	3:45-3:55	Kisby, Brent	Dr. George Henderson/Dr. Petar Grozdanov
10	4:00-4:10	Mahmud Syed, Mosharaf	Dr. George Henderson/Dr. Petar Grozdanov
11	4:15-4:25	Mazzitelli, Mariacristina	Dr. George Henderson/Dr. Petar Grozdanov
12	4:30-4:40	Mullins, Caitlyn	Dr. George Henderson/Dr. Petar Grozdanov
13	3:00-3:10	Presto, Peyton	Dr. Josee Guindon/ Dr. Andrey Karamyshev
14	3:15-3:25	Sanchez Villalobos, Cesar	Dr. Josee Guindon/ Dr. Andrey Karamyshev
15	3:30-3:40	Spontarelli, Kerri	Dr. Josee Guindon/ Dr. Andrey Karamyshev
16	3:45-3:55	Sweazey, Ryan	Dr. Josee Guindon/ Dr. Andrey Karamyshev

3. Basic Science – Postgraduates

Posters	Time	Presenter	Judges
17	4:15-4:25	Blanton, Henry	Dr. Guangchen Ji/ Dr. Igor Ponomarev

4. Clinical – Undergraduate/Medical Students

Posters	Time	Presenter	Judges
18	3:00-3:10	Bassett, Ashley/Rodaniche, Alyssa	Dr. Volker Neugebauer/Dr. Jenny Wilkerson
19	3:15-3:25	Hall, Rebecca	Dr. Volker Neugebauer/Dr. Jenny Wilkerson
20	3:30-3:40	Manal, Nabeela	Dr. Volker Neugebauer/Dr. Jenny Wilkerson
21	3:45-3:55	Ray, Nandini	Dr. Volker Neugebauer/Dr. Jenny Wilkerson
22	4:00-4:10	Ray, Sparsh	Dr. Volker Neugebauer/Dr. Jenny Wilkerson
23	4:15-4:25	Reddy, Akhila	Dr. Volker Neugebauer/Dr. Jenny Wilkerson

5. Clinical – Graduate Students

Posters	Time	Presenter	Judges
24	3:00-3:10	Ali, Kiran	Dr. Dr. Chanaka Kahathuduwa/Dr. J. Josh Lawrence
25	3:15-3:25	Bammel, Alexandra	Dr. Dr. Chanaka Kahathuduwa/Dr. J. Josh Lawrence
26	3:30-3:40	De Simon, Daniel	Dr. Dr. Chanaka Kahathuduwa/Dr. J. Josh Lawrence
27	3:45-3:55	Dennis, Victoria	Dr. Dr. Chanaka Kahathuduwa/Dr. J. Josh Lawrence
28	4:00-4:10	Iweh, Marvelyn	Dr. Dr. Chanaka Kahathuduwa/Dr. J. Josh Lawrence
29	4:15-4:25	Shahi, Sadisna	Dr. Dr. Chanaka Kahathuduwa/Dr. J. Josh Lawrence

6. Clinical – Postgraduates

Posters	Time	Presenter	Judges
30	4:00-4:10	Kurt, Hatice	Dr. Josee Guindon/Dr. Andrey Karamyshev
31	4:15-4:25	Park, Micah	Dr. Josee Guindon/Dr. Andrey Karamyshev

Abstracts

1. Basic Science – Undergraduate / Medical Students

Halbgewachs, Karsyn

Blood-based lipidomic analyses in Alzheimer's disease: investigating relationships between dysregulated lipid species and molecular mechanisms of oxidative stress

Karsyn Halbgewachs[1], Masoud Zabet-Moghaddam[2], J. Josh Lawrence[3,4], and Andrew C. Shin[5]

[1]TTUHSC School of Medicine, [2]TTU Biotechnology and Genomics, [3]TTUHSC Pharmacology and Neuroscience, [4]TTUHSC Center of Excellence for Translational Neuroscience and Therapeutics, [5]TTU Nutritional Sciences, Lubbock, TX

Approximately 6.5 million Americans are living with Alzheimer's disease (AD), a neurodegenerative disorder most common amongst the elderly. AD is the 5th leading cause of death in individuals 65 and older, and the Alzheimer Association projects that the number of individuals with AD will increase as the elderly population grows. Approximately 12.7 million Americans could have AD by 2050. If left untreated, AD will kill millions. Understanding the molecular mechanisms of AD is imperative. According to the Mitochondrial Free Radical Theory of Aging, across a lifespan, mitochondria cause oxidative stress (OS) by producing excess reactive oxidative species (ROS), which cause oxidative damage to species like lipids. The correlation between increased oxidative damage and AD is well established. Lipid integrity is essential to the brain due to its many functions, such as lipid bilayers, synaptic transmission, and signal transduction. There is already some evidence to suggest that lipid species are dysregulated in individuals with AD. We hypothesize that individuals with AD will have dysregulated lipid species compared to age-matched controls. Moreover, we expect to find elevated counts of saturated or oxidized lipid species in blood compared to age-matched individuals without AD. In collaboration with the Texas Alzheimer's Research and Care Consortium, 10 blood samples from Alzheimer's patients and age-matched control patients were analyzed with mass spectrometry to evaluate lipid species contained within the blood. Use of the Lipid Maps Structural Database enabled unambiguous identification of 16 lipid species. We exported the data from the analyses into Integration Pathway Analysis (IPA) to assess the difference in lipid species between the AD and control groups. We detected 5 significantly dysregulated signaling pathways, which included ceremide signaling (p=4.49E-3) and sphingosine-1-phosphate (4.49E-3). Consistent with previous work, dysregulation of ceremide signaling has been shown previously in AD. The top IPA network included 7 lipid species. We also discovered the predicted dysregulation of cytochrome c oxidase and NQO1, an Nrf2-related antioxidant defense enzyme relevant to oxidative stress. Because lipidomics within the Ingenuity Pathway Analysis (IPA) database was limited, we also used LipidMaps' BioPAN, which recognized 252 lipid species, 42 of which were involved in reactions. BioPAN detected a novel suppressed pathway, biosynthesis of PE(40:6) to PC(40:6) involving the gene PEMT, which has been associated with sporadic AD. Using these observations as a foundation, future studies will investigate molecular mechanisms that connect dysregulated lipid species to oxidative stress, determine how lipidomic and metabolomic species mechanistically interrelate, examine relationships between oxidized lipid species and measured lipophilic antioxidants, and integrate these data into multi-omic analyses.

Loewen, Jocelin

Increased levels of SARS CoV-2 ACE2 receptors and TMPRSS enzyme in an age-dependent manner in Alzheimer's and Huntington's mouse models

Jocelin Loewen[1], Shreya Uppala[1], Erika Orlov[1], Hallie Morton[1], Neha Sawant[1], Murali Vijayan[1], Arubala P Reddy[2], and P. Hemachandra Reddy[1,3]

[1]Department of Internal Medicine, Texas Tech University Health Sciences Center, [2]Department of Nutritional Sciences College of Human Sciences, Texas Tech University, [3]Center of Excellence for Translational Neuroscience and Therapeutics, Texas Tech University Health Sciences Center, Lubbock, TX

The purpose of our study is to assess the levels of angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS) in mouse models of Alzheimer's disease and Huntington's disease. SARS CoV-2, commonly known as COVID-19, has been the cause of a global outbreak since 2019. The virus is spread directly via respiratory droplets and utilizes receptors like ACE2 to enter host cells and then primed by TMPRSS. SARS CoV-2 is most known for the severe respiratory distress it can cause, most often affecting older individuals as well as those with comorbidities, such as Alzheimer's, Huntington's, diabetes, kidney disease, etc. Neurodegenerative disorders have also been reported in those infected with COVID-19 and show correlations to both ACE2 and TMPRSS levels, suggesting a connection to increased susceptibility to SARS CoV-2. Our initial investigation makes use of mouse cerebellum models to understand the correlation between age and enzyme levels of ACE2 and TMPRSS. It is believed that there is an upregulation of these levels with age and age-related neurological diseases such as Alzheimer's and Huntington's. Our methods include using brain tissues from 2-, 6-, 12- and 20-month-old wild-type (WT) and age-matched transgenic mouse models of Alzheimer's disease (APP and Tau) and Huntington's disease (BACHD and HD-knockin) to measure levels of ACE2 and TMPRSS. We found that levels of both ACE2 and TMPRSS increased in an age-dependent manner in WT, APP, Tau, BACHD, and HD mice. A comparative analysis of 1) WT to APP, 2) WT to Tau, 3) WT to BACHD mice also revealed increased levels in APP, Tau, BACHD, and HD mice. These observations suggest that ACE2 and TMPRSS levels increase with disease progression in Alzheimer's disease and Huntington's disease in an age-dependent manner. Our study findings suggest that age and neurodegenerative diseases result in increased susceptibility to acquiring COVID-19.

May, Harry

Synergistic effects of DNA-PK inhibitors with standard chemotherapeutic drugs in neuroblastoma

Harry May, In-Hyoung Yang, Min H Kang

TTUHSC School of Medicine, Dept. of Pediatrics, Lubbock, TX

In neuroblastoma, c-MYC oncogene expression is reported as one of the bad prognosis factors. In our previous studies in neuroblastoma, we found that c-MYC is transcriptionally activated by OCT4, a stem cell factor, and OCT4 is phosphorylated by MAPKAPK2 and DNA-PKcs at S111 and S93 residues, respectively. This activation pathway is mostly observed in progressive disease neuroblastoma models independent of MYC genomic amplification. In our previous study, we also studied and confirmed the DNA-PKcs-OCT4- c-MYC axis being active in neuroblastoma models.

The methods used for the current study includes western blotting, DIMSCAN, a semi-automated cytotoxicity assay system, copy number determination using PCR, and gene expression by RT-PCR. We found that narciclasine, one of the agents we discovered as the inhibitors of the protein interaction between OCT4 and DNA-PKcs, inhibits phosphorylation of DNA-PKcs and reduces c-MYC expression in neuroblastoma.

Since we discovered that new agents act as DNA-PKcs inhibitors that interfere with the protein interaction between DNA-PKcs and OCT4, we aimed to characterize the activity of the agents in comparison to commercially available DNA-PKcs inhibitors. The purposes of the study are to investigate single-agent cytotoxicity of five DNA-PKcs inhibitors and to identify combination cytotoxicity of DNA-PKcs inhibitors with the standard of care chemotherapeutic drugs such as DNA-damage drug, 4-HC, and Bcl-2 inhibitor, ABT199.

We confirmed the effect of the single agents and especially the combination on c-MYC expression and synergistic cell kill effect. Further work is warranted to investigate the activity of narciclasine and its combination in xenograft models. Also, focus of the future plan includes identifying various c-MYC expression status of neuroblastoma cell lines we used.

Ortiz, Yuma

Mitragynine Reverses Paclitaxel Chemotherapy-Induced Peripheral Neuropathy and is Mediated via Opioid Receptor Involvement

Yuma Ortiz[1], Marco Mottinelli[2], Christopher McCurdy[2], Lance McMahon[3,4], Jenny Wilkerson[3,4]

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2. University of Florida, College of Pharmacy, Medicinal Chemistry. Gainesville, FL
3. Texas Tech University Health Sciences Center, Department of Pharmaceutical Sciences, Amarillo, TX
4. Texas Tech University Health Sciences Center, Center of Excellence for Translational Neuroscience and Therapeutics, Lubbock, TX

Chemotherapy-induced peripheral neuropathy (CIPN) is a problematic side effect in patients receiving chemotherapeutic cancer treatments. Clinical use of approved analgesic drugs often does not adequately control the pathological pain arising from CIPN and does not account for potential abuse with opioid therapeutics. Mitragyna speciosa (kratom) contains the alkaloid mitragynine, which exhibits analgesic properties. However, the underlying pharmacological mechanisms that underlie these analgesic properties are complex and not completely understood. Male and female C57bl/6 mice received 8 mg/kg intraperitoneal injections of paclitaxel, a taxane class chemotherapeutic, every other day over the course of 7 days. To confirm the development of CIPN, the von Frey assay was utilized to determine the onset mechanical allodynia, which arises when a previously non-painful stimulus is perceived as painful. Intraperitoneal mitragynine and the prototypical opioid agonist morphine both dose-relatedly reversed CIPN-induced mechanical allodynia. Effective doses (ED)50 were as follows – morphine: 7.02 (6.56 – 7.51) mg/kg, mitragynine: 109.80 (104.27 – 115.62) mg/kg. Pretreatment with the opioid antagonist naltrexone 0.032 mg/kg, intraperitoneally produced a rightward shift in both morphine and mitragynine dose-response curves. Effective doses (ED)50 were as follows – naltrexone + morphine: 27.93 (24.84 – 31.40), naltrexone + mitragynine: 245.41 (211.76 – 284.39), resulting in a 3.98 and 2.24 fold shift of dose response curves, respectively. Here we show that mitragynine reverses mechanical allodynia associated with paclitaxel CIPN. We also show that opioid receptors mediate such activity, though additional data suggest a role for adrenergic and serotonin receptors as well. Mitragynine may be an effective analgesic treatment option for patients experiencing painful CIPN.

Uppala, Shreya

Investigating levels of SARS CoV-2 ACE 2 receptor and TMPRSS enzymes in post mortem brain tissues from Alzheimer's, stroke, and diabetes patients

Shreya Uppala[1], Jocelin Loewen[1], Erika Orlov[1], Hallie Morton[1], Neha Sawant[1], Murali Vijayan[1] , Arubala P Reddy[2] , and P. Hemachandra Reddy[1,3]

[1]Dept. of Internal Medicine, Texas Tech University Health Sciences Center, [2]Dept. of Nutritional Sciences College of Human Sciences, Texas Tech University, [3]Center of Excellence for Translational Neuroscience and Therapeutics, Texas Tech University Health Sciences Center, Lubbock, TX

The purpose of our study is to assess the levels of angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS) by utilizing post-mortem brain models of Alzheimer's disease (AD), diabetes, and stroke patients. The SARS CoV-2 virus, commonly known as COVID-19, has been the cause of a global outbreak since the first reported case in China in late 2019. The virus is spread directly person-to-person via respiratory droplets and utilizes receptors such as the angiotensin-converting enzyme 2 to enter host cells and then primed by the enzyme TMPRSS. COVID-19 is most known for the severe respiratory distress it can cause, most often affecting individuals who are older as well as those with other comorbidities, such as Alzheimer's, Huntington's, diabetes, obesity, and stroke. Additionally, neurological manifestations have also been reported in those infected with the virus. These include neurodegenerative disorders which have correlations to both ACE2 and TMPRSS levels, also suggesting a connection to increased susceptibility to SARS CoV-2. Our investigation makes use of postmortem human brain models that have AD, diabetes, or strokes to understand the correlation between these comorbidities and levels of ACE2 and TMPRSS. We found that both ACE2 and TMPRSS levels were increased in postmortem brain tissues with AD, diabetes, and stroke when compared to brain tissues with healthy control subjects. These observations suggest that ACE2 and TMPRSS levels are increased with disease progression in AD, diabetes, and stroke patients, which also indicates an increased susceptibility to contracting COVID-19.

2. Basic Science – Graduate Students

Gomez, Alejandra

CRES and CRES subgroup members as functional amyloids in the brain.

Alejandra Gomez[1], Petar Grozdanov[1,3], Jeremy D. Bailoo[1,2,3], Aveline Hewetson[1], Gail A. Cornwall[1]

[1]Dept. of Cell Biology and Biochemistry, Texas Tech University Health Sciences Center. [2]Dept. of Environmental and Construction Engineering, Texas Tech University, [3]Center of Excellence for Translational Neuroscience and Therapeutics, Texas Tech University Health Sciences Center, Lubbock, TX

Amyloids are highly ordered cross β-sheet aggregates that are typically associated with disease states such as neurodegeneration and diabetes. However, growing evidence shows that some amyloids can carry out biological roles including as structural scaffolds and signaling complexes and are categorized as functional amyloids. We previously demonstrated an amyloid matrix is present throughout the normal mouse epididymal lumen with proposed functions in sperm protection and maturation. The epididymal amyloid matrix is composed of several members of the highly amyloidogenic reproductive CRES (cystatin-related epididymal spermatogenic) subgroup of cystatin cysteine protease inhibitors suggesting it is a complex functional amyloid. In the mammalian brain, studies suggest amyloids are important structural components of synapses as well as being involved in regulating synapse structure and function making them potential key players in synaptic plasticity and memory maintenance. We hypothesize CRES and CRES subgroup members are also found in the brain and may carry out functional roles as amyloids. Preliminary RT-PCR and Western blot showed CRES and other subgroup members are present in the mouse hippocampus and other brain regions as well as in a mouse hippocampal neuronal cell line. Cognitive-behavioral studies between wild-type (WT) mice and a global CRES knockout (KO) mouse model highlight that male, but not female, KO mice displayed impairments in learning in a 2-choice water-escape task as well as behavioral inflexibility during reversal (they perseverate on the previously learned escape location) when the location of the platform to escape is changed. These findings suggest CRES and CRES subgroup members may be implicated in learning and memory processes and provide a basis to further study their role as potential functional amyloids in the brain.

Hernandez, Sarah

Novel Role of TRiC/CCT in the Regulation of alpha-Synuclein Biogenesis

Sarah Hernandez[1,2], Elena B. Tikhonova[1], Andrey L. Karamyshev[1,2,3]

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Parkinson's disease (PD) is a neurodegenerative disorder that is associated with the formation of Lewy bodies (LBs) in the human brain. The major component of LBs is aggregated alpha-Synuclein (aSyn). The biogenesis of aSyn, including folding and interacting factors, has yet to be elucidated. TRiC/CCT is a chaperonin involved in the proper biogenesis of proteins containing hydrophobic pockets or large complexes, encompassing 5-10% of the entire proteome. TRiC/CCT is involved in the proper folding of other aggregation-protein proteins, such as HTT. We propose that TRiC/CCT is involved in the biogenesis of aSyn and that loss of TRiC/CCT involvement results in the dysregulation of aSyn biogenesis, causing disease. Here we demonstrate that TRiC/CCT is involved in the proper biogenesis of aSyn through regulation at both the mRNA and protein levels. Depletion

of CCT2 results in the degradation of mRNA and loss of protein synthesis. Reduction of mRNA and protein is vital for the attenuation of substrate protein unable to be processed by TRiC/CCT2 to avoid the accumulation of unfolded proteins and aggregation. Here we present a novel quality control mechanism activated by the loss of TRiC/CCT subunit CCT2.

Jaramillo-Martinez, Valeria

Therapeutic development of Na+-coupled citrate transporter (NaCT) corrector molecules

Valeria Jaramillo-Martinez[1], Vadivel Ganapathy[2,3], Ina L. Urbatsch[2,4]

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Citrate participates in multiple catabolic and anabolic pathways and serves as a bridge between carbohydrate and fatty acid metabolism. It also generates ATP via the citric acid cycle. Neurons, with their high energy demand, rely on the Na+-coupled citrate transporter (NaCT) for citrate supply from the circulation. Loss-of-function mutations in NaCT cause a severe neurologic disease known as early infantile epileptic encephalopathy-25 (EIEE-25). EIEE-25 leads to epilepsy, impaired speech, limited motor skills, developmental delay, and tooth defects in children. However, no treatment is currently available for patients with EIEE25, despite the discovery of approximately 40 disease-causing mutations. Only eight of the 22 missense mutations have been studied for protein expression, with conflicting results, making differentiation for treatment difficult. We propose to differentiate NaCT mutants that traffic to the plasma membrane surface normally but lack citrate transport (Class I) from those mutants that severely affect protein folding, and thus are retained as core-glycosylated protein in the endoplasmic reticulum (ER) and are degraded prematurely (Class II); i.e. these mutation cannot escape the ER quality control and never reach the plasma membrane surface. In this study, NaCT was modified with RGS-His10, Twin-Strep and the SUMOstar domain to facilitated detection of NaCT by immunohistochemistry and western blot. When transiently expressed in HEK293 cells, recombinant NaCT proteins underwent complex glycosylation, compartmentalized with the plasma membrane, and exhibited citrate transport activity similar to the non-tagged protein. Surface NaCT expression was enhanced by the presence of SUMOstar on the N-terminus. Using this approach, we further propose that Class II mutations can be rescued by small molecules that 'correct' the folding defect in the ER (herein named "corrector molecules" or "correctors"), and thus promote trafficking through the Golgi apparatus where they attain complex glycosylation and proceed to the plasma membrane cell surface where they can now execute their citrate transport function. We identified a first 'corrector' molecule (proprietary information) among 30 test compounds. Strikingly, this first 'corrector' hit compound partially restores surface expression of the trafficking defect mutant S427L (Class II). This promising result in the preliminary screening serves as a proof-of-principle that small molecule therapeutics could be used to correct the folding defect of NaCT mutants and promote trafficking to the cell surface. This "corrector" could serve as the lead compound whose molecular scaffold can be used to synthesize new derivatives for more potent rescue activity than the parent compound.

Kisby, Brent

Cell-type specific gene expression changes in the mouse Prefrontal Cortex after chronic ethanol drinking

Kisby, Brent R.[1]; McManus, Michelle M.[2]; Shanmugam, Sambantham[2]; Ponomarev, Igor[2,3]

[1]Translational Neuroscience and Pharmacology, [2]Dept. of Pharmacology and Neuroscience, [3]Center of Excellence for Translational Neuroscience and Therapeutics, Texas Tech University Health Sciences Center, Lubbock, TX

Excessive alcohol (ethanol) consumption is one of the criteria for alcohol use disorder (AUD). Every-other-day (EOD) alcohol drinking in mice increases ethanol consumption over weeks, however, it is unclear which brain cell-types are key for regulating this drinking behavior. One of the primary brain regions affected by ethanol and involved in regulation of ethanol consumption is the Prefrontal Cortex (PFC). The goal of this study was to identify cell-type-specific gene expression changes within the PFC after alcohol drinking in mice. Male C57BL/6J male mice (n=4/ group) were randomly assigned to either the ethanol drinking group or water drinking group. We used the (EOD) drinking paradigm for a total of 17 alcohol sessions, which resulted in higher levels of ethanol drinking at the end of the procedure, compared with baseline. Twenty-four hours after the last drinking session, brains were harvested and cell nuclei from the PFC were isolated for single nucleus RNA Sequencing (snRNA-Seq). We identified 27,207 nuclei which were organized into 30 discrete clusters. To identify cell-type clusters, we used known molecular markers of various cell types, such as astrocytes (*Slc1a3*), microglia (*C1qa*), endothelial cells (*Flt1*), and inhibitory and excitatory neurons. In addition, we identified rare cell types such as pericytes (*Rgs5*). We used DESeq2 to identify differentially expressed genes (DEGs) in different cell types between the two drinking groups. With respect to global DEGs, we identified 1,337 genes at nominal p value of less than 0.05 with 731 genes down-regulated and 606 genes up-regulated in the ethanol drinking group compared with the water drinking group. We further identified DEGs in specific cell types. Cell types most responsive to ethanol exposure were certain inhibitory neurons (i.g., DEGs: *Vip*, *Gad2*), some excitatory neurons (i.g., DEGs: *Kcnq5*, *Kcnh7*), endothelial cells (i.g., DEGs: *Ptprm*, *Pltp*), and microglia (i.g., DEGs: *Hexb*, *Cst3*). The data taken together suggest a large heterogeneity of responses in PFC cell types to prolonged drinking in mice. Some of these cell type-specific DEGs may mechanistically underlie the transition from moderate to high alcohol consumption in our mouse model.

Mahmud Syed, Mosharaf

Dysregulated Glucocorticoid Signaling is Associated with Vitamin A Deficiency in Alzheimer's Disease

Mosharaf Mahmud Syed[1], Anne Pierre[1], and J. Josh Lawrence[1,2,3]

[1]Department of Pharmacology and Neuroscience,[2]Garrison Institute on Aging, [3]Center of Excellence for Translational Neuroscience and Therapeutics, Texas Tech University Health Sciences Center, Lubbock, TX

Alzheimer's Disease (AD) is a neurodegenerative disorder impacting ~5.8 million people in the United States. AD is the 6th leading cause of death and estimated to be the 3rd cause of death among the elderly population. The incidence of AD doubles every 5 years, projected to expand to 14 million people by 2060, with annual costs of >$500 billion. Therefore, it is of utmost importance to determine molecular causes. There are increasing evidence linking Vitamin A/retinol (VA) deficiency in AD. All-trans retinoic acid (ATRA) is the bioactive derivative of VA. Previous studies suggest that VA improves symptoms of AD and its progression in vitro and in vivo – inhibition of amyloid fibril formation and reduction of proinflammatory cytokines/chemokines. Moreover, VA deprived mice exhibit impaired learning. In this study, we investigated the most dysregulated ATRA-sensitive pathways in the human hippocampus in AD. We performed an in silico experiment via Ingenuity Pathway Analysis (IPA) from the publicly available human AD hippocampal transcriptomic data generated by van Rooij and colleagues (2019) using 673 ATRA-sensitive genes. The top canonical pathway was glucocorticoid receptor (GR) signaling (p=4.86E-34). The most dysregulated ATRA-

sensitive gene was UQCRC2 (p=6.51E-16), which was downregulated in complex III located within mitochondria. A total of 36 genes, including NDUFA genes, in the Mitochondrial Dysfunction pathway were dysregulated (p=2.27E-21), further linking ATRA deficiency to mitochondrial dysregulation in human AD. Several previous studies have implicated the importance of dysregulated GR signaling in AD. Finally, our IPA analysis highlighted that the top Upstream Regulator was tretinoin (ATRA itself), validating the ATRA sensitivity of our enriched gene set and the regulation of the GR pathway. Our study provides a wealth of new knowledge regarding interactions between ATRA availability, GR signaling, and mitochondrial function. Understanding these pathways can help identify novel therapeutic strategies for AD.

Mazzitelli, Mariacristina

Different roles of mGluR2 and mGluR3 in the modulation of CeA-CRF neurons in an arthritic model of pain

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The amygdala is critically involved in the regulation of emotional-affective components of pain and in pain modulation. The central nucleus of amygdala (CeA) serves major output functions and receives purely nociceptive information via the external lateral parabrachial nucleus (PB) and polymodal information from the cortex and thalamus via the basolateral nuclei of amygdala (BLA). The CeA contains the highest density extra-hypothalamic corticotropin releasing factor (CRF), which is implicated in several neuropsychiatric disorders. CeA-CRF containing neurons project to other brain regions involved in behaviors and pain. Gi/o-coupled group II metabotropic glutamate receptors (mGluR2 and 3) are expressed in different brain regions, including the amygdala. Their activation can decrease neurotransmitter release and regulate synaptic plasticity, but effects of the modulation of group II mGluR subtypes on CeA-CRF neurons remain to be determined. Here, we address this knowledge gap in an arthritic pain model. Brain slice physiology was performed to determine the effects of a group II mGluR agonist (LY379268 disodium salt), a positive allosteric modulator (PAM) selective for mGluR2 (LY487379 hydrochloride), and the combination of a group II mGluR agonist (LY379268) with a negative allosteric modulator (NAM) selective for mGluR2 (VU6001966) on CeA-CRF neurons. To visualize CRF neurons, a Cre-inducible viral vector expressing red fluorescent protein (mCherry) was injected into the CeA of transgenic Crh-Cre rats (original breeding pairs kindly provided by Dr. Robert Messing, UT Austin). A viral vector coding channelrhodopsin 2 (ChR2) fused to enhanced yellow fluorescent protein under the control of CaMKII promoter was injected into the PB for optical activation of glutamatergic inputs to CeA-CRF neurons. An electrical stimulator was placed in the BLA to stimulate the BLA-CeA inputs. Whole-cell patch-clamp recordings in brain slices from arthritic rats (5-6 h postinduction of a kaolin/carrageenan-monoarthritis) were used to investigate neuronal excitability, monosynaptic excitatory postsynaptic currents (EPSCs), and glutamate-driven inhibitory postsynaptic currents (IPSCs) evoked from PB and BLA inputs. Application of LY379268 decreased neuronal excitability and EPSCs and IPSCs in the arthritis condition. Application of LY487379 resulted in decreased EPSCs, whereas selective activation of mGluR3 (combination of LY379268 with VU6001966) mimicked the effects of the group II mGluR agonist on the modulation of CeA-CRF neurons in pain. These results suggest that mGluR2 and 3 have different roles in controlling functions and pain-related changes of CRF neurons in the amygdala, providing important insights into the subtype-specific roles, which may help identify appropriate therapeutic strategies for pain management.

Mullins, Caitlyn

BT2 alleviates AD-related brain pathology and improves neurotransmitter status in Alzheimer's disease mouse model

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Six million Americans live with Alzheimer's disease (AD) today without a cure or effective treatment. High circulating branched-chain amino acids (BCAAs) are associated with metabolic and brain dysfunctions. Our lab has recently shown elevated plasma BCAAs and their metabolites in both AD patients and mice. Further observations of dose-dependent neuronal damage induced by BCAA supplementation prompted us to hypothesize that BT2, a small molecule shown to increase BCAA breakdown and thereby lower plasma BCAAs, will alleviate AD-related pathology and metabolic impairment. To test this, we used 2-month-old wildtype (WT) and 5xFAD mice, a widely used transgenic AD mouse model.
Mice received daily doses of either BT2 (60 mg/kg/day) or vehicle intraperitoneally for 30 days. 5xFAD mice had elevated fasting blood glucose compared to WTs at baseline, however, after BT2 treatment their blood glucose was significantly lowered matching WT levels. As expected, 5xFAD controls had significantly higher Aβ-42 levels, a pathological hallmark of AD, compared to WT controls in the cortex, but this was completely reversed following BT2 treatment. This decreased amyloid burden may be due to elevated insulin-degrading enzyme (IDE) in the cortex, an enzyme known to degrade Aβ. Our data also demonstrate that BT2 treatment partially restored levels of key neurotransmitters such as norepinephrine, dopamine, and serotonin in both the cortex and hippocampus of 5xFAD mice. These findings suggest that BT2 may improve systemic glucose metabolism and neurotransmission while effectively lowering amyloid peptides in the brain, indicating the potential of BT2 as a novel therapeutic strategy to prevent/treat AD.

Presto, Peyton

CGRP1 receptor blockade in the amygdala in neuropathic pain: cellular and behavioral effects

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The amygdala has emerged as a key player in the emotional-affective aspects of pain and pain modulation. The laterocapsular region of the central amygdala nucleus (CeLC) is defined as the "nociceptive amygdala" due to its high content of neurons that process pain-related information. The CeLC is the target of the spino-parabrachio-amygdaloid pain pathway, which is the major source of calcitonin gene-related peptide (CGRP). Changes in CeLC neurons have been observed in pain models and synaptic plasticity in the CeLC has been linked to pain-related behaviors. CGRP has been shown to be involved in peripheral and spinal mechanisms and in pain-related synaptic plasticity in the amygdala. However, the role of CGRP-mediated plasticity in the amygdala in neuropathic pain behaviors remains to be determined. Here we tested the hypothesis that the CGRP1 receptor is involved in neuropathic pain-related amygdala plasticity and that blockade of this receptor can inhibit neuropathic pain behaviors. Sensory and affective behaviors were measured in adult chronic neuropathic rats (4 weeks after spinal nerve ligation, SNL). For blockade of the CGRP receptor, a selective CGRP1 receptor antagonist (CGRP 8-37) was administered stereotaxically into the CeLC by microdialysis. Inhibition of the CGRP1 receptor reduced emotional responses to noxious stimuli (audible and ultrasonic

vocalizations) and mechanical hypersensitivity (hindlimb withdrawal reflexes). Tonic aversive aspects of pain relief by CGRP 8-37 were detected in the conditioned place preference (CPP) test. In brain slices containing central amygdala corticotropin releasing factor (CeA-CRF) neurons from neuropathic rats, multiphoton imaging showed that CGRP1 receptor blockade reduced calcium signals evoked by electrical stimulation of presumed PB input. Together these findings may suggest that CGRP1 receptors in the CeLC are involved in neuropathic pain-related plasticity and contribute to nociceptive and emotional-affective pain responses. CGRP1 receptors in the amygdala may serve as a therapeutic target for pain relief.

Sanchez-Villalobos, Cesar Augusto

A machine learning analysis on a recent human hippocampal transcriptome elucidates multivariate differentiating genes in Alzheimer's Disease

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Alzheimer's Disease (AD) is the most common cause of dementia and 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 novel work, we apply machine learning (ML) algorithms on transcriptomic data obtained for 30 subjects from a publicly available dataset from van Rooij et al. (2018). The data consisted of 14564 genes from the hippocampus of 30 brains (20 AD, 10 agematched controls). We implemented data-driven feature selection algorithms, such as ReliefF and Sequential Forward Search, to reduce the number of predictors to a set of only 14 genes. Through this analysis, we found KCNIP1 and HHAT to be the highly discriminating genes. To our knowledge, these novel results have not yet been reported in the AD literature. One possible explanation for this result is that KCNIP1 is a potassium voltage-gated channel interacting protein linked to epilepsies and heart disorders, but not yet to AD. While this gene plays a vital role in a cell's ability to generate and transmit signals, HHAT catalyzes N-terminal palmitoylation; one disease associated with this is the Nivelon-Nivelon-Mabille Syndrome (NNMS), which could include infantile-onset seizures. Therefore, there is a connection between KCNIP1, linked to epilepsies (a seizure disorder), and HHAT related to a disease that takes form in seizures, suggesting strong mechanistic links between epilepsy and AD. Finally, we implemented a Random Forest (RF) classifier to differentiate between AD and control groups, giving an out-of-bag error of 0%. We conclude that for this dataset, an RF classifier will distinguish appropriately between the AD and control groups, using only a discriminative group of genes from the original dataset.

Spontarelli, Kerri

Heterozygous ATP1A1 knockout mice do not develop neuropathies

Kerri Spontarelli[1] & Ryan Sweazey[1], Alexandria Padro[1], Jeannie Lee[2], Tulio Bueso[2], Roberto Hernandez[2], Jongyeol Kim[2], Jeremy Bailoo[3,4,5], Pablo Artigas[1]

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Charcot-Marie-Tooth disease (CMT), one of the most common heritable diseases effecting the peripheral nervous system, presents with distal muscle atrophy and weakness, loss of sensation, absent reflexes, and *pes cavus*. The pathology of CMT is impaired propagation of action potentials through peripheral axons, with two major types being due to demyelination (CMT1) or axonal degeneration (CMT2). CMT has been linked to mutations in over 90 genes, including *ATP1A1*, the gene encoding the α_1 subunit of the Na^+/K^+-ATPase (NKA). The NKA hydrolyzes ATP to export three Na^+ and import two K^+ across the cellular membrane, establishing the electrochemical gradients required for normal resting and action potentials, as well as secondary active transport. The NKA is an αβ heterodimer, the catalytic α subunit has 4 major isotypes with α1, expressed in all tissues, as the predominant ortholog in peripheral axons. It has been proposed that the CMT-causing *ATP1A1* mutations are loss-of-function mutations. Here we evaluated heterozygous *ATP1A1* knockout mice, *ATP1A1*$^{+/-}$, to test the hypothesis that haploinsufficiency would suffice to cause disease as the mice age, mimicking observations in families with mutations with low penetrance. We used a combination of behavioral analysis, mouse electromyography, nerve histology, neuromuscular junction immunohistochemistry in both wild-type and *ATP1A1*$^{+/-}$ mice. The behavioral tests chosen evaluate strength, coordination, balance, and endurance, with loss of strength being the most obvious CMT2 symptom. Mice were evaluated at 1, 3, 6, 12, and 18 months old. No significant differences were found between WT and heterozygous mice across the whole life span. Our results indicate that the pathophysiology of *ATP1A1*-driven CMT probably require more than simply haploinsufficiency (at least in mice). We are currently developing methods to study the expected dominant-negative effects of the neuropathy causing mutations to understand the disease mechanism underlying each mutation.

Sweazey, Ryan

Characterization of diseases associated with mutations in the Na+/K+ pump α1 gene ATP1A1

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The Na^+,K^+-ATPase (NKA) is an essential membrane protein that establishes Na^+ and K^+ gradients across the plasma membrane. By exporting 3 Na^+ ions out of the cell, in exchange for 2 K^+ ions, the NKA establishes electrochemical gradients for both ions which in turn, are utilized for other essential processes such as cell excitability and secondary active transport. A functional NKA enzyme requires the formation of a heterodimer, which consists of an α and β subunit, and is often accompanied by an auxiliary FXYD subunit. Four α subunit isoforms (α1-4) as well as three β subunit isoforms (β1-3) are found in humans, allowing for the formation of multiple, unique, heterodimer combinations that differ in their distributions and kinetic properties. Located within the α subunit are the ion-binding sites and catalytic machinery required for ion transport. The α1 subunit is ubiquitously expressed and generally intolerant to mutations due to its dysfunction rendering cells nonviable. However, it has since been discovered that multiple diseases such as Complex Spastic Paraplegia (CSP), Charcot-Marie-Tooth syndrome (CMT) and Hypomagnesemia Accompanied by Seizures and Cognitive Delay (HASCD) are associated with germline mutations in *ATP1A1*, the gene encoding the α1 subunit. Due to the widespread distribution and importance of the α1 subunit, mutations that disrupt its function should, in theory, result in similar phenotypes. However, there is great variability in the age of onset, severity, and

nature of symptoms experienced by individuals harboring disease associated *ATP1A1* mutations. We aim to improve current understanding of these diseases by characterizing specific *ATP1A1* mutations using a combination of electrophysiological and biochemical methods. Determining the relationship between certain *ATP1A1* mutations and their associated diseases will assist in identifying and understanding the manifestation of unique disease states, while also providing potential future treatments for these debilitating disorders.

3. Basic Science – Postgraduates

Blanton, Henry

Combination of cannabidiol and beta-caryphyllene synergistically mitigate inflammatory pain

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Introduction. Pain, one of the most common reasons adults seek medical care. Current pain treatment options are limited, often ineffective, and have associated side effects. Cannabis contains a high number of potentially therapeutic phytochemicals including cannabinoids and terpenes. While cannabinoids and terpenes have been investigated in pain models in isolation, there has been very little research investigating the potential analgesic effects of cannabinoids and terpenes in combination. The aim of the present study was to determine if a more effective analgesic effect could be obtained through the combination of two major constituents of the cannabis plant, the phytocannabinoid cannabidiol (CBD) and the sesquiterpene beta-caryophyllene (BCP) without producing the adverse effects associated with CNS cannabinoid receptor-1 (CB1) activation, and to characterize the nature of the potential interaction between these two compounds.
Methods: Experiments were performed using sixteen-week-old male C57BL6/J mice purchased from Jackson Laboratories (Bar Harbor, Maine, USA). First, we determined the analgesic potency and efficacy of CBD and BCP individually in the formalin inflammatory pain model through dose-response studies. After determining the ED50 for each compound, we tested the analgesic effect of several fixed-ratio combinations of CBD and BCP and monitored any adverse effects on body temperature, motor impairment, and locomotor activity. We also determined the effect of this combination on inflammation. Analysis of cytokines from plasma was performed using a Mouse XL Cytokine Array Kit (R&D Systems; Minneapolis, MN, USA). This kit allows simultaneous measurement of 111 mediators/markers in a single sample. Statistics were performed in Graph Pad Prism 9 (GraphPad Software; San Diego, USA). Two and One-Way ANOVA with Dunnett's Post Hoc Tests. Significance was set at $p < 0.05$.
Results: CBD was administered at doses of 1, 2.5, 10, 25, and 50 mg/kg. BCP was administered at doses of 1, 3, 10, and 30 mg/kg. Administration of CBD and BCP resulted in dose-dependent reductions in pain behaviors in the inflammatory phase of the formalin test from minutes 20 to 40 post-formalin injection. We tested several fixed ratio combinations (based on the ED50 of each compound), and using isobolographic analysis, it was found that the analgesic effect of CBD and BCP in combination is synergistic. We also tested this combination for common CB1-associated side effects. We found that CBD and BCP in combination did not produce, hypothermia, sedation and motor incoordination. Finally, the synergistic analgesic effect of the CBD and BCP in combination involves an anti-inflammatory mechanism.
Conclusions: This study has demonstrated that a minor cannabinoid and terpene found in the cannabis plant can be used as a pharmacological tool to produce an enhanced analgesic effect without side effects commonly seen with CB1 acting cannabinoids. The idea that CBD and BCP in combination can produce a synergistic analgesic effect set the stage for future studies that will test if the beneficial effect of this combination can be reproduced in other inflammatory/neuropathic pain models.

4. Clinical – Undergraduate / Medical Students

Bassett, Ashley and Rodaniche, Alyssa

Effects of Repetitive Transcranial Magnetic Stimulation on Immediate Post-Intervention Chronic Daily Headache Frequency: A Systematic Review and Meta-Analysis

Ashley Bassett[1] *, Alyssa Rodaniche[1] *, Rebecca Hall[1] *, Emily Stephens[2], Chathurika S. Dhanasekara[3], Christina Robohm-Leavitt[2], Chwan-Li Shen[4,5,6], Chanaka N. Kahathuduwa[1,5,6,7]

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Background: Chronic daily headache (CDH) is a group of devastating headaches characterized by occurrence of headaches for >15 days for at least 3 months. CDH exerts a severe psychosocial and economic burden on the affected individuals and their families. Treatment of CDH often includes pharmacological options, despite limited response rates and increased risk of medication overuse. Thus, there is a critical need to establish effective non-pharmacological options for the management as well as prevention of CDH. A systematic review and meta-analysis was conducted to determine the utility of repetitive transcranial magnetic stimulation (rTMS) on reducing the frequency of CDH.
Methods: All procedures were conducted in accordance with PRISMA guidelines. Specific, predefined keyword combinations were used to search PubMed, Scopus, ProQuest, and Web-of-Science for peer-reviewed reports of clinical trials that have examined the effects of rTMS on CDH. Each record was reviewed by two independent reviewers using pre-determined eligibility criteria and discrepancies were resolved by a senior tie-breaker. Randomized controlled trials (RCTs) examining the change in CDH frequency following rTMS were identified and the relevant data were extracted. DerSimonian-Liard random effects meta-analyses were conducted using meta package in R (4.0.3). A reduction of headache frequency by one episode / month was considered as the minimal clinically important difference (MCID).
Results: Seven RCTs (70 rTMS participants; 65 sham-control participants) examining the effects of rTMS on the change of CDH frequency in the immediate post-intervention period or after a duration of follow-up compared to the baseline were identified. Meta-analysis pooling the pre-intervention vs. post-intervention change in CDH frequency among rTMS vs. sham control groups showed an overall decrease in CDH frequency by five episodes / month following rTMS (Δ = -5.07 [-10.05, -0.11], p = 0.045). This result also exceeded the MCID of one episode/month. Even though the random effects meta-analysis showed marked heterogeneity between studies, subsequent meta-regression analyses failed to explain this residual heterogeneity. Meta-analysis examining the effects of rTMS on CDH frequency between post-intervention follow-up vs. pre-intervention states (seven RCTs, 106 rTMS participants; 100 sham-control participants) showed a decrease of three headache episodes / month (Δ = -2.62 [-5.35, 0.12], p = 0.061). Even though not statistically significant, the difference exceeded the MCID of one episode / month. These results also revealed notable heterogeneity between studies. On exploratory meta-regression analyses, the proportion of females in the treatment group decreased the residual heterogeneity and emerged as significantly moderators, suggesting that the beneficial effects rTMS may decay faster among females following cessation of the intervention. Furthermore, the anatomical site of rTMS also significantly decreased residual heterogeneity and was a negative moderator, indicating that the effects of rTMS may last longer for CDH prevention when applied over the primary motor cortex vs. the pre-frontal cortex.

Conclusion: Addressing the pre-existing ambiguity in the literature regarding the utility of rTMS for CDH prevention, our meta-analysis suggested that rTMS may be useful for decreasing CDH frequency in the short-term. However, this beneficial effect seems to decay with time following cessation of treatment. Considering the high cost of equipment and requirement of trained personnel for administration, utility of rTMS as a therapeutic strategy for long-term management of CDH remains questionable. More evidence is needed to fully understand the optimal anatomical site and frequency of rTMS to extend the benefits of rTMS for the long-term management of CDH.
Acknowledgements: The study was partially funded by the TTUHSC School of Medicine Medical Student Summer Research Program (2021).

Hall, Ashley

Effects of Repetitive Transcranial Magnetic Stimulation on Immediate Post-Intervention Chronic Daily Headache Intensity: A Systematic Review and Meta-Analysis

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Background: Headaches encompassing the most common reason for analgesic use in the general population. Chronic daily headaches (CDH), defined as suffering from ≥15 headache episodes per month for ≥3 months is a group of devastating headaches that often results in analgesic misuse, despite limited response rates. In fact, medication overuse headaches are a common form of CDH. Regardless of the etiology, more effective non-pharmacological treatments are needed to decrease the intensity of CDH. Even though repetitive transcranial magnetic stimulation (rTMS) has emerged as a promising non-pharmacological modality for management of CDH, the evidence regarding the efficacy of rTMS in decreasing CDH intensity remains ambiguous. We conducted a systematic review and meta-analysis to determine the effects of rTMS on CDH intensity.
Methods: PRISMA guidelines were followed. Pre-specified keyword combinations were used to search PubMed, Scopus, ProQuest, and Web-of-Science databases for peer-reviewed records of randomized clinical trials (RCTs) examining the effects of rTMS on CDH. The records were pooled and screened by two independent reviewers using pre-determined eligibility criteria; discrepancies were resolved by a tie-breaker. Studies reporting the effects of rTMS on CDH intensity in the immediate post-intervention period and a no-intervention follow-up were identified and the outcomes were extracted. DerSimonian-Liard random effects meta-analyses were conducted using meta package in R (4.0.3). A reduction in headache intensity by 0.5 standardized units was considered as the minimal clinically important difference (MCID).
Results: The meta-analysis on immediate post-intervention effects of rTMS (eight studies; 91 rTMS participants; 87 sham-control participants) revealed that compared to sham control interventions, exposure to rTMS significantly decreased the standardized headache intensity in the immediate post-intervention period vs. pre-intervention state among patients with CDH ($g = -0.95$ [-1.76, -0.14], $p = 0.021$). This improvement exceeded the MCID threshold of Hedge's $g = 0.5$. Even though significant between-study heterogeneity was a concern ($\tau^2 = 1.092$, $p < 0.001$), subsequent exploratory meta-regression analyses failed to significantly reduce the residual heterogeneity. The meta-analysis that compared the standardized post-follow-up vs. pre-intervention changes in headache intensity (six studies; 105 rTMS participants; 100 sham-control participants) did not reveal a statistically or clinically significant beneficial effect ($g = -0.43$ [-0.96, 0.10], $p = 0.109$).

Significant between-study heterogeneity remained a concern ($\tau^2 = 0.26$, $p = 0.013$). In subsequent meta-regression analyses, motor threshold substantially decreased the residual heterogeneity ($\tau^2 = 0.06$, $p = 0.199$) and emerged as a negative moderator, indicating that use of an increased motor threshold seems to result in a long-lasting decrease in headache intensity after the cessation of the rTMS intervention
Conclusion: Compared to sham control interventions, exposure to rTMS significantly reduced the standardized headache intensity in the immediate post-intervention period vs. pre-intervention state among patients with CDH. However, the beneficial effects of rTMS were found to decline after cessation of treatment. Thus, considering the cost and the expertise required to perform the intervention, the utility of rTMS for long-term management of CDH remains questionable. We emphasize the need to conduct exploratory studies to optimize the rTMS parameters (e.g. motor threshold) in order to improve the overall efficacy of rTMS.
Acknowledgements: The study was partially funded by the TTUHSC School of Medicine Medical Student Summer Research Program (2021).

Manal, Nabeela

Gaisbock syndrome: A review of contemporary studies, pathogenesis, complications, and possible treatment

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Gaisbock syndrome is the term ascribed to several conditions initially observed by Felix Gaisbock, MD, (from Innsbruck, Tyrol, Austria) in 1905 when he described a group of hypertensive male patients who had high hematocrit levels, normal leukocyte counts, and no splenomegaly. These patients had an overweight, stocky habitus, a plethoric appearance with suffusion of the eyes, tense and anxious personalities, a cigarette smoking habit, vascular disease, headaches, and facial rubor. Later studies identified alcoholism, diuretic therapy, and physical or emotional stress as additional risk factors that might contribute to the onset of this syndrome. This review revisits Gaisbock syndrome based on recent literature, and will highlight contemporary studies that have established an association between erythrocytosis and hypertension and associated risk factors. Several mechanisms help explain the pathophysiology underlying Gaisbock's observations, and these include psychiatric disorders resulting in chronic stress, volume contraction secondary to diuretics and hypertension, and obstructive sleep apnea with nocturnal hypoxemia and erythropoietin production. Complications associated with this syndrome include the formation of microthrombi with cerebral infarction; treatment should focus on the management of hypertension and a reduction in risk factors, such as obesity, cigarette smoking, and alcohol use. Gaisbock syndrome involves several clinical disorders, has a complex pathogenesis, and leads to a better understanding of the causes of erythrocytosis during patient evaluation.

Ray, Nandini

An unusual presentation of rounded atelectasis complicated by pulmonary embolism

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Rounded atelectasis is a unique form of lung collapse that occurs when redundant pleura separates from the chest wall, creating a false mass-like appearance. Rounded atelectasis is often asymptomatic, making it

difficult to diagnose in the absence of a computed tomography (CT) scan. This case illustrates an association between unprovoked pulmonary embolism and rounded atelectasis.
A 40-year-old female with a history of hypothyroidism and endometriosis presented to the internal medicine clinic with a 3-day history of shoulder and back pain on her left side that worsened on inspiration and movement following strenuous exercise. Vital signs were all within normal limits and a chest x-ray showed no acute injury to bony structures, obvious soft tissue swelling, or pneumothorax. She returned to the emergency department three weeks later with a similar presentation of intermittent pleuritic chest pain and shortness of breath. Upon admission, she had stable vital signs, but a chest CT scan without contrast revealed a wedge-shaped pleural-based opacity in the left lower lung, consistent with rounded atelectasis. A second scan with pulmonary embolism protocol showed bilateral tiny emboli, compatible with unprovoked pulmonary embolism. She was discharged with a full dose of anticoagulation. Upon follow-up, the patient stated that her shortness of breath, chest tightness, and back pain were improving. Her labs revealed an elevation in factor VIII, an elevated lupus type anticoagulant profile, and a negative COVID-19 IgG antibody. Further testing revealed no malignancies.
The characteristic findings of rounded atelectasis upon imaging in which the lesion adheres to the pleura of the lung may suggest a possible malignancy, but the mismatch in clinical symptoms and radiologic findings may prolong the path to initial diagnosis. However, signs of pulmonary embolism should be monitored in patients with radiographic evidence of rounded atelectasis to ensure proper treatment or management of the underlying cause.

Ray, Sparsh

Neurorehabilitation Challenges following Surgical Correction of Congenital Kyphosis

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Introduction: Congenital Kyphosis is an uncommon disorder that is associated with a forward curvature of the spine of typically 30 – 60o. This deformity can be attributed to either a failure of formation of the anterior vertebrae (Type I), failure of segmentation of the anterior vertebrae (Type II), or a mixture of both (Type III). If untreated, Congenital Kyphosis can progress rapidly and lead to neurological symptoms including paraplegia.
Case Report: A 6-month old male presented to the clinic with curvature of the spine in the lumbar region. AP and Lateral views of the lumbar spine were consistent with Congenital Kyphosis with the apex at L2 and curvature of approximately 35o. Initial plan was for re-evaluation in 3 months with repeat films and MRI as well as echo and renal ultrasound studies to rule out cardiac and renal abnormalities. Films during follow up revealed progression of kyphosis to 50o. Surgical intervention was recommended in order to stop progression and correct deformity. Following procedure, patient was placed into custom clamshell TLSO brace. Post-op X-Rays were taken two weeks after confirming correction.
Discussion: Congenital kyphosis has many complications including spinal cord compression, respiratory, and even cardiac issues. As a result, post-surgical management of kyphosis is a crucial component of successful recovery. With congenital kyphosis being a having a rare incidence, there are very little studies looking at long term rehabilitation techniques for this. The journal of rehab medicine discussed manual mobilization and techniques to improve thoracic kyphosis in elderly post-menopausal patients. Following this rehab, the improvement with 6+/-3 degree reduction in kyphosis was seen following just 3 months of exercise therapy. Starting earlier intervention with compliance in children may offer improvement of overall posture and

function. Especially younger children as they grow into adolescence, early and consistent intervention can help improve their posture and prevent potential complications.

Reddy, Akhila

Pregnancy Outcomes in Patients with COVID-19

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It is understood that pregnant women are at higher risk for severe COVID-19 illness compared to non-pregnant people. Because of this, careful monitoring and research of this population should be carried out. The purpose of this study was to identify the clinical characteristics, neonatal outcomes, and population demographics of COVID-positive pregnant women admitted the UMC Health Center in Lubbock, Texas.
We reviewed the charts of 35 pregnant patients with confirmed COVID-19 admitted to the UMC Medical Center between April 12, 2020 and January 25, 2021.
It is understood that pregnant women are at higher risk for severe COVID-19 illness compared to non-pregnant people (CDC 2021). Because of this, careful monitoring and research of this population should be carried out. The purpose of this study was to identify the clinical characteristics, neonatal outcomes, and population demographics of COVID-positive pregnant women admitted to the UMC Health Center in Lubbock, Texas. We reviewed the charts of 35 pregnant patients with confirmed COVID-19 admitted to the UMC Medical Center between April 12, 2020 and January 25, 2021. The average patient age was 29 ± 4.8 years, and 71.43% of patients identified their ethnicity as Hispanic or Latino origin. Average LOS was 3.33 ± 3.56 days, and average number of weeks at delivery was 37.79 ± 2.27 weeks. No deaths were reported among the mothers, but there were three pregnancies that did not result in live birth. Notable findings were an increased rate of pre-term birth (18.18%), an increased rate of NICU admission (16.67%), and an increased rate of gestational diabetes (13.89%) compared to national averages among pregnant women.
Many of our findings confirmed the existing literature concerning pregnancy outcomes among COVID-19 positive pregnant women, including relatively high preterm birth and NICU admission rates. The amount of women who identified their ethnicity as Hispanic or Latino was over-represented, which may be reflective of Lubbock's overall demographics or health inequities in West Texas. Furthermore, our gestational diabetes rate was also higher than the national average, potentially reflective of Lubbock's high obesity rates. We recommend further research on the mechanisms of preterm birth in COVID-19 illness and ways to improve the health and healthcare equity of West Texas residents.

5. Clinical – Graduate Students

Ali, Kiran

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.

Bammel, Alexandra

Executive Functioning Deficits as a Criminal Risk Factor for Justice-Involved Youth

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Moffitt's (1993) model of antisocial behavior identifies neuropsychological deficits as a foundational risk factor for persistent criminal offending. Research has generally supported this model, with neuropsychological differences between justice-involved (JI) and non-JI adults becoming well-established in the years following its development (LaDuke et al., 2017). Research has begun to apply these findings to JI youth as well. In one study comparing youth in public school to incarcerated youth, incarcerated youth exhibited notable neuropsychological deficits compared to their public-school peers (Cauffman et al., 2005). Still, only a small number of studies have evaluated this link in JI youth using a formal neurocognitive measure as opposed to a biological indicator. Besides Cauffman et al.'s (2005) study, those that have used a sample of only male juveniles (Moffitt et al., 1994; Raine et al., 2005) or only African-American youth (McGloin et al., 2006; Piquero, 2001).

To examine the relationship between neuropsychological functioning and offending in a diverse juvenile sample, we analyzed data from 41 JI youth in Lubbock, Texas. Youths' ages ranged from 12-17 (M = 14.37, SD = 1.24), with just over half being male (n = 22, 53.7%) and the rest being female (n = 19, 46.3%). Criminal risk was measured using the Youth Level of Service/Case Management Inventory (YLS/CMI; Hoge & Andrews, 2002). Executive functioning was measured using the Delis-Kaplan Executive Function System (D-KEFS) Towers subtest, which measures spatial planning, rule-learning, and behavioral inhibition (Delis et al., 2001).

Results from a one-way ANOVA found no significant relationship between our Towers subtest composite score and criminal risk ($p = 0.062$). To increase the discriminatory power of the Towers subtest, a new Towers composite score was created using only the last four items (i.e., items 6, 7, 8, and 9) of the D-KEFS Towers subtest. Items on the Towers subtest gradually grow more difficult, and most individuals perform well on the earlier items. Considering this, we increased measure sensitivity by using only the last four Towers subtest items to form new Towers composite scores ranging from 1-4. Our next analysis revealed a highly significant association between this new Towers composite score and criminal risk such that lower Towers scores were associated with greater criminal risk ($F = 4.082$, $p = 0.013$). JI youth with a new Towers composite score of one scored about 14.11 points higher on average on our criminal risk measure compared to JI youth with a score of three ($p = 0.032$, 95% CI [0.8338, 27.3969]).

Thus, the latter portion of the D-KEFS Towers subtest was significantly associated with criminal risk. This suggests that D-KEFS Towers subtest items may predict reoffense for JI youth. Furthermore, this high predictive power of the Towers subtest suggests that spatial planning, rule-learning, and behavioral inhibition may be particularly relevant in predicting criminal risk. These areas may be worthwhile targets of criminal risk interventions. Additionally, the increased predictive power when considering only the final (rather than all) Towers subtest items indicates a potential ceiling effect. Scores were generally high on the Towers subtest, and the easier, earlier items were not useful in discriminating between higher and lower neuropsychological functioning. Our results suggest that executive functioning may provide valuable insight into criminal risk for JI youth. However, more sensitive measures should be explored, given that most neurocognitive measures are intended to evaluate obvious brain dysfunction.

De Simon, Daniel

Preoperative Transcortical Mapping by Navigational Brain Stimulation in a Case of Temporal Astrocytoma

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Case Description: The patient presented with a 24-hour history of word finding difficulty and memory deficits associated with blurred vision. MRI revealed a centrally enhancing cystic lesion in the left temporal lobe, with mass-effect along the left temporal lobe and occipital horn. Due to the proximity of the tumor to the speech center of the brain, she underwent preoperative transcortical mapping by navigational brain stimulation (NBS) prior to resection.
Assessment/Results: Brain mapping was performed by loading prior high-resolution T1 MRI images on the NBS system for neuro-navigated transcranial magnetic stimulation (TMS). Responses to magnetic stimulation were obtained using surface electromyography. The patient was videotaped performing object naming of simple black and white images. A 3D map of the cortical speech area was created for operative planning.
During surgical resection, remnants of tumor were left posteriorly along the superficial surface in an effort to preserve speech function. Intraoperative guidance with precise brain mapping resulted in greater resection of the astrocytoma without typical postoperative complications and speech deficits.
Discussion: NBS is a non-invasive method for localizing cortical areas of interest. Clinical studies suggest that this results in an increase of gross tumor regression by over 35% and an expansion in surgical indication by 14.8%.
Conclusion: This case demonstrates how brain mapping using NBS can be used to optimally plan surgical resection of tumors that are near critical cortical regions to reduce the risk for post-operative neurological deficits and improve functional outcomes.
Level of Evidence: Level V

Dennis, Victoria

Neuropsychological abilities in justice-involved youth: Differences observed in risk for re-offense

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Neuropsychological deficits occur in 60-80% of justice-involved youth (JIY; Cauffman et al., 2005; Sukyirum, 2016; Wynkoop, 2008), and multiple studies have found significant differences in neurocognitive abilities among JIY when compared to the general population (Nigg & Huang-Polluck, 2003; Oglivie, et al., 2011). Despite decades of research, juvenile delinquency remains a costly issue with negative emotional, physical, and economic consequences not only for individual youth and their families, but also for the community (De Vries et al., 2015; Welsh et al., 2008). Given these costs, this study sought to examine whether re-standardizing juvenile intelligence scores to reflect the sample mean rather than the average intellectual functioning of the general population would result in significant differences in total scores for risk for re-offense. We hypothesize that youth will display significant differences in total risk scores when compared across newly standardized intelligence scores. Intelligence is defined as the full-scale intelligence quotient (FSIQ).
Youth (N = 53) ranged in age from 12-16 years (M_{age} = 14.25, SD = 1.15; male = 28) and were primarily Latino/a/x (n = 17), White (n = 16), Black (n = 14), Asian (n = 1), and Other (n = 1); two participants were missing race/ethnicity information. Youth demonstrated an average FSIQ of 82.08 (SD = 10.94, range: 58-116) and an average total risk score of 12.31 (SD = 6.25, range: 3-26). To assess if re-standardizing juvenile intelligence scores would result in significant differences in youth's risk scores, we created a "new" normal distribution of intelligence scores. We converted FSIQ's into z-scores in which the distribution of scores centered our justice-involved sample's mean FSIQ rather than the general population mean FSIQ of 100. A

one-way ANOVA was performed to compare total risk scores across the three groups generated from "re-standardizing" our sample's FSIQ scores. Risk for re-offense was measured using the Youth Level of Service/Case Management Inventory (YLS/CMI) and intelligence was measured with the 7-core subtests of the Wechsler Intelligence Scale for Children (WISC-V).
Contrary to our initial hypothesis, comparisons did not reveal a significant difference in risk scores across the three groups, $F(2, 43) = .68$, $p = .51$. This suggests it may not be helpful to compare risk scores of JIY across intelligence scores within their own population. To further explore potential differences in intelligence across risk categories, one-way ANOVA were run to assess differences in FSIQ, VCI (verbal comprehension), and FRI (fluid reasoning) scores between different risk subgroups. We identified a significant difference in both FSIQ and VCI scores across Peer Relation risk levels $F(1, 49) = 7.55$, $p = .008$, Hedge's $g = .78$; $F(1, 48) = 5.56$, $p = .02$, Hedge's $g = .68$. This subcategory indicates whether youth's acquaintances are known offenders who exhibit antisocial attitudes. Youth who scored low on Peer Relations risk displayed a mean FSIQ of 86.91 ($SD = 12.88$) and a mean VCI of 91.01 ($SD = 12.39$) and those who scored high on Peer Relations risk displayed a mean FSIQ of 78.77 ($SD = 8.04$) and a mean VCI of 83.41 ($SD = 10.58$).
Our initial finding suggested it may not be helpful to compare risk scores of JI youth across intelligence scores within their own population. However, our additional analyses revealed a significant difference in FSIQ scores across the YLS/CMI Peer Relations risk subgroup. This finding may imply that distinct areas of neuropsychological abilities have specific relations with different criminogenic risk factors. Specifically, this study identified IQ as a potential mechanism for antisocial peer association among youth. Future research should continue to examine to what extent intellectual abilities are related to peer criminogenic risk factors among JIY.

Iweh, Marvelyn

The Epidemiology of Multi-systemic Inflammatory Disease (MIS-C) and Acute COVID-19 of Children in West Texas

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Over the past two years, COVID-19 has spread worldwide, resulting in changes in healthcare, public health, and the introduction of novel diseases. The clinical characteristics of COVID-19 in children differ significantly from adults. We compared the clinical and demographic characteristics of children requiring hospital admission in our region for acute COVID-19 and MIS-C during the first year of the pandemic.
We aimed to explore the associations of patient demographic characteristics and presentation with severe acute COVID-19 and MIS-C as well as resource utilization. Additionally, we estimated the hospital rate of admission of children with Acute COVID-19 and MIS-C in West Texas
We conducted a retrospective review of pediatric patients (< 18 years) admitted from April 1, 2020, through March 31, 2021, with MIS-C or acute COVID-19. We collected demographic and clinical information via direct chart review. We generated descriptive statistics of patient characteristics for acute COVID and MIS-C admissions. We generated population-based estimates of hospital admission in children in our region.
There were 159 subjects in the cohort including 39% (n=63) with acute COVID-19, 27% (n=41) with MIS-C, and 34% (n=55) with incidental COVID. Excluding patients with an incidental diagnosis of COVID-19, there were 105 patients hospitalized secondary to acute COVID-19 or MIS-C. While males represented most cases for acute COVID, 59.7% (n=38) and MIS-C,53.7% (n=22), there was no significant association. The median age was 4 for acute COVID and 9 years for MIS-C. Length of stay was 4.1 days for MIS-C versus 3.5 days for acute COVID. For the largest county in the hospital catchment area there were 22 children hospitalized with acute COVID-19

(0.03% of the county's children) and 19 hospitalized with MIS-C (0.026% of the county's children). Resource utilization was similar for both acute COVID and MIS-C.
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.

Shahi, Sadisna

Developing a Novel Class of DAT Inhibitor for the Treatment of Addiction

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Dopamine Active Transporters (DAT) is an important recognition site for cocaine and mediates its acute behavioral and reinforcing effects that contribute to abuse liability. In vitro studies have shown that cocaine blocks the uptake of the monoamines like dopamine, serotonin, and norepinephrine, with behavioral effects being attributed mostly to inhibition of dopamine uptake. Thus, compounds that target DAT are viewed as a potential pharmacological treatment of cocaine abuse, addiction, and dependence. Several preclinical studies demonstrate that DAT inhibitors can effectively attenuate cocaine self-administration, whereas drug effectiveness is correlated with DAT occupancy. In addition, recent reports showed selected DAT inhibitors, like modafinil, to reduce the rewarding effects of selected drugs and decrease abuse and addiction liability. Recently, our lab has reported a novel class of achiral urea analogs capable of inhibiting DAT with a high degree of selectivity and potency. Favorable pharmacokinetic profile, the ability to cross the BBB in vivo, and metabolic stability prompt us to evaluate the lead compound in the experimental autoimmune encephalomyelitis (EAE) mouse model. We have observed that this compound has lowered neuroinflammation, a pathological marker associated with chronic drug abuse. Here we present the project's status, providing more information on our compound's typical vs. atypical inhibitory properties and its ability to modulate responses to illicit drug exposure.

6. Clinical – Postgraduates

Kurt, Hatice

Sociodemographic Factors as Moderators of the Association between Resilience and Suicidality in a Group of Youth with Depression

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INTRODUCTION: Suicide, known to be the second leading cause of death in people between ages 15-29, continues to be a major public health issue. Identifying the risk factors of suicidal thoughts and behaviors is as important as understanding the protective factors to prevent this tragic outcome. While depression is widely reported to significantly increase the risk of suicidality, research to identify parameters affecting the predictive strength of depression or other risk factors on suicidality is ongoing. Resilience has been the focus of expanding research in recent decades as a factor that can attenuate the risk and suicidality. However, the moderating factors of resilience as related to depression and or suicidality are yet to be well defined.
OBJECTIVES: To explore the socio-demographic moderators of the well-established association between resilience and depression among youth with depression or suicidal ideation in a secondary analysis.
METHODS: Cross-sectional baseline data collected at a regional node of a larger state-wide longitudinal registry study (Texas Youth Depression and Suicide Research Network) were analyzed using R (4.1.3). The study sample was made-up of youth (age 8-20 years) with clinical depression or suicidal ideation. Numerous variables including severity of depression (Patient Health Questionnaire – Adolescents; PHQ-A), suicide propensity and suicidal thoughts (Concise Health Risk Tracking-Self Report; CHTR), resilience (Connor-Davidson Resilience Scale) as well as sociodemographic variables including age, sex, race, annual house-hold income and parental education level were obtained. Linear correlations between baseline resilience vs. PHQ-A, suicide propensity and suicidal thoughts was examined. Moderator effects of each socio demographic variable on these associations was explored in multiple regression models.
RESULTS: Data of seventy-two participants were included in the analyses. Resilience was negatively and moderately associated with PHQ-A ($r = -0.360$, $p = 0.002$), suicide propensity ($r = -0.335$, $p = 0.005$) and suicidal thoughts ($r = -0.230$, $p = 0.050$). Multiple regression analyses revealed that increasing age was associated with significantly decreased severity of depression, suicide propensity and suicidal thoughts when controlled for resilience. Furthermore, age was a significant moderator of the association between resilience and each of severity of depression, suicide propensity and suicidal thoughts. While sex and race were not observed to have direct or moderator effects on the association between resilience and depression or suicidal thoughts, an annual house-hold income of $100,000-$199,000 and having at least one parent with a Bachelor's degree significantly decreased the risk of suicidal thoughts and moderated the association between resilience and suicidal thoughts.
CONCLUSIONS: It is reiterated with the current work that increased resilience seems to be associated with decreased depression severity, suicidal propensity and suicidal ideation among children and adolescents. The protective effects of age, income above $100,000 and higher parental education of the association between resilience and depression / suicide risk are novel findings worth further exploration.
ACKNOWLEDGEMENTS): The study was conducted using data collected as part of the Texas Youth Depression and Suicide Research Network with the help of the clinical research coordinators from the TTUHSC Clinical Research Institute. The study was funded by the Texas Child Mental Health Care Consortium.

Park, Micah

Moderator effects of acculturation and ethnic identity on the association between resilience and self-reported medication adverse effect burden among youth with depression and suicidal ideation: a secondary analysis

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Background: Multiple environmental and socioeconomic factors can affect resilience in children and adolescents. Studies of resilience in immigrant and refugee children show that acculturation and ethnic identities can affect and moderate the effects of resilience on health outcomes. Protective effects of resilience against mental illness, particularly depression, have been well-established. Furthermore, beneficial effects of resilience among immigrant children have been well-documented. However, specific associations between resilience and treatment outcomes such as medication adverse effect burden (AE) among youth with depression and suicidal ideation remains to be explored. Moreover, the effects of acculturation as well as ethnic identity on this potential association remains to be elucidated.

Objectives: To examine whether resilience among youth with depression or suicidal ideation is associated with acculturation as well as affirmation, exploration, and resolution as related to ethnic identity, and to examine whether acculturation and ethnic identity will moderate the predictability of future self-perceived medication AE in a secondary analysis.

Methods: Data collected at a regional node of a larger state-wide longitudinal registry study (Texas Youth Depression and Suicide Research Network) were analyzed using an intention-to-treat approach. The study recruited youth (age 8-20 years) with depression or suicidal ideation and collected multiple variables including resilience (Connor-Davidson Resilience Scale), acculturation (Brief Acculturation Scale for Hispanics), and ethnic identity (Ethnic Identity Scale) at baseline, and self-perceived medication adverse effect burden (Frequency, Intensity, Burden of Side Effects Rating) at baseline, month 1, and multiple bi-monthly visits. Pair-wise Spearman correlations were performed between resilience, acculturation, and ethnic identity variables at baseline. The association between baseline resilience and cumulative AE of participants followed-up for at least 6 months was examined in a univariate linear regression model. Moderator effects of acculturation, affirmation, exploration, and resolution of the above association were examined in four separate multiple regression models.

Results: Baseline data of 72 participants were included in correlation analyses. Thirty-one participants who were managed with anti-depressants and followed-up for at least 6 months were included in the regression analyses. Resolution was significantly correlated with acculturation ($\rho = -0.331$, $p = 0.005$) and exploration ($\rho = 0.509$, $p < 0.001$). Resilience was a significant predictor of cumulative AE within the first 6 months of treatment ($\beta = -0.250$, $p = 0.004$) suggesting that youth with increased baseline resilience had a decreased self-perceived AE. Acculturation or the ethnic identity variables failed to significantly moderate this association ($p > 0.050$).

Conclusions: Resiliency was a significant predictor of patient's self-perception of AE. Those who report less AE may be more compliant with their pharmacologic treatment, and therefore more likely to achieve improvement or remission of their psychiatric condition. Future studies should aim to establish the effects of self-perceived AE in mediating the association between resilience and treatment response among youth with depression and suicidal ideation.

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