Maine Biological and Medical Sciences Symposium: Opioid Session Summary

Introduction
Maine is one of 23 IDeA states, with MDI Biological Laboratory as the lead institution for the NIH-funded INBRE (IDeA Network of Biomedical Research Excellence) program. Additionally, Maine has multiple NIH-funded COBRE centers, with one specifically focused on the study of pain and sensory function, an important component of the opioid crisis. NIH recognizes that these ready-made networks are poised to leverage their biomedical research infrastructure to potentially contribute to strategies to addressing this public health crisis and has issued a call to action. The most recent data from the National Institute on Drug Abuse ranks Maine among the top 10 states with the highest number of deaths involving opioids. The rate was 29.9 deaths per 100,000 persons compared to a national average of 14.6 deaths per 100,000 persons in 2017.

In response to these data and the call to action for IDeA states, we incorporated a session on the opioid crisis, from a research perspective, in our annual INBRE-supported Maine Biological and Medical Sciences Symposium held on April 26-27, 2019 at MDI Biological Laboratory.

Session Title: The Science Behind the Opioid Crisis: From Genetics to Prescribing Practices

The panelists included:

**Moderator:** Karen L. Houseknecht, Professor and Associate Provost of Research and Scholarship, University of New England (UNE)

**Speaker:** Ian Meng, Professor and Director, Center of Biomedical Research Excellence for the Study of Pain and Sensory Function (COBRE), UNE. Topic: Role of pain in opioid abuse and addiction

**Speaker:** Elissa Chesler, Professor, The Jackson Laboratory. Topic: The genetics of addiction

**Speaker:** Vivek Kumar, Assistant Professor, The Jackson Laboratory, Topic: Modeling addiction behaviors in the mouse.

**Speaker:** Leslie Ochs, Associate Professor and Chair, Department of Social and Administrative Pharmacy, UNE. Topic: The role of prescribing practices in the opioid crisis

Introduction to the Opioid Crisis in the US and Maine
Houseknecht, K.

The opioid crisis in the US is well known; today more than 2 million Americans live with addiction to opioids. Chronic pain is an important underlying cause of the opioid crisis as more than 50 million Americans live with chronic pain and treatment protocols often rely on opioid medications. In Maine, rates of opioid misuse and related deaths exceed the national average. The NIH is making large strategic investments in research strategies designed to combat this crisis, including investments in basic research as well as clinical and translational approaches.
Goals of this session included:
1. Highlighting important factors contributing to the opioid crisis
2. Reviewing the biology underlying chronic pain and addiction
3. Exploring the role of prescribing behaviors on opioid abuse and diversion
4. Identifying areas of research expertise within Maine relating to the opioid crisis
5. Exploring areas of collaborative research and education opportunities in Maine
6. Identifying next steps relating to research solutions

Opioid Systems in Pain and Reward
Meng, I.

The brain’s opioid system regulates both pain and reward. This presentation examined the distinct and overlapping pathways through which opioids can inhibit pain and produce reward. Much of the overlap involves the negative emotional consequences of pain and the ability of pain relief to act as a reward. The opioid system includes mu, delta, and kappa receptors. The opposing actions of mu-opioid receptors and kappa-opioid receptors in pain and addiction were discussed, along with changes that occur after chronic exposure to morphine. Dr. Meng provided insight on how the intertwining of pain and reward systems creates challenges when trying to develop new medications for chronic pain that do not have the potential for addiction.

Genetics of addiction and the opioid crisis
Chesler, E.

This presentation focused on individual differences in addiction vulnerability, which are driven by life history, sex differences, genetics and drug exposure. These differences play a role in all stages of addiction and can influence when and how individuals initiate drug use, the amount of drug use necessary to develop an addiction and even the preference for particular classes of drugs. These biological differences in basic behavioral characteristics, drug response and the effects of lasting drug use are evident across species. Genetic studies of addiction provide insights into the biological basis of addiction risk, the molecular mechanisms of addiction and may one day lead to advances in the treatment of addiction. Genetic studies in laboratory mice provide precise and powerful discovery of biological mechanisms of addiction vulnerability, and in the study of effects of addictive substances under carefully controlled conditions. Dr. Chesler shared how using new, advanced mouse populations and bioinformatics tools, it is now possible to connect findings within and across species to understand the interplay of biological variation, drug seeking, drug exposure and biobehavioral effects of drugs.

Actin regulation in drug addiction
Kumar, V.

In another take on genetics and addiction, this presentation focused on drugs of abuse that induce neuroadaptations, including synaptic plasticity, which are critical for transition to addiction, and genes and pathways that regulate these neuroadaptations, which are potential therapeutic targets. Using forward genetic approaches Kumar’s lab has found that members of the Rac and Rho signaling cascade regulate acute, sensitized, and self-administration of cocaine. These include WAVE Regulatory Complex member Cyfip2. In addition, they recently discovered that actin capping protein TMOD2 regulates cocaine responses and that Tmod2.
Tropomodulin 2 (Tmod2) is an actin-regulating gene that plays an important role in synapse maturation and dendritic arborization and has been implicated in substance-abuse in humans. During this presentation, Dr. Kumar provided compelling evidence (using multimodal data from genomics, imaging, and electrophysiology), that Tmod2 is a major regulator of plasticity in the mesolimbic system and regulates the reinforcing and addictive properties of cocaine. In addition, he shared outcomes of efforts to systematically mine data from the Mouse Knockout Project, which included identifying dozens of genes that potentially regulate addiction.

Understanding the Opioid Crisis: Getting to the Heart of the Matter
Ochs, L.

During this presentation, Dr. Ochs shared her research regarding the unnecessary use and overuse of prescription opioids and prescribing practices of these medications. Opioid use and overuse are a source of great concern for families and communities in Maine and throughout the United States. Together with the increasing use of illicit opioids, overuse and misuse of prescription opioids represents an epidemic that contributes to dependency, addition, overdose and death. Dr. Ochs reported data on opioid use and misuse, including the volume of opioid prescriptions, overuse of opioid prescriptions, and prescribing trends for opioid medications in concert with other medications of potential abuse.

Panel Discussion
- There was a lot of discussion around opioid prescribing data and about how we got to the point of overusing and overprescribing opioid medications. There were questions on the pharmaceutical industry’s role in the current situation. The discussion also included role of health care providers and patients in addressing this problem and how it will be essential for all entities to work together in developing solutions. Session participants expressed concern and had questions about the quantity of medications returned unused during Medication Take Back Programs in the state of Maine and around the country. In addition, the audience was surprised to learn that 75% of prescription pain medications are returned unused. The discussion quickly turned to questions about the health care costs associated with the return of these medications, and more importantly that these unused medications may be obtained from family members and/or friends or stolen from unsecured medicine cabinets. There were questions about why large quantities of prescription medications are being prescribed as well as the environmental impact of the disposal of these medications.
- The speakers discussed the many possible synergies with existing COBRE and INBRE partners that may help to address the opioid crisis
- Panelists from The Jackson Laboratory described the new JAX Center on Addiction Biology, which brings together addiction biologists with genetics and genomics experts at The Jackson Laboratory. The Center is willing and able to organize statewide meetings to facilitate collaboration.
- There was mention of the fact that there are not many researchers studying addiction in Maine relative to the scope of the problems and breadth of research opportunities. Those that are doing research in this area are distributed throughout many institutions state wide and a unifying organization would foster further collaboration and growth of research in this area.
- Infrastructural needs including model organism behavioral research facilities for access by investigators across Maine, and a need for state funded faculty positions were also highlighted to expand the available expertise for Maine researchers and clinicians to draw on.
• There was some discussion about next steps including a possible follow-up full day event including presentation of clinical research ongoing in Maine and collaboration with policy makers on science funding in this area
• It was noted that Northern New England Clinical and Translational Research (CTR) is engaged in opioid-related clinical research and should be part of future events/discussion on building collaborative research networks in Maine/the region around this issue. They have funding from NIGMS to study the role of statewide legislation in controlling opioid prescriptions and hospital visits for opioid overdose. In addition, the CTR funded a pilot project on morphine use and bone loss in mice. They also funded a project thru CTR on endocarditis prevalence and drug abuse in northern New England.

Outcomes and Optimism for the Future

The opioid crisis in Maine is at a turning point. There are multiple strategies being implemented throughout the state to combat this significant public health threat. Maine Governor Janet Mills named Gordon Smith, MD as Director of Opioid Response in Maine, and in July 2019 the Governor’s office convened an Opioid Summit “Turning the Tide” which included federal and state leaders in healthcare, policy, law enforcement who discussed interdisciplinary solutions for the state and region (http://www.cvent.com/events/2019-maine-opioid-summit-turning-the-tide-maine-s-path-forward-in-addressing-the-opioid-crisis-me-80/custom-19-db20cfeaaaaa04b26a01d884108fa6c3a.aspx).

As an outcome of the opioid session at the Maine Biological and Medical Sciences Symposium, MDI Biological Laboratory developed an INBRE short course for undergraduates from Bates College called “Gut Biology”. Students in the course helped to pilot a study on the effects of cocaine addiction on the microbiomes of mice. This was a collaborative effort with scientists from Elissa Chesler’s research team at The Jackson Laboratory working with leading microbiome expert George Weinstock of The Jackson Laboratory for Genome Medicine in Farmington, CT. In addition, Dr. Chesler spoke with undergraduate honors students in their seminar at Colby College last spring. Panelist Vivek Kumar was invited to return to MDI Biological Laboratory to present a Science Café titled The Genetics of Addiction for a general audience in September 2019. As another next step, University of New England is hosting a harm reduction conference in October 2019. Future plans include developing areas of research synergy and opportunities to build out the opioid and other addiction research capacity in Maine.