

# The Helping to End Addiction Long-term (HEAL)

## HEAL Partnership Committee

### FNIH Informational Interviews - Executive Summary

The HEAL Partnership Committee (HPC) has witnessed the development of the HEAL Initiative from its very beginnings. In 2018, the NIH led a workshop on Biomarkers to Develop Non-Addictive Therapeutics for Pain which convened scientific leaders from academia, industry, government and patient advocacy groups to discuss progress, challenges, gaps and ideas to facilitate the development of biomarkers and end points for pain. The outcomes of this workshop are published in [Nature Reviews Neurology](#). The pain therapeutic field has evolved over the course of the last 2 and a half years since the launch of HEAL and the NIH sought to hear from the HPC members what has changed particularly in regards to biomarker development, as biomarkers are recognized as being important for all aspects of therapeutic development. To gather this information, FNIH conducted interviews with members of the HPC to solicit their expertise on biomarker development, and to assess what has changed in the field.

The following questions were developed by NIH and FNIH to help gather information for the NIH, as part of ongoing efforts to advance pain therapeutics through the NIH HEAL Initiative and below is a summary of the HPC member responses.

#### **What is the pipeline for pain therapies that are coming to clinical trials in the next 5 years?**

Most respondents could not identify specific drug assets that are upcoming within pain therapy pipelines. The pain research field appears to be shifting away from ion channel-focused therapies and broad pharmacotherapies toward more specific mechanisms of action or non-pharmacologic therapies (e.g., mindfulness, Cognitive Behavior Therapy). Respondents emphasized that the field needs to focus on understanding the underlying mechanisms of pain and to use information about those mechanisms to match patients with specific pain therapies, and in order to identify the mechanisms driving pain conditions, researchers need access to better mouse models and human biospecimens.

Therapies with novel mechanisms of action are appealing to many in the pain field, but these therapies tend to have unfavorable safety profiles. Respondents expressed interest in developing biomarkers of (1) central pain sensitization, (2) specific pain indications (to identify homogeneous populations for clinical trials), including visceral pain and pain that differentially affects specific racial groups (e.g., sickle cell disease-mediated pain), and (3) placebo effect prediction. Biomarkers that can help select therapies for patients should be prioritized over objective measures of pain.

#### **What decision(s) are most impacted by the availability of biomarkers during non-addictive pain therapy development?**

Respondents agreed that the pain research field would benefit from prognostic biomarkers (to identify patients at increased risk for progressing to severe pain) as well as biomarkers that enable patient stratification (to identify patients that would most likely benefit from a specific therapy). However, the current state of science may not support the development of such biomarkers and thus more basic science investigations are needed to uncover target mechanisms that cause specific pain types. Respondents noted that increasing the number of biomarker studies that integrate multiple omics types may lead to identification of more robust biomarkers.

Some respondents emphasized the need for therapies to include mindfulness and quality-of-life measures because many of the symptoms that patients are concerned about are not related to pain, but instead to loss of feeling or loss of sleep. Biomarkers of quality-of-life measures may be helpful to assess these symptoms during Phase II studies.

**If you have no pain pipeline, would the availability of appropriate biomarkers encourage you to reenter the pain therapy space? What types of biomarkers would be most needed?**

- Diagnostic biomarkers
- Prognostic biomarkers for patient stratification
- Target engagement biomarkers

Also discussed, but had less consensus from respondents

- Biomarkers of placebo effect, Biomarkers of addiction potential, Biomarkers evaluating the neuro immune relationship in relation to pain, and Standardized Digital Monitoring Biomarkers

**In your experience, what degree of validation for pharmacodynamic biomarkers is necessary for the purposes listed below?**

- a. Internal decision making*
- b. Support an IND package*
- c. Phase I trial*
- d. Surrogate endpoint*

Most respondents noted that pharmacodynamic biomarkers are most helpful for internal decision making, particularly to ensure the asset in development deserves continued funding for development. Respondents emphasized that the pain research field does not yet have the evidence base to begin validating biomarkers.

**How can a NIH clinical trial setting be most useful in developing a pain biomarker (any type)?**

- a. To provide an appropriate setting for a prospective designed study to identify new biomarkers*
- b. As a source for standardized, annotated retrospective and prospective samples*
- c. To provide an appropriate setting for definitive, multi-site studies or trials specifically designed to validate a set of biomarkers*

Most respondents preferred option (a) to facilitate prospective clinical trials that are required to collect multi-dimensional measures and samples, and that are either analyzed in a biomarker add-on study to the clinical trial or stored in a repository for later analyses; some respondents emphasized that these clinical trials should focus on multiple pain indications in order to identify common biomarkers. Respondents noted that the quickest method to identify biomarkers would be to leverage existing datasets from past or ongoing clinical trials and perform analyses, possibly using artificial intelligence or machine learning tools. Some respondents favored option (b), emphasizing that the pain research field would benefit from well-phenotyped patient samples. One respondent recommended pursuing these options in order, beginning with (a) as the logical first step to evaluate biomarkers. One respondent noted that option (c) is preferred only if an existing set of biomarkers are ready for validation, which the pain field does not appear to have available.

**What are the biggest challenges to matching the timing of biomarker development from academic groups to the drug development cycle time for a pain therapeutic?**

Respondents noted that most challenges in the pain biomarker field are not related to timing, and that most companies have left the field because of the opioid epidemic and a resulting fear of creating more agents with abuse liabilities. However, one respondent emphasized that companies will not become involved with academic groups until studies are sufficiently underway. The fact that an academic group is assessing biomarkers for a specific agent may then lead to that agent being prioritized within a company's pipeline. Some respondents emphasized that the development of biomarkers in academia will likely incentivize collaborations between academic and industry organizations within the pain therapeutic field. One respondent recommended that NIH create a network of academic centers of excellence with the overarching goal to facilitate pain biomarker studies across multiple pain indications; such infrastructure would help enable academia-industry partnerships.

**In general, how could NIH play the most effective role? How should NIH provide resources and best disseminate information?**

Suggestion from respondents were as follows:

- Use NIH resources to facilitate collaborations by holding workshops/meetings that convene pain basic science researchers and clinicians.
- NIH could release RFAs to fund basic research on the mechanisms that drive pain in both the preclinical and clinical settings.
- NIH funded prospective trials should involve the collection of multi-dimensional measures, imaging data, and omics data types for use and analysis of the scientific community.
- NIH could create a network of centers that investigate biomarkers across pain conditions.
- NIH could create a repository of multiple types of samples from well-phenotyped patients and make those samples available to researchers for biomarker studies.
- NIH could focus research on the transition from acute to chronic pain.
- NIH could focus on (1) developing, standardizing, and validating digital biomarkers, (2) facilitating standardized clinical trials that test multiple agents across multiple pain conditions, and (3) evaluating biomarkers for neuroimmune interactions.