

# Discovery and Validation of Biomarkers to Develop Non-Addictive Therapeutics for Pain

*Washington Marriott Wardman Park*

*2660 Woodley Road N.W., Washington, DC 20008*

**November 14-15, 2018**

## **Introduction**

More than 25 million Americans suffer from daily chronic pain, a highly debilitating medical condition that is complex and difficult to manage. In recent decades, there has been an overreliance on the prescription of opioids for chronic pain, contributing to an epidemic of opioid overdose deaths and addictions. Innovative scientific solutions to develop alternative treatment options for pain management are thus needed. NIH recently released a research plan for a broad and aggressive effort to accelerate scientific solutions to address the opioid crisis. The [NIH HEAL \(Helping to End Addiction Long-Term\) Initiative](#) will advance research to develop safer therapies for people with pain through a multi-pronged approach.

The challenges facing the development of non-opioid alternative pain medications include: challenging and costly clinical design requirements, poor predictive power of preclinical models, and a paucity of validated targets. In addition, patient populations are heterogeneous across multiple pain conditions, with broad variability in individual responses to interventions. Another major barrier to advancing new pain treatments is the inability to measure objectively the biological effect of a treatment in these complex patients.

The NIH HEAL Initiative provides funds for research to discover and validate biomarkers for pain that can serve as such objective measures that will help define patient populations for clinical trials. The use of objective biomarkers and endpoints throughout the drug discovery and development process is critical, as it would help to define pathophysiologic subsets of pain, evaluate target engagement of new drugs, and predict analgesic efficacy of new drugs. Nevertheless, such biomarkers and endpoints remain limited and very few have been validated.

Therefore, the overarching purpose of this workshop is: 1) to inform the community about current regulatory standards and guidelines for the development of biomarkers and endpoints, 2) to evaluate the state of the science in pain biomarker development and 3) to explore potential scientific and collaborative approaches that could facilitate the discovery and validation of robust biomarkers and endpoints that would provide the tools necessary for the diagnosis and treatment of pain conditions.

## **Workshop Goals**

- Inform the community about current regulatory standards and guidelines for the development of biomarkers and endpoints
- Explore the state-of-the-science of different types and modalities of biomarkers for chronic pain and identify the research needed to stimulate their development in a manner that will withstand rigorous validation
- Identify roadblocks and gaps in the development of strong candidate biomarkers and endpoints for chronic pain indications that will withstand rigorous validation
- Identify opportunities to address challenges and gaps
- Convene academic, biopharmaceutical industry, and government scientists working on biomarker identification and discovery to share and discuss progress, successes, challenges, gaps, and potential solutions going forward

## **Workshop Deliverables**

- Recommendations/guidelines for best practices in biomarker discovery and validation
- Publication of a white paper summarizing workshop findings/guidelines
- Formation of a core working group representing government, academia and industry that regularly convenes to evaluate progress and remaining challenges in the area of pain biomarker and endpoint development

## AGENDA

**Wednesday, November 14, 2018**

<b>7:00 AM – 4:35 PM</b>	<b>REGISTRATION</b>
<p>8:00 – 8:15 AM</p> <p>8:15 – 8:35 AM</p> <p>8:35 – 8:45 AM</p>	<p><b><u>Session I: Welcome and Overview of the Workshop</u></b>            Session Chair: <i>Simon Tate, PhD</i></p> <p><b>Workshop Goals, Logistics, and Charge to Audience</b></p> <ul style="list-style-type: none"> <li>○ <i>Mary Ann Pelleymounter, PhD, NINDS, and Simon Tate, PhD, Bridge Valley Ventures, Co-Chairs Workshop Organizing Committee</i></li> <li>○ <i>Victoria Smith, PhD, NINDS, Co-Chair Workshop Organizing Committee</i></li> <li>○ <i>Dave Thomas, PhD, NIDA, Workshop Organizing Committee</i></li> </ul> <p><b>Opening Remarks: Clinical Significance/Context for Workshop/NIH HEAL Initiative</b></p> <ul style="list-style-type: none"> <li>○ <i>Walter J. Koroshetz, MD, NINDS Director</i></li> <li>○ <i>Wilson M. Compton, MD, MPE, NIDA Deputy Director</i></li> </ul> <p><b>The Need for Predictive Markers in Non-Addictive Pain Management: A Patient's Perspective</b></p> <ul style="list-style-type: none"> <li>○ <i>Christin Veasley, BSc, Co-Founder and Director, Chronic Pain Research Alliance</i></li> </ul>
<p>8:50 – 9:05 AM</p> <p>9:05 – 9:30 AM</p> <p>9:30 – 9:50 AM</p>	<p><b><u>Session II: Overview of the Biomarker Discovery and Development Process</u></b>            Session Chair: <i>David Wholley, MPhil</i></p> <p><b>Introduction to Session: Pain Biomarkers in the Era of Personalized Medicine-based Clinical Design – Sean Mackey, MD, PhD</b></p> <p><b>Biomarkers 101: Biomarker Types, Modalities, and an Overview of the Biomarker Development Process – Christopher Leptak, MD, PhD</b></p> <p><b>Clinical Outcome Assessments in Medical Product Development – Elektra J. Papadopoulos, MD, MPH</b></p>
<b>9:50 – 10:00 AM</b>	<b>BREAK</b>
<p>10:00 – 10:15 AM</p> <p>10:15 – 10:35 AM</p>	<p><b>Biomarker Development in the Pharmaceutical Industry: Challenges and Approaches – Michael E. (Ted) Burczynski, PhD</b></p> <p><b>Panel Discussion Led by Speakers</b></p> <ul style="list-style-type: none"> <li>○ <i>Discussion Questions: What degree of validation is necessary for Phase II and Phase III clinical trials? How is context of use decided? How will this apply to pain indications?</i></li> </ul>

	<p><b><u>Session III: Biomarker Types: Advances and Special Challenges</u></b>  Session Chair: <i>Christine Sang, MD, MPH</i></p> <p>10:35 – 10:45 AM      <b>Overview of Biomarker Types: Advances and Special Challenges</b>  – <i>Christine Sang, MD, MPH</i></p> <p>10:45 – 11:00 AM      <u>Treatment Response Prediction Biomarkers</u>  <b>Predicting Analgesic Response to Acupuncture – Preliminary Results from Two Clinical Trials</b> – <i>Jiang-Ti Kong, MD, MS</i></p> <p>11:00 – 11:15 AM      <b>Development of a Chronic Pain Treatment Prediction Tool</b>  – <i>Karen Davis, PhD, FCAHS</i></p> <p>11:15 – 11:30 AM      <u>Diagnostic Pain Condition Biomarkers</u>  <b>Stratifying Neuropathic Pain by Spinal Electrophysiology</b> – <i>Nigel Calcutt, PhD</i></p> <p>11:30 – 11:45 AM      <b>Sleep Interruption as a Biomarker of Spontaneous Neuropathic Pain</b>  – <i>Clifford J. Woolf, MB, BCh, PhD</i></p> <p>11:45 AM – 12:00 PM      <u>Biomarkers for Progression of Pain – Multimodal Approach</u>  <b>Multimodal Models Predicting Transition to Chronic Pain and Placebo Response in Patients with Chronic Pain</b> – <i>Vanya Apkarian, PhD</i></p> <p>12:00 – 12:15 PM      <u>Biomarkers for Target Engagement</u>  <b>PET Imaging as a Biomarker for Target Engagement</b> – <i>Mike Iadarola, PhD</i></p> <p>12:15 – 12:35 PM      <b>Panel Discussion Led by Speakers</b></p> <ul style="list-style-type: none"> <li>○ <i>Discussion Questions: What are the “low hanging fruit” for pain and pain treatment outcome biomarkers and how can we use lessons learned from their development to most quickly provide tools for non-addictive therapy development?</i></li> </ul>
<p><b>12:35 – 1:20 PM</b></p>	<p><b>LUNCH</b></p>
	<p><b><u>Session IV: Biomarker Modalities – Advances and Special Challenges</u></b>  Session Chair: <i>Irene Tracey, MA (Oxon), DPhil, FRCA, FMedSci</i></p> <p>1:20 – 1:35 PM      <u>Overview of Session:</u> <i>Irene Tracey, MA (Oxon), DPhil, FRCA, FMedSci</i></p> <p>1:35 – 1:50 PM      <u>Imaging Biomarkers</u>  <b>Imaging Pain and Analgesics: Brain and Peripheral Biomarkers</b>  – <i>David Borsook, MD, PhD</i></p> <p>1:50 – 2:05 PM      <b>Neuroimaging-based Biomarkers for Pain: From Measures to Interventions</b>  – <i>Tor D. Wager, PhD</i></p>

2:05 – 2:20 PM	<b>Functional and Neurochemical Brain Markers of Diagnosis and Treatment Prediction in Chronic Pain – Richard E. Harris, PhD</b>
2:20 – 2:35 PM	<u>Quantitative Sensory Testing Biomarkers</u> <b>Potential Utility of Quantitative Sensory Testing as a Biomarker</b> – Roger B. Fillingim, PhD
2:35 – 2:50 PM	<b>Quantitative Sensory Testing in the Research Setting – Challenges and Opportunities</b> – Roy Freeman, MD
<b>2:50 – 3:00 PM</b>	<b>BREAK</b>
3:00 – 3:15 PM	<u>Fluid Biomarkers (Genetic/Proteomic/Metabolomic)</u> <b>Biopsychosocial and Genomic Biomarkers for Individualized Integrative Pain Care – The Horizon</b> – William Maixner, DDS, PhD
3:15 – 3:30 PM	<b>Epiregulin Signals Through Epidermal Growth Factor Receptor to Produce Pain</b> – Luda Diatchenko, MD, PhD
3:30 – 3:45 PM	<u>Biomarker “Fingerprint” or Signatures</u> <b>Neural Pain Signatures for Rats, Dogs, and Humans: Hardware and Software</b> – Carl Saab, MS, MA (Hon), PhD
3:45 – 4:00 PM	<b>Biomarker Signatures for Neurological Disorders: Building and Validating Predictive Models</b> – Hartmuth Kolb, PhD
4:00 – 4:20 PM	<b>Panel Discussion Led by Speakers</b> ○ Discussion Questions: How will challenges be overcome? Where do each of these biomarker modalities fit in the future of therapeutic development and clinical practice? What are the special challenges with biomarker signatures?
4:20 – 4:35 PM	<b>Introduction to Clinical Endpoints</b> <b>Bedside Sensory Testing of Chronic Pain Patients: An Example of Development and “Commercialization” of a Predictive Biomarker for Clinical Trials</b> – Nathaniel Katz, MD, MS
<b>4:35 – 6:00 PM</b>	<b>Networking Session</b>

Thursday, November 15, 2018

<p>8:00 – 8:15 AM</p> <p>8:15 – 8:30 AM</p> <p>8:30 – 8:45 AM</p> <p>8:45 – 9:05 AM</p>	<p><b><u>Session V: Clinical Endpoints for Pain and Device Therapeutics</u></b>            Session Chair: <i>Ajay D. Wasan, MD, MSc</i></p> <p><u>Development of Brain and Spinal Cord-based Behavioral/Psychosocial Biomarkers</u></p> <p><b>The Neural Correlates of Chronic Pain and the Impacts of Negative Affect on Pain Treatment Response – <i>Ajay D. Wasan, MD, MSc</i></b></p> <p><b>Functional Neuroimaging of Psychosocial States: The Identification of “Process” Biomarkers – <i>Robert R. Edwards, PhD</i></b></p> <p><b>Device-based Chronic Pain Therapies, Biomarkers and Digital Tools – <i>Juan Hincapie, PhD</i></b></p> <p><b>Panel Discussion Led by Speakers</b></p> <ul style="list-style-type: none"> <li>○ <i>Discussion Questions: What is the optimal strategy to validate COAs and endpoints for pain?</i></li> </ul>
<p>9:05 – 9:20 AM</p> <p>9:20 – 9:40 AM</p> <p>9:40 – 9:55 AM</p> <p>9:55 – 10:10 AM</p>	<p><b><u>Session VI: Emerging Tools and Approaches in Biomarker Discovery and Development</u></b>            Session Chair: <i>Martin S. Angst, MD</i></p> <p><u>New CNS Biomarkers: Challenges Along the Way and How They Were Met</u></p> <p><b>CNS Biomarkers: Lessons Learned and New Opportunities – <i>Lino Becerra, PhD</i></b></p> <p><b>Predictive Validity of Human Laser-EPs in Extended Phase-I IND Analgesic Research – <i>Klaus Schaffler, MD</i></b></p> <p><u>Multomic and Computational Approaches to Biomarker Discovery</u></p> <p><b>Use of Machine Learning to Guide Pain Biomarker Development – <i>Jing Wang, MD, PhD</i></b></p> <p><b>Emerging Tools and Approaches in Biomarker Discovery and Development: Mass Cytometry and Data Integration – <i>Martin S. Angst, MD</i></b></p>
<p><b>10:10 – 10:20 AM</b></p>	<p><b>BREAK</b></p>
<p>10:20 – 10:35 AM</p> <p>10:35 – 10:55 AM</p>	<p><u>Mobile Detection Devices/Signatures for Endpoints and Clinical Outcomes</u></p> <p><b>Using Wearable, Sensor, and Behavior Signals to Develop Digital Biomarkers – <i>Ernesto Ramirez, PhD</i></b></p> <p><b>Panel Discussion Led by Speakers</b></p> <ul style="list-style-type: none"> <li>○ <i>Discussion Questions: How realistic are these new approaches and how can we encourage people to work on “out of the box” approaches? How can we better educate the community to form multi-disciplinary teams?</i></li> </ul>

	<p><b><u>Session VII: Technical and Decision-related Challenges in Translating Biomarkers and Endpoints into Therapeutic Development and Clinical Practice</u></b>  Session Chair: <i>Simon Tate, PhD</i></p> <p><u>Biomarker Development in the Context of Clinical Trials; Decision-Making Variables</u>  <b>Use of Human Experimental Models of Pain as a Biomarker for Unprecedented Analgesic Targets</b> – <i>Eric Nisenbaum, PhD</i></p> <p><b>What Makes a Biomarker Valuable for a Clinical Trial in Pain?</b>  – <i>Joachim Scholz, MD</i></p> <p><b>Of Platforms, Baskets, and Biomarkers: Adaptive Clinical Trials in Other Diseases to Pain Research</b> – <i>Donald A. Berry, PhD</i></p> <p><u>Biomarker Development Process in the Context of Clinical Practice; Decision-making Variables</u>  <b>Neuroethical Issues Related to the Adoption of Biomarkers for Pain Diagnostics and Treatment</b> – <i>Karen Davis, PhD</i></p> <p><b>The Challenge of Inequities, Diversity, and Inclusion: The Need for New Science and Policy to Improve Quality of Care and Life</b> – <i>Carmen R. Green, MD</i></p> <p><b>Panel Discussion Led by Speakers</b></p> <ul style="list-style-type: none"> <li>○ <i>Discussion Questions: What is the real problem in developing non-addictive therapeutics for pain? What is the real issue in developing biomarkers to guide treatment decision-making in clinical situations?</i></li> </ul>
<p><b>12:30 – 1:15 PM</b></p>	<p><b>LUNCH</b></p>
	<p><b><u>Session VIII: Moving Forward</u></b>  Session Chairs: <i>Martha A. Brumfield, PhD, and Joseph Menetski, PhD</i></p> <p><u>Overview of Session</u>  <b>Potential Pathways for Facilitating Biomarker Development</b>  – <i>David Wholley, MPhil</i></p> <p><u>Driving Innovation in Clinical Trial Strategies</u>  <b>Challenges and Opportunities for Innovation</b> – <i>Joachim Scholz, MD</i></p> <p><b>Biomarkers to Address Clinical Hypotheses and Trial Endpoints for Pain</b>  – <i>Andrew H. Ahn, MD, PhD</i></p> <p><u>Public Private Partnerships</u>  <b>How the FNIH Biomarker Consortium Has Achieved Impact: Multiple Paths to Success</b> – <i>Joseph Menetski, PhD</i></p>

2:05 – 2:20 PM	<p><b>Advancing Innovation in Regulatory Science through Public Private Partnerships – A Focus on Biomarker Development</b>  – <i>Martha A. Brumfield, PhD</i></p>
2:20 – 2:35 PM	<p><u>Collaborative Science for Advancing from Discovery to Clinic</u>  <b>Collaborative Approaches to Advance Translational Research</b>  – <i>Lara Mangravite, PhD</i></p>
2:35 – 2:55 PM	<p><b>Panel Discussion</b> – <i>Martha A. Brumfield, PhD, and Joseph Menetski, PhD</i></p> <ul style="list-style-type: none"> <li>○ <i>How can biomarkers have the greatest impact on clinical trials?</i></li> <li>○ <i>What is the most effective way to facilitate collaborative approaches to biomarker and endpoint development?</i></li> </ul>
2:55 – 3:10 PM	<p><b>Workshop Summary and Panel Discussion:</b> <i>Simon Tate, PhD</i></p> <ul style="list-style-type: none"> <li>○ <i>Workshop Recommendations: Best Practices, Meeting Challenges</i></li> </ul>
3:10 – 3:30 PM	<p><b>Closing Remarks:</b> <i>Mary Ann Pelleymounter, PhD</i></p>
<b>After Workshop</b>	<p><b>1) White Paper Outline and Organization discussion for 30 minutes with email/phone follow-up, 2) Working Group Formation/Outline Concept for Dynamic Problem-Solving Forum</b></p>