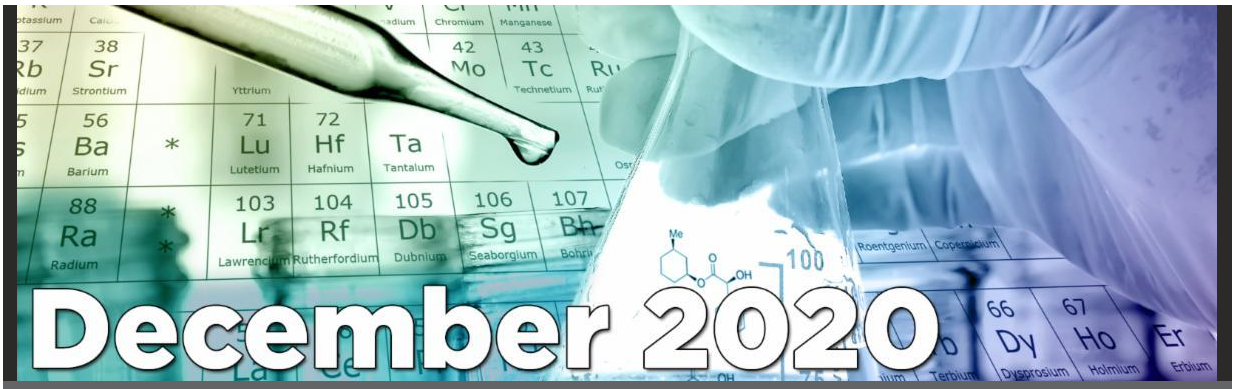
UNIVERSITY of MARYLAND
CENTER TO ADVANCE CHRONIC PAIN RESEARCH



RELIEVING PAIN IN AMERICA

Change in CACPR Executive Leadership

Greetings CACPR members! At the end of this year, I will be stepping down as Co-Director of CACPR, and Dr. Man-Kyo Chung will be assuming this role. I feel that I am leaving CACPR in very good hands.

As I look back on the history of CACPR, I feel proud of what we have accomplished. Susan Dorsey and I worked with Dean Jane Kirschling, Dean Mark Reynolds, and President Jay Perman to develop this center, with considerable collaboration from Drs. Richard Traub, Cynthia Renn, and Ron Dubner. On Feb. 24, 2014, UMB formally established our Center to Advance Chronic Pain Research, in recognition of the large amount of talent involved in pain research on campus. Although I haven't done a formal survey, I think CACPR is the largest Center focused on pain research in the world. I'm confident in saying that it has the largest breadth of expertise with the largest range of thematic initiatives in the world.

Two of the CACPR initiatives that I am particularly pleased with are the annual symposia and the PIG meetings. Our five annual CACPR symposia included great presentations from local and invited speakers, lively panel discussions, and time for further discussions over lunch. Our bi-weekly PIG meetings afford opportunities for members to present their most recent work and new ideas for consideration by the rest of CACPR membership. Both venues have led to the development of new collaborations and project ideas, which is one of the principle objectives of CACPR.

While I will be stepping back from my leadership role in CACPR, I will continue to be invested in its success. There are other initiatives in development for CACPR, which will be rolled out over the course of 2021-2022. I look forward to seeing the growth of CACPR, and the continued achievements of its members. Excelsior!

Joel D. Greenspan, PhD

CACPR Member Spotlight

Introducing the CACPR's newest Co-Director, Dr. Man-Kyo Chung

Dr. Man-Kyo Chung DMD PhD is a Professor in the Department of Neural and Pain Sciences. He received DMD PhD from the Kyung Hee University, Seoul Korea. After postdoctoral training at the Johns Hopkins University, Dr. Chung joined the University of Maryland School of Dentistry in 2008. Since then, he has been studying neurobiological mechanisms of craniofacial muscle and neuropathic pain focused on the roles of trigeminal nociceptive afferents. Dr. Chung is an expert in electrophysiological, biophysical and genetic analysis of nociceptors and nociceptive ion channels including transient receptor potential vanilloid 1 (TRPV1). His current interest is to determine neuroplastic changes associated with chronic neuropathic pain. In collaboration with Drs. Feng Wei and David Seminowicz, his team currently investigates how TRPV1-expressing nociceptors lead to the neuroplasticity in brain and contribute to the maintenance of chronic craniofacial neuropathic pain. These studies may suggest manipulation of peripheral nociceptors can be a disease-modifying treatment for chronic pain with fewer adverse side effects. As a dentist scientist, Dr. Chung has also long been interested in the roles of dental and periodontal primary afferents. He hypothesizes that nociceptive afferents in periodontal tissues not only contribute to pain but also pathophysiological remodeling of bone surrounding teeth. This study

determines how nociceptive afferents regulate bone destruction in periodontal diseases or bone remodeling in orthodontic treatments, which may suggest manipulation of nociceptors as novel methods for the management of dentoalveoalr disorders. The merit of his project regarding dual roles of trigeminal nociceptors in chronic pain and alveolar bone remodeling was recognized by the National Institute of Dental and Craniofacial Research (NIDCR), and Dr. Chung recently received an R35 NIDCR Award for Sustaining Outstanding Achievement in Research, which supports $8 million for 8 years.

Throughout his career at the UMB, Dr. Chung has been serving to enrich UMB pain research community by organizing campus wide pain journal club, pain seminar series, and joint pain research workshop between CACPR and Johns Hopkins University. He is now taking on a bigger role by serving as a co-Director of CACPR. “It is an honor to represent this unique group of pain research community. I recognize that CACPR has indeed remarkably advanced chronic pain research in the UMB campus under the leadership of co-Directors, Drs. Joel Greenspan and Susan Dorsey, during last six years. CACPR members’ publication and funding has increased by more than two folds. CACPR has cultivated wonderful collaborative environments not only for basic and translational pain research, but also for pain-related policy and overall care of pain patients. I look forward to working with Dr. Susan Dorsey, executive board members and all CACPR members, and do all that I can do to further promote multidisciplinary research, education, and management of chronic pain in the UMB campus”.

CACPR Member Laurels

Highlights of recent grant awards, publications, and presentations.

Vinita Agarwal, PhD

Agarwal, V. (2020). *Dialogic and relational ethics of food in Ayurveda: Ecology as body/self embodiment in integrative patient-centered pain care*. NCA virtual conference, November 2020, Applied Communication Division

Luana Colloca, MD, PhD, MS

What Should Clinicians Tell Patients about Placebo and Nocebo Effects? Practical Considerations Based on Expert Consensus.
Evers AWM**, Colloca L**, Blease C, Gaab J, Jensen KB, Atlas LY, Beedie CJ, Benedetti F, Bingel U, Büchel C, Bussemaker J, Colagiuri B, Crum AJ, Finniss DG, Geers AL, Howick J, Klinger R, Meeuwis SH, Meissner K, Napadow V, Petrie KJ, Rief W, Smeets I, Wager TD, Wanigasekera V, Vase L, Kelley JM, Kirsch I;
Consortium of Placebo Experts. Psychother Psychosom. 2020 Oct 19:1-8. doi: 10.1159/000510738. Online ahead of print. PMID: 33075796

This article is an Expert Consensus based on a Delphi Survey on how clinicians may want to inform patients about the occurrence of placebo and nocebo effects.

Joel D. Greenspan, PhD

Gaynor SM, Bortsov A, Bair E, Fillingim RB, **Greenspan JD**, Ohrbach R, Diatchenko L, Nackley A, Tchivileva IE, Whitehead W, Alonso AA, Buchheit TE, Boortz-Marx RL, Liedtke W, Park JJ, Maixner W, Smith SB. Phenotypic profile clustering pragmatically identifies diagnostically and mechanistically informative subgroups of chronic pain patients. Pain. 2020 Nov 30. doi: 10.1097/j.pain.0000000000002153. Epub ahead of print. PMID: 33259458.

Using a supervised clustering approach in a cohort of temporomandibular disorder (TMD) cases and controls from the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) study, we recently developed and validated a rapid algorithm (ROPA) to pragmatically classify chronic pain patients into three groups that differed in clinical pain report, biopsychosocial profiles, functional limitations, and comorbid conditions. This study examined the generalizability of this clustering procedure in two additional cohorts: patients with chronic overlapping pain conditions (Complex Persistent Pain Conditions (CPPC) study), and a real-world clinical population of patients seeking treatment at Duke Innovative Pain Therapies (DIPT). In each cohort, we applied ROPA for cluster prediction, which requires only four input variables: pressure pain threshold (PPT) and anxiety, depression, and somatization scales. In both cohorts, we distinguished three clusters, including one with more severe clinical characteristics and psychological distress. We observed strong concordance with observed cluster solutions, indicating the ROPA method allows for reliable subtyping of clinical populations with minimal patient burden. The ROPA clustering algorithm represents a rapid and valid stratification tool independent of anatomic diagnosis. ROPA holds promise in classifying patients based on pathophysiological mechanisms rather than structural or anatomical diagnoses. As such, this method of classifying patients will facilitate personalized pain medicine for patients with chronic pain.

Marcela Romero- Reyes, DDS, PhD

1.“Orofacial pains and headaches as a source of non-odontogenic pains” *Dolores Orofaciales y Cefaleas como Fuente de Dolores No-Odontogenicos* invited by the Latinoamerican Academy of Orofacial pain , Temporomandibular Disorders and Sleep, *Academia Latinoamericana de Dolor Facial, Trastornos Temporomandibulares y del Sueño (ALDOTS).* 10/20/2020

The lecture discussed the importance of the diagnosis of different sources of craniofacial pain that can resemble dental pain, in addition to their pathophysiology and evidence-based management.

2. “Headaches as a source of non-odontogenic pains and their relationship with temporomandibular disorders” Cefaleas Como fuente de dolores no-odontogenicos y su relación con los Desordenes Temporomandibulares invited by the MS program of Orofacial Pain and TMD of the University of the Basque Country (Universidad del Pais Vasco), School of Dentistry and the Complutense University of Madrid (Universidad Complutense de Madrid). 11/10/2020

The lecture discussed migraine pathophysiology with a bench to bedside approach including other primary headache disorders with atypical presentations and localization in the face as well as a discussion of the comorbidity between migraine and TMD.

3. Lecturer and organizer with the TMD, Cervical Spine and Orofacial Pain section and the Procedural Headache Medicine Section of the AHS. Pre-course “The Anatomy of Headache and Orofacial Pain: An Interventional Based Cadaver Course”. American Headache Society virtual 2020 Scottsdale Headache Symposium. 11/21/2020

The online pre-course described TMD diagnosis and management, cranial neuralgias and the different pharmacological approaches of management including nerve blocks and a dissection of the different anatomical craniofacial structures.

Joyce Teixeira da Silva, PhD

Pain modulatory network is influenced by sex and age in a healthy state and during osteoarthritis progression in rats.
Joyce T. Da Silva, Christina Tricou, Youping Zhang, Amir Tofighbakhsh, David A. Seminowicz, Jin Y. Ro.

This study has just been accepted for publication in Aging Cell. We used functional MRI to determine the effects of sex and age on periaqueductal gray functional connectivity (PAG FC) in a healthy state (pre-OA) and during the early and late phases of monosodium iodoacetate (MIA)-induced OA in rats. We then examined how sex and age affect longitudinal changes in PAG FC in OA. Overall, our findings show that PAG FC is modulated by sex and age in a healthy state. A widespread PAG network in the early phase of OA pain may contribute to the transition from acute to chronic OA pain and the increased risk of developing chronic pain for females. Enhanced PAG FC with the reward system may represent a potential mechanism underlying chronic OA pain in elderly patients.

Junfang Wu, BM, PhD

1. Ritzel RM, He J, Li Y, Cao T, Khan N, Shim B, Sabirzhanov B, Aubrecht T, Stoica BA, Faden AI, Wu L-J, **Wu J**. Proton extrusion during oxidative burst in microglia exacerbates pathological acidosis following traumatic brain injury. Glia, 2020, Oct 22. doi: 10.1002/glia.23926. PMID: 33090575.

This paper showed that TBI causes significant intracellular (e.g., microglia) and extracellular (i.e., perilesional cortex) acidification that persists for months. Acidosis was associated with higher NOX2 expression and reactive oxygen species (ROS) production in microglia, and increased oxidative stress in the cortex. Microglia depletion attenuated brain acidosis, oxidative stress, and the induction of pro- and anti-inflammatory mediators. We demonstrate that Hv1 proton channel is present in phagocytes and functions as an acid extruder responsible for alleviating intracellular acidosis during oxidative burst and is consequently required for ROS formation. Genetic ablation of Hv1 exacerbated microglia acidification, but reduced the severity of brain acidosis, oxidative stress, and neuroinflammation. These early changes had a profound and lasting impact on neurological outcome, as evidenced by enhanced functional recovery and reduced lesion size months after TBI. Together, we demonstrate that activated microglia increase the extrusion of protons and ROS across the plasma membrane into the extracellular space after TBI, contributing to pathological brain acidosis, chronic neurodegeneration, and related functional deficits.

2. Khan N, Cao T, He J, Ritzel RM, Li Y, Henry RJ, Colson C, Stoica1 BA, Faden AI, **Wu J**. Spinal cord injury alters microRNA and CD81+ exosome levels in plasma extracellular nanoparticles with neuroinflammatory potential. Brain, Behavior, and Immunity, (2020), doi: https://doi.org/10.1016/j.bbi.2020.12.007

We provide the first known characterization of plasma EV dynamics after mouse SCI. We used multiple, complementary techniques in our analysis as technical limitations associated with EV isolation and detection technologies need to be thoroughly considered in data interpretation. The most dramatic changes in EVs occurred at 1d post-injury. We observed a decrease in the total plasma EV count with a concurrent increase in a specific subset of EVs carrying the tetraspanin marker, CD81. Surface CD81 expression was decreased in astrocytes at the injury site, which may be associated with CD81+ plasma EV release. microRNA content was also significantly modified in ultracentrifugation-isolated plasma EVs at 1d post-injury, with changes similar to that reported in EVs released by astrocytes after inflammatory stimulation in vitro. Furthermore, intracerebroventricular (ICV) injection of plasma EVs from SCI mice increased pro- and anti-inflammatory gene expression in the brain as well as reactive astrocyte gene expression. Subsequent ICV injection experiments demonstrated significant intracellular cytokine changes in brain astrocytes specifically. Together, we demonstrate that plasma EVs may be sufficient to promote brain inflammation after SCI.

3. Murugan M, Zheng J, Wu G, Mogilevsky R, Zheng X, Hu P, **Wu J#**, Wu L-J#.The voltage-gated proton channel Hv1 contributes to neuronal injury and motor deficits in a

mouse model of spinal cord injury. Molecular Brain, 2020, Oct 20;13(1):143. doi: 10.1186/s13041-020-00682-6. PMID: 33081841 (#correspondent)

We investigate whether Hv1 mediates microglial/macrophage activation and aggravates secondary damage following SCI. Following contusion SCI, wild-type (WT) mice showed significant tissue damage, white matter damage, and impaired motor recovery. Mice lacking Hv1 (Hv1−/−) showed significant white matter sparing and improved motor recovery. The improved motor recovery in Hv1−/− mice was associated with decreased interleukin-1β, reactive oxygen/nitrogen species production and reduced neuronal loss. Further, deficiency of Hv1 directly influenced microglia activation as noted by decrease in microglia numbers, soma size, and reduced outward rectifier K+ current density in Hv1−/− mice compared to WT mice at 7 d following SCI. Our results therefore implicate that Hv1 may be a promising potential therapeutic target to alleviate secondary damage following SCI caused by microglia/macrophage activation.

The OPPERA Grand Finale

Authored by Joel Greenspan

In 2005, a multi-site study began that was directed at identifying the underlying causes for chronic orofacial pain, formally recognized as Temporomandibular Disorders (TMD). This condition is characterized by persistent pain and dysfunction of the temporomandibular joint (TMJ) and associated muscles in the orofacial region. While acute TMD is often associated with injury or infection in the region of the TMJ or surrounding regions of the jaw, the causes for chronic TMD – lasting for months or years – are not easily identified, if at all.

Over the last 15 years, four dental schools in the eastern US have conducted a large-scale study with the aim of identifying the risk factors for chronic TMD pain. This study, identified as *Orofacial Pain: Prospective Evaluation and Risk Assessment*(OPPERA), was funded by the National Institute of Dental and Craniofacial Research, National Institutes of Health. Scientists and clinicians at the Univ. of Maryland, Baltimore, University of North Carolina, Chapel Hill, University of Florida, and University at Buffalo, recruited thousands of research participants over the course of several years, and followed them for up to seven years. Over this period of time, over fifty scientific papers have been published based on the study, including two special issues of *The Journal of Pain* (2011 and 2013).

While this study formally ended this summer, several more research papers are forthcoming. Of particular note is the recent publication of a special issue of the *Journal of Oral and Facial Pain and Headache* devoted to the most recent results from the OPPERA study. This series of papers evaluated the impact of co-morbid pain conditions upon the likely development and severity of TMD pain, and *vice versa*. Among the significant discoveries was the relatively high frequency of TMD co-occurring with other chronic pain conditions of interest in this study: headache (migraine and tension-type), low back pain, irritable bowel syndrome, and fibromyalgia. While previous studies have

documented such co-morbidities as occurring at a greater frequency than expected by independent, random occurrence, this study was the first large scale study of this type that relied on in-person assessment of the various pain conditions, using the recognized "gold standards" for diagnoses.

It would be difficult to adequately summarize all the findings from this most recent compendium of papers. But some of the highlights are as follows. Among the 182 chronic TMD cases that were formally assessed for the four other pain conditions noted above, 77.5% of them had at least one of those other conditions. Another important finding was that TMD patients with multiple co-morbid pain conditions experienced greater TMD symptoms, both in terms of severity and frequency of orofacial pain. This is a novel observation that chronic pain localized to one body site can impact the pain experienced at another body site. This supports a model of much current interest which proposes that a prolonged pain condition changes how the nervous system processes signals indicative of injury very broadly, regardless of the bodily origin of those signals. The process is often referred to as central sensitization, which has been explicitly documented as a consequence of injury in animal models.

Paralleling this pattern, psychological distress measures - such as depression, trait anxiety, perceived stress, somatic symptom burden, and pain catastrophizing - also became more severe with increasing numbers of pain conditions. Previous OPPERA papers took advantage of longitudinal data to document that several of these measures of psychological distress were significant risk factors for the development of TMD. Additionally, as TMD became chronic, the psychological distress increased, characterizing a mutually reinforcing relationship between psychological state and the incidence/severity of chronic TMD pain. A similar pattern was observed for fatigue and sleep disturbance, both in terms of showing a "mutually reinforcing" relationship with chronic pain susceptibility and severity, and in terms of increased sleep disturbance with increasing numbers of chronic pain conditions.

The principle message from these papers is that individual chronic pain conditions should not be viewed in isolation, but in the broader context of co-morbidities, particularly other pain conditions and psychological distress. Indeed, focused attention to treat a single pain condition is likely to be less successful if the presence and severity of other co-morbid conditions are not considered as well.

Papers from the special issue of the *Journal of Oral and Facial Pain and Headache*:

Slade GD, **Greenspan JD**, Fillingim RB, Maixner W, Sharma S, Ohrbach R. Overlap of Five Chronic Pain Conditions: Temporomandibular Disorders, Headache, Back Pain, Irritable Bowel Syndrome, and Fibromyalgia. *J Oral Facial Pain Headache*. 2020;34: s15-s28.

Sharma S, Slade GD, Fillingim RB, **Greenspan JD**, Rathnayaka N, Ohrbach R. Attributes Germane to Temporomandibular Disorders and Their Associations with Five Chronic Overlapping Pain Conditions. *J Oral Facial Pain Headache.* 2020;34: s57-s72.

Sanders AE, **Greenspan JD**, Fillingim RB, Rathnayaka N, Ohrbach R, Slade GD. Associations of Sleep Disturbance, Atopy, and Other Health Measures with Chronic Overlapping Pain Conditions*. J Oral Facial Pain Headache*. 2020;34: s73-s84.

Ohrbach R, Sharma S, Fillingim RB, **Greenspan JD**, Rosen JD, Slade GD. Clinical Characteristics of Pain Among Five Chronic Overlapping Pain Conditions. *J Oral Facial Pain Headache.* 2020;34: s29-s42.

Ohrbach R, Fillingim RB, **Greenspan JD**, et al. Authors' Response: When You Come to the Fork in the Road, Take It! Future Research into Chronic Pain as a General Condition*. J Oral Facial Pain Headache*. 2020;34: s12-s14.

Greenspan JD, Slade GD, Rathnayaka N, Fillingim RB, Ohrbach R, Maixner W. Experimental Pain Sensitivity in Subjects with Temporomandibular Disorders and Multiple Other Chronic Pain Conditions: The OPPERA Prospective Cohort Study*. J Oral Facial Pain Headache*. 2020;34: s43-s56.

Fillingim RB, Ohrbach R, **Greenspan JD**, et al. Associations of Psychologic Factors with Multiple Chronic Overlapping Pain Conditions. *J Oral Facial Pain Headache*. 2020;34: s85-s100.

These papers can be accessed here:
http://www.quintpub.com/journals/ofph/journal_contents.php?iss_id=1704&journal_name=JOFPH&vol_year=2020&vol_num=34#.X8VO0GhKjcv

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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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