UNIVERSITY of MARYLAND
CENTER TO ADVANCE CHRONIC PAIN RESEARCH

FEBRUARY 2021

A Message from CACPR Leadership

We are deeply saddened to announce the passing of former CACPR Co- Director, **Joel D. Greenspan**. Dr. Greenspan was instrumental in the vision, creation, and growth of the Center to Advance Chronic Pain Research (CACPR). A special edition newsletter coming this March will highlight Dr. Greenspan's outstanding accomplishments, mentorship, and career. His extensive research and contributions within the neuroscience and pain fields will leave a lasting impact, and he will be greatly missed by all.

Best regards,

Susan G. Dorsey, PhD, RN, FAAN
Professor and Department Chair,
Department of Pain and Translational Symptom Science & Department of Anesthesiology
School of Nursing

Man-Kyo Chung, DMD, PhD
Professor, Department of Neural and Pain Sciences
School of Dentistry

CACPR Member Spotlight

Joyce T. Da Silva, Ph.D.

Joyce T. Da Silva, Ph.D., a fourth-year postdoctoral researcher in Dr. David Seminowicz's lab in the Department of Neural and Pain Sciences at the University of Maryland School of Dentistry (UMSOD) has received three awards from the Society for Neuroscience (SfN) and the NIH-funded BUILD2 ASCEND program, which were highlighted at the 2020 UMSOD State of the School by Dr. Mark Reynolds.

As an underrepresented postdoctoral fellow, I am passionate about programs that promote diversity and inclusion in STEM fields. I was selected to be part of the Neuroscience Scholar Program (NSP) from the SfN to promote diversity and inclusion in biomedical science. The NSP is a two-year online training program open to underrepresented graduate students and postdoctoral researchers. Building on a 30-year history, NSP provides resources focused on career advancement issues, the research process, and cutting-edge scientific content. The NIH-funded BUILD2 ASCEND program is a partnership between UMB and the HBCU Morgan State University (MSU), designed to increase diversity in the biomedical community through mentoring underrepresented MSU undergraduate students. This year I will mentor 2-3 MSU undergraduate students pursuing biomedical research careers with training in hypothesis testing, project design

and implementation. In addition, I was fortunate to receive another award from the SfN, the “Trainee Professional Development Award”, which recognizes students and postdoctoral fellows who demonstrate scientific merit and excellence in research.

Being part of a community that supports underrepresented groups in science is empowering! I am really proud to be the UMSOD's representative at these diversity awards.

As osteoarthritis (OA) is a worldwide cause of disability with higher prevalence among women than men, I became motivated to investigate sex differences in OA. Thus, throughout my collaboration with Dr. Jin Ro, we showed that brain networks associated with endogenous pain inhibition are modulated by sex and age in a healthy state and during OA progression. This study was just published in a flagship journal of the aging field (Aging Cell). We demonstrated that both age and enhanced periaqueductal gray connectivity with the reward system impact OA-like pain, making aged rats, especially females, more vulnerable to chronic pain. These findings suggest that therapeutic strategies that strengthen the pain inhibitory system may represent a potential avenue of early pain management to help prevent chronic OA pain. Dr. Ro and I have received an invitation from the Pain Research Forum to give an interview about our recent publications. Our Aging Cell paper was also highlighted as the “Editors' Pick” in the Pain Research Forum.

My career development goal is to transition into an independent research program that will employ an innovative, multiscale, interdisciplinary approach to

evaluating the role of sex in how OA pain drives comorbid emotional disorders, such as anxiety and depression, and how sex and OA pathological changes affect behavior. The ultimate goal of this research is to yield novel insights for personalized OA therapy. I have submitted a proposal for the NIH K99/R00 Pathway to Independence Award that hopefully will allow me to develop my research program and put me on a path to becoming an independent investigator.

Highlights from the United States Association for the Study of Pain (USASP) inaugural conference: Transforming Pain Science & Care in Challenging Times, December 9-11, 2020.

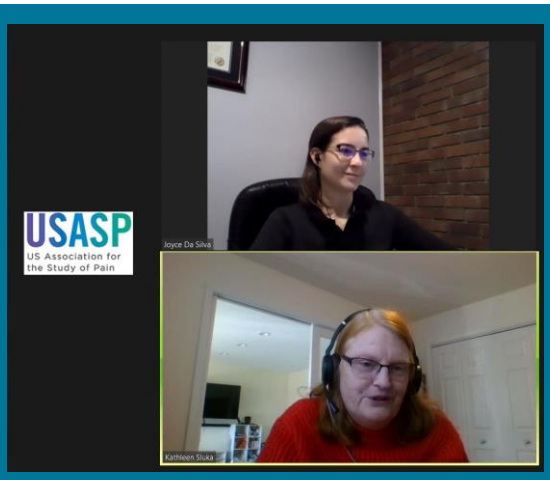
United States Association for the Study of Pain (USASP) is to promote scientific advances that reduce the burden of pain and their goal is to bring diverse perspectives, including those of scientists, clinicians, health-care providers, and policymakers, together to stimulate and support the study of pain and to translate that knowledge into improved pain relief. This is Inaugural conference organized by USASP with having three half-day sessions that includes keynote speaker, plenary speakers, concurrent sessions, early career programming, a data blitz and posters. I would like to thank the 0rganizing Committee of the United States Association for the Study of Pain (USASP) inaugural conference for giving me the opportunity to attend and present my work entitled "**Capsaicin-induced depolymerization of axonal microtubules mediates analgesia for trigeminal neuropathic pain"**.

I will describe briefly below some elements in the meeting. The meeting touched upon the key aspects which

are very much important in the present scenario like “Evolving Relationship of Opioid Prescribing with Opioid Overdose and Suicide” and “Remote Treatment of Chronic Pain using E-Health Interventions in the Era of Covid-19”. Another feature of the meeting is that having concurrent sessions that went into covering the broad range of topics in the pain field, one of the important session is of particular interest to me was “ Translational aspects of central sensitization in the trigeminal system” and discussed the complications from dental procedures such as surgical interventions and root canal treatments leads to the iatrogenic trigeminal nerve injuries, which can result in trigeminal neuropathic pain. Other important aspect of the meeting that all the three days have sessions for the of the early career researchers i.e. Early Career Programming, Meet, Connect, Collaborate: Networking Opportunities and sessions on the NIH grants writing. Participants debated a broad array of issues career in industry vs academia, grants available for international students, setting up a new lab and many more.

The meeting truly gave me the opportunity to learn and interact with Key opinion leaders; Prof Michael S. Gold and Prof Francis J. Keefe in the pain filed. I find it was an enriching experience for me and excellent platform to connect, discuss new strategies and engage scientific conversation to advance my knowledge and learning in the field of pain.

Vipin Arora, Ph.D
Post- Doctoral Fellow, Department of Neural & Pain Sciences.



My experience attending the 2020 virtual US Association for the Study of Pain (USASP) meeting.

The 2020 USASP meeting was the first virtual conference that I participated in and I confess that I was really surprised about how much I was able to benefit from a virtual conference!

First, the networking sessions were incredibly useful for early career researchers like me who are seeking to transition to independent positions. The range of topics in the “Early Career Programing and Networking” sessions was very appealing and I was able to easily change breakout rooms to talk to different people I wanted to connect with. I felt very fortunate to have the opportunity to have a one-on-one conversation with Dr. Kathleen Sluka about the development of my research niche. She gave me valuable tips for starting a new lab. Second, the ability to find people in the attendees list and message them through the app was a very efficient resource. A professor from Washington University in St. Louis saw my poster, messaged me, and we had a Zoom meeting afterward to discuss a potential collaboration. Third, I was also able to network through the lectures. I was watching the excellent session "Translating the “pain versus pain” phenomenon: From rodents to humans and back again" and Dr. Anne Murphy from Georgia State University asked in the chat if there were any manuscripts showing sex differences in

descending pain modulatory pathways, so I just jumped in and typed: “Yes! We have published sex and age differences in descending pain modulatory pathways in rats. Please see the paper in www.pubmed" She immediately replied: “Great! We have our new Pain Journal Club paper.” I have to admit it was much easier for me to walk up to the “microphone” in the virtual space and say, “Please check out our paper in www.pubmed” than it would have been in a big conference room.

Last but not least, I would like to thank the USASP president Dr. Michael Gold, the USASP treasurer Dr. Jennifer Haythornthwaite and the entire USASP team for the excellent organization of this inaugural virtual meeting that allowed us to gain so much.

Joyce T. Da Silva, Ph.D.

CACPR Member Laurels

Highlights of recent grant awards, publications, and presentations.

Simon Akerman, PhD

1. **Akerman S**, **Romero-Reyes M**. Preclinical studies to dissect the neural mechanism for the comorbidity of migraine and temporomandibular disorders (TMD): the role of CGRP. Br J Pharmacol 2020. (https://pubmed.ncbi.nlm.nih.gov/32929719/).
Here, we demonstrate a unique preclinical approach to study the co-morbidity of migraine and TMD. The only approach that directly translates to the clinical co-morbid phenotype. Using this approach, we begin to dissect the neural mechanisms involved, highlighting the likely importance of the release of CGRP in these mechanisms.

2. Summ O, Andreou AP, **Akerman S**, Holland PR, Hoffmann J, Goadsby PJ. Differential actions of indomethacin: clinical relevance in headache. Pain 2020. (https://pubmed.ncbi.nlm.nih.gov/32796319/).

Here, we demonstrate the unique ability of indomethacin, over other common OTC NSAIDs, to inhibit nitric oxide-induced migraine-like dural-trigeminovascular neuronal changes, compared to similar effects in response to glutamate. It highlights its potential differential mechanism of action, via disruption of nitric oxide signaling, and why it might be specifically efficacious in the treatment of paroxysmal hemicrania and hemicrania continua.

Man-Kyo Chung, DMD, PhD

Presentation

Dr. Chung gave a plenary lecture at 25th Annual meeting of Japanese Society of Orofacial Pain for dentists, orofacial pain specialists and pain researchers. The title was “Neural Pathways of Craniofacial Muscle Pain and Implications for Novel Treatments”. He discussed peripheral and central neural pathways involved in craniofacial muscle pain in the context of temporomandibular joint disorders.

Publications

1. Orthodontic force induces nerve injury-like transcriptomic changes driven by TRPV1-expressing afferents in mouse trigeminal ganglia. Wang S, **Chung MK**. Mol Pain. 2020 Jan-Dec;16:1744806920973141. doi: 10.1177/1744806920973141.

Transcriptomic assay in mouse trigeminal ganglia showed that orthodontic force produces transcriptomic changes resembling nerve injury in the trigeminal ganglia and that nociceptive inputs through TRPV1-expressing afferents leads to subsequent changes in gene expression not only in TRPV1-positive neurons, but also in TRPV1-negative neurons and non-neuronal cells throughout the ganglia. Orthodontic force-induced transcriptomic changes might be an active regenerative program of trigeminal ganglia in response to axonal injury following orthodontic force.

2. Fight fire with fire: Neurobiology of capsaicin-induced analgesia for chronic pain. Arora V, Campbell JN, **Chung MK**. Pharmacol Ther. 2020 Nov 10:107743. doi: 10.1016/j.pharmthera.2020.107743.

Capsaicin, the pungent ingredient in chili peppers, produces intense burning pain in humans. Capsaicin selectively activates the transient receptor potential vanilloid 1 (TRPV1), which is enriched in nociceptive primary afferents, and underpins the mechanism for capsaicin-induced burning pain. Paradoxically, capsaicin has long been used as an analgesic to treat chronic pain conditions,

such as neuropathic pain. In this paper, we reviewed current understanding about molecular and neurobiological mechanisms underlying capsaicin-induced analgesia for neuropathic pain mainly focused on long-term analgesia associated with capsaicin-induced TRPV1/calcium/calpain-dependent ablation of TRPV1-expressing afferent terminals.

Marianne Cloeren, MD, MPH

Marianne Cloeren, MD, MPH, Associate Professor, Department of Medicine, was author of an article in the *On Being a Patient* series: "Missing the Forest for the Trees," which was published in the *Annals of Internal Medicine* on January 19, 2021.

This account describes the journey of Dr. Marianne Cloeren, Associate Professor of Medicine, as she struggled with painful loss of vision shortly after her arrival here. It offers food for thought for any providers working with patients whose conditions impact their day-to-day functioning and threaten their livelihood.

Susan G. Dorsey, PhD, RN, FAAN

Function and Mechanisms of Truncated BDNF Receptor TrkB.T1 in Neuropathic Pain.
Cao T, Matyas JJ, Renn CL, Faden AI, **Dorsey SG**, Wu J. Cells. 2020 May 11;9(5):1194. doi: 10.3390/cells9051194. PMID: 32403409

This is a review paper outlining the pathological role(s) for the brain-derived neurotrophic factor (BDNF) receptor, truncated trkB.T1, in chronic pain.

Joel D. Greenspan, PhD

Pain. 2020 Dec;161(12):2710-2719. doi: 10.1097/j.pain.0000000000001976.

Understanding the relationship between features associated with pain-related disability in people with painful temporomandibular disorder: an exploratory structural equation modeling approach.

Miller VE(1), Chen DG(2)(3), Barrett D(2), Poole C(4), Golightly YM(4), Sanders AE, Ohrbach R, **Greenspan JD**, Fillingim RB, Slade GD.

Pain-related disability is a multifaceted construct that refers to the impact of pain on an individual's capacity to fulfill their self-defined and social

roles. This research examined the relationship between clinical, psychological, and pain sensitivity factors and pain-related disability among adults with chronic temporomandibular disorder (TMD). We analyzed data from a cross-sectional community-based sample of 1088 men and women with chronic TMD. Jaw functional limitation and psychological unease was strongly related to pain-related disability. Experimental pain sensitivity was removed from our model because of weak direct effect and the burden of performing experimental pain sensitivity testing in a clinical setting. The final model explained 78% of the variance in pain-related disability.

J Neurophysiol. 2021 Jan 1;125(1):305-319. doi: 10.1152/jn.00492.2020. Epub 2020 Dec 16.Meeker TJ, Emerson NM, Chien JH, Saffer MI, Bienvenu OJ, Korzeniewska A, **Greenspan JD**, Lenz FA.

A pathological increase in vigilance, or hypervigilance, may be related to pain intensity in some clinical pain syndromes and may result from attention bias to salient stimuli mediated by anxiety. During a series of painful stimuli requiring subjects to respond to targets, we separated response willingness from ability to discriminate targets from nontargets. Response willingness declined during the task, with no change in subjects' ability to discriminate, consistent with previous vigilance studies. High trait anxious subjects were less willing to respond and showed slower reaction times to hits than low anxious subjects. This study reveals an important role of trait anxiety in pain vigilance.

Front Neurosci. 2020 Dec 22;14:594588. doi: 10.3389/fnins.2020.594588. eCollection 2020.Menstrual Cycle Variations in Gray Matter Volume, White Matter Volume and Functional Connectivity: Critical Impact on Parietal Lobe.Meeker TJ, Veldhuijzen DS, Keaser ML, Gullapalli RP, **Greenspan JD**.

The role of gonadal hormones in neural plasticity remains unclear. This study aimed to examine the effects of naturally fluctuating hormone levels over the menstrual cycle in healthy females. Gray matter, functional connectivity (FC) and white matter changes over the cycle were assessed by using functional magnetic resonance imaging (fMRI), resting state fMRI, and structural MRIs, respectively, and associated with serum gonadal hormone levels. Moreover, electrocutaneous sensitivity was evaluated in 14 women in four phases of their menstrual cycle (menstrual, follicular, ovulatory, and luteal). Electrocutaneous sensitivity was greater during follicular compared to menstrual phase. Additionally, pain unpleasantness was lower in follicular phase than other phases while pain intensity ratings did not change over the cycle. Significant variations in cycle phase effects on gray matter volume were found

in the left inferior parietal lobule (IPL) using voxel-based morphometry. Subsequent Freesurfer analysis revealed greater thickness of left IPL during the menstrual phase when compared to other phases. Also, white matter volume fluctuated across phases in left IPL. Blood estradiol was positively correlated with white matter volume both in left parietal cortex and whole cortex. Seed-driven FC between left IPL and right secondary visual cortex was enhanced during ovulatory phase. A seed placed in right IPL revealed enhanced FC between left and right IPL during the ovulatory phase. Additionally, we found that somatosensory cortical gray matter was thinner during follicular compared to menstrual phase. We discuss these results in the context of likely evolutionary pressures selecting for enhanced perceptual sensitivity across modalities specifically during ovulation.

Marcela Romero-Reyes, D.D.S., PhD

Publication

1. **Akerman S**, **Romero-Reyes M**. Preclinical studies to dissect the neural mechanism for the comorbidity of migraine and temporomandibular disorders (TMD): the role of CGRP. Br J Pharmacol 2020. (https://pubmed.ncbi.nlm.nih.gov/32929719/).

Here, we demonstrate a unique preclinical approach to study the co-morbidity of migraine and TMD. The only approach that directly translates to the clinical co-morbid phenotype. Using this approach, we begin to dissect the neural mechanisms involved, highlighting the likely importance of the release of CGRP in these mechanisms.

Presentation

2. Participation in the UASAP Inaugural conference: Transforming pain science and care in challenging times on 12/11/2020

Topic/Title for the session symposium: Translational aspects of central sensitization in the trigeminal system

Lecture: Central sensitization in Headache and Orofacial Pain

Conversation from the bench to the clinical setting about the clinical features of central sensitization in headache disorders and trigeminal neuropathic pain.

Announcement

Change in Leadership, Department of Neural & Pain Sciences

Effective February 1, 2021 following the retirement of Joel D. Greenspan, Dr. Richard Traub will become the interim chair of the Department of Neural and Pain Sciences in the School of Dentistry. NPS has 17 faculty, 10 with a focus on pain research spanning basic, translational, and clinical science. The department is also home to the Brotman Facial Pain Clinic. Dr. Traub was vice-chair of the department for 7 years which helped prepare him to lead the department moving forward. NPS has a research portfolio exceeding $15 million and is strongly situated as a leader in pain research. Dr. Traub is looking forward to helping the faculty to develop new ideas and collaborative opportunities within the department, university and beyond.

The UM Center to Advance Chronic Pain Research (CACPR) is a multidisciplinary center composed of nationally and internationally renowned clinical and preclinical translational scientists whose principle research focus is on the physiological, genetic, and psychosocial underpinnings of the development and persistence of debilitating chronic pain conditions.

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