



Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress David Geffen School of Medicine at UCLA

From the Desk of Emeran A. Mayer, MD, PhD Center Director



In this Spring 2015 edition of our newsletter, we are once again highlighting exciting news from the Programs of the Oppenheimer Center. Each of the Programs addresses a different aspect of brain gut interactions by studying biological mechanisms in health and disease. In the current issue, we are highlighting three such aspects: The gut microbiome, chronic pain and obesity. For details of the Oppenheimer Center and its individual Programs, please visit our website at uclacns.org.

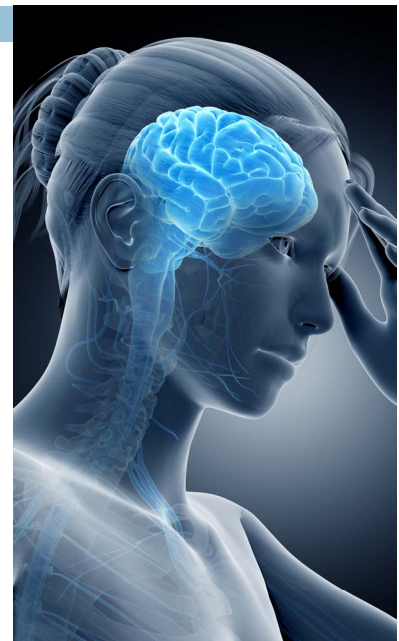
We would like to thank the small group of individuals who have continued to generously support the research portfolio of the Oppenheimer Center. Even though all the Programs have been highly successful in competing for federal funding, philanthropic support remains essential to provide infrastructure support, support junior researchers to launch their careers, and to start high risk pilot/high yield projects which may lead to federally funded grants. Such high risk/high yield projects include the development of a web based pain treatment program, research into how dietary changes may affect the gut microbiome and the mind, and research into finding new obesity treatments aimed at the brain gut axis.

Focus on the Gut Microbiota

Research into the makeup and function of the organisms that live in the gastrointestinal tract (the gut microbiome) continues to excite investigators, funding agencies, the media and the lay public more than any other topic in biomedical science. The potential of novel therapies coming out of this research has also gotten the attention of the biotech industry who now sees the possibilities for completely new therapeutic approaches to a wide range of chronic diseases, from autism to obesity and from irritable bowel syndrome to Parkinson’s disease.

Center investigators have been at the forefront of research into brain gut

Continued on page 2



Inside

Focus on the Gut Microbiota ..... 1
What Causes Chronic Pelvic Pain? Progress Toward an Answer ..... 3
CNS Visiting Scholar Program — Featured Trainee ..... 4
CNS Translational Seminar Series — Spotlight on Obesity ..... 4

CHS 42-210
10833 Le Conte Avenue
Los Angeles, CA 90095-7378
(310) 206-0192
uclacns.org
painrepository.org



## Focus on the Gut Microbiota

*Continued from cover*

microbiome communication in human subjects. While a growing number of papers has reported on connections between the gut microbiome and rodent behavior, only very few studies in humans have been published, and none of them has replicated the dramatic animal findings to date. Center investigators Kirsten Tillisch, Jen Labus and Emeran Mayer were the first to demonstrate that manipulation of the healthy gut microbiome by regular intake of a probiotic yogurt influenced the way the brain responds to emotional stimuli (Tillisch et al, *Gastroenterology*, 2013). In follow up research, they have found a relationship between structural brain measures and the composition of the microbiota and gut microbial metabolites

The Center has several ongoing NIH funded studies in this area. One aims to identify the role of gut microbes in weight loss following weight loss surgery and another to characterize the potential role of gut microbiota in the effectiveness of non-pharmacological therapies like cognitive behavioral therapy or mindfulness meditation in irritable bowel syndrome. A donor-supported study on the effects of a vegetarian diet on gut microbial metabolites, brain activity and symptoms is in the planning phase. The Center is actively seeking support from donors, industry and from the NIH to expand and accelerate these research efforts.

Center investigators have not only led the research efforts in this area, but have represented the field to the scientific and lay communities. Kirsten Tillisch participated in a symposium organized by Emeran Mayer at the 2014 Annual Meeting of the Society for Neuroscience in Washington, DC entitled: "Gut Microbes and the Brain: Paradigm Shift in Neuroscience" which was attended by several thousand neuroscientists. Besides Tillisch, speakers included Rob Knight

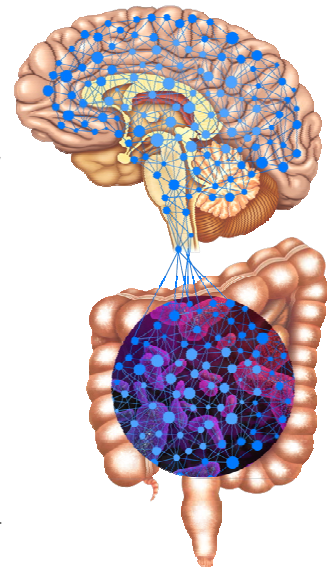
from the University of California in San Diego, Sarkis Mazmanian from the California Institute of Technology and John Cryan from the University of Cork in Ireland. A review article with the same title was published in the prestigious *Journal of Neuroscience*.



*Left to Right: Emeran Mayer, Michael Moss, Paul Simon*

Emeran Mayer was one of 3 invited speakers at the recent 19th Annual UCLA Health Care symposium. The symposium was entitled "A Gut Reaction to Obesity: The Impact of Diet, the Microbiome, and the Environment." Mayer spoke on the role of the gut microbiota in the bidirectional interaction between the gut and the brain in regulating food intake, in particular in the context of food addiction. New York Times bestselling author Michael Moss talked about the board room strategies of America's most recognizable food brands, and the role of the hidden connections between health, nutrition, politics and corporate interests in the current obesity epidemic. Paul Simon, the director of the Division of Chronic Disease and Injury Prevention at the LA County Department of Health talked about some remarkable LA success stories in the fight against obesity, outlined the remaining challenges and talked about novel strategies to fight the obesity epidemic.

Over the next few years we expect that medical researchers, clinicians and the public will be learning much more about the key role for microbiota in maintaining health and how manipulations of the microbiota can help with a variety of illnesses. CNS plans to be a key player in this area given our interest in and unique expertise and abilities to work with the complex systems involved in brain-gut microbiome interactions.



## What Causes Chronic Pelvic Pain? Progress Toward an Answer

Millions of American adults suffer from chronic pain in the pelvic region. This pain can make bladder function, sexual intercourse, even sitting down in a chair excruciatingly painful. This pain can really take a toll on quality of life, and impacts adults of all ages.

Researchers at the Center have been leading a nationwide brain imaging effort to figure out what is causing this pain. This research is part of the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) network, which is sponsored by the National Institutes of Health. The first phase of the study ran from 2008 to 2013, and now center researchers are embarking on the second ambitious 5 year phase of the study.

The MAPP research network studies individuals with urological chronic pelvic pain (UCPPS), that includes overlapping conditions of interstitial cystitis/painful bladder syndrome (IC/PBS) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). In the United States, it is estimated that IC/PBS symptoms affect 2.7% of women and 1.3% of men. It is estimated that CP/CPPS occurs in between 1.8-6.4% of men in the US. These conditions are a tremendous burden to patients and their families, and come at a great economic cost to the healthcare system.

In the first phase of the MAPP study, the UCLA team discovered that patients with chronic pelvic pain were unlike healthy individuals in activity signals coming from certain regions of the brain. One particular region of interest involves processing sensory information and properly controlling pelvic floor muscles. These findings are important, because clinicians have long suspected problems with pelvic floor muscles in people with chronic pelvic pain, but the cause was a mystery. These findings were published in 2014 in the *Journal of Urology*.

Other groups in the MAPP network have made other exciting discoveries about individuals with chronic pelvic pain. MAPP network researchers from Stanford University used computer machine learning algorithms to discover potential predictors of chronic pelvic pain in brain imaging data (published in the journal *Pain* in 2014). And researchers at the University of Michigan discovered that women with chronic pelvic pain have changes in the volume of gray matter in regions of the brain associated with sensation from the pelvic floor (published in the *Journal of Urology* in 2015). Researchers throughout the network continue to look for innovative ways to unite these exciting findings into a comprehensive framework to understand and predict chronic pelvic pain progression based on the structure and function of the brain.

The second phase of the MAPP study to be led by the UCLA team is critical. It will be the first time researchers will be able to see how brain signals change in chronic pelvic pain patients over time. What makes the pain get worse? What makes it get better? The answers to these vexing questions are not far off.



PAIN 

PAIN Repository

All MAPP II neuroimaging data will be uploaded to and curated by the Pain and Interoception Imaging Network (PAIN)

Repository, a newly created NIH funded neuroimaging data repository that aims to accelerate scientific discovery regarding brain mechanisms in all chronic pain conditions, providing more rapid benefits to pain patients, through the harmonization of efforts and data sharing.

To learn more, visit [painrepository.org](http://painrepository.org)

## CNS Visiting Scholar Program – Featured Trainee

Kewin Siah, a Singapore National Medical Research Council (NMRC) research fellow, joined the CNS family January this year. He is a practicing gastroenterologist from National University of Singapore. He completed his undergraduate studies at Royal Free and University College Medical School, London.



Dr. Siah is interested in cross-cultural issues in functional GI diseases research. During his time with CNS, he will be working on a Rome Foundation Research Award project entitled "The Chinese and Caucasian Brain Study: A Neuroanthropological Evaluation of the ROME III criteria." It is a collaborative study by CNS, Singapore's National University Hospital, and China's Sun Yat-Sen University. We plan to use structural and functional brain imaging to characterize brain signatures of patients in two socio-cultural milieu (Chinese vs. American) who present with bloating and fullness as their most bothersome symptoms. The study aims to test the validity of the Rome criteria and fidelity of linguistic translatability of symptom questionnaire as it relates to cultural adaptation of English words to Chinese terms. The study is also a neuro-anthropological exploration of the socio-cultural factors that influence the language that we employ in describing symptoms that are perceived to arise from the gastrointestinal tract.

## CNS Translational Seminar Series – Spotlight on Obesity

As part of its regular CNS Translational Seminar Series, the Center hosted a seminar on Ingestive Behavior and Obesity in which keynote speaker Dr. Helen Raybould spoke on the "Beneficial Effects of Prebiotics in Rodent Diet-Induced Obesity."



Dr. Raybould, a professor of anatomy at UC Davis and a recipient of the Outstanding Women in Gastroenterology Award by the American Gastroenterological Association, presented new research results on the effect of using a milk-derived prebiotic on weight control and appetite, and how these effects may be related to changes in gut microbial composition. Dr. Raybould spoke about studies performed in mice where obesity was induced by a high fat diet. In this model, vagal afferent neurons, the primary nerve pathways that signal food-related information from the GI tract to the brain, no longer respond to the action of the satiety hormone leptin, resulting in an inability to convey intestinal satiety signals to the hypothalamus. This results in hedonic eating, when food intake exceeds the homeostatic need of the animal, e.g. hyperphagia. It appears that this change in the vagal afferent pathway is sufficient to induce obesity, as genetically modified (transgenic) mice that no longer have a receptor for leptin in vagal afferent neurons are hyperphagic, eat larger and longer meals and become obese. These mechanisms can partially explain the development of food addiction in humans, driven by the consumption of the typical American high fat diet.

Dr. Raybould then presented unpublished data that help to understand possible pathways and mechanisms by which these neurons become leptin-resistant. Her laboratory is focusing on identifying the possible role of the gut microbiota and their metabolites in this process, specifically, how high-fat diets produce an inflammatory state of the gut epithelium, alter gut epithelial barrier function to make the gut more "leaky," and possibly allowing for the passage of bioactive molecules produced by the gut microbes to cross the gut epithelium. By this mechanism the microbial metabolites can gain access to vagal nerve terminals and alter their properties. Finally, she presented data to show that addition of complex carbohydrates contained in milk, so called prebiotic milk oligosaccharides, can "rescue" the obesity related changes in mice, by partially restoring the microbial dysbiosis and by preventing the change in barrier function. Dr. Raybould's presentation opened an interesting discussion on the possible benefits of using this intervention on human subjects. These discussions emphasized the importance of interdisciplinary interactions between the various research groups within the Oppenheimer Center to advance knowledge in this field.