

NIH HEAL INITIATIVE

Helping to End Addiction Long-term

June 9, 2021

HEAL Partnership Committee (HPC) Meeting

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National Institutes of Health
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Agenda

- Welcome, Review of Agenda, and HEAL Director's Update
  Rebecca Baker, Director, HEAL Initiative, Office of the Director, National Institutes of Health

- Update: EPPIC Net
  Linda Porter, Director, National Institutes of Health's Office of Pain Policy

- HPC Interviews Discussion
  Joe Menetski, Vice President, Research Partnerships at FNIH
  - Original HPC Biomarker Recommendations from 2018
  - HPC Responses Overview
  - Group Discussion

- Translational Science Training Discussion
  Christine Colvis, Director, Drug Development Partnership Programs, National Center for Advancing Translational Sciences (NCATS) – Discussion Lead

- Next Steps and Closing
  Rebecca Baker, NIH Office of the Director

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Director's Update

June 9, 2021

Rebecca Baker,

Director, HEAL Initiative, Office of the Director, NIH

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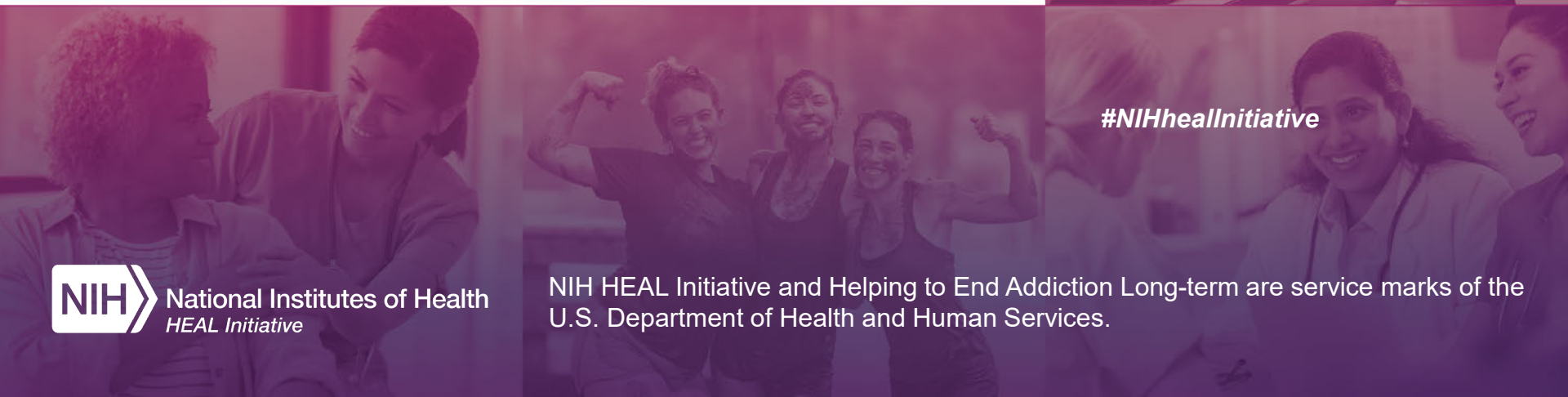

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HEAL Initiative

Joining the Power of Science with the Strength of Community

- Over $1.5 billion in research
- More than 500 research projects
- Promotes teamwork across disciplines, communities, and care settings
- Partnership with stakeholders

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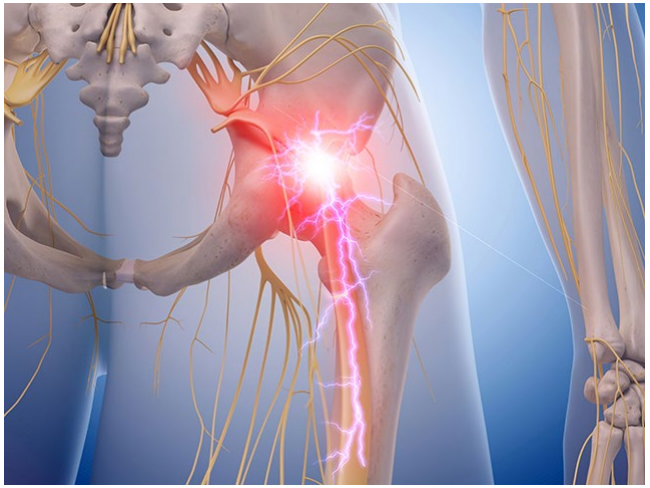
NIH HEAL INITIATIVE RESEARCH OVERVIEW

Preclinical and Translational Research in Pain Management

- Discovery/validation of targets
- Optimizing therapeutics
- Devices
- Human-based model systems
- Candidate testing for nociception, addiction, and overdose
- Biomarkers, signatures and endpoints

Accomplishments in Preclinical and Translational Research in Pain Management

- 2 patents for small molecule modulators of pain receptors; for chronic pain and migraine
- Portable thermoelectric device to inhibit pain signals in two different peripheral nerves
- Investigational New Drug (IND) for a first-in-class non-additive drug candidate for the treatment of chronic pain



Clinical Research in Pain Management

- Early Phase Preclinical Investigation Network (EPPIC Net)
- Back Pain Consortium (BACPAC)
- Hemodialysis Opioid Prescription Effort (HOPE)
- Pain Effectiveness Research Network (Pain ERN)
- Pragmatic and Implementation Studies for Management of Pain to reduce opioid prescribing (PRISM)

Clinical Research Accomplishments in Pain Management

- Data harmonization through core Common Data Elements
- Iterative model - precision medicine for chronic low back pain
  - from anxiety to tissue damage, psychotherapy to surgery
- IND for buprenorphine in multidisciplinary pain management for people on dialysis

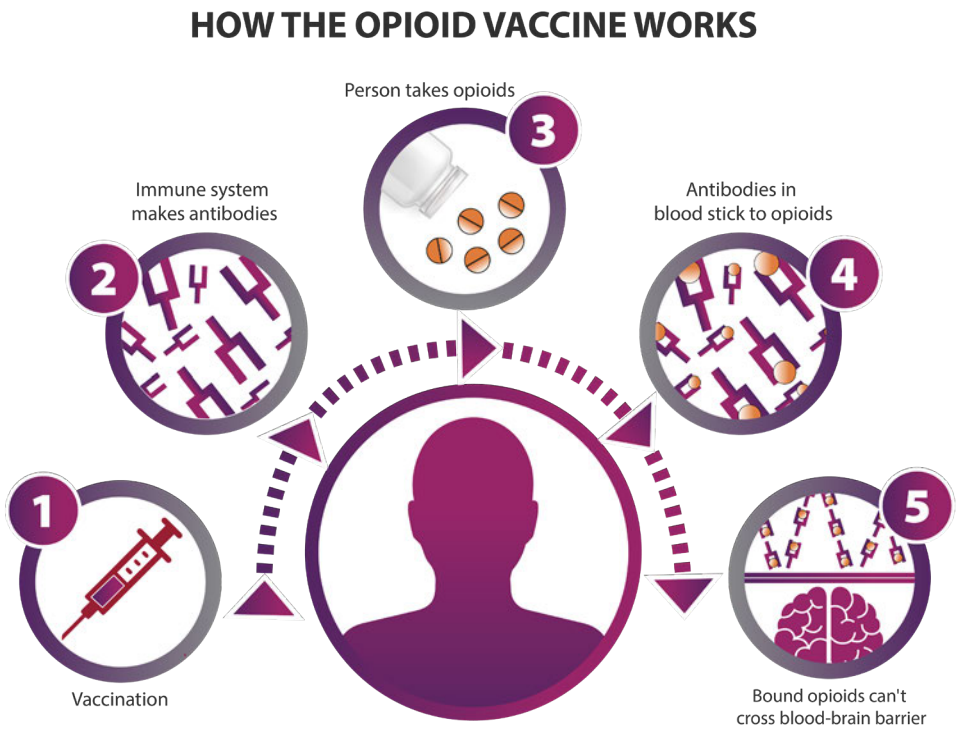
Novel Therapeutic Options for Opioid Addiction and Overdose

Novel medications, immunotherapies, and devices to treat withdrawal, craving, progression, and relapse

- 32 New Molecular Entities (NME) and 23 repurposed medications.
- 50+ compounds being developed from early preclinical to late clinical phases
- Anti-opioid immunotherapies (vaccines and monoclonal antibodies)

Therapeutic Development Research Accomplishments:

- 16 INDs been filed with FDA
  - Exceeding HEAL Initiative goal of 15 INDs in 5 years
- *Biologics:* First study in humans of an opioid vaccine
- *Devices:* One IDE to study Deep Brain Stimulation for OUD



Enhancing Outcomes for Infants and Children

- ACT-NOW now enrolling for all three studies in 23 sites nationwide
- MRI compatible crib to improve imaging of sleeping newborns and infants
- 2 small business received FDA Breakthrough Devices Designation for non-pharmacological, noninvasive treatments for NOWS

Prevention and Treatment for OUD

- Enhanced Rx opioid registry with harmonized EHR for:
  - Monitoring opioid dose reduction, tapering
  - Examining changes in opioid Rxs for acute pain, surgery
- PHARMSCREEN validated OUD-risk measure to identify high risk opioid use patterns for early intervention

Translation of Research to Practice for OUD

- Local communications campaigns
- Data tools
- National opinion surveys on perceptions of OUD and stigma
- Emerging best practices for criminal justice agencies

Adapting Research Interventions for COVID-19

- Strategies for social connection in virtual setting
  - e.g. virtual cooking sessions
- Participants recruited in the ED followed by phone after discharge
  - Choice of communication medium (phone, video chat, What's Ap or mail)

Data-driven collaboration and discovery

- Data and information sharing is a cross-cutting theme
- ***Vision***: an integrated, FAIR biomedical data ecosystem
- HEAL Data Ecosystem resources accelerate discoveries

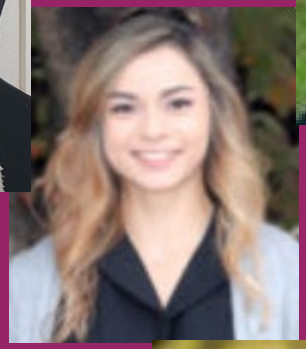
HEAL Annual Report

High-level summary of progress achieved by the end of 2020

- Strengthening existing strategies
- Advancing promising therapeutics through the clinical trial pipeline
- Building infrastructure and tools
- Defining non-opioid targets for both pain and OUD

And much more…







HEAL Community Partner Committee

- Patients, advocates, liaisons, and family members
- Input on key issues faced by individuals affected by pain and addiction
- Identify, refine, and prioritize engagement activities and links to HEAL science

Annual HEAL Investigators Meeting

- Resilience and ingenuity of the scientific community
- Responsive to changing landscape and emerging trends
- Focus on health equity and culturally tailored interventions
- Strength-based approaches for patients

Open funding opportunities... and more to come!

Early Phase Pain Investigation Clinical Network (EPPIC-Net) Pain Research Asset Application OTA-21-005

Small Business Innovation Research

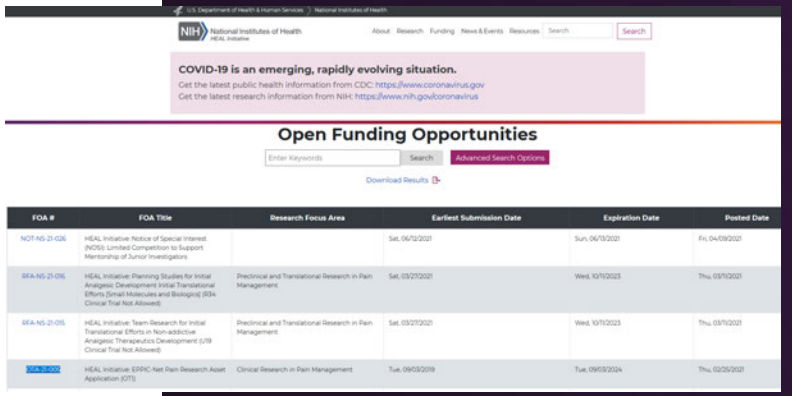
- Development of Therapies and Technologies Directed at Enhanced Pain Management RFA-NS-20-009; RFA-NS-20-011
- America's Startups and Small Businesses Build Technologies to Stop the Opioid Crisis RFA-DA-19-019; RFA-DA-19-020

Medication Development

- Development of Medications to Prevent and Treat Opioid Use Disorders and Overdose PAR-20-092

Preclinical Analgesic Development

- Planning Studies for Initial Analgesic Development Initial Translational Efforts [Small Molecules and Biologics] RFA-NS-21-016
- Team Research for Initial Translational Efforts in Non-addictive Analgesic Therapeutics Development RFA-NS-21-015
- Non-addictive Analgesic Therapeutics Development [Small Molecules and Biologics] to Treat Pain RFA-NS-21-010



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Update: EPPIC Net

June 9, 2021

Linda Porter, Director OPPP

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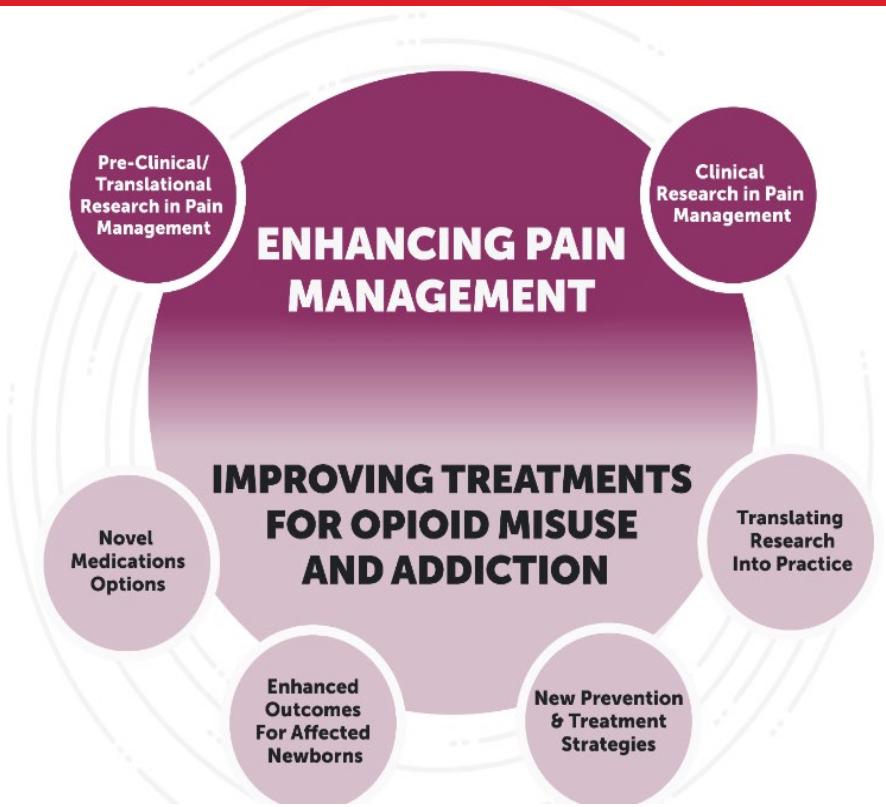
EPPIC-Net Update

Linda Porter, PhD

Barbara I. Karp, MD

June 9, 2021



Genesis of EPPIC Net: 2017 Meetings to Address the opioid crisis

Goal: reduce the time for drug development by half

Strategy: a program to accelerate pain therapeutics

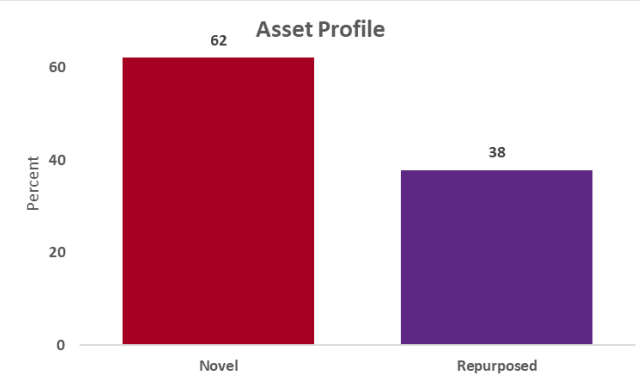
Problem: 2005-2015: 1/16 compounds failed in the pipeline, most at phase 2

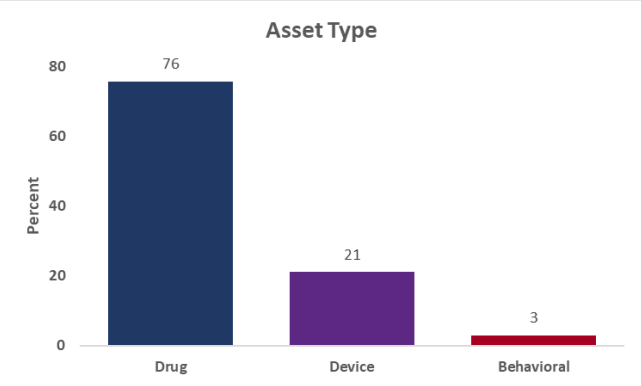
Response: EPPIC Net :

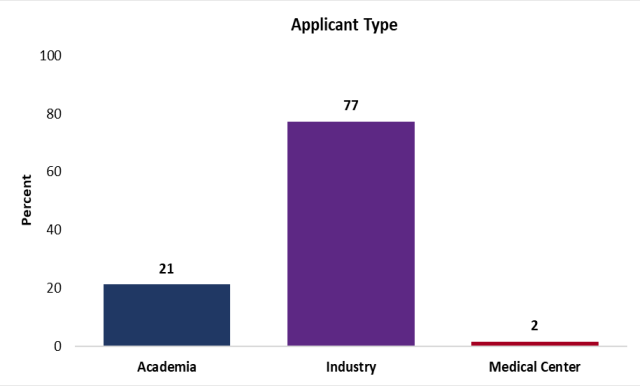
- provide high quality, innovative and efficient trials
- develop objective biomarkers and endpoints
- attract promising assets
- renew industry interest in analgesic development
- mitigate regulatory hurdles of risk in high prevalence, heterogenous populations

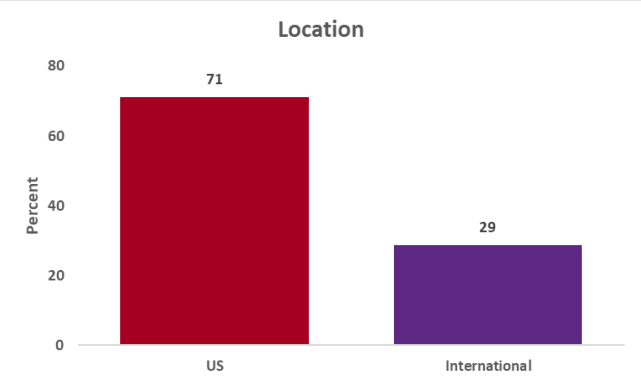
Asset Applications

66 preliminary applications reviewed between Oct 30, 2019 and Apr 28, 2021









<u>Primary reasons preliminary applications did not move forward:</u>

- Not phase 2 ready (35%)
- No improvement over current treatments (27%)
- Weak scientific basis (16%)
- Safety concerns (adverse events, narrow therapeutic window, no safety data) (12%)
- Commercially available/no need for phase 2 (6%)
- Not a pain therapeutic or pain biomarker (2%)
- Opioid with addiction potential (2%)

Asset Summary

- Small molecules targeting a wide range of pain receptors and pathways
- Topical analgesics
- Neuromodulation devices
- Anesthetic blocks
- Biobehavioral apps

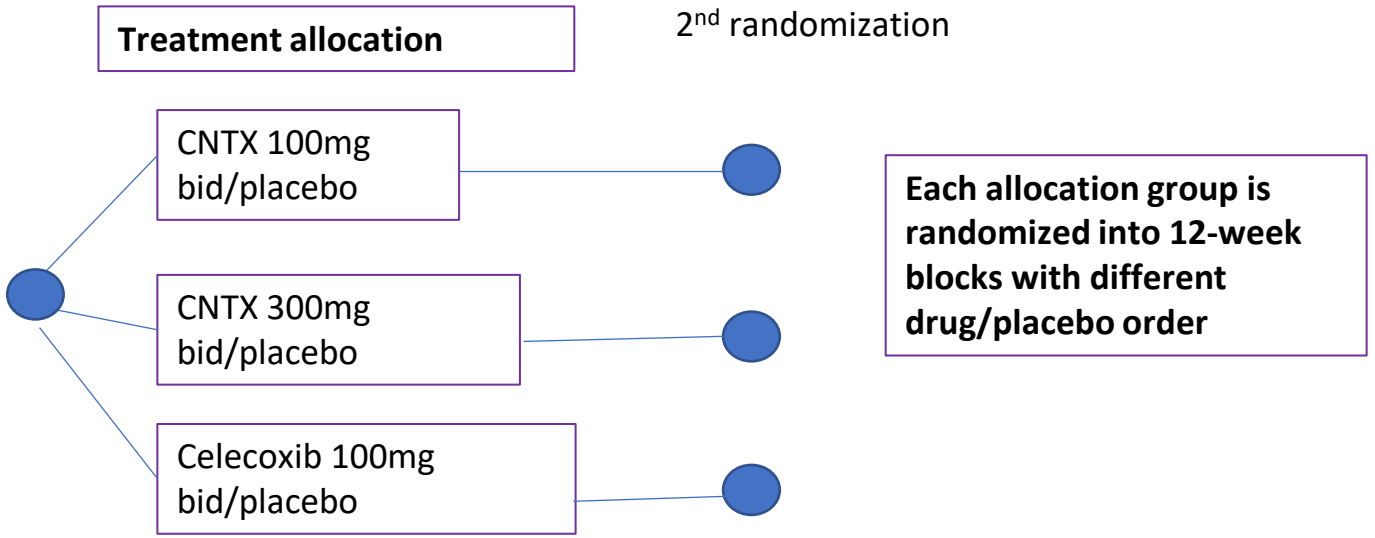
Targeted conditions

- Acute/post-surgical pain
- Neuropathies/neuropathic pain
  - Diabetic
  - Chemotherapy-induced
  - Small fiber
- Low back pain
- Osteoarthritis
- Headache (migraine/non-migraine)
- Post-herpetic neuralgia
- Fibromyalgia
- Skin graft pain
- Complex regional pain syndrome
- Chronic central pain
- Traumatic neuralgia
- PTSD pain
- Erythromelalgia
- Bladder pain
- Chronic pelvic pain

EN01: A 24-week Week Study to Evaluate the Safety and Efficacy of CNTX-6970 in Subjects with Moderate to Severe Knee Osteoarthritis Pain

CNTX-6970: Small molecule, chemokine receptor 2 (CCR2) > CCR5 antagonist

Enrollment planned for **August 2021**



EPPIC-Net Master Protocol for Platform Trials

Why a master protocol?

- Applicant interest
- Efficiencies:
  - Minimize start-up time to enrollment
  - Common procedures
  - Common equipment
  - Shared resources/training
  - Shared controls (placebo/active comparator)

Pain condition of focus?

- Neuropathy is target indication for many preliminary applications
- Common condition/access to diverse population of patients

Input from HPC

- Ways to enhance outreach and bring in more high quality assets?
- Master platform protocol
  - What special features to consider in design of the platform?
- Many preliminary applications fail because the asset is not phase 2 ready.
  - Should EPPIC-Net provide earlier phase resources to applicants to help meet these needs?

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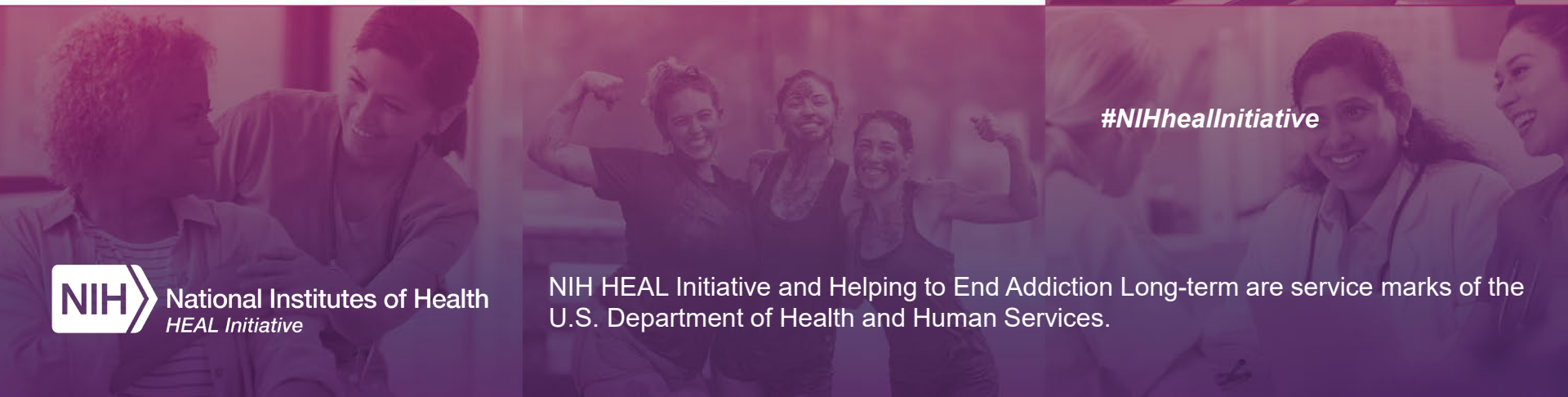
HPC Interviews Discussion

June 9, 2021

Joe Menetski,

Vice President, Research Partnerships at FNIH



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Original HPC Biomarker Recommendations from 2018

- **Focus on pharmacodynamic and predictive biomarkers**
- **Priority uses for pharmacodynamic and predictive biomarkers:**
  - Monitor therapeutic efficacy
  - Stratify patients into biological mechanism-defined subgroups for clinical testing
  - Serve as adjunct endpoints for efficacy but not replace subjective pain perception
- **Biomarkers of interest:**
  - Mechanistic markers associated with numerous and diverse pain conditions
  - Multiple markers whose combined effects (signature) are more powerful and clinically meaningful as objective markers of pain unique to the condition
  - Quantitative sensory testing, brain imaging, biofluid omics assays, genetic markers, and patient report measures

HEAL Biomarker Efforts To-date

- ✓ Initial input received from NIH/HEAL stakeholders was to focus on biomarkers to accelerate development of pain therapeutics:
  - pharmacodynamic
  - predictive biomarkers to stratify patients in clinical trials.
- ✓ Published two 5-year funding opportunities with partnership of 14 participating NIH Institutes and Centers in 2018.
  - Didn't receive any pharmacodynamic or predictive biomarker proposals
  - Funded nine projects primarily prognostic/diagnostic biomarkers for patient stratification in clinical trials across multiple conditions
- ✓ Solicited PD and target engagement biomarkers as part of therapeutics development programs.
- ✓ Held 2018 NIH HEAL Workshop to evaluate the status of pain biomarker research published in Nature Reviews Neurology:
  - Importance of composite biomarker "signatures" to treat complex disease/conditions
  - Patient stratification biomarkers
- ✓ Now further evaluating the HEAL Biomarker Program relative to development with ongoing pain therapeutic program.

Biomarker Efforts Integrated Into the Target Discovery and Therapeutic Development Programs

HEAL FOAs
***RFA-NS-21-016**
***RFA-NS-21-015**
Initial Efforts in Analgesic Development

HEAL FOA
***RFA-NS-21-010**
Pharmacodynamic Biomarkers Used for PK/PD

HEAL Biomarker Program
Biomarker Discovery:
Patient stratification/
Prognostic/Diagnostic Biomarkers
9 projects across 8 pain conditions

A2CPS (Common Fund)
Post-Surgical
Acute to Chronic Pain
Deep Phenotyping
BACPAC (HEAL)
Chronic Back Pain
Deep Phenotyping

HEAL FOAs
***OTA-20-002**
(EPIC-NET) Ph II
Sample/Data Repository
Biomarker Development Included

Remaining Gaps
- **Discovery of biomarker in context of pain pathophysiology**
- **Surrogate Endpoints**

***Active Funding Opportunity**

Background for Interview Request

- HEAL launched many programs in 2019 and is now systematically evaluating areas for new opportunities and programs based on the current state of the science.

- The interviews are being used to assess the current field in order to capture what has :
  - changed over the last 2 years, or
  - stayed the same over the last 2 years.

HPC Member Interviews

- Interviewed 10 HPC Members representing FDA, Industry, Academia, and Patient Advocates

- 7 Questions designed to help identify potential areas of future opportunities for pain biomarker research and advancing therapeutic development in pain

Question 1:

In terms of biomarkers, from your perspective, what is the pipeline for pain therapies that are coming to clinical trials in the next 5 years?

a) Are those therapies directed to a specific pain indication and if so, please list which conditions?

Q1 Areas of general agreement:

- Not many therapies in the pipeline
  - Mechanisms that drive pain are unknown and therefore the field is not ready for biomarker development
- There has been an exodus from the pain therapeutic space
- A better understanding of the underlying mechanisms of pain is required, only then can patients be matched with specific pain therapies
- Biomarkers that can help select therapies for patients should be prioritized over objective measures of pain.

Question 2:

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

a) In your opinion, where in the therapeutic development process do you encounter challenges/barriers where you would need a biomarker?

b) Is there a specific category of biomarker that is particularly needed for specific decision points in the therapy development process? Could you provide examples of specific categories of biomarkers that are needed at specific decision points in the therapy development process?

Q2 Areas of general agreement:

- The pain research field would benefit from biomarkers including those that:
  - Identify patients at increased risk for progression to a given severe pain indication
  - Identify biomarkers that would enable patient stratification based on pain mechanism
- **Current state of science may not support the development of such biomarkers**
- **More basic science investigations are needed to uncover target mechanisms that underly specific pain types.**

Q2 Areas for further discussion:

- Biomarkers of quality of life should be explored
- Biomarkers of placebo effect – high placebo response
- **Clinical and research fields are traditionally siloed** and do not engage in regular communication. This likely prevents progress in the field of pain biomarkers and therapeutic clinical trials.

Question 3:

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?

Q3 Areas of general agreement:

- Diagnostic biomarkers
- Biomarkers for patient stratification
- Target engagement biomarkers
  - normally done by the therapy sponsor, but need tools

Q3 Areas for further discussion:

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

Question 4:

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

a) Internal decision making

b) Support an IND package

c) Phase I trial

d) Surrogate endpoint

Q4 Areas of general agreement:

- Biomarkers are most helpful for internal decision making, particularly to ensure the asset in development deserves continued development.
- The pain research field does not yet have the evidence base to begin validating biomarkers of any type.

Question 5:

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

1. To provide an appropriate setting for a prospective designed study to identify -new biomarkers
2. As a source for standardized, annotated retrospective and prospective samples
3. To provide an appropriate setting for definitive, multi-site studies or trials specifically designed to validate a set of biomarkers - Validation level based on previous question 4 if biomarker type is pharmacodynamic

Q5 Areas of general agreement:

- Option 1
  - Use of a trial to prospectively identify a new biomarker
- Option 2
  - Use of a trial as a source of standardized, annotated samples for retrospective identification of a biomarker
- Option 3
  - Use of a trial to validate a biomarker

General Response

Most liked

Next most liked

Field not ready

Q5 Areas for further Discussion:

- Set of collaborative infrastructures to work across pain would be helpful.
  - Importance of fostering collaboration between oncologists and pain specialists
- Utilization of existing biobanks; MAPP or OPERA
  - Use of machine learning or deep learning AI methods to identify biomarkers from existing biobank data
- Clinical trials network for a prospective study looking at multi-dimensional measures
  - Evaluate pain responses and improvement with known analgesic agents to have benchmarks and understand what opioids do to these biomarkers
  - Pain phenotyping
- Discovering biomarkers to differentiate people with chronic pain

Question 6:

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?

a) If you have partnered with an academic group to develop a biomarker how have you resolved those timing issues?

b) What are the additional challenges to academic collaborations focused on delivery of a biomarker for use in pharma besides timing?

Q6 Areas of general agreement:

- Timing doesn’t tend to be a problem and there are multiple ways on how companies work with academia to address
- Some companies prefer that an academic biomarker project must be advanced in order to match the needs of the company
- Certain types of biomarkers (target engagement, for example) are typically developed by the company rather than an academic collaborator

Question 7:

In general, how could NIH play the most effective role?

How should NIH provide resources and best disseminate information?

Q7 Areas for Further Consideration:

- Facilitate collaborations by holding workshops/meetings that convene pain basic science researchers and clinicians.
- Fund basic research on the mechanisms that drive pain in both the preclinical and clinical settings.
- Prospective trials should involve the collection of multi-dimensional measures, imaging data, and omics data types for use and analysis of the scientific community.
- Create a network of centers that investigate biomarkers across pain conditions.
- Create a repository of multiple types of samples from well-phenotyped patients and make those samples available to researchers for biomarker studies.
- Focus research on the transition from acute to chronic pain.
- Focus on:
  - developing, standardizing, and validating digital biomarkers
  - facilitating standardized clinical trials that test multiple agents across multiple pain conditions
  - evaluating biomarkers for neuroimmune interactions.

Discussion

- Surprises?
- Anything missing?
- Priorities and Timeframe



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Translational Science Training Discussion

Christine Colvis, Director, Drug Development Partnership Programs, National Center for Advancing Translational Sciences (NCATS)

June 9, 2021

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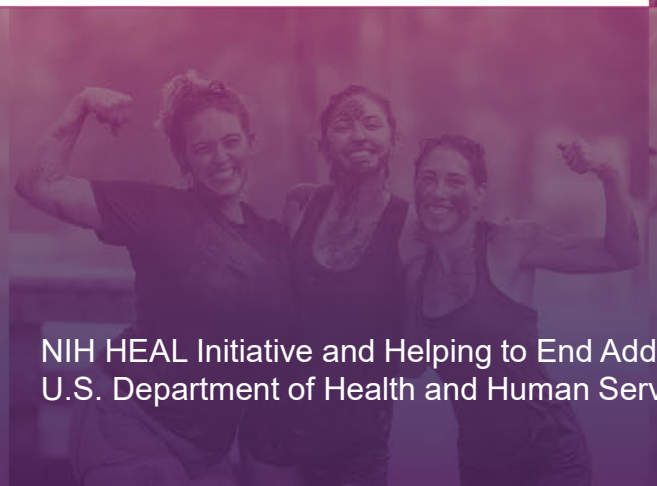


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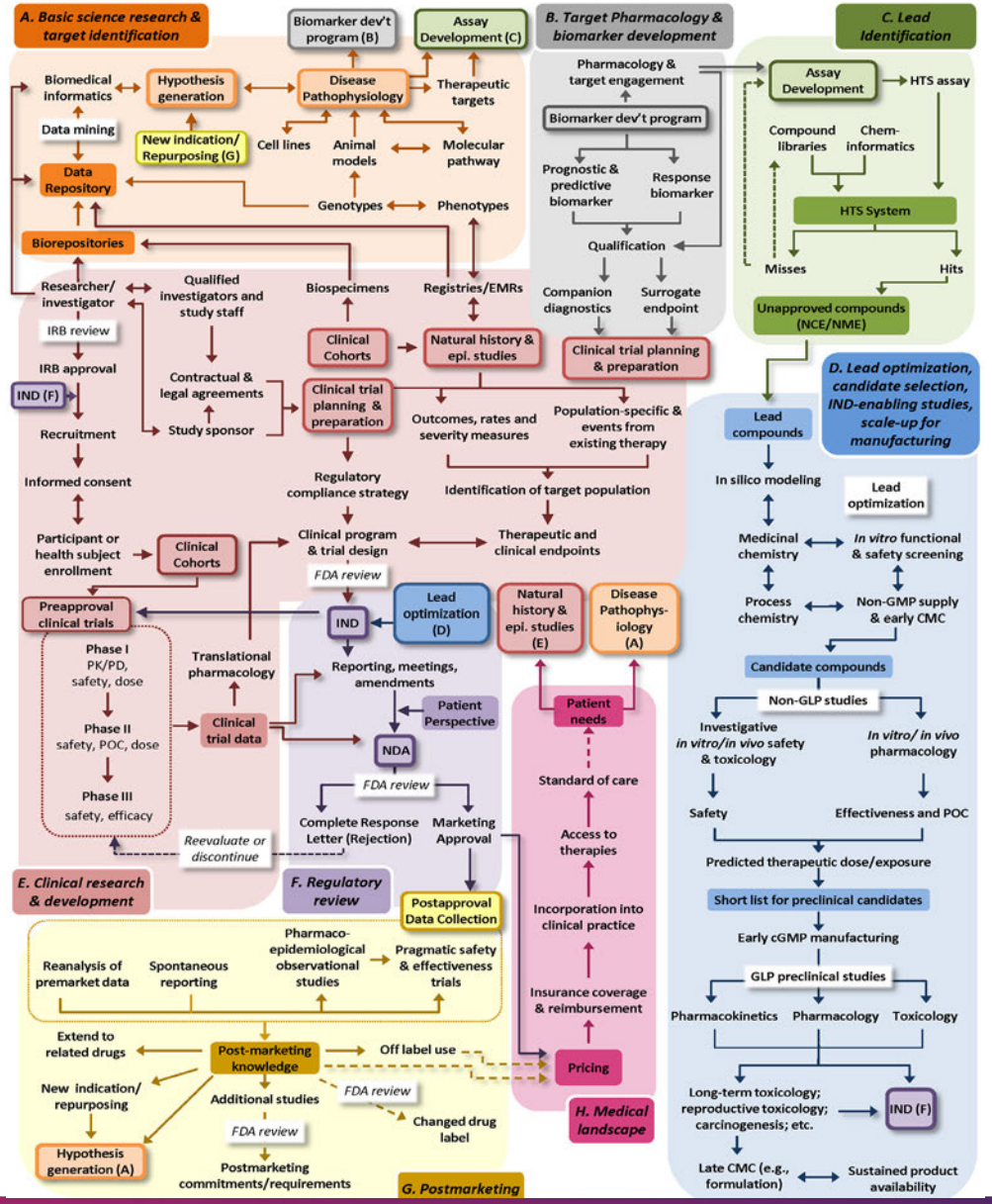
Background

- Drug discovery, development and deployment is extraordinarily complex
- Academic science often focuses on basic mechanism
- Biomedical training within academia often sacrifices breadth of knowledge for deep expertise in a specific field



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Background

- Lack of workplace diversity in biomedical research, particularly within therapeutic discovery and development

Diversity in science: next steps for research group leaders

Many institutions publicly pledged their commitment to inclusion in research after Black Lives Matter protests this year. And academics emphasize the need to maintain momentum. **By Nikki Forrester**

Sparked by the global reaction to the police killing of George Floyd, an unarmed Black man, in Minneapolis, Minnesota, in May, universities, departments and faculty members rapidly issued statements and policies highlighting their commitment to diversity and equity in academia. Conversations on how to create a more equitable research environment erupted on social media, and data on the lack of diversity in academia were thrown into stark relief.

In the United States, for instance, 13% of the population is Black, but Black researchers comprise just 6% of faculty positions in science, technology, engineering and mathematics (STEM). According to the Pew Research Centre in Washington DC, 62% of Black STEM employees in the United States say they have experienced racial or ethnic discrimination at work, and 57% say their workplaces do not pay enough attention to racial and ethnic diversity.

Although some scientists feel hopeful about

OUR COMPANY

Johnson & Johnson to Address Racial and Social Injustice Through Platform that Aims to Eliminate Health Inequities for People of Color

Johnson & Johnson commits $100 million over the next five years to invest in and promote health equity solutions

Bristol Myers Squibb and the Bristol Myers Squibb Foundation Commit $300 Million to Accelerate and Expand Health Equity and Diversity and Inclusion Efforts

Five–year commitment builds on long-standing investment in health equity

Research Need

- Provide HEAL funding to support early- and mid-career scientists with pain or opioid abuse expertise to receive immersive training in therapeutic development at an academic or government translational research center or in an industry setting

- Directly address the lack of workplace diversity in drug development by specifically providing translational training to individuals from underrepresented groups

Goal: Build a workforce of investigators better equipped to translate scientific discoveries into clinical breakthroughs

Initiative Details

- Two separate FOAs
  - One that is general for scientists in pain, addiction, and overdose field
  - One for scientists from “Underrepresented Populations in the U.S. Biomedical, Clinical, Behavioral and Social Sciences Research Enterprise”

- Funding directed to individual scientists in pain, addiction, and overdose field to receive training at site doing drug development.
  - Funding to cover:
    - Up to 12m salary/fringe benefits
    - Small amount for research development costs

Opportunity Objectives

- This opportunity will populate the pain, addiction, and overdose fields with **scientists better equipped** to design experiments with a focus on **translating discoveries to impact health**

- Cultivate a **diverse workforce** that holds a broad understanding of the translational process to enable **development of therapeutics** to treat pain, addiction, and overdose

- An **inclusive workforce** will be better equipped **to find scientific solutions** to address health inequalities that affect minority populations

Initiative Details

- Trainees to be embedded in translational research environment within:
  - Academia
  - Government
  - Industry

Discussion

Specific questions for the HPC:

- Are there skills and expertise that you think are vital, yet often lacking, in new hires?

- How do we make participation attractive to industry?
  - What are the primary barriers to participation?

- How do we ensure training sites will facilitate training across multiple steps in the translational pipeline?

Additional Comments?


THANK
YOU