Executive Summary
HEAL Pain Research Priorities Workshop: Non-Addictive Pain Therapeutics Development
Friday, November 15th, 2024 10am-2pm ET

Subcommittee members: John Markman, MD (co-chair); Ted Price, PhD (co-chair); Joyce T. Da Silva, PhD; Kristy Fischmann, JD; David Julius, PhD; Anne-Marie Malfait, MD, PhD; Ana Moreno, PhD; Daniela Salvemini, PhD; Will Schwalbe; Prasad Shirvalkar, MD, PhD; Todd Vanderah, PhD; Beth Winkelstein, PhD

Lived Experience Perspectives on Chronic Pain – Will Schwalbe and Kristy Fischmann, JD, Persons with Lived Experience (PWLE)
People using prescription pain medications often face a burdensome tradeoff: pain relief for side effects. Compromised sleep, cognitive ability, and weight gain in particular seriously impact quality of life, although experience is very personalized. These PWLE emphasized the need for more basic science to understand the mechanisms behind chronic pain, which will lead to more therapeutic choices for people living with pain, including topical agents. A representative from the US Pain Foundation recommended conducting a survey of PWLE on the very individualized experience of treatment side effects.

Why Basic Research Remains an Essential First Step in Assessing and Treating Chronic Pain – David Julius, PhD; Panelists: Joyce T. Da Silva, PhD, Will Schwalbe, Anne-Marie Malfait, MD, PhD, [moderated by Ted Price, PhD]

Takeaways:

- Basic science is essential to medical breakthroughs; the only way medicine can lead to cures is through a mechanism-based approach.
- We need to be targeted but patient; therapeutic research and development takes years beyond initial discovery, and sometimes “failure” needs another route to development.
- Drugs targeting peripheral cells may be the best strategy to avoid central side effects.
- Researchers still have much to learn about DRG neuronal connections and communications
- We really still need biomarkers for pain mechanisms and target engagement.
- Pain affects different tisues with different mechanisms, and we need to understand these to resolve them.

Discussion: Panelists voiced concerns about the cost of (and need for support for) preclinical research using complex models and aged animals; and the need to validate mouse findings in human tissues as in the HEAL PRECISION network. The great hope is that basic science will identify the biology to halt or reverse the disease processes of pain. Panelists agreed that prevention and disease-modifying therapeutics should be investigated further.

Disease-Specific Mechanism Discovery for Pain and Disease Modification – Anne-Marie Malfait, MD, PhD; Panelists: John Markman, MD, Prasad Shirvalkar, MD, PhD, Will Schwalbe and Kristy Fischmann, JD; [moderated by Ted Price, PhD]

Takeaways:

- Osteoarthritis (OA) and joint pain diseases make up a large share of chronic pain. We should be looking for peripheral drivers of chronic pain in these conditions.
- Need to study condition-specific mechanisms using tissue obtained from people. The HEAL REJOIN network is using basic science to understand the joint tissue environment.
- OA is a complex, dynamic disease involving changes in all joint tissues and cells, and affected by age, weight, other health conditions, and pain itself. It is difficult to model in animals – how should that be pursued?

- The discordance between damage seen with imaging and pain (in OA, back pain) remains mysterious – understanding that could help us understand the biology.
- Mechanisms behind rare and common diseases are not understood, from Ehlers-Danlos Syndrome (EDS) to low back pain, and many are not being studied at all but could offer important clues.

Discussion: By better profiling pain phenotypes, we may learn what is driving each specific condition, and different targets may emerge. It may be beneficial to target a condition/ tissue feature, like a cellular change, that occurs across several conditions, rather than focus on an OA treatment per se. Also: Studies of mechanism of action for devices (SCS, TMS) would spur more FDA approval for these effective treatments with limited access.

Therapeutic Discovery for Pain – Daniela Salvemini, PhD; Panelists: Ted Price, PhD, Todd Vanderah, PhD, and Kristy Fischmann, JD [moderated by John Markman, MD]

Takeaways:

Focus on resolution of [neuropathic] pain: G-protein-coupled receptors (GPCRs) are druggable targets, including 120 orphan receptors withunknown endogenous ligands. Example of work to characterize and de-orphanize GPCR160, a receptor found to be upregulated in neuropathic pain states in rodents; expressed in human microglia; required for maintenance of pain; and now an endogenous ligand transcript is being characterized. An antagonist blocks pain behavior, allodynia in mice. This is an example of HEAL basic research making progress. It's critical to continue these programs, provide tools to translate innovative ideas from bench to bedside, improve care and basic biology understanding, especially without industry investment.

Discussion:

Price agreed that HEAL support has "been totally transformative for the kind of work we do," from basic discovery to Phase I/II trial transition. Support from the NIH comes not just in the form of funding but also from advisors and contractors who assist with the drug-development process. Much success in drug delveopment has come from back-translation of detailed phenotyping – in other words, taking indepth information from people with pain conditions and applying that to a mechanistic model back at the lab bench. Not all basic science is hypothesis-driven; sometimes a keen sense of observation by clinicians learning from PWLE and by researchers in human tissues that has led to new insights. Discussion emphasized moving high quality targets into drug development for pain as an important step to developing alternatives to opioids.

Small Business Innovation for Pain – Ana Moreno, PhD; Panelists: Daniela Salvemini, PhD, Ted Price, PhD [moderated by John Markman, MD]

Takeaways:

Overview of Moreno's experience taking her basic science research as a graduate student to development at a startup company, including with HEAL SIBR grants. The therapy uses epigenetic suppression of Nav1.7. She expressed a major need for biomarkers specific to de-risk drug development processes like target engagement, metabolism, etc.

A comment from the webinar chat summarized many points of discussion during the session: "Most rodent models and outcome measures in pain are mainly focused on the biology of nociceptive processing and resulting behaviors, but not chronic pain. The emotional, subjective, individual health & comorbid (or co-occuring) health condition components are missing in these models, and are difficult to assess. As mentioned earlier, emphasis on reverse-translational approach to model human pain conditions and associated disease & comorbid conditions to understanding the biology of ongoing human pain conditions are the needs for the field, which have been ignored or sidelined for decades."