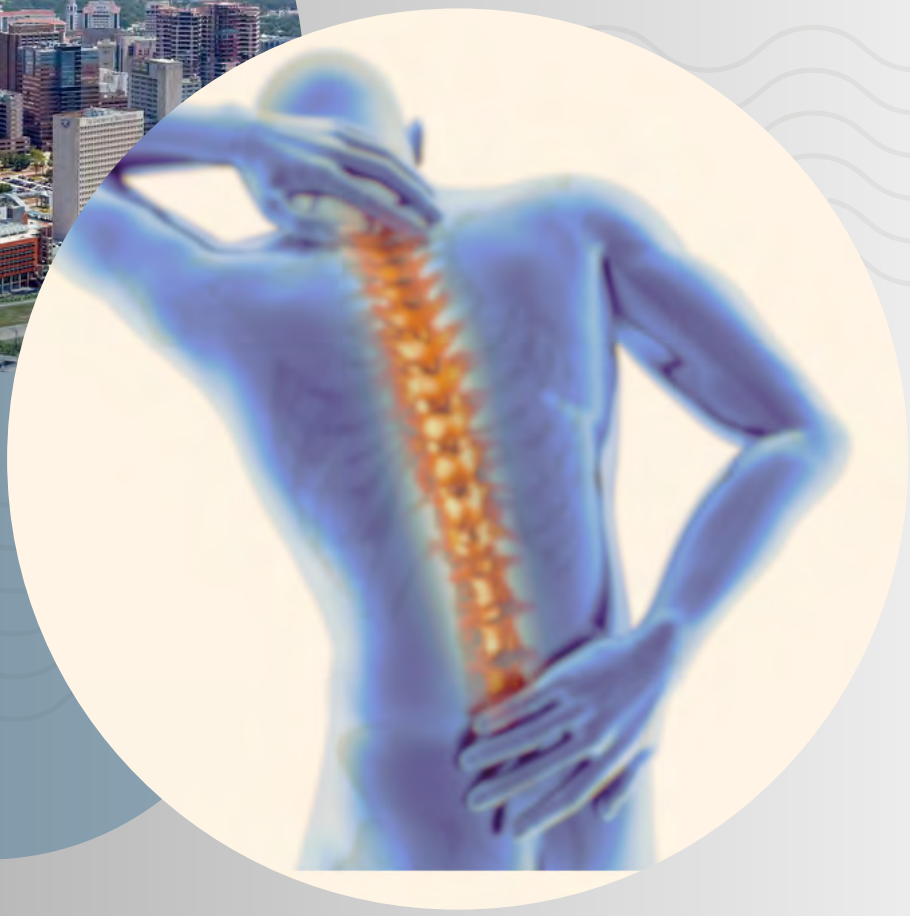
HOUSTON, TEXAS

March 26-27, 2024



13TH ANNUAL GCC TRANSLATIONAL PAIN CONFERENCE

Gulf Coast Consortia

QUANTITATIVE BIOMEDICAL SCIENCES

Gulf Coast Consortia
QUANTITATIVE BIOMEDICAL SCIENCES

The Gulf Coast Consortia (GCC), located in Houston, Texas, is a dynamic, multi-institution collaboration of basic and translational scientists, researchers, clinicians, and students in the quantitative biomedical sciences, who benefit from joint training programs, topic-focused research consortia, shared facilities and equipment, and exchange of scientific knowledge. Working together, GCC member institutions provide a cutting-edge collaborative training environment and research infrastructure beyond the capability of any single institution. GCC research consortia gather interested faculty around research foci within the quantitative biomedical sciences and currently include Translational Pain Research, Antimicrobial Resistance, Cellular and Molecular Biophysics, Innovative Drug Discovery and Development, Immunology, Integrative Development, Regeneration, and Repair, Mental Health Research, and Single Cell Omics. GCC training programs currently focus on Biomedical Informatics, Computational Cancer Biology, Molecular Biophysics, Pharmacological Sciences, Precision Environmental Health Sciences, and Antimicrobial Resistance. Current members include Baylor College of Medicine, Rice University, University of Houston, The University of Texas Health Science Center at Houston, The University of Texas Medical Branch at Galveston, The University of Texas M. D. Anderson Cancer Center, Institute of Biosciences and Technology of Texas A&M Health Science Center and Houston Methodist Research Institute.

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Gulf Coast Consortia - Research

Agenda

Day 1

10:00-10:30 Registration-Pre-function Area
and Poster Set Up-Event Hall

10:30-10:35 Welcome
Suzanne Tomlinson, Gulf Coast Consortia
Jun-Ho La, University of Texas Medical Branch at Galveston

Convener: **Jun-Ho La**, University of Texas Medical Branch at Galveston
10:35-11:15 **Keynote presentation**
More Than Pain: Functions and Mechanisms of Ongoing Activity in Nociceptors
Edgar (Terry) Walters, University of Texas Health Science Center Houston

Convener: **Stacey Gorniak, University of Houston**
11:15-11:30 *Novel Therapeutic Approaches Targeting Nerve Barrier Disruption in Diabetic Painful Neuropathy*
Munmun Chattopadhyay, Texas Tech Health Science Center

11:30-11:45 *Deciphering the Molecular Landscape of Human Peripheral Nerves: Implications for Diabetic Peripheral Neuropathy*
Diana Tavares Ferreira, University of Texas Dallas

11:45-12:00 *Opioid-sparing Effects of the Nrf2 Activator Diroximel Fumarate in Mice*
Mohd Sami Ur Rasheed, MD Anderson Cancer Center

12:00-12:15 *Pathology-Activated Prodrugs Targeting Nrf2 to Treat Neuropathic Pain*
Fátima Rivera-Escalera, MD Anderson Cancer Center

12:15-12:20 *GCC-TPR Scholars Program*
Chrystine Gallegos, University of Texas Health Science Houston
Isabella Casmedes, Tarleton University
Ramesh Pariyar, University of Texas Medical Branch

12:20-1:20 Networking Lunch-event hall

Convener: **Carmen Dessauer**, University of Texas Health Science Houston
1:20-2:00 **Keynote presentation**
Unlocking the Role of Satellite Glial Cells in Sensory Neuron Function in Healthy and Disease States
Valeria Cavalli, Washington University

Convener: **Helen Lai**, University of Texas Southwestern
2:00-2:15 *Elucidating the Neural Oscillations of the Sensory-Discriminative and Affective-Motivational Dimensions of Pain Using EEG*
AmberHarris Bozer, Tarleton State University

2:15-2:30 *Endogenous Dopaminergic Signaling in the Lateral Parabrachial Nucleus Modulates Mechanical Nociception*
Jun-Ho La, University of Texas Medical Branch Galveston

Agenda

2:30-2:45 *The Potential of Stem Cells as Catalysts for Innovation.*
Nikita Ruparel, University of Texas Health Science Center at San Antonio

2:45-3:00 *Precision Medicine fMRI Neuromodulation Enhances Swallow Control Targeted for Lower Cranial Neuropathy Patients*
T. Dorina Papageorgiou, Baylor College of Medicine

Convener: **Patrick Dougherty**, MD Anderson Cancer Center
3:00-3:40 Data Blitz

3:40-3:45 Move to the event hall for the poster session
3:45-4:45 Even # poster session
4:45-5:45 Odd # poster session

5:45-6:45 Reception-pre-function

Day 2
8:00-8:55 **Mentoring Breakfast-**Event Hall
Panelists: **Valeria Cavalli**, Washington University
Isaac M. Chiu, Harvard Medical School
Carmen Dessauer, University of Texas Health Science Center Houston
Andrew Shepherd, MD Anderson Cancer Center
Edgar (Terry) Walters, University of Texas Health Science Center Houston

Moderators: **Andrew Shepherd,** MD Anderson Cancer Center
Chrystine Gallegos, University of Texas Health Science Center Houston

9:00-9:05 Welcome
Jun-Ho La, University of Texas Medical Branch at Galveston

Convener: **Shivani Ruparel**, University of Texas Health Science San Antonio
9:05-9:20 *PACAP-Mediated Activation of MRGPRX2+ Meningeal Mast Cells Leads to Migraine-like Pain*
Sami Sbei, University of Texas Medical Branch

9:20-9:35 *PACAP38 Mediates Stress-Induced Headache Via Mast Cell-Specific Receptor*
Yu Shin Kim, University of Texas Health San Antonio

9:35-9:50 *TRPA1 Agonist-Responsive Nociceptors Drive Central Sensitization by Suppressing Spinal GABAergic Interneurons through Somatostatin 2A Receptors*
Ramesh Pariyar, University of Texas Medical Branch

9:50-10:05 *Cell-Type Map of Pain and Non-Pain Somatosensory States in the Spinal Cord*
Allan-Hermann Pool, University of Texas Southwestern Medical Center

Convener: **Andrew Shepherd**, MD Anderson Cancer Center
10:05-10:45 **Keynote presentation**
Neuronal Interactions with Microbes in Pain and Itch
Isaac M. Chiu, Harvard Medical School

10:45-11:15 Networking Break

Agenda

Convener: **Diana Tavares Ferreira**, University of Texas Dallas

11:15-11:30 *Peripherally Acting Recombinant LIGHT Inhibits Oral Cancer Pain*
Jaclyn Merlo University of Texas Health Science Center at San Antonio

11:30-11:45 *Prolonged Analgesia in Neuromuscular Trauma with a Single Dose of Non-Opioid Nanomedicine in Rodents and Non-Human Primates*
Jelena Janjic, Duquesne University

11:45-12:00 *SARS-CoV-2 Pain Mechanisms*
Ken Hargreaves, University of Texas San Antonio

12:00-12:15 *Pro-Nociceptive Role of IgG After Peripheral Nerve Injury*
Nathan Fiore, MD Anderson Cancer Center

12:15-12:30 Presentation of awards and closing remarks
Jun-Ho La, University of Texas Medical Branch at Galveston

Presenters in alphabetical order

Valeria Cavalli, PhD
Robert E. and Louise F. Dunn Professor of Biomedical Research
Professor of Neuroscience
Washington University School of Medicine

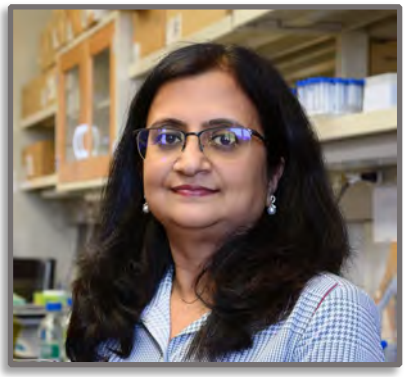
Unlocking the Role of Satellite Glial Cells in Sensory Neuron Function in Healthy and Disease States

Research in my laboratory focuses on elucidating the principles and mechanisms by which peripheral nervous system neurons regenerate, and to identify therapeutic targets to improve neuronal recovery following axon injury. To understand why regeneration occurs in the peripheral but not the central nervous system, our lab studies a unique cell type that spans both systems: sensory neurons of the dorsal root ganglia. The cell bodies of sensory neurons are located in the dorsal root ganglion, a structure that sits just outside the spinal cord. These sensory neurons have a unique pseudo-unipolar morphology with a single axon which bifurcates within the ganglion; one axon proceeds along peripheral nerves and the other proceeds centrally along the dorsal root into the spinal cord. Importantly, the peripheral axon has a much greater regenerative capacity than the central axon.

Using this system, we have discovered epigenetic, transcriptional, and translational pathways employed by peripheral neurons to increase their growth capacity. While we continue to study the signaling pathways elicited in sensory neurons, we recently turned our attention to the possibility that other cells residing in dorsal root ganglia contribute to the nerve repair process. We focused on the glial cells that envelop the sensory neuron soma, known as satellite glial cells (SGC). We discovered that the Fasn-PPARalpha signaling pathway in SGC contribute to nerve repair and this pathway is conserved across rodent and human SGC. In our recent studies we found that SGC receives signals from macrophages after nerve injury that contribute to promote axon regeneration. Our recent studies suggest that the endothelin signaling pathways in SGC contribute to age-dependent axon regenerative decline.

While we continue our studies on mechanism nerve repair, we have also recently been interested in understanding how SGC contribute to sensory dysfunction in mouse models of autism. Together, our studies point to the importance of better understanding the contribution of DRG resident cells in nerve injury responses, which may pave the way for improved efficiency in translating discovery into new treatments of nerve injury and disease.

Keynote presenter



Munmun Chattopadhyay, MSc, PhD
Associate Professor
Chair, IACUC
Paul L. Foster School of Medicine
COE in Diabetes and Metabolism
Texas Tech Health Science Center El Paso
Novel Therapeutic Approaches Targeting Nerve Barrier Disruption in Diabetic Painful Neuropathy

Dr. Munmun Chattopadhyay is an Associate Professor in the Department of Molecular and Translational Medicine at Texas Tech University Health Sciences Center El Paso and Chair of the Institutional Animal Care and Use Committee at TTUHSC El Paso. Dr. Chattopadhyay received her MS degree in Zoology and Ph.D. in Neurosciences from Jiwaji University, Gwalior, India. After her post-doctoral training in Molecular Genetics at the National Institute of Immunology, New Delhi, India, she joined the University of Pittsburgh as a post-doctoral fellow in the Department of Neurology. She became a junior faculty in the Department of Neurology at the University of Michigan in 2010 and joined TTUHSC El Paso as an Assistant professor in 2014. Her research is focused on determining the impact of inflammatory mediators on the pathogenesis of diabetic complications. Her lab is currently investigating on the novel early biomarkers of inflammation and epigenetic modulators (histone modifications) involved in the progression of neuropathy, cardiac dysfunction and gastroparesis in diabetic animals and human subjects. She is also investigating how natural compounds and exercise could alter the progression of these complications. Dr. Chattopadhyay has been funded by NSF, NIH, ADA and other foundations; published more than 43 articles and 2 book chapters. Dr. Chattopadhyay received Faculty Service Award by Student Government Association, TTUHSC El Paso (2020), Women Worth Watching in STEM (2022) by Profiles in Diversity Journal and nominated for 3D Printing Industry (2021). She serves as an associate editor and editorial board member in a number of peer reviewed journals and panel member in several grant review committees including NIH, ADA, DoD, NSF and other international review panels including NIHR.

Isaac M. Chiu, PhD
Associate Professor
Department of Immunology
Blavatnik Institute
Harvard Medical School

Neuronal Interactions with Microbes in Pain and Itch

Dr. Chiu's main research focus is on the role of neuroimmune interactions in pain, itch, and immunity. He is an associate professor at Harvard Medical School in the Department of Immunology. Dr. Chiu received his PhD training in Immunology at Harvard Medical School with Dr. Michael Carroll. He completed postdoctoral fellowships at Harvard University with Dr. Tom Maniatis, and at Boston Children's Hospital with Dr. Clifford Woolf. He started as an assistant professor at Harvard Medical School in 2014 and was promoted to associate professor in 2021.

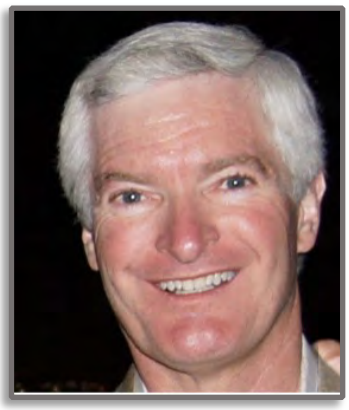
The Chiu lab uses interdisciplinary approaches from neurobiology, microbiology, and immunology. He has found that nociceptive sensory neurons directly detect bacterial pathogens and their secreted mediators to produce pain and itch. These neurons signal to immune cells in the skin, lungs, and gut to regulate barrier tissue immune responses. Dr. Chiu has received the Chan-Zuckerberg Initiative Ben Barres Early Career Award, NIH Director's New Innovator Award, and Burroughs Wellcome Fund Investigators in the Pathogenesis of Infectious Disease Award.

http://chiulab.med.harvard.edu

Keynote presenter

Nathan Fiore, PhD
Research Scientist
MD Anderson Cancer Center
Pro-Nociceptive Role of IgG After Peripheral Nerve Injury

Dr. Fiore is a Research Scientist at UT MD Anderson in the Grace laboratory with a research background in research in the fields of Neuroscience and Neuroimmunology. He completed his PhD at University of Sydney in the fields of neuroimmunology and neuropathic pain. The research utilized rodent models of neuropathic pain and neuropathy to identify individual differences in behavior and corresponding neuro-immune signatures at multiple levels of the nervous system. His PhD research also expanded into characterizing immune system dysfunction in chronic pain patients. He completed postdoctoral training in the Neuropathic Pain Research group at University of New South Wales (UNSW). The research focused on identifying unique sex-specific microglial signatures and effects of immunomodulatory treatments in mouse models of peripheral nerve injury and chemotherapy-induced peripheral neuropathy. He is currently investigating the role of B cells in the development neuropathic pain, with a particular focus on the pro-nociceptive role of IgG after peripheral nerve injury.



Ken M. Hargreaves, DDS, PhD
Diplomate, American Board of Endodontics
Professor
Dept Endodontics
University of Texas Health San Antonio
SARS-CoV-2 Pain Mechanisms

Ken Hargreaves received his DDS from Georgetown University, his PhD in physiology from the Uniformed Services University of the Health Sciences in Bethesda, MD, and his certificate in Endodontics from the University of Minnesota. Ken spent 5 years in Ron Dubner's Neurobiology and Anesthesiology Branch of the NIDCR and 7 years as an associate professor of Endodontics and Pharmacology at the University of Minnesota. He joined the University of Texas Health Science Center at San Antonio in 1997. Ken has published more than 250 articles and has edited two textbooks.

Amber Harris Bozer, PhD
Associate Professor
Psychological Sciences
Tarleton State University

Elucidating the Neural Oscillations of the Sensory-Discriminative and Affective-Motivational Dimensions of Pain Using EEG

Amber Harris Bozer is currently an Associate Professor of Psychological Sciences at Tarleton State University. She earned a BS in Psychology (2008) and an MS in Educational and Experimental Psychology (2010) at Tarleton State University under the mentorship of Drs. Jason Lyons and Robert Newby. At the University of Texas at Arlington, she obtained an MS (2013) and a PhD (2015) in Experimental Psychology with a focus on Neuroscience and Health Psychology under the mentorship of Drs. Perry Fuchs and Yuan Bo Peng. During her graduate studies, her primary focus was the development of novel, multi-dimensional preclinical pain assays and the investigation of local field potentials that underlie the multi-dimensional nature of pain in rats. In the Behavioral Neuroscience and Psychophysiology lab at Tarleton, the current research focus is to explore the cortical mechanisms that underlie the multidimensional pain experience in humans (including pain approach-avoidance) and the cortical mechanisms of cannabinoid analgesia using EEG.

Jelena M. Janjic, PhD
Associate Professor
Pharmaceuticals
Duquesne University
Prolonged Analgesia in Neuromuscular Trauma with a Single Dose of Non-Opioid Nanomedicine in Rodents and Non-Human Primates

Jelena M. Janjic, PhD, also known as “Dr. J”, is a tenured Associate Professor of Pharmaceutics and Founder/Co-Director of the Chronic Pain Research Consortium (CPRC, www.duq.edu/pain [duq.edu]) at Duquesne University in Pittsburgh, USA. She received her pharmacy degree at Belgrade University, Form. Yugoslavia in 1998 and her Ph.D. at the University of Pittsburgh School of Pharmacy in 2005. She completed her post-doctoral training at Scripps Florida (2006) and Carnegie Mellon University (2009). The primary focus of her research is the implementation of Quality by Design to the manufacture of nanomedicines for imaging-supported drug delivery. In her 17-year long career in nanotechnology, she has developed multiple imaging and drug delivery platforms and biomaterials, which resulted to date in 3 patents, more than 60 publications, and numerous invited presentations at national and international meetings. Her research interests lie at the intersection of immunology and neuroscience in control of neuroinflammation in pain, trauma, and regenerative medicine. Specifically, her work has focused on nanomedicines, which simultaneously image and modulate immune cells for therapeutic intervention in trauma and post-surgical pain, pain following neuromusculoskeletal injuries, neuropathic and chronic inflammatory pain. She also works in organ transplantation and rejection control, regenerative medicine, and organ preservation. Her designs have been successfully validated in experimental small and large animal models of transplant rejection, neuroinflammation, neuroregeneration, and pain. She is the inventor of the first nanoparticle-based oxygen delivery agent tested on human organ/tissue preservation, and the inventor of the first neuroinflammation-

Yu Shin Kim, PhD
Associate Professor
Dentistry
University of Texas Health San Antonio
PACAP38 Mediates Stress-Induced Headache Via Mast Cell-Specific Receptor

Dr. Yu Shin Kim graduated Johns Hopkins University and did postdoc at Johns Hopkins University. Currently, he is an associate professor in the School of Dentistry at the University of Texas Health at San Antonio (UTHSA) where it is well known for its strong group in pain research. His research is focused on the function and regulation of sensory modalities, including pain, itch, and gentle touch, and on understanding the cellular and molecular mechanisms of pain by studying neural circuit activities evoked by pain in normal and disease conditions like chronic pain and temporomandibular disorders (TMD). His lab developed in vivo GCaMP calcium and voltage sensor voltage imaging of intact dorsal root ganglia (DRG) and trigeminal ganglia (TG) to study molecular and cellular mechanisms of somatosensory system.

Jun-Ho La, DVM, PhD
Associate Professor
Neurobiology
University of Texas Medical Branch
Endogenous Dopaminergic Signaling in the Lateral Parabrachial Nucleus Modulates Mechanical Nociception

Dr. La is an Associate Professor in the Department of Neurobiology and the Cecil H. and Ida M. Green Distinguished Chair in Neuroscience and Cell Biology at the University of Texas Medical Branch. Dr. La has a longstanding research interest in chronic pain and the development of therapeutic tools to manage this debilitating condition. His current research focuses on unraveling the endogenous mechanisms that modulate nociceptive circuits at both spinal and supraspinal levels. Using preclinical animal models and employing behavioral and Ca2+-imaging approaches, his laboratory is investigating how the ongoing activity of nociceptors modulates nociceptive circuits in the dorsal horn, leading to pain hypersensitivity. Additionally, the research delves into understanding how endogenous dopaminergic signaling in the lateral parabrachial nucleus contributes to nociception. Beyond these efforts to comprehend chronic pain mechanisms, Dr. La's laboratory is developing novel pain therapeutics designed to facilitate endogenous pain resolution mechanisms, aiming to convert chronic pain back to normally resolving pain.

Jaclyn N. Merlo, MS
Graduate Student
Integrated Biomedical Sciences Program
University of Texas Health San Antonio
Peripherally Acting Recombinant LIGHT Inhibits Oral Cancer Pain

Jaclyn Merlo, MS, is a current a PhD student in the Integrated Biomedical Sciences Program at UT Health San Antonio (UTHSCSA). She received her masters degree in Immunology and Infection at UTHSCSA and is under the tutelage of Dr. Shivani Ruparel, in the Pain Lab of the Department of Endodontics. Jaclyn is currently studying peripheral mechanisms of oral tumorigenesis and pain associated with cancer treatment. This includes identifying novel treatments for oral cancer-induced pain. Her specialized training track is through the Craniofacial Oral-Biology Student Training in Academic Research (COSTAR) program which supports advanced research training in Craniofacial Oral-Biology at the UTHSCSA Dental School. She is the current Vice-President of Public Relations of the UTHSCSA Toastmasters Chapter and a member of the Initiative on Maximizing Student Development (IMSD) Program.

T. Dorina Papageorgiou, PhD, MHSc
Assistant Professor of
Psychiatry, Neuroscience,
Physical Medicine and Rehabilitation
Baylor College of Medicine

Precision Medicine fMRI Neuromodulation Enhances Swallow Control Targeted for Lower Cranial Neuropathy Patients

Dr. T. Dorina Papageorgiou obtained a BA in Psychology and Sociology (University of Georgia), a M.H.Sc. in Psychiatric Epidemiology (Johns Hopkins Bloomberg School of Public Health), and a Ph.D. in the Biomedical Sciences The (University of Texas - M.D. Anderson Cancer Center; MDACC) with a focus on human brain neuroimaging, specifically the effects of morphine in the pain matrix networks. She continued with three postdoctoral fellowships: (i) neuroimaging of cancer symptoms and its treatment (MDACC); (ii) cortical neuromodulation of speech using real-time functional MRI neurofeedback (Baylor College of Medicine; BCM); and (ii) cortical neuromodulation of visual perception in cortical blindness (BCM). As an Assistant Professor of Psychiatry, Neuroscience, Physical Medicine and Rehabilitation, Center for Space Medicine, Dan L. Duncan Comprehensive Cancer Center at BCM and an Adjunct Assistant Professor of Electrical and Computer Engineering, Neuroengineering, and Applied Physics at Rice University her lab's research focuses on the development and application of targeted, and individualized real-time fMRI NeuroModulation (iNM) translational applications and computational methods to elucidate the causal spatiotemporal mechanisms of cortical plasticity in health, and disease. Clinical applications focus on the neurorehabilitation of chronic pain syndromes following the side effects of cancer treatments, such as radiation induced lower cranial neuropathy, post-mastectomy pain syndrome following lymph node dissection, as well as cortical blindness, cognitive impairment. The principle of precision medicine iNM is based on promoting the reorganization of networks by bypassing lesioned pathways and capitalizing on redundant, intact but functionally associated networks to the injured ones. The Papageorgiou - Investigational Targeted Brain Neurotherapeutics Lab's research is funded by the McNair Medical Institute, the McNair Foundation, the TIRR Foundation, various other foundations, and NIH mechanisms. She is the Chief Editor of the internationally successful book "Advanced Brain Neuroimaging Topics in Health and Disease – Methods and Applications" (ISBN: 978-953-51-1203-7; DOI: 10.5772/58256; eBook (PDF) ISBN: 978-953-51-7209-3), which has been downloaded ~58K times to date. She has presented her lab's work at several international conferences, such as the Brain Stimulation Conference, Vancouver (2019) the International Real-time NeuroImaging Conference (Maastricht, 2019; and at Yale School of Medicine, 2022), the International Cognition and Cancer Task Force, the 2nd Annual NIH Meeting on Interoception Meeting for Investigators (2023), American Academy of Neurology (2023), and others. Finally, she is co-editor to the Special Issue of Neuroimaging Neuromodulation, expected to be published by the Philosophical Transactions of the Royal Society in 2024.

Ramesh Pariyar, PhD
Research Scientist-I
Neurobiology
University of Texas Medical Branch Galveston
TRPA1 agonist-responsive nociceptors drive central sensitization by suppressing spinal GABAergic interneurons through Somatostatin 2A receptors

Dr. Pariyar currently serves as a postdoctoral fellow at the University of Texas Medical Branch, in the Dr. Chung/La laboratory. His research focuses on understanding the mechanisms of central sensitization in the spinal cord underlying nociplastic pain. Dr. Pariyar received his PhD in neuropharmacology and a master's in pharmacology form the Wonkwang University (South Korea), where he studied molecular mechanism of neuronal cell death in neurodegenerative diseases.

Allan-Hermann Pool, PhD
Assistant Professor
Department of Neuroscience, Department of Anesthesiology and Pain Management, O'Donnell Brain Institute
University of Texas Southwestern Medical Center
Cell-Type Map of Pain and Non-Pain Somatosensory States in the Spinal Cord

Allan-Hermann Pool is an Assistant Professor at University of Texas Southwestern Medical Center (UTSW) where his lab studies the cellular mechanisms mediating central pain and pain relief states and develops new cell-type specific therapeutic avenues to target these circuit nodes. Dr. Pool received his PhD from UC Berkeley where he dissected food and water intake regulatory circuits in the fruit fly uncovering a pair of neurons preventing indiscriminate consumption in insects. He went on to perform postdoctoral work at California Institute of Technology where he discovered mammalian central sensory neurons detecting the need for water and minerals and orchestrate corresponding appetites. His lab at UTSW deploys high-throughput cellular methods to discover pain and pain-relief engaged neuron types, dissects their functional role in driving adaptive and mal-adaptive pain behaviors and develops antibody and viral methods to render these circuits precisely druggable.

Mohd Sami Ur Rasheed, PhD
Postdoctoral Fellow
Symptom Research
MD Anderson Cancer Center
Opioid-sparing Effects of the Nrf2 Activator Diroximel Fumarate in Mice

Dr. Rasheed obtained his PhD in Biological Sciences from the Academy of Scientific and Innovative Research (India) in 2020 where he studied the role of Nrf2-Keap1 pathway in Parkinson's disease.

Developing a keen interest in understanding the role of Nrf2 as a therapeutic approach in the treatment of neuropathic pain, he joined the lab of Dr Peter Grace as a postdoctoral fellow (2020- present). Currently he is working on an NIH-HEAL project to investigate the role of Nrf2 activators in protection against opioid-induced side effects.

Fátima Rivera-Escalera, PhD
Research Scientist
Symptom Research
MD Anderson Cancer Center

Pathology-Activated Prodrugs Targeting Nrf2 to Treat Neuropathic Pain

Dr. Rivera-Escalera is originally from Puerto Rico and obtained her PhD in Neuroscience from the University of Rochester in 2015 where she studied the role of neuroinflammation and microglial phagocytosis in Alzheimer's disease pathogenesis. She then completed postdoctoral training at both the University of Virginia and the University of Rochester in the fields of neuroimmunology and immunology, with a focus on investigating the function of tissue-resident macrophages in acute and chronic inflammation, cancer immunotherapy resistance, hematologic malignancies, aging, and demyelinating disease. She is currently a Research Scientist in the Grace Lab where she is investigating the NRF2-KEAP1 pathway in modulating oxidative stress in neuropathic pain and cancer-related chronic pain.

Nikita B. Ruparel, MS, DDS, PhD
Endodontics
Director, Advanced Program in Endodontics
Carlos E. del Rio Chair in Endodontics
University of Texas Health Science Center at San Antonio

The Potential of Stem Cells as Catalysts for Innovation

Dr. Ruparel is Board certified Endodontist who practices in San Antonio at UT Faculty Endodontics. She is the Director of the Advanced Program in Endodontics at UT San Antonio. She received her clinical certificate in Endodontics in 2013 after receiving her doctoral (PhD) and DDS at The University of Texas Health Science Center at San Antonio. Her practice in Endodontics includes all aspects of modern endodontics. Her current research projects are focused in two broad themes in the area of pain and stem cells: 1) development of novel non-opioid drugs using human tissues and stem cells to treat infection-induced pain using an clinically translational orofacial model of apical periodontitis-induced pain; 2) differential regulation of the trigeminal system in patients suffering from pain induced by apical periodontitis and investigating gender-related differences in patients with post-endodontic pain using human transcriptomic and bioinformatic analysis of human tissue biopsies. She has been funded by Clinical and Translational Science Awards (CTSA) and the NIH.

Sami Sbei
Graduate Student
University of Texas Medical Branch Galveston
PACAP-mediated activation of MRGPRX2+ Meningeal Mast Cells Leads to Migraine-like Pain

Sami Sebi is currently a Ph.D. candidate and a TL1 predoctoral fellow in the Human Pathophysiology and Translational Medicine program at the University of Texas Medical Branch (UTMB) in the lab of Dr. Dustin P. Green. His research in the field of Neuroimmunology is aimed at studying the interaction between mast cells and the nervous system in the context of pain. His current work focuses on characterizing the role of the connective-tissue mast cell-exclusive Mas-Related G Protein-Coupled Receptor (Mrgpr)B2 and its human homolog MRGPRX2 receptors in pain.

Diana Tavares Ferreira, PharmD/MS, PhD
Assistant Professor
Neuroscience
University of Texas Dallas

Deciphering the Molecular Landscape of Human Peripheral Nerves: Implications for Diabetic Peripheral Neuropathy

Diana is originally from Portugal and graduated with a PharmD/MS in Pharmaceutical Sciences from the University of Coimbra. Then, she moved to the UK, where she completed her PhD in neuroscience at the University of Sheffield studying the role of resolvin receptors and microRNA following nerve injury. During her PhD studies, Diana spent six months at Eli Lilly Research as a visiting scientist and received training in bioinformatics. Then, she moved to the US to do a postdoc in Dr. Theodore Price's lab at UT Dallas, where she worked on translational control and transcriptome profiling of the peripheral nervous system. Diana will start as an Assistant Professor of Neuroscience in January 2024 at UT Dallas. Her lab research will focus on axonal transport and RNA regulation in neuropathies and neurodegenerative diseases, leveraging a variety of omics and computational approaches.

Edgar (Terry) Walters, PhD
Professor
Integrative Biology and Pharmacology
Fondren Chair in Cellular Signal
Univ. of Texas Health Science Center Houston
More Than Pain: Functions and Mechanisms of Ongoing Activity in Nociceptors

Edgar (Terry) Walters received his Ph.D. in Physiology from Columbia University in 1980. In 1982 he became a faculty member at the University of Texas Medical School in Houston (now McGovern Medical School), where he is currently Professor of Integrative Biology and Pharmacology and holder of the Fondren Chair in Cellular Signaling. His early research was on plasticity in nociceptive sensory neurons related to tissue and nerve injury in invertebrate models (Aplysia, squid), with discoveries of unexpected mechanistic overlap and potential evolutionary links with neural plasticity underlying learning and memory. More recent research, with valued colleagues and collaborators, has been on the contributions of nociceptor plasticity to persistent pain in mammals, including pain induced by spinal cord injury, surgical procedures, or chemotherapy. Current emphases are on the functions and mechanisms (including specific excitability alterations and associated ion channels and cell signaling pathways) that drive spontaneous electrical activity in mouse, rat, and human nociceptors to persistently promote pain after biologically significant injuries.

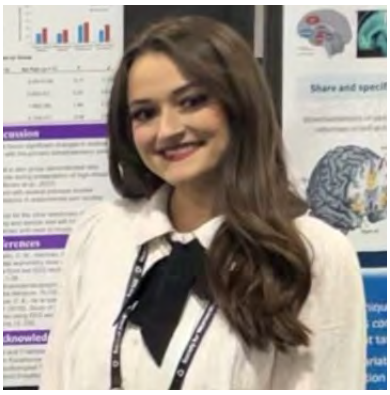
Keynote presenter

G.C.C. T PR SCHOLARS
Translational Pain Research

Steering Committee Members

Ramesh Pariyar
University of Texas Medical Branch
Postdoc Chair

Chrystine Gallegos
University of Texas Health Science Center Houston
Student Chair



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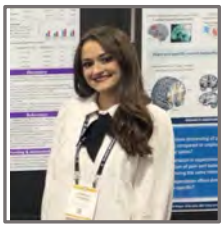

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Poster 1

Identification of Trigeminal Sensory Neurons Innervating the Temporomandibular Joint

Jessie Alfaro[1], Karen Lindquist[1], Anahit Hovhannisyan[2], Jennifer Mecklenburg[2], Armen N. Akopian[1,2,3]

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Temporomandibular joint disorders (TMJD) are functionally heterogenous conditions of the mastication system affecting the jaw joint, masticatory muscles, and ligaments. Despite approximately 5-12% of the population suffering from some type of TMJD, treatment remains ineffective. To gain an improved understanding of the pathophysiology of TMJD, the subtypes of sensory neurons that innervate the temporomandibular joint (TMJ) and connected lateral pterygoid muscle (LPM) were identified using immunohistochemistry (IHC) and various established markers. TMJ neurons were primarily C fibers (NFH-), while the LPM has about equal amounts of A fibers (NFH+) and C fibers. Approximately 1/5 of TMJ C fibers were labeled as peptidergic nociceptors and 2/5 in LPM C fibers. Of the A fibers in TMJ, most were Htr3a expressing. The A fibers in the LPM had almost equal amounts of Htr3a+ and CGRP+ expressing fibers. There was little to no MrgprD expression in both TMJ and LPM as well as minimal amounts of PV in TMJ. Our findings convey that the sensory neurons innervating the TMJ and LPM are distinct from each other, and subsequent studies with additional markers will further categorize the subtypes of sensory neurons present. Following, we will use patch clamp electrophysiology to obtain the electrophysiological characteristics of the sensory neurons innervating the TMJ. The goal of the present study is moving towards uncovering the sensory neurons responsible for TMJD pain to develop more specific and long-lasting treatment for TMJD inflicted chronic pain.

Acknowledgements: This work is supported by the National Institutes of Arthritis and Musculoskeletal and Skin Diseases UC2 AR082195 and a T32 Craniofacial Oral-Biology Student Training in Academic Research training grant.

Poster 19

Widespread Latent Hyperactivity of Nociceptors Outlasts Enhanced Avoidance Behavior Following Incision Injury

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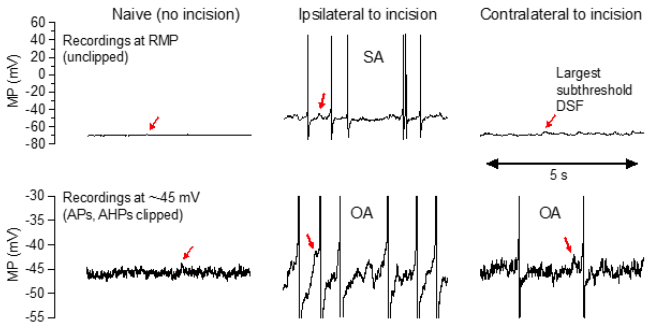
Current treatments for persistent pain are often ineffective, highlighting the need for better understanding of physiological and molecular mechanisms that may reveal better therapeutic targets. Nociceptors with somata in dorsal root ganglia (DRGs) exhibit an unusual readiness to switch from an electrically silent state to a hyperactive state of tonic, nonaccommodating, low-frequency, irregular discharge of action potentials (APs). Ongoing activity (OA) during this state is present *in vivo* in rats months after spinal cord injury (SCI), and has been causally linked to SCI pain. OA induced by various neuropathic conditions in rats, mice, and humans is retained in nociceptor somata after dissociation and culturing, providing a powerful tool for investigating its mechanisms and functions. An important question is whether similar nociceptor OA is induced by painful conditions other than neuropathy.



The present study shows that probable nociceptors dissociated from DRGs of rats subjected to postsurgical pain (induced by plantar incision) exhibit OA. The OA was most apparent when the soma was artificially depolarized to a level within the normal range of membrane potentials where large, transient depolarizing spontaneous fluctuations (DSFs) can approach AP threshold (the panel shows representative 5-second traces from somal recordings at RMP and -45 mV in neurons isolated from DRGs of naïve rats and DRGs ipsilateral or contralateral to a unilateral plantar incision made 7 days before dissociation). This latent hyperactivity persisted for at least 3 weeks, whereas behavioral indicators of affective pain – hindpaw guarding and increased avoidance of a noxious substrate in an operant conflict test – persisted for 1 week or less. An unexpected discovery was latent OA in neurons from thoracic DRGs that innervate dermatomes distant from the injured tissue. The most consistent electrophysiological alteration associated with OA was enhancement of DSFs (red arrows indicate the largest subthreshold DSFs). Other pain models, including SCI, chemotherapy-induced peripheral neuropathy, chronic constriction injury of sciatic nerve, and *in vitro* exposure to inflammatory agents (serotonin, MIF) produce similar enhancement of DSFs, suggesting that DSF enhancement is a fundamental driver of nociceptor hyperactivity in diverse pain conditions. Potential *in vivo* functions of widespread, low-frequency nociceptor OA consistent with these and other findings include amplifying hyperalgesic priming and driving anxiety-related hypervigilance. Further characterization of the molecular mechanisms underlying DSFs may yield promising targets for treating chronic neuropathic pain.

Acknowledgements: This work was supported by National Institute of Neurological Diseases and Stroke Grant NS111521 to E.T. Walters and M.X. Zhu; NS091759 to C.W. Dessauer and E.T. Walters; and the Fondren Chair in Cellular Signaling (E.T. Walters).

Poster 20

Intranasal Mesenchymal Stem Cells Require B and T cells to Resolve Chemotherapy-induced Neuropathy

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Background & Aims- Chemotherapy-induced peripheral neuropathy (CIPN) is a common, often severe side effect that considerably reduces the quality of life of cancer survivors. Neuronal mitochondrial dysfunction is a key pathogenic mechanism involved in CIPN. Currently, there are no effective FDA-approved drugs to prevent or treat this condition. We previously showed that nasal administration of mesenchymal stem cells (MSC) reverses CIPN in mice and that IL-10 signaling is critical for resolution of CIPN. The aim of this study is to investigate the cellular mechanisms underlying the therapeutic effects of MSC on neuropathic pain after chemotherapy.

Methods- Mice received cisplatin or saline for 2 cycles of 5 daily injections of 2.3 mg/kg with 5 days of rest in between. Adoptive transfer of T cells and/or B cells to mice deficient in T cells and/or B cells was performed 2 weeks before cisplatin treatment. MSC were administered nasally at 48 and 96 h after the last dose of cisplatin. CIPN was monitored before and after chemotherapy and MSC administration. Mechanical allodynia was evaluated using von Frey tests; spontaneous pain was measured using a conditioned place preference operant test. Mitochondrial function of dorsal root ganglia (DRG) was determined by Seahorse Flux analysis. Intracellular IL-10 production after MSC administration was assessed by flow cytometry.

Results- Nasal MSC administration resolved cisplatin-induced mechanical allodynia, spontaneous pain and restored mitochondrial function in DRG of wild-type mice. In contrast, MSCs did not resolve mechanical allodynia, spontaneous pain, or mitochondrial function in mice deficient in B cells ($muMt^-$), or both B and T cells ($Rag2^{-/-}$). Adoptive transfer of T cells but not B cells to $Rag2^{-/-}$ mice prior to cisplatin treatment partially reversed mechanical allodynia but not DRG mitochondrial dysfunction. Reconstitution of $muMt^-$ mice with B cells and $Rag2^{-/-}$ mice with B and T cells was necessary for MSC to fully resolve CIPN symptoms. Whereas administration of $IL\text{-}10^{-/-}$ B cells to $muMt^-$ mice failed to reverse cisplatin-induced mechanical allodynia, suggesting a role for B cell-derived IL-10 in resolving CIPN.

Conclusion- Nasal administration of MSC resolves CIPN via a mechanism involving B cells and T cells that is dependent on IL-10 signaling.

Acknowledgements- This research was supported by the National Institute of Health grant R01CA208371- Mesenchymal Stem Cells to Repair Chemobrain, grants CA 227064 and MD Anderson foundation.

Poster 21

Targeting STAT3 Signaling to Promote Recovery from Neuropathic Pain

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Increased production of Angiotensin II (Ang II) at sites of nerve injury and expression of type 2 Ang II receptors (AT2R) on infiltrating macrophages have emerged as potential drivers of neuropathic pain. The binding of Ang II to AT2R has been shown to activate STAT3 signaling, which increases inflammation, oxidative stress, and impaired barrier function in the injured nerve. We hypothesize that STAT3 signaling in macrophages is a key pathway leading to neuropathic pain following nerve injury. We have previously developed a small-molecule STAT3 inhibitor, TTI-101, that is the most promising STAT3 inhibitor currently in clinical development. Here, we aimed to determine if inhibition of STAT3 by TTI-101 reduces neuropathic pain caused by spared nerve injury (SNI) and chronic constriction injury (CCI) and promotes lasting functional recovery in mice by suppressing inflammation. SNI and CCI were carried out in 8-week-old C57BL/6 mice. Seven days following injury, animals received TTI-101 (100 mg/kg) in Labrasol/PEG-400 (vehicle) or vehicle alone by oral gavage once daily for 5 consecutive days. Mechanical sensitivity was assessed using von Frey and mechanical conflict avoidance tests. Paw placement and gait parameters were assessed using Catwalk digital gait analysis. Behavioral tests were conducted before surgery and then once a week for up to 8 weeks. After the last behavioral test, mice were euthanized, and the contralateral and ipsilateral sciatic nerves were sectioned and stained for detection of macrophage infiltration. The administration of TTI-101 for 5 consecutive days promotes the recovery of neuropathic pain induced by SNI and CCI for up to 56 days. TTI-101 reverses SNI and CCI-induced mechanical hypersensitivity; however, we do not see major gait changes between TTI-101 treated mice in comparison to vehicle-treated suggesting that this loss of pain hypersensitivity was not associated with further loss of sensation or motor coordination. Surprisingly, our IHC staining revealed that STAT3 inhibition by TTI-101 did not alter the increased macrophage density in the injured sciatic nerve of mice at 12 dpi. Considering that CD68 is a pan-macrophage marker, instead of reducing the population number, TTI-101 may be shifting the macrophage phenotype from a pro-inflammatory to an anti-inflammatory pro-resolution state, contributing to nerve regeneration to promote a long-lasting recovery. Further studies will be conducted to assess the effect of TTI-101 on inflammatory mediator production, oxidative stress, and nerve barrier function in mice subjected to SNI and CCI.

Acknowledgments: This work was supported by the Department of Defense and the Cancer Center Support Grant for the core facilities at MD Anderson Cancer Center.

Poster 2

Exploring the Connections Between Neural Oscillations, Pain, THC, and Attention: An EEG Study

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Pain in an interruptive stimulus that demands an organism's attention. However, the use of certain recreational drugs like tetrahydrocannabinol (THC) can further alter cognitive functioning. This study aims to investigate the potential effects of THC and acute experimental pain on neural oscillations and visual selective attention. We hypothesized that there would be a significant difference in gamma band frequency (31-100 Hz), between non-THC users and THC users at the prefrontal electrodes (Fp1, Fp2, F7, F8) during a baseline EEG recording. We also hypothesized that THC users would have slower reaction times on the Flanker Task during a baseline recording. Additionally, we hypothesized that THC users would have slower reaction times during concurrent administration of the Cold Pressor Task (CPT) and Flanker Task compared to non-THC users. Participants were separated into non-THC users (n=8) or THC users (n=8) and subsequently went through a baseline EEG recording followed by a cold pressor task EEG recording while completing the Flanker Task. Participants were presented with 167 trials consisting of congruent (HHHHH or SSSSS) and incongruent (HHSHH or SSHSS) stimuli presented randomly. Trials were split into three rounds, with different response deadlines (1500ms, 600ms, 300ms). After an impedance check, EEG was recorded using iMotions software on a 20 cortical electrode B-Alert x-24 EEG. Data were exported into Matlab (EEGlab) to apply a low and high pass filter (.02 - 50 Hz), assign electrode channel locations, and manually delete artifacts. Cartool was used to perform Fast Fourier Transforms. Mixed ANOVAs were computed for each electrode of interest to compare groups (THC users/non-THC users) by gamma activity over time (baseline/CPT). There was no support for the hypothesis that non-THC users would have significantly more gamma activity in the prefrontal cortex (Fp1, Fp2, F7, F8) compared to THC users in our baseline recording. Mixed ANOVAs were computed for congruent and incongruent stimuli by group (THC users/non-THC users) by Flanker Task scores over time (baseline/CPT). Contrary to the hypothesis that THC users would have slower response times and less accurate scores on the Flanker Task as compared to non-THC users, we did not find a significant difference between groups on the Flanker Task during the baseline or the CPT recording. Findings could be explained by a low sample size, and heterogeneity of cannabinoid use in the sample. Past research has shown that attention, pain, and THC can increase gamma activity, specifically in the prefrontal regions. While we did not replicate that effect in the current study, we did find that at the F3 electrode location, THC increased gamma oscillations which is consistent with past studies. Further research on the combinatorial effects of pain and THC on neural oscillatory disruption and cognitive performance is needed.

Acknowledgements: The research was supported by the Tarleton Provost's Research and Creative Activities Travel Grant and Tarleton President's Fund for Excellence.

Poster 3

Peripheral Nerve Injury Induces Long-Lasting Upregulation of Microglia and endothelial cells-Associated Translocator Protein 18kDa (TSPO) in Brain

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Neuropathic pain has an underlying neuroimmune component. However, it is a challenge to determine neuroimmune signaling in the central nervous system *in vivo*. Efforts have been made to identify biomarkers of neuroimmune activity in patients with chronic pain. TSPO 18kDa, a mitochondrial protein found in steroid-synthesizing tissues such as brain, is a possible biomarker of neuroimmune activity. Indeed, TSPO is upregulated in discrete brain regions such prefrontal, insular and cingulate cortices of patients with chronic pain. In preclinical studies, however, just a few studies have focused on TSPO expression in the brain, and none in neuropathic pain. Furthermore, the cells expressing TSPO are unknown. In this study, we explored the longitudinal expression of TSPO in vivo after a peripheral nerve injury in male and female Sprague Dawley rats. TSPO expression was monitored using positron emission tomography (PET). The cells expressing TSPO were identified using immunohistochemistry. Moreover, to test whether TSPO expression is sensitive to drug treatment, we treated nerve-injured rats with diroximel fumarate (DRF), a nuclear factor- erythroid 2 related factor 2 (NRf2) activator with potent anti-inflammatory and antioxidant properties. Beginning 4 weeks after peripheral nerve injury, TSPO was upregulated in brain regions encoding emotional and motivational dimensions of pain such as medial prefrontal cortex, cingulate cortex, and nucleus accumbens of both male and female rats. Additionally, females expressed high levels of TSPO in the ventral tegmental area and pons. TSPO mostly upregulated in microglia and endothelial cells, but not in astrocytes or neurons. The treatment with DRF for 7 days starting at week 3 post surgery showed a preventive effect on TSPO upregulation at week 4 in both males and females that coincided with attenuation of mechanical and cold allodynia. In conclusion, TSPO is upregulated in microglia and endothelial cells after peripheral nerve injury, and its expression is responsive to anti-nociceptive treatments. TSPO-PET imaging is a potential translational biomarker for neuroimmune signaling in the brain that could be used to confirm target engagement in the context of neuropathic pain.

Poster 4

Investigating the Cortical Activity Associated with the Impact of Acute Pain on Working Memory Using EEG

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Chronic pain affects about 100 million adults in the United States and has an annual cost of roughly $300 billion, outweighing the annual costs of heart disease, cancer, and diabetes combined. Pain is highly interruptive for cognitive processes, such as memory, encoding, and retrieval. This study aimed to examine how cold-induced acute pain affects working memory. Right-handed participants between the ages of 18-30 were randomly assigned into either a cold pressor task (CPT) pain stimulus group (n=11) or the control group (n=10). Participants completed two rounds of a working memory task that measured their ability to both recall and recognize the last word of presented sentences. EEG data were recorded with iMotions software and a B-Alert 20-electrode system (10-20 electrode placement referenced to mastoids) after an impedance check. Matlab, Notepad++, and Cartool were used to filter (.05-50Hz) data, reject artifacts, and compute fast fourier transforms. Band data for all 5 frequencies (0-50Hz) were extracted for all 20 electrodes. Independent samples t-tests were run to compare cortical activity (power spectral density of all EEG electrodes) by group (pain/no pain). Electrodes Fp1, Fp2, and F8 are thought to represent cortical areas that are associated with pain perception and working memory. Previous pain research also suggests most changes in brain activity recorded from EEG result in a decrease in alpha power, but findings have been heterogeneous. This study expected that a decrease in alpha power, and possible increases in delta and beta power, would occur upon administration of cold-induced acute pain. Independent samples t-tests indicated that there were no significant differences in the alpha band (8-13 Hz) across groups. The cold pressor task pain stimulus group demonstrated significantly higher gamma frequency band (31-50 Hz) activity for the electrode F7 ($p=0.035$). Gamma frequencies are associated with working memory and directed attention while F7 records data from a number of brain areas residing in the frontal cortex that are often associated with both pain processing and working memory function. These results indicate the necessity for further research examining the frequency oscillations in pain processing and working memory, specifically with the aim to understand the electrophysiology of the pain effects on working memory.

Acknowledgements: The research was supported by the Tarleton Provost's Research and Creative Activities Travel Grant and Tarleton President's Fund for Excellence.

Poster 5

A Novel High Content Screening Assay for Analgesics Utilizing hIPSC-Derived Nociceptors

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Pain is a multifaceted and subjective experience that alerts individuals to potential or actual tissue damage and triggers protective responses. However, chronic pain, which lasts beyond normal healing, impairs the quality of life and well-being of millions of people worldwide. Current pain management treatments are often inadequate, ineffective, or associated with side effects such as addiction. Moreover, very few effective analgesics options aside from opioids are currently available to circumvent the present need. This is partly due to the poor translation of results from experimental models to successful clinical trials. Therefore, robust and rigorous tools for rapidly and effectively identifying new analgesics are needed. One approach is the use of high-throughput screening (HTS). Traditional HTS methods use non-human sensory neurons or artificial systems. These methods, however, have limitations due to species differences, low output, ethical issues, and lack of physiological relevance. More advanced models that recapitulate the complexity of human nociceptors are essential. In this regard, human iPSCs are a valuable resource for generating nociceptor-like cells for HTS and, more importantly, high content screening applications. In the present study, we used a high content screening-based MultiWell MicroElectrode Array (MEA) platform to monitor the spontaneous and evoked activities of hiPSC-derived nociceptors using 48 (16 electrodes/well) and 96 (8 electrodes/well)-well plates. Using these settings, we were able to simultaneously record extracellular action potentials from multiple sensors per well, and measure parameters such as mean firing rates, spike counts and cell impedance. To optimize our experimental conditions, we adjusted culture parameters such as seeding techniques, densities, and coating substances. To evaluate the performance of our model, we calculated the classical and robust Z' factors, which are statistical measures used to assess the robustness and reliability of HTS assays. A Z'-factor between 0.5 and 1 indicates an excellent test. After fine-tuning seeding densities, we achieved nearly 100% active electrode yield (sensor functionality) from the second week of culture. We were able to maintain stable mean firing rates or total spike counts for at least two weeks with densities ranging from 35,000 to 65,000 cells/well. Using lidocaine, we obtained impressive robust Z' factors of 0.7 with 35,000 cells per well with the 48-well or a 0.6 Z' at 15,000 cells/well with the 96-well plate. Logarithmic transformations further improved Z' factor values, reaching 0.9 for both classic and robust calculations. Comparatively, we observed that hiPSC-derived nociceptors exhibited a susceptibility to inflammation upon exposure to cytokines, mirroring the natural response observed in human dorsal root ganglia. This finding suggests a strong resemblance between hiPSC-derived nociceptors and their human counterparts. Overall, the method we hereby developed, combining hiPSC-derived nociceptors and a high content screening-based MEA system, can be effectively and reliably used to screen for new therapeutic agents.

Acknowledgements: The organization's programs and core facilities are supported by the National Institutes of Health (NIH) R61 AT011938 (BJK, GD, JP).

Poster 22

Effects of Satellite Glial Cell Signaling and Stimulation on Isolated DRG Nociceptors

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While neuronal participation in signaling related to ongoing pain is well explored, the potential contribution of support cells such as satellite glial cells (SGCs) has been largely overlooked. SGCs in the dorsal root ganglion (DRG) wrap around neuron somas, and this unique morphology and placement makes SGCs opportune targets for circulating physiological signals or pharmacological manipulation. However, SGC pharmacology and the roles of SGCs in driving chronic pain remain mysterious. We hypothesize that the prolonged elevation of inflammatory signaling factors after trauma, such as spinal cord injury (SCI), stimulate SGCs and encourage SGCs to secrete neuroactive signaling molecules that physiologically alter neurons in the DRG, driving increased excitability of nociceptors and maintaining a state of chronic pain. Using bulk RNA-sequencing of our neonatal SGCs, we show that they are highly similar in expression to SGCs from adult rat DRGs. As increased ATP levels are associated with nociceptor sensitization and increased neuronal excitability, we also examined SGC responses to ATP analogues by measuring changes in the intensity of ERK phosphorylation or Fluo-8AM, with increased intensity indicating pathway activation for ERK or calcium signaling, respectively. We show that ATP analogues are key players for increasing intracellular calcium levels in isolated SGCs as well as elevating ERK signaling, which is a requirement in neurons for hyperexcitability. Additionally, we have identified an inflammatory factor, which shows sustained elevation after SCI, that increases glial fibrillary acidic protein (GFAP), a classical glial activation marker. We further show using high content microscopy that increasing GFAP in SGCs requires SMAD signaling pathway activation, but not ERK, STAT, or calcium signaling. Ongoing studies are examining the effects of how SGCs treated with inflammatory factors alter nociceptor excitability.

Poster 6

Fibroblast-derived PI16 Drives the Physiological Process of Immune Cell Recruitment and Activation During Inflammatory Response

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Slow, long-term inflammation, or chronic inflammation, is characterized as lasting for several months to years, and affects over one-quarter of United States citizens (Dydyk, 2023). The extent and impact of chronic inflammatory pain is determined by myeloid cell-driven induction and resolution of inflammation. In previous studies, we have shown that PI16 (peptidase/protease inhibitor 16), a fibroblast-derived protein of unknown function, controls neuropathic pain by facilitating crosstalk between fibroblasts at the endothelial barrier (Sighmar, 2020). We also showed that PI16 sustains Complete Freund's Adjuvant (CFA)-induced inflammatory pain (Garrity, 2023). $Pi16^{-/-}$ mice recovered more rapidly from CFA-induced hypersensitivity due to an increase in $CD206^{hi}$ (anti-inflammatory) macrophages in the DRG meninges and paw skin. However, the nature of the fibroblast-macrophage crosstalk was unclear. We next investigated PI16's interaction with myeloid cells in the CFA model. Through RT-qPCR we detected a higher expression of genes associated with myeloid cells in our $Pi16^{-/-}$ mice compared with their WT littermates following inflammation. Using immunohistochemistry, we saw reduced fibroblast marker expression following hindpaw CFA injection in $Pi16^{-/-}$ mice compared to their WT littermates. Altogether, these studies suggest PI16 drives pro-inflammatory crosstalk between myeloid cells and their surrounding environment. Collectively, our data suggest that fibroblast PI16 facilitates recruitment and polarization of pro-inflammatory myeloid cells, delaying recovery from inflammatory pain. Myeloid cells are attractive analgesic targets. Therefore, targeting PI16 may be leveraged to manipulate neuro-immune crosstalk to achieve relief of chronic pain. Our study also adds to the growing body of evidence that fibroblasts have potential for the discovery of new pain targets and therapeutics with fewer side effects for pain sufferers.

Acknowledgements: This work was funded by R01NS116704 and a Rita Allen Foundation Award in Pain (to AJS). The organizations core facilities used to carry out flow cytometry was supported by the MD Anderson Cancer Center Support Grant from NIH/MCI under award number P30CA016672.

Poster 23

Gabapentinoids Potentiate Opioid Effects by Inhibiting Depolarization-driven Opioid Resistance in Primary Nociceptors After Spinal Cord Injury

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Chronic, neuropathic pain is a common complication after spinal cord injury (SCI). A growing body of evidence has shown that chronic pain is linked to alterations of primary nociceptors, where increased excitability is linked to increased and prolonged pain. Using a rat model of SCI, we have shown that this hyperexcitability is linked to a 5-6-fold decrease in opioid inhibition of cAMP production in nociceptors isolated from naïve animals, and that membrane depolarization reduces opioid actions. In the present study, we link these effects to the activity of voltage-gated calcium channels (VGCC), which modulate both opioid sensitivity and electrical excitability in sensory neurons via the activation of components of the ERK cascade after SCI. We show that VGCC inhibitors, including gabapentinoids, can restore opioid sensitivity and electrical excitability to naïve levels after SCI, providing the first *in vitro* evidence of gabapentinoid potentiation of opioid effects. We further show that SCI effects on opioid sensitivity are restricted to non-peptidergic nociceptors, being mimicked in naïve neurons by VGCC agonists, Ca^{2+} ionophores or proinflammatory cytokines targeting this neuronal subpopulation.

Our study provides evidence of a previously unrecognized role for VGCCs after SCI, promoting nociceptor hyperexcitability while decreasing opioid sensitivity. This discovery provides a mechanistic rationale for the clinically observed potentiation of opioid effects by gabapentinoids and other VGCC inhibitors, which reverse the opioid-insensitive state induced in sensory neurons by SCI. This novel, clinically translatable knowledge may have direct application in pain therapies to improve the quality of life for patients, while contributing to the understanding of the processes driving chronic pain.

Acknowledgements**:** This work was supported by National Institute of Neurological Diseases and Stroke Grant NS091759 to C.W.D. and E.T.W., and Craig H. Neilsen Foundation Grant 545880 to C.W.D.

Poster 24

IGF1 and IGF2 Produced by Primary Sensory Neurons and Myeloid Cells Do Not Contribute to Pain Hypersensitivity Following Postoperative Pain

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Objectives: Insulin-like growth factors (IGF), including IGF1 and IGF2, and their signaling pathways are frequently upregulated in pain disorders. The role of IGF signaling in pain remains controversial. We sought to genetically delete IGF1 and IGF2 production in primary sensory neurons and/or myeloid cells (monocytes, mature macrophages, and granulocytes) to test IGF's role-generated from these cell types in postoperative pain (incision) model.

Methods: Surgical incision of the hind-paw was used as a model of surgical (postoperative) pain. Mechanical and thermal pain sensitivity were tested by von Frey and Hargreaves tests, respectively. Neutralizing antibodies for IGF1 and IGF2 were injected into mice after surgical incision of the hind paw. IGF1 and IGF2 were injected into mice prior to pain tests and *in vivo* calcium imaging of intact lumbar 5 dorsal root ganglion (DRG) using GCaMP3 fluorescent calcium indicator and confocal scanning microscopy. IGF1-fx and IGF2-fx are conditional alleles of IGF1 and IGF2, respectively, that can be deleted in primary sensory neurons and myeloid cells by Pirt-Cre and Lyz2-Cre transgenes, respectively.

Results: Neutralizing antibodies to IGF1, but not IGF2, reduced mechanical and thermal pain after surgical incision. Both IGF1 and IGF2 increased sensitivity to mechanical and thermal pain and increased neuron responses to mechanical and thermal stimulation in the DRG. Deletion of IGF1 and IGF2 in primary sensory neurons and myeloid cells slightly increased sensitivity to mechanical and thermal stimuli.

Conclusions: Both IGF1 and IGF2 which are produced by primary sensory neurons and myeloid cells cannot account for their effects on surgical incision pain and it appears not to reduce surgical pain.

Poster 25

Evaluating GPR37 Agonism as a Novel Therapy to Erase Spinal Pain Memory in a Spinal Nerve Ligation Mouse Model

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Chronic pain affects approximately 20% of the US population, contributing to the serious public health crisis presented by the ongoing opioid epidemic. Novel non-opioidal analgesics are needed to address both this health crisis and the issue of how to effectively and safely treat those with chronic pain. In order to achieve this goal, a more complete understanding of the mechanisms that underlie chronic pain and identification of the novel targets responsible for the development and maintenance of chronic pain is necessary. GPR37 is one such novel target, an orphan GPCR with only recently identified ligands, protectin D1 (PD1) and TX14A, which have been shown to have neuroprotective effects, inhibit increased nociception, and affect long-term synaptic plasticity. We propose that one of GPR37's natural functions at the spinal level is to reverse these chronic changes to spinal nociceptive circuitry that are a key mechanism underlying chronic pain. We used the L5 spinal nerve ligation (SNL) model to produce robust, long-lasting neuropathic mechanical hypersensitivity. The effect of GPR37 agonism on the sensory-discriminative domain of this hypersensitivity was assessed by von Frey filament assays. With repeated i.th. administration of GPR37 agonist TX14A and PD1, we saw a robust acute alleviation of mechanical hypersensitivity. This rapid effect did not diminish with repeated injections, indicating tolerance to repeated treatment with GPR37 agonists does not develop.
In addition, this repeated treatment gradually resolved mechanical hypersensitivity. These results suggest that repeated activation of GPR37 may attenuate mechanical hypersensitivity produced by the SNL model of neuropathic pain.

Acknowledgements: This project is supported by the University of Texas Medical Branch at Galveston and by funding from the Department of Defense.

Poster 26

Role of Protease Inhibitor 16 in Attenuating Paclitaxel-induced Neuropathic Pain

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Chemotherapy-induced peripheral neuropathy is one of the prevalent dose- and therapy-limiting side effects of several anti-cancer agents, including paclitaxel (PTX). Although very effective in blocking tumor growth, PTX induces neuropathic pain with numbness, allodynia, tingling, and burning sensations on hands and feet in 60–70% of cancer patients. Pharmacological treatment options are very limited, as there are currently no recommended treatment strategies for effective prevention of PTX-induced neuropathic pain (PINP). Therefore, this study aimed to explore the role of protease inhibitor 16 (Pi16) in attenuating PINP. It was evident from this investigation that there were no significant differences in PTX-induced mechanical allodynia observed between WT and Pi16-/- mice until day 7 post-PTX injection. Moreover, mechanical allodynia persisted for ≥8 weeks in both male and female WT mice. Pi16-/- mice, however, began recovering on day 9 and returned to pre-injection levels of mechanical sensitivity by day 17 post-PTX injection, which indicates deletion of Pi16 protects against PTX-induced persistent mechanical allodynia in experimental animals. Furthermore, an increased density of CD206+ macrophages was observed in the hindpaw skin and associated DRG of Pi16-/- mice as compared to their WT counterparts. In addition, there were no significant differences observed in the expression of inflammatory markers, i.e., TNF-α, IL-1β, iNOS, Arg-1, IL-4, and IL-10 in untreated Pi16-/- bone marrow-derived macrophages (BMDMs) as compared to the WT BMDMs. Additionally, no significant differences in the expression of Thy1, vimentin, CCL2, IL-4, and IL-6 were observed in untreated Pi16-/- fibroblasts as compared to the WT fibroblasts. However, a significant increase in the expression of TNF-α and FAP-α were noted in Pi16-/- fibroblasts, suggesting a complex role of Pi16 in acute inflammation and corresponding pain resolution. Overall, deletion of Pi16 demonstrates protection against PTX-induced pain hypersensitivity and is prospectively a potential target for managing PINP.

Acknowledgements: This project was funded by NIH (project number: R01NS116704-01)

Poster 27

Biomarkers for SCI Neuropathic Pain

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Chronic neuropathic pain (NP) is a debilitating condition that occurs in 40-70% of persons with spinal cord injury (SCI). Unfortunately, NP is frequently refractory to treatment. Given this, the identification of objective markers that can identify people at risk for developing NP may improve diagnosis, increase our understanding of the underlying pathophysiology, and may lead to the development of new treatments. An autoimmune response can be generated as a consequence of the trauma disrupting the blood-spinal cord barrier, allowing CNS proteins/peptides to enter the bloodstream (or immune cells to enter the spinal cord) where they can stimulate an immune response. We hypothesized that if autoantibodies are produced after SCI, they may have clinical utility in identifying SCI patients at risk for developing NP.

Capillary westerns were used to measure the immunoreactivity of plasma samples from SCI patients to antigens identified by a 2-D western screen. The levels of immunoreactivity in SCI patients who subsequently developed NP (as defined by the International Spinal Cord Injury Pain Classification system), and those who did not, were compared to identify prognostic biomarkers. The classification of each patient was assigned a level of confidence (high or low) by a pain specialist based on the availability of data. For this study, 64 patients were classified as having NP whereas 19 were considered negative (No NP) by 6-months post-injury. Autoantibodies that could differentiate between the two groups were used to generate a biomarker signature.

A regression model was generated that included the following independent variables: Age, Sex, Race, Ethnicity, Cervical Level Injury, Complete Injury, Injury Etiology, and Biomarker levels. The final model found that anti-BSCIP-001 (*pseudonym*) was the strongest predictor of NP, OR=1.44 (95% CI=1.10, 1.89), p=.008. Anti-BSCIP-001 antibodies were found to be “good” at differentiating between SCI patients who will develop NP and those who will not with an AUC of 0.82. Examining only those patients whose pain status was unequivocal, the AUC for anti-BSCIP-001 antibodies increased to 0.88, p=.037. The addition of anti-BSCIP-002 and anti-BSCIP-003 improved the AUC to 0.96.

A second cohort will independently validate the prognostic accuracy of an optimized assay for determining future NP after SCI. A clinical grade test that can predict the future development of NP would aid in selection of pain medications and possibly preventive measures, and would lessen the use (and misuse) of opioids as these are ineffective in treating NP.

Acknowledgements**:** This research was supported by the National Institutes of Health through the NIH HEAL Initiative under award number R61NS113329. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or its NIH HEAL Initiative.

Poster 7

Cell-Type Map of Pain States in the Spinal Cord

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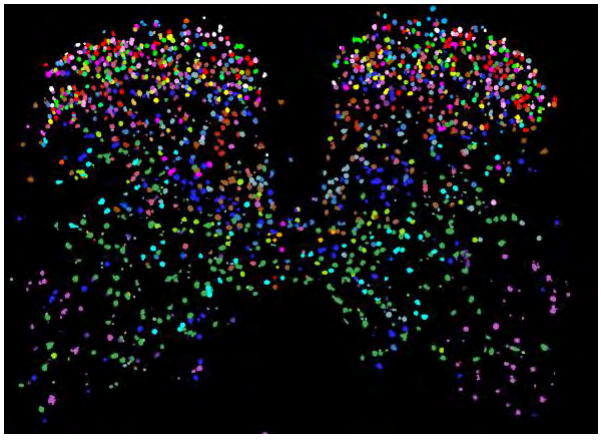
The spinal cord is the first central pain relay that is essential for mediating most peripheral somatosensory states. Recent spinal cord cell-type atlases have revealed a high degree of cell-type diversity in the mammalian spinal cord, with over 40 transcriptomic neuron types detectable in this structure. However, how different somatosensory states are mapped to spinal cord neural classes and which neuron types relay pain information to higher order pain centers remain poorly understood. Here, we developed a high-throughput and unbiased spatial transcriptomics-based approach to identify which neural classes are engaged by which pain states. First, we deployed a panel of different pain and non-noxious somatosensory assays and examined the resulting populations of activated neurons in the dorsal horn of the spinal cord using the immediate-early gene Fos. Second, because existing atlases lacked many known cell types, we generated a high-quality atlas of spinal cord neuron types using single-nucleus RNA-sequencing, which revealed at least 74 distinct neuron types. Most of the known genetic markers for pain and non-pain somatosensory processing labeled dozens of neuron types in our cell type atlas, indicating the need for functional annotation of the atlas in an unbiased manner. Based on the atlas, we designed a spinal cord probe set for Multiplexed Error Robust Fluorescent In Situ Hybridization (MERFISH) spatial transcriptomics mediated stimulus-to-cell-type mapping that included a panel of immediate early gene probes to identify activated neural classes. This allowed us to identify somatosensory stimulus-activated neural classes in intact tissue with higher sensitivity and without cell fall-out problems than previous approaches. We show that distinct pain and non-pain states engage a unique and partially overlapping set of spinal cord neuron types, with half a dozen to a dozen cell classes engaged by each pain/somatosensory state. This establishes the cell-type logic of how somatosensory states are represented in the spinal cord. Finally, we used retrograde viral tracing with MERFISH to reveal the diversity and transcriptomic identity of the spinal cord output neurons. In summary, our work reveals an unbiased cell-type map of pain and non-pain states as well as the anatomical output logic of the mammalian spinal cord.



Acknowledgements: This work is supported by UTSW Endowed Scholars Program.

Poster 28

Charting the Course: Exploring Traumatic Spinal Cord Injury Neuropathic Pain Management Strategies

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The U.S. confronts an opioid crisis that causes over 220 deaths per day from drug overdoses. In response, healthcare professionals strive to balance pain management for traumatic spinal cord injury (SCI) patients without overprescribing opioids. In addition to musculoskeletal/nociceptive pain, about 50% of these patients develop neuropathic pain (NP), which is generally refractory to opioids. The current go-to guideline for treating SCI-NP is the *CanPain SCI practice guidelines for rehabilitation management of neuropathic pain* (CanPain).

We aimed to determine the adherence rate to the CanPain SCI-NP medication treatment guidelines for patients diagnosed with SCI-NP at one-month post-SCI.

Traumatic SCI patients with a diagnosis of SCI-induced NP at one month post-injury enrolled. Patients completed the Self-report Leeds Assessment of Neuropathic Symptoms and Signs (SLANSS) and visual analog pain intensity score. The Medication Quantification Scale III (MQSIII) quantified their active medication regimen. Utilizing the CanPain guidelines, we classified medication by first, second, third or fourth-line treatment. Following medication classification, each patient's treatment was categorized as *CanPain Compliant* or *CanPain Non-compliant* based on adherence to guidelines. Group comparisons were performed using the Student's t-test or Mann-Whitney Rank Sum Test, SigmaPlot (Systat Software, San Jose, CA). A p-value of 0.05 was considered significant.

We evaluated 44 SC-NP patients' treatment. They were an average age of 43 ± 8 years, and 82% were male. Patients' treatment adhered to CanPain guidelines in 40/44 (90% of cases). The medications most commonly prescribed were acetaminophen, lidocaine patches, and gabapentin was the gabapentinoid of choice. At one-month post-injury, 45.5% were prescribed opioid medications (primarily tramadol), with no significant difference in the rate of opioid prescription between CanPain-compliant vs non-compliant groups (48.6% vs 33.3%, p = 0.48). MQSIII did not differ between the compliant and non-compliant groups, 21.53 ± 9.6 vs 16.31 ± 8.76, p=0.15. The median pain intensity score between compliant (7.0 (IQR 4.0-9.0)) and non-compliant (5.0 (IQR 1.5-8.0), p = 0.36) groups, and the median SLANSS scores for those in compliance 14 (Q12.3-16.3) vs non-compliance 15 (IQR 0-17.3), p=0.95 did not differ.

Our data indicate adherence to guidelines, not prescribing high-impact opioids if unnecessary, was achieved in the cases studied. There was no group difference between the pain intensity or the SLANSS, indicating that pain control was similar between the compliance groups. Almost half of SCI-NP patients continue to require relief for musculoskeletal and nociceptive pain. Future studies on the six-month medication rate will determine rates of chronic opioid use.

Acknowledgements: This research was supported by the National Institutes of Health through the NIH HEAL Initiative under award number 1R61NS113329-01.

Poster 8

Investigating the Role of PRDM12 in Adulthood

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The peripheral nervous system contains numerous cell types, each responsible for detecting unique sensations such as noxious stimuli, temperature, touch, itch, and proprioception. Maintaining these cell identities is crucial for proper function, yet the mechanisms governing their identity maintenance remain unclear. This gap in knowledge impairs our ability to rationally design ways to differentiate and maintain specific sensory neuron cell types *in vitro* which could be used to understand their etiology and develop targeted therapies for somatosensory disorders. This project investigates the role of the transcription factor PRDM12, which is required for the development of nociceptors, during adulthood and tests the hypothesis that PRDM12 regulates the maintenance of nociceptors by repressing transcription of alternate cell fate markers. Overall, this project will progress the field's understanding of how somatosensory neuron identity is maintained, specifically as it pertains to nociceptors.

Acknowledgments: Rita Allen Foundation, O'Donnell Brain Institute Sprouts Grant

Poster 29

Unveiling Antibodies to MAP4K3/GLK: A Breakthrough Biomarker for Neuropathic Pain in Chronic Spinal Cord Injury Patients

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Background: 40-70% of people with traumatic spinal cord injury (SCI) develop chronic neuropathic pain. Neuropathic pain, described as “pins and needles”, “electric shock-like”, and “burning” pain, contributes to suffering, poor rehabilitation outcomes, and reduced quality of life. Currently, available neuropathic pain medications produce undesirable side-effects and have limited efficacy. Biomarkers for neuropathic pain can help phenotype patients, objectively identify candidate patients for drug trials, and serve as a proxy measure for medication selection and responsiveness. Autoantibodies are associated with multiple pain-producing autoimmune diseases and may be useful as biomarkers for neuropathic pain after SCI. We conducted a pilot study to determine whether levels of antibodies to MAP4K3/GLK distinguish SCI patients with chronic neuropathic pain from those without neuropathic pain.

Objectives: The study aimed to investigate the levels of antibodies to MAP4K3/GLK, a candidate autoantibody discovered during biomarker screening, in plasma samples of patients after chronic SCI with or without neuropathic pain and healthy volunteers.

Method: Antibodies to recombinant human protein MAP4K3/GLK (ThermoFisher PV6350) were measured by capillary western blotting (ProteinSimple, San Jose, CA) in 18 plasma samples of SCI patients with neuropathic pain (pain n=6), SCI patients without neuropathic pain (no pain n=6) and healthy volunteers (HV n=6). Peak detection, the area under the curve (AUC), was calculated using Compass software (ProteinSimple, San Jose, CA). Results were normalized between plates using standard curves and expressed as ng/ml of MAP4K3/GLK protein. Levels of antibodies to MAP4K3/GLK were compared by one-way analysis of variance.

Results: There were no differences in sex (5 males and one female/group) or age (p=0.2) between the three groups. Time post-SCI did not differ between injured groups (15.4 ±13.4 years vs 20.3±10.8 years, p=0.5). Levels of antibodies to MAP4K3/GLK were significantly higher in the pain group (6.16 (IQR 4.5 - 7.7) ng/mL) compared to both no pain (1.9 (IQR 0.37 – 5.47) ng/mL) and HV (0 (IQR 0 -2.4) ng/ml) groups ($H(2) = 28.03$, $p<.001$).

Conclusion: Antibodies to MAP4K3/GLK present in human plasma distinguished the SCI patients with chronic neuropathic pain from SCI without neuropathic pain and HV. MAP4K3/GLK is involved in apoptosis, autoimmune systemic lupus erythematosus (SLE), and Still’s disease. While it is unclear whether the presence of antibodies to MAP4K3/GLK has a biological role in SCI neuropathic pain, this pilot study indicates it may have utility as a diagnostic maker. Future studies will validate the presence of the antibody in larger groups.

Acknowledgements: This research was supported by the National Institutes of Health through the NIH HEAL Initiative under award number 1R61NS113329-01.

Poster 37

Selective Silencing of Spinal Output Pathways

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The perception of pain is multidimensional; upon pinch of our skin, we recognize the location and identity of the stimuli (discriminatory), turn our body and head towards the stimuli (motor), and feel bad/hurt (emotional). In other words, pain perception involves multiple distinct aspects of sensation and reaction. The complexity of pain perception may stem from the unique "modular" organization of the anterolateral pathway, a major ascending spinal pathway that conveys a variety of somatosensory signals from the spinal cord to multiple regions in the brain. The anterolateral pathway consists of multiple independent ascending modules - distinct spinal projection neuron (PN) subtypes - innervating different brain targets, including the pons, midbrain tectum, and thalamus. Thus, these distinct spinal PNs innervating different brain target regions may contribute to different aspects of pain sensation. To test this idea, we need tools that enable the silencing of distinct spinal PN subtypes in an acute, selective, and stoichiometric manner. To this end, we have generated and characterized an axon terminal silencing mouse line that allows us to selectively silence distinct spinal PNs innervating different brain target regions of the anterolateral pathway. We first used this mouse line to examine the effect of silencing spinal PNs innervating the lateral parabrachial nucleus of the pons on behavioral responses to noxious thermal stimuli.

Acknowledgements: The organization's programs and core facilities are supported the Cancer Prevention and Research Institute of Texas (CPRIT).

Poster 10

Mechanism of NK1 Receptor Antagonists in Spine-Surgery Induced Sensitization in Mice.

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Background: Back pain is a leading cause of healthcare costs, impacting both individuals and healthcare systems. As many as 1% to 3% of adults in the United States undergo spine surgery annually, with this number likely to rise further in the future. Unfortunately, an estimated 10-40% of patients following back surgery experience what is known as failed back surgery syndrome (FBSS). This means that a significant portion of people undergo back surgery without finding a definitive cure, highlighting the importance of pre-operative efforts to reduce the development of FBSS.

Our previous study demonstrated that laminectomy induced pain hypersensitivity in the hind paw of mice, suggesting central sensitization. This hypersensitivity was mitigated by a novel approach using intraoperative spinal cord stimulation (SCS). Interestingly, intrathecal injections of the NK1 receptor agonist L-760735 prior to laminectomy also led to decreased postoperative pain. Based on these intriguing findings, we propose to investigate the expression of the NK1 receptor in the lumbar spinal cord using Western blot analysis. Through this analysis, we aim to elucidate whether pre-emptive administration of NK1 receptor agonists achieves similar pain-relieving effects as intraoperative SCS and explore the potential mechanisms underlying this phenomenon, with a specific focus on its feasibility as a therapeutic strategy.

Methods: Left-sided laminectomy was performed in mice at the T13 level. Prior to the laminectomy, mice were given intrathecal injections of normal saline and NK1 receptor antagonist L-760735 at the L4-5 level. One day post-surgery, spinal cord tissue was extracted from the mice and prepared for Western blot. Anti-NK1R antibody was used for specifically targeting protein receptors. After sample preparation, electrophoresis was performed according to sample loading quantities calculated by BCA. Following membrane transfer, non-specific antibody binding was blocked using 5% skim milk. The primary antibody was incubated with the membrane, followed by the secondary antibody. After protein detection using fluorescent substrate, the image was captured and analyzed using ImageJ.

Results: While data and Western blot collection are ongoing, preliminary studies and available data provide initial support for our hypothesis that the control group receiving intrathecal saline injections prior to laminectomy will exhibit a notable difference in NK1 receptor expression.

Conclusion: The preliminary studies suggest the involvement of receptor antagonists in the mechanism of spine-surgery induced central sensitization. We hypothesize that our Western blot results may aid in elucidating the mechanism by which intraoperative spinal cord stimulation mitigates postoperative pain.

Poster 30

Characterizing the Transcriptomic Profile of Human C2 Dorsal Root Ganglia from Patients with Neck Pain using Next Generation Sequencing Technologies

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Neck pain is a highly prevalent condition and a leading cause of disability with a disease burden of roughly 134.5 billion dollars annually. Current pharmacological treatments for chronic neck pain, like opioids, have limited efficacy and cause dose-limiting adverse side effects. Alternative treatments include cognitive-behavioral therapy, steroid injections, nerve ablations, and surgery, such as the Atlanto-axial (C1-C2) fusion surgery. Despite our current efforts, many patients continue to suffer from daily pain, decreasing their quality of life. Identifying the molecular mechanisms driving human chronic neck pain will allow us to better address this health condition by developing target-specific therapeutics. Therefore, we aimed to characterize and compare the transcriptomic profile of human cervical (C2) Dorsal Root Ganglia (DRG) from patients with acute and chronic neck pain using next-generation sequencing technologies.

We retrieved fresh frozen DRG from patients with acute pain (<3 months) or chronic pain (≥3 months) undergoing C1-2 fusion surgery. The patients completed quantitative sensory testing (QST) and self-report measures of pain-related outcomes before the surgery. Next, the samples were assessed for quality control and sequenced. We complemented the whole-tissue resolution results from bulk RNA sequencing (n=17; 10 acute pain, 7 chronic pain) with the near single-cell resolution from 10X genomics Visium spatial sequencing technology (n=13; 6 acute pain, 7 chronic pain). Using the computational packages CONOS and scCamel in R we classified neuronal populations in the C2 DRG by comparing their molecular landscapes to those previously described in lumbar human DRG.

We found 66 genes differentially expressed in C2 DRG from patients with chronic pain, compared to patients with acute pain. Among 33 significantly upregulated genes, we identified GFRA3, GRIK3, and ADGRB3. These genes are associated with osteoarthritis pain and cell-to-cell communication. The integrated results from both sequencing techniques suggest that the upregulation of these genes may sensitize nociceptors. Overall, our data shows significant differences in the transcriptomic profile of the patients with chronic versus acute neck pain, revealing potential changes to neurons or other cell types in the C2 DRG. We will continue to further characterize the molecular landscape of C2 DRG to unveil molecular targets for existing or new therapeutic strategies to resolve chronic neck pain.

Acknowledgments: This project is supported by NIH grants U19NS130608 to TJP and MC, and NIH 1R01AR078192-01A1 to MC, CPH, and TJP

Poster 11

Analgesic Signaling in *Drosophila* Larvae

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Like humans, *Drosophila* has evolutionarily conserved nociceptive pathways to detect potentially damaging stimuli and initiate escape responses. *Drosophila* larvae exhibit a nociceptive escape response (aversive rolling) to harmful stimuli. It is unclear whether *Drosophila* has a functional analgesic signaling pathway shared with humans. Our recent evidence suggests a putative G-protein coupled receptor orthologous to somatostatin receptor-2 (SSTR2)- allatostatin receptor 1 (AstCR-1) is responsible for opioid-induced analgesia (OIA). Interestingly, previous work demonstrated SSTR2 binds morphine within vertebrate cells. Our goal is to establish a genetically tractable *Drosophila* model of analgesia- dampened nociceptive responses. We used a controlled heat probe behavior assay to measure larval nocifensive responses to noxious heat after consumption of non-lethal doses of opioids. We found that opioid consumption leads to analgesia-reduced responsiveness to highly noxious thermal stimuli. We further demonstrated that AstCR-1 is genetically required for thermal OIA. Expression analysis using an *AstC-R1$^{T2A\text{-}Gal4}$* line revealed that AstC-R1 is expressed within the larval peripheral and central nervous systems (CNS). Using the GFP-reconstitution across synaptic partners (GRASP) labeling technique we identified synaptic connections between class IV multidendritic sensory neurons (which do not express AstC-R1 but do mediate thermal nociception) with AstCR-1-expressing ventral nerve cord neurons known to be situated within the nociceptive circuit- basin interneurons. Preliminary genetic experiments using an in vivo tissue-specific RNAi approach suggest that these basin interneurons are the functional site of AstC-R1-mediated thermal analgesia. We are currently testing whether other AstC-R1-expressing cells also play a role in thermal OIA as well as exploring the possible binding and activation of AstC-R1 by both endogenous peptide ligands (AstC) and exogenous opioids. Our results indicate *Drosophila* larvae can serve as a functional model to study OIA and will likely be useful for studying the evolution and basic function of this important biology.

Poster 12

Evaluation of MIF in Mediating Stem Cell Analgesia in a Model of Orofacial Pain

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Despite the efficacy of root canal treatments at eliminating pain associated with apical periodontitis (AP), a form of infection-induced pain, an estimated 2 million patients will experience persistent pain six months after treatment. This pain reduces quality of life and increases the intake of analgesic drugs. However, chronic use of currently available analgesics is accompanied with adverse effects. Therefore, development of a novel class of analgesics that can prevent the development of persistent dental pain, with no adverse effects, will provide relief to millions of patients. Stem cell-induced analgesia is a promising therapeutic that has shown efficacy in pre-clinical and clinical studies. Our preliminary data demonstrates that i.v. injections of human stem cells of the apical papilla (hSCAP) reverses mechanical hypersensitivity in a model of AP. Additionally, our data suggests the cytokine macrophage migration inhibitory factor (MIF) may be mediating this effect. Lasty conditioned media from primed hSCAP attenuates capsaicin (CAP) evoked Ca2+ response from trigeminal ganglia neurons and is reversed with pre-treatment of a MIF antibody. This data supports a novel direct hypothesis of stem cell anti-nociception, possibly mediated by MIF. We hypothesis that MIF is mediating hSCAP-induced anti-nociception. Pulp exposures of maxillary left 1st molars of mice were performed to induce AP. Mice received i.v. injections of hSCAP or Saline once a week for three weeks after pulp exposures. Conditioned placed preference was then done to evaluate the role of an intra-oral injection of a MIF antibody in reversing hSCAP anti-nociception. Additionally, hSCAP was treated with CRIPSR to develop a MIF knockout cell line. This cell line was used to generate conditioned media for in vitro Ca2+ imaging experiments to evaluate the role of MIF in mediating attenuation of CAP evoked Ca2+ responses. Mice receiving an intra-oral injection of a neutralizing MIF antibody displayed higher preference for a morphine paired chamber than those given an IgG control. Additionally, conditioned media from a MIF knockout hSCAP cell line saw higher Ca2+ accumulation when compared to both a non-treated and non-targeting control cell lines. This data provides evidence for a novel, previously undiscovered anti-nociceptive role of MIF in mediating hSCAP-indued pain relief.

Acknowledgments: Research reported in this poster is supported by NIDCR F-30 DE033587, T-32 DE14318, R01 DE031352, and R03 DE027780

Poster 13

Activation of Pro-Inflammatory Keratinocyte-Macrophage Axis Controls Resolution of Painful Chemotherapy-Induced Peripheral Neuropathy

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Painful Chemotherapy-Induced Peripheral Neuropathy (CIPN) is a main cause for chemotherapy dose reduction and/or treatment cessation, leading to increased cancer mortality. In addition, surviving patients have reduced quality of life. It is known that a subset of painful CIPN patients will have a resolution of pain while some continue to have persistent pain. The mechanisms that mediate pain resolution are unknown and constitute a large gap of knowledge. Using Paclitaxel (PTX), we developed a resolving painful CIPN by measuring behavior (Von Frey) over time then performed bulk RNA sequencing at the periphery (hind paw and DRG) at multiple time points. We found in the hind paw preceding pain resolution; an up-regulation of genes related to the immune system (particularly myeloid related genes). This led us to hypothesize that inflammatory up-regulation at the site of pain promotes pain resolution. To test this, we ablated CD11b+ and Iba1+ cells using the diphtheria toxin/receptor system and found that CD11b+ depletion led to pain persistency. Using flow cytometry, we found that within both the hind paw and DRG that there were no quantitative changes in immune cell populations, suggesting qualitative changes in myeloid cells. Evaluating myeloid related genes, we saw an upregulation of CCR2 within the hind paw during resolution time course. This led us to hypothesize that macrophage activation via CCL2/CCR2 axis activation promotes pain resolution. Using both pharmacological (anti-CCR2 antibody) and genetic (CCR2 KO) means we found CCR2 is necessary for pain resolution. Through immunohistochemistry, we found CCL2 is expressed in keratinocytes and through RNA sequencing found an upregulation of CCL2 in keratinocytes after PTX treatment. We performed conditional knockout of CCL2 in KRT14+ keratinocytes and also saw that this was required for pain resolution. Lastly, to test if CCL2 is sufficient for pain resolution, we first developed and characterized a model of persistent painful CIPN, then applied recombinant CCL2 intraplantar and/or intrathecally and found that intra-plantar CCL2 treatment is sufficient to resolve pain. We also saw that treatment with intraplantar IL-4+IL-10 did not reverse this persistency, suggesting the actions of CCL2 are not acting through an anti-inflammatory mechanism. Overall, this study points to a novel mechanism at the site of pain for the permanent resolution of painful CIPN.

Acknowledgements: Research was supported by National Institute of Health (NIH)

Poster 14

The Role of NR1 and NR2 Receptor Antagonism in the Mitigation of Spine Surgery Induced Sensitization in Mice

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The rising rate of spine surgeries correlated with low back pain incidence in the United States is associated with the risk of developing chronic pain, particularly in the form of failed back surgery syndrome (FBSS) which presents significant management challenges. With the current limited options to treat FBSS-related pain, there is a critical need to elucidate the mechanism of FBSS development after surgery. Therefore, managing postoperative pain may be crucial in mitigating this issue, as intense postoperative pain is a known risk factor for chronic pain following surgery.

In our previous studies, we developed laminectomy-induced pain hypersensitivity model in mice, which might be consistent with central sensitization. Although we found that intraoperative SCS significantly reduced hind paw mechanical hypersensitivity, the further exploration of the mechanism of this model is needed. This also suggests a potential preventive effect against postoperative pain. In our preliminary data, intrathecal injection of the NMDA receptor antagonist (AP-5) significantly reduced postoperative pain, as assessed using von Frey filament testing. We hypothesize that the laminectomy-induced pain hypersensitivity in hind paws is associated with NMDA receptors. We will conduct immunohistochemistry to assess the expression and localization of (phosphorylated) GluN1 and GluN2B subunits of the NMDA receptor in the lumbar spinal cord in mice. This analysis will provide insights into the molecular mechanisms underlying central sensitization after spine surgery and the potential of SCS and NMDA receptor antagonism as therapeutic strategies.

To model spine surgery-induced central sensitization, we performed a left-sided T13 laminectomy in mice. Prior to laminectomy, mice were intrathecally injected at the L5-L6 level with the NMDA receptor antagonist AP5 and normal saline. Spinal cord segments (T12-L1) were dissected and processed for immunohistochemical staining. Sections were blocked in normal serum, then incubated with primary antibodies against the GluN1, GluN2B, followed by incubation with fluorophore-conjugated secondary antibodies. Control sections underwent the same process without primary antibody incubation. Immunoreactivity was visualized and analyzed using fluorescence microscopy and ImageJ software.

Currently data is still being collected for our immunohistochemistry and Western blots. However, with our preliminary studies and current limited data, we observed that the control group undergoing LMX with saline intrathecal injections exhibited differences in NMDA receptor quantity (e.g., increased protein expression and/or phosphorylation). This finding suggests a potential hypothesis that NMDA receptors are associated with the mitigation of LMNx-induced central sensitization, possibly mediated by intraoperative spinal cord stimulation. Our preliminary Western blot results suggest a correlation between the observed mechanism of the receptor antagonism and the expected central sensitization induced by spine surgery. We anticipate that the dorsal horn tissue samples obtained for protein qualification with immunochemical staining can be further utilized to screen for additional cellular targets of interest in future studies.

An Intervention for Alleviation of Post-Mastectomy Neuropathic Pain Following Lymph Node Using Individualized fMRI Neuromodulation.

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Although 85% of patients with BCA currently live >5 years (~4 million survivors worldwide) due to improved treatment, 60% of them develop chronic post-mastectomy pain syndrome (PMPS). PMPS is caused by peripheral and primary afferent receptors' sensitization, producing crippling neuropathic pain on the thorax, shoulder, and/or arm. PMPS is exacerbated by inspiration, expiration, and trunk movement. This results in 54% of PMPS patients physical and mental well-being is detrimental affected Physical therapy and pharmacological agents do not effectively alleviate PMPS. The Papageorgiou Lab has developed a safe, non-invasive, individualized intervention (U.S. Patent No. 16/954,256), which targets each patient's unique anatomical and functional brain areas (1mm resolution) activated in response to arm motor and sensory/pain stimulation. We apply our Individualized fMRI-closed-loop NeuroModulation (iNM) of central pain and motor system mediators to alleviate PMPS. Our intervention extracts optimal fMRI signals, as a function of each breast cancer patient's brain motor and pain network spatial extents and signal intensity with the goal to effectively manage arm and torso mobility and alleviate neuropathic pain. We have developed two iNM interfaces to provide this individualized neurorehabilitation to patients with PMPS: 1. An interface that upregulates each patient's unique anatomical and functional cortical and subcortical motor networks to strengthen arm movement, while the patient engages in arm movement; 2. An interface that downregulates each patient's unique anatomical and functional cortical and subcortical pain networks to alleviate neuropathic pain during arm movement. Our individualized iNM guides and regulates neural response patterns by modulating the flow of oxygenated hemoglobin (HbO2) in targeted motor and pain areas. Through a visual interface, the patient can view changes in signal intensities and brain network - extents that correspond to arm-shoulder-torso motor and pain control. Although we don't have data yet on PMPS patients, we have provided iNM to 30 healthy participants to test feasibility and to a chronic lower cranial neuropathy patient with motor and sensory/pain impairments associated with swallowing and tongue movement. The patient underwent 6 iNM sessions and showed significant changes in motor control and pain alleviation ($p<0.001$):1. Increase in oxygenated hemoglobin (HbO2) signal intensity by 84%; 2. Enhanced speech intelligibility by 60%; 3. Decrease in self-reported neuropathic pain by 60%. Our immediate goal is assessing iNM efficacy in breast cancer patients to alleviate neuropathic pain and strengthen arm movement.

Acknowledgments: This study is funded by grants to T.D. Papageorgiou: McNair Medical Institute, Robert and Janice McNair Foundation, TIRR/Mission Connect, IP Award, The Institute of Rehabilitation Research, Breast Cancer SPORE/BCM, Center for Alzheimer's and Neurodegenerative Disease, Jan and Dan Duncan Neurological Research Institute, Naman Basic Science Faculty Award, Baylor College of Medicine, NIH-F32, NEI; NIH-F32, NINDS

Poster 15

Enhanced Efferocytosis Alleviates Neuropathic Pain and Promotes Clearance of Apoptotic Cells in the Injured Nerve

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Chronic inflammation is an important contributor of the development and maintenance of neuropathic pain. Upon nerve injury, damaged cells secrete pro-inflammatory signaling molecules that recruit circulating immune cells to the site of injury. The persistent inflammation can activate nociceptive hypersensitivity through immune mediators and result in chronic pain. The resolution of inflammation and maintenance of tissue homeostasis depends upon the clearance of apoptotic cells by infiltrating phagocytes through a process known as efferocytosis. Macrophages are the key cells responsible for the efferocytotic clearance of damaged cells through different specialized receptors like tyrosine kinase MER (MerTK). However, MerTK can be cleaved in an inflammatory environment, dysregulating efferocytosis. In this study, we used knockin mice which are resistant to proteolytic cleavage of MerTK ($Mertk^{CR}$ mice) to test whether a cleavage resistant MerTK can enhance the efferocytosis of damaged cells by macrophages and thus help in the alleviation of neuropathic pain. Following chronic constriction injury (CCI) of the sciatic nerve, Male $Mertk^{CR}$ mice had higher von Frey thresholds, compared to wild-type littermate controls. We confirmed that MerTK expression on macrophages was downregulated in wild-type mice compared to $Mertk^{CR}$ mice. At the nerve injury site, we observed that apoptotic markers (caspase 3 and cleaved caspase 3), as well as necroptotic markers (pRIPK3), were decreased in $Mertk^{CR}$ mice, compared to wild-type controls, as assessed by western blot analysis and immunohistochemistry. Reciprocally, cleaved, and total caspase 3, and pRIPK3 levels were increased when Mertk was knocked out in macrophages ($Lysm2^{Cre/-}Mertk^{fl/fl}$ mice). Efferocytosis was assessed as a percentage of $TUNEL^{+}$ live macrophages through flow cytometry. We observed an increase in $TUNEL^{+}$ live macrophages in $Mertk^{CR}$, compared to wild-type mice, suggesting that the presence of cleavage-resistant macrophages enhances the efferocytotic clearance of apoptotic cells at the site of nerve injury in $Mertk^{CR}$ mice. These results indicate that MerTK is downregulated at the peripheral nerve injury site, and its protection from cleavage accelerates the clearance of apoptotic cells to ultimately alleviate neuropathic pain.

Acknowledgment: This work is supported by National Institutes of Health Grant R01 NS126252-01.

Poster 32

Spatial Transcriptomics Identifies a Distinct Neuronal Signature of Human Sympathetic Chain Ganglia (SCG)

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The sympathetic chain ganglia (SCG) are a set of autonomic ganglia that extend from the base of the skull to the coccyx. SCG neurons receive input from the spinal cord and extend axons through peripheral nerves to control the “fight-or-flight” response. Symptoms of sympathetic dysfunction, ranging from cardiovascular issues to incontinence, are common in many diseases and disorders such as diabetes, infections, and neurological conditions. Since the SCG and dorsal root ganglia (DRG) share common anatomical landmarks, sympathetic nerve block can be an effective method for controlling ectopic nerve activity contributing to neuropathic pain, particularly in complex regional pain syndrome (CRPS). We **aim** to use spatial transcriptomics to characterize the transcriptomic signature of SCG neurons. We hypothesize that SCG neurons have a unique gene expression profile that differs from DRG neurons and that these differences can be exploited to develop novel therapeutics with limited side effects. Furthermore, using SCG from diabetic and non-diabetic individuals, we aim to identify a distinct neuronal gene set corresponding to diabetes. We obtained human lumbar (L2) SCGs from organ donors that were then cryo-sectioned and stained with hematoxylin and eosin (H&E), followed by Visium Spatial Transcriptomics kit (10X Genomics) for gene sequencing. Computational analysis consisted of using 10x Loupe Browser to select neuronal barcodes, Pycharm to sort gene expression and Seurat to analyze and identify neuronal clusters. We identified 4 neuronal clusters in lumbar SCGs that all express canonical sympathetic neuronal markers (*TH*, *DBH*, *PHOX2B*). When comparing DRG neurons to SCG neurons, we found that SCG neurons do not express *SCN10A* (Nav1.8) but express *SCN9A* (Nav1.7), both of which are commonly used markers of nociceptors. Diabetic SCG neurons have significantly elevated expression of insulin-linked autophagy genes like *DEPP1*, and metabolism genes like *ADH1B*, compared to non-diabetic SCG neurons. Human SCG neurons cluster into unique gene populations that are transcriptionally distinct from sensory neurons of the DRG. Enrichment of insulin-linked and metabolism-related gene sets suggests diabetes influences the transcriptome of SCG neurons. This data provides an invaluable resource to identify and target the sympathetic nervous system for treating autonomic dysfunction.

Acknowledgements: We would like to thank the donors, their families, and the Southwest Transplant Alliance. This project was funded by Merck & Co, National Institutes of Health (U19 NS130608, R01 DK134893), and University of Texas at Dallas Undergraduate Research Student Award.

Poster 16

Pathology Activated Prodrugs Targeting Nrf2 for the Treatment of Neuropathic Pain

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The antioxidant nuclear factor erythroid 2-related factor 2 (Nrf2) is a desirable therapeutic target for neuropathic pain. However, systemically distributed Nrf2 activators have adverse systemic side effects due to the ubiquitous expression of Nrf2, indiscriminate interactions with protein thiols, and activity at other receptors. To overcome the detrimental side effects of fumarates, we created a prodrug for MMF that selectively activates Nrf2 at sites of oxidative stress associated with neuropathic pain. Compound 1c, DRF, or vehicle were orally administered daily, beginning 6 months after spared-nerve injury (SNI) or sham surgery. Peroxide decomposition catalysts (PDCs) were administered intrathecally to decompose endogenous peroxides. The von Frey test, brush test, and conditioned place preference task were used to measure evoked and ongoing pain. Western blot and qPCR were used to quantify Nrf2 translocation and antioxidant transcripts in the ipsilateral L4/5 dorsal root ganglia (DRG). Oral treatment with compound 1c reversed evoked and ongoing pain in the SNI model and preferentially increased Nrf2 nuclear translocation in the ipsilateral L4/5 DRG, in a peroxide sensitive manner as PDCs blocked the activation of Nrf2 and prevented pain relief. Compound 1c failed to reverse allodynia in Nrf2 deficient SNI mice compared to WT SNI mice, confirming that Nrf2 is the therapeutic target. In contrast to DRF, compound 1c did not reduce plasma glutathione levels, or induce flushing. These results highlight the potential for compound 1c to reverse neuropathic pain via Nrf2 with in mice with reduced side effects.

Acknowledgements: This work was supported by National Institutes of Health grants RF1NS113840 (P. Grace), UG3NS127251 (A. Abell, P. Grace), and in part by P30 CA016672 (animal housing and care in the MD Anderson Research Animal Support Facility); Australian Research Council grants CE140100003 and DP180101581 (A. Abell), and a Rita Allen Foundation Award in Pain (A. Shepherd).

Poster 33

PACAP-Mediated Activation of MRGPRX2$^+$ Meningeal Mast Cells Leads to Migraine-like Pain

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Background: As one of the key effector cells in the inflammatory process, mast cells have essential functions in allergies and fighting infections. More recently, mast cells have been shown as important links between the nervous and immune systems. Mast cells can be found in close proximity to peripheral nerve endings and, due to their significant spatial advantages over other immune cells, are one of the first to respond to sensory nerve activation. We recently showed that mast cell specific receptors, MrgprB2 and its human homologue MRGPRX2, are involved in neurogenic inflammation and pain. Using a humanized mouse line that expresses MRGPRX2 on meningeal mast cells, we studied the role of this receptor in migraine-like pain *in vivo.*

Methods: Calcium imaging was used to study MRGPRX2$^+$ cell activation by PACAP1-38. Calcium imaging and β-hexosaminidase release assays were used to find the dose response. Minimally invasive dural stimulation model was used to apply PACAP1-38 to the MrgprB2-Cre$^+$ MRGPRX2$^+$ (X2$^+$) or MrgprB2-Cre- X2$^+$ (X2$^-$) mouse meninges. Facial mechanical hypersensitivity was measured in male mice prior to dural injection and then 1hr, 2hrs, 4hrs, and 24hrs after dural stimulation with PACAP1-38 (n=11-10/per group) using Von Frey filaments. Flow Cytometry was utilized to quantify X2$^+$ cells in the extracted meninges of dural-stimulated vs sham X2$^+$ and X2$^-$ mice.

Results: The mast cell receptor MrgprB2/X2 is expressed in the meninges and its activation leads to migraine-like pain behavior. The neuropeptide PACAP1-38 activates of MrgprB2, therefore stimulating mast cell release leading to migraine-like pain. Similarly, PACAP1-38 activates mouse meningeal mast cells that express the human MRGPRX2 receptor.

Conclusions: Here, we demonstrate, for the first time, a novel transgenic mouse line that functionally expresses the human MRGPRX2 in connective tissue mast cells, including meningeal mast cells, and responds to PACAP1-38 to contribute to migraine-like pain, in mice.

Acknowledgements: This study was conducted with the support of the Institute for Translational Sciences at the University of Texas Medical Branch, supported in part by a Clinical and Translational Science Award NRSA (TL1) Training Core (TL1TR001440) from the National Center for Advancing Translational Sciences, National Institutes of Health.

Poster 34

Twik1, Potassium Ion Channel Is Essential to Maintaining Sensitivity to Mechanical, Thermal, and Cold Stimuli Following Nerve Injury Condition

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Twik1 is a two-pore inward rectifying potassium channel whose expression and conductance properties change in a diverse array of tissues during disease states, but its role in somatosensation and primary sensory neuron function are unknown. Here, we use a nerve injury pain model to investigate Twik1's role in the somatosensory system. A mouse strain containing a conditional knockout Twik1 (Twik1-fx) was deleted in primary sensory neurons of Pirt-Cre animals. Chronic constriction injury (CCI) nerve injury model was performed on Pirt-Cre/Twik1-fx and wild type animals and sensitivity to mechanical, thermal, and cold pain was measured using von Frey, Hargreaves, and cold plantar tests, respectively. Ca^{2+} activities and responses to stimuli in lumbar 5 dorsal root ganglion (DRG) were measured using *in vivo* GCaMP3 fluorescent indicator Ca^{2+} imaging of intact DRG by confocal scanning microscopy. Compared to wild type animals, Pirt-Cre/Twik1-fx mice (Twik1 specifically deleted in primary sensory neurons) had indistinguishable mechanical, thermal, and cold sensitivity, but showed less mechanical sensitivity following CCI. Following CCI, compared to wild type, they showed insensitivity to thermal and a striking, persistent insensitivity to cold stimuli. During DRG Ca^{2+} imaging, compared to wild type-CCI, Pirt-Cre/Twik1-fx-CCI animals (Twik1 specifically deleted in primary sensory neurons) showed persistent, greatly reduced responses to stimuli in both cell counts and amplitudes of Ca^{2+} transients. By 30 days after CCI, Ca^{2+} transient amplitudes had become statistically indistinguishable but the number of cells responding to stimuli remained very low. Twik1 plays an essential role in maintaining somatosensory sensitivity and integration of primary sensory neurons following CCI. However, Twik1 does not appear to play a role in maintaining somatosensory sensitivity of primary sensory neurons under normal, non-injured physiological conditions.

Acknowledgements: Yu Shin Kim, my mentor, Jae-Yong Park for kindly providing Twik1 flox strain, the COSTAR program, and technical assistance from Ruben Gomez and Dr Yan Zhang were particularly vital to producing this research.

Funding provided by:

NIH T32 DE014318

NIH R01 NS128574

NIH R01 DE031477

NIH R01 DE026677

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Anatomical Analysis of Anterolateral Pathway

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Ascending somatosensory pathways consist of multiple independent spinal tracts that convey pain, temperature, and touch information from the spinal cord to the brain. The anterolateral pathway forms one of the major ascending spinal pathways and is an attractive therapeutic target for treating pain because nociceptive signals emanating from the periphery are channeled through this pathway en route to the brain. However, the organizational logic of the anterolateral pathway remains poorly understood. We have been anatomically characterizing *Phox2a*$^{+}$ anterolateral pathway projection neurons using a new mouse line in combination with histological and viral-tracing approaches.

Acknowledgements: The organization's programs and core facilities are supported the Cancer Prevention and Research Institute of Texas (CPRIT).

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Enhancing Swallow Control Targeted for Spinal Cord Injury Patients Through Precise fMRI-Guided Neuromodulation

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Targeted brain-computer interfaces have revolutionized the rehabilitation of neurological and psychiatric disorders. The Papageorgiou lab developed an individualized real-time fMRI closed-loop neuromodulation (iNM) to strengthen swallowing by targeting swallow motor and sensory control cortical networks in patients after spinal cord injury (SCI), or anterior discectomy and fusion surgery (ADFS). The purpose of this study was to elucidate the spatiotemporal mechanisms and efficacy associated with swallow motor and sensory control via iNM. On study-day one, we decoded 30 healthy participants' cortical magnitude and spatial patterns of activity during swallow and tongue motor and sensory control, interleaved with periods of baseline-tongue-at-rest. On study-day two, participants underwent iNM and control-No-iNM conditions. Brain networks were decoded using linear support vector machines (SVMs) trained to distinguish brain activity during swallow compared to tongue movement under iNM and control conditions. SVM modeling was trained on 1 participant and tested on 29 participants in an iterative fashion using a sliding window. iNM resulted in higher classification accuracies for swallow versus tongue cortical direction selectivity (up: 80.8%; down: 76.3%; left: 83.3%; right: 82.0%) compared to control condition (up: 69.2%; down: 73.0%; left: 78.5%; right: 69.6%). Enhanced activity was noted for motor cerebellum, basal ganglia, insula and claustrum. iNM increased the HbO2 magnitude during swallow control by 22% in the motor, 34% in the sensory, and 66% in the attention networks. There was a decrease in the variance of the magnitude of the signal by 11% in the motor, 11% in the sensory, and 25% in the attention networks. We cross-validated our findings by elucidating the dynamic brain states via causal modeling (Hidden Markov Model) during swallow control: 1. a dominant state generated by signal from areas that regulate swallowing in 78% of iNM trials (45% of control trials); and 2. a non-dominant state – noise - identified as tongue motor interference in 22% of iNM trials (55%% of control trials). iNM strengthened the physiological response of swallow and increased the signal-to-noise ratio by inhibiting signals from pain areas and enhancing motor control. With no current evidence-based standard of care, iNM can serve as a valuable tool to delineate optimal neurorehabilitative targets in SCI and ADFS patients.

Acknowledgments: This study is funded by grants to T.D. Papageorgiou: The McNair Medical Institute, The Robert and Janice McNair Foundation, TIRR Mission Connect, Baylor College of

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Medicine Junior Faculty Award, BCM - NRI and Houston Methodist Collaborative grant, and NIH – T32

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Hormonal Associations with Self-reported Neck and Back Pain in Full Busted Women

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Approximately 130 million individuals in the US (39% of the US population) are living with chronic musculoskeletal pain. Women experience more localizations of self-reported pain across their lifespan. Women report significantly more pain in the neck and back due to the presence of breast tissue. Neck and back pain has been strongly linked to bra cup size. While the primary source of pain in these women may be mechanical, emerging evidence suggests non-mechanical pain pathways that may contribute to pain expression in women. Specifically, evidence of sex-hormone influences in female animal models with respect to chronic musculoskeletal pain has emerged; however, concurrent work in human is a gap in the evidence base. To address this gap, our group is working on understanding sex-hormone contributions to pain in women. In the current study, 20 healthy physically active women with bra cup sizes E-H (33 ± 12 years of age, BMI = 30.2 ± 6.5 kg/m^2) were recruited to investigate the relationship between self-reported neck and back pain and serum-based hormonal markers. Questions which combined neck and back pain indicators were negatively associated with estradiol levels ($p < 0.001$) but positively associated with progesterone levels ($p < 0.005$). Questions specific to neck pain were negatively associated with estradiol levels ($p < 0.001$) and age ($p < 0.05$) but positively associated with a self-reported history of numbness in the torso and/or arms ($p < 0.01$). Questions specific to back pain were negatively associated with estradiol levels ($p < 0.001$), testosterone levels ($p < 0.05$), and number of children born ($p < 0.001$). These data indicate a significant influence of hormonal markers on neck and back pain perception in healthy physically active women. Additional work to understand the interaction between these hormonal influences and other non-mechanical pain pathways in pain perception in women is warranted.

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Mapping Microglia in the Brain After Nerve Injury Reveals Sustained Activity in Regions Encoding Affective Dimensions of Pain

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Microglia are the resident macrophages of the central nervous system, regulating homeostasis through various means such as cell surveillance, phagocytosis, and release of soluble factors. Microglia have historically been categorized as either active or inactive, though burgeoning research has demonstrated a higher degree of heterogeneity across microglial populations than previously appreciated. Microglial morphology similarly exists on a spectrum, encompassing ramified, surveillant microglia which, upon detection of some insult, enter a reactive state typically characterized by a distinct, amoeboid phenotype. After peripheral nerve injury for example, microglia in the spinal cord become reactive and begin releasing pro-inflammatory cytokines, initiating and maintaining pain. Similar microglial responses within the brain, however, have yet to be fully mapped. Here, we sought to elucidate microglial reactivity within the full brain, emphasizing regions associated with pain processing.

We assigned sham or sciatic nerve constriction conditions to male and female Sprague-Dawley rats (N=6 per group, total N=48), using the chronic constriction injury (CCI) model for neuropathic pain. Whole brains were extracted from each rat at either 7- or 28-days post-injury. Brains were fully coronally cryosectioned at 30 µm per section and were then immunostained for CD11b. Using software for automated analysis (HALO®, Indica Labs, Albuquerque, New Mexico), we assessed morphological changes in microglia across the span of the entire brain following nerve injury. Morphological assessment was cross-referenced with densitometry analysis.

We observed transformations in microglial morphology in brain regions involved in pain processing. Interestingly, while regions associated with sensory processing (such as insular cortex, somatosensory cortex, periaqueductal grey) saw transient responses from microglia, regions associated with affective processing (such as nucleus accumbens, ventral tegmental area, substantia nigra) displayed sustained responses across the experimental time course. These data provide a rationale for investigating a possible differential role for microglia in affective and motivational versus sensory dimensions of neuropathic pain.