Review of NIH Programs for Developing and Testing Pain Treatments

HEAL Partnership Committee Meeting
March 5, 2019

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NIH HEAL Initiative: Priorities for Enhancing Pain Management

- Understand the biological underpinnings of chronic pain
- Accelerate the discovery and pre-clinical development of non-addictive pain treatments
- Advance new non-addictive pain treatments through the clinical pipeline
- Establish the best pain management strategies for acute pain and numerous chronic pain conditions

Read about the 2019 research plan:

www.nih.gov/heal-initiative

NIH - Helping to End Addiction Long-term
In 2017, NIH invested $516 million on pain research

Pain cuts across all 27 NIH Institutes and Centers

The NIH Pain Consortium was established with the goal of enhancing pain research and promoting collaboration across NIH
HEAL Programs for Pain Cover the Research Spectrum

- **Discovery**
  - Acute to Chronic Pain Signatures
  - Discover and Validate Novel Targets for Safe and Effective Pain Treatment
  - Preclinical Screening Platforms + Novel Drug Development
  - Translating Discoveries Into Effective Devices For Pain Treatment
  - Discovery and Validation of Biomarkers, Biomarker Signatures, and Endpoints for Pain Indications
  - Data & Asset Sharing Partnership
  - Back Pain Research Consortium
  - Hemodialysis Pain Management

- **Preclinical Development**

- **Clinical Trials**
  - Early Phase Pain Investigation Clinical Network

- **Implementation/Dissemination**
  - Pain Effectiveness Research Network
  - Pragmatic and Implementation Studies for the Management of Pain

**NIH**
National Institutes of Health
Turning Discovery Into Health
Understand the biological underpinnings of chronic pain
Understand the biological underpinnings of chronic pain

- Acute to Chronic Pain Transitions Program
- Objective biosignatures to identify susceptibility or resilience to chronic pain
  - Phenotyping, genotyping, sensory tests, imaging, -omics
- Prevention Outcomes
  - Mechanisms; Novel therapeutic targets
  - Cohort stratification
    - Risk of chronic pain
    - Risk of long term opioid use
- Structure: Clinical Coordination Center, Clinical Centers, Omics Data Generation Centers, Data Integration and Resource Center
- Awards expected Spring 2019
Accelerate the discovery and pre-clinical development of non-addictive pain treatments

- Discovery and Validation of Biomarkers, Biomarker Signatures, and Endpoints for Pain Indications
- Discover and Validate Novel Targets for Safe and Effective Pain Treatment
- Preclinical Screening Platforms + Novel Drug Development
- Translating Discoveries Into Effective Devices For Pain Treatment
- Acute to Chronic Pain Signatures
Discover and Validate Novel Targets for Safe and Effective Pain Treatment

- To promote the basic science discovery and validation of **novel targets** for the treatment of pain that can be used to develop treatments that have minimal side effects and little to no abuse/addiction liability.

Discover and Validate Novel Targets for Safe and Effective Pain Treatment

• **Target Discovery**
  • For small molecules
    • Channels, lipids, enzymes
  • For biologics
    • Peptides, cell-based therapies, antibodies
    • DREADD (Designer Receptors Exclusively Activated by Designer Drugs) technique
  • For devices
    • Nerves for neuromodulation devices, electrophysiological signatures of pain, sites for combination pumps

• Projects also include a strong rationale and/or experiments to demonstrate that the target does not pose a significant abuse liability

RFA-NS-18-043 – R01
RFA-NS-18-042 – R21
NOT-NS-18-073 – Administrative Supplements
Reduce reliance on opioids through the enhanced targeting and reduced invasiveness of diagnostic and therapeutic devices to manage pain.

- Leverage ongoing mapping / target discovery activities in BRAIN, SPARC, and other HEAL Initiatives
- Late stage device development
- Verification and validation to accelerate regulatory approval
- Early clinical studies to de-risk new and improved pain treatments
Translating Discoveries into Effective Devices for Pain Treatment

An Amygdalar Neural Ensemble Encodes the Unpleasantness of Pain
Corder G, Ahanonu B, Grewe BF, Wang D, Schnitzer

- Can BRAIN Initiative science translate circuit activity into an assay for developing non addictive therapeutics?
  - Silencing BLA neurons in people with chronic low back pain?
Human Cell-based Screening Platforms and Novel Drugs to Treat Pain, Addiction, and OD

- Support preclinical optimization and development of safe, effective, and non-addictive small molecule and biologic therapies to treat pain
- Develop human cell/tissue models
  - Peripheral and central nervous system
  - Normal and disease states
  - iPSC-derived neurons, 3D printed organoids, tissue chips
- Advance investigational drugs for new targets
  - Human tissue constructs to identify new probes/drug leads
  - Automated chemical synthesis
  - Artificial Intelligence to identify new chemical structures
  - IND-enabling studies: Optimization of Non-addictive Therapies [Small Molecules and Biologics] to Treat Pain

RFA-NS-19-010
RFA-NS-19-020 (SBIR)
Preclinical Screening Platform for Pain (PSPP)

• Establish a one-stop preclinical testing platform that promotes the testing and characterization of non-addictive modalities for the treatment of pain
• Incentivize academia & industry to accelerate discovery of non-addictive, effective therapies
• Develop or refine animal models of pain conditions-available to research community
• Generate high quality data to support partnerships, translational programs
• Provide access to research community

Preclinical Screening Platform
• In vitro μ-opioid receptor screening
• Acute pain models
• Chronic pain/disease models
• In vivo addiction screening

Small molecules  Biologics  Devices  Natural products

Successful compounds/devices move to clinical trials
• Goal: facilitate the discovery and development of high-quality biomarkers to accelerate the development of non-addictive therapeutics for the treatment of pain conditions

• Advanced analytical and clinical validation of pain biomarkers, biomarker signatures, and/or endpoints using retrospective and/or prospective methods: RFA-NS-18-046

• Identification and initial biological, analytical and clinical validation of pain biomarkers, biomarker signatures, and/or endpoints: RFA-NS-18-041
Discovery and Validation of Biomarkers, Biomarker Signatures, and Endpoints for Pain Indications

Discover and Validate Novel Targets for Safe and Effective Pain Treatment

Preclinical Screening Platforms + Novel Drug Development

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Data & Asset Sharing Partnership

Early Phase Pain Investigation Clinical Network

Back Pain Research Consortium

HEAL Programs for Pain Cover the Research Spectrum
Early Phase Pain Investigation Clinical Network + Data and Asset Sharing Partnership

*Improve quality, consistency, efficiency of early phase pain clinical trials*

- EPPIC-net will test compounds and devices judged highly meritorious in peer review that come from industry and academia
- Clinical Coordination Center, Data Coordination Center, 10 specialized clinical sites (hub and spoke design)
- Incentivize, accelerate Phase II trials
- Focus on well-defined pain conditions with high-unmet need
- Reduce the time to start, enroll, run, and complete trials
- Incorporate biomarker studies
- Accommodate platform trial designs

**Data and Asset Sharing Partnership**

- EPPIC-net Data Coordination Center will host data and biosample repositories from HEAL programs and industry partners
- FNIH and the HEAL Partnership Committee will encourage submission of assets for phase 2 clinical trials

**More info coming later today!**
**Mission:** To improve the treatment of acute and chronic pain and reduce the reliance on opioids, by accelerating the early phase testing of promising non-addictive therapeutics and devices to relieve pain.

**Goals**
- Develop a highly effective infrastructure for the rigorous early phase testing of promising pain treatments (small molecules, biologics, devices) from academia and industry.
  - Take advantage of existing pain expertise in both academia and industry
  - Advance pain clinical research though a learning network
  - Train new clinical investigators,
  - Design and test innovative clinical trial paradigms,
  - Establishing well-phenotyped patient cohorts (e.g. BACPAC),
- Incorporate biomarkers of target engagement or proof-of-principle into clinical trial design for new non-addictive pain treatments whether small molecules, devices, or biologics.
EPPIC-Net Infrastructure

Data Coordination Center
- Statistical expertise
- Trial expertise

Repositories:
Industry and HEAL biosamples, neuroimaging, and data

Clinical Coordination Center
- Clinical expertise
- Pain expertise
- Organizes hubs
- Protocol design (with hubs)

10 Specialized Clinical Centers (hubs + spokes)
- Protocol design (with CCC)
- Trial execution
- Ready access to patient populations and expertise in multiple specific pain conditions
- Access to patients with and expertise in low back pain

Coordination centers and clinical sites all solicited through funding opportunities, planned to award at May council
**Candidate Assets**
- Basic information on asset to be entered into submission template
  - Specialized for small molecules, biologics and devices
- Draft template(s) are being developed now by NINDS, with FDA, and will go to HEAL Partnership Committee for input
  - Contents include: e.g., asset type, completed clinical and preclinical studies, pain type, competing products, primary outcomes
- Template submission will be open to anyone and available online

**Outreach to Submitters**:
- Academic networks: e.g., NIH Guide Notice, listservs, blogs
- Connections through partners on HEAL Partnership Committee: PhRMA, BIO, AdvaMed
- The whole process will occur with use of Other Transaction Authority
Panel of non-conflicted academic, industry experts perform rolling review of assets (based on template)
Rolling review of dossiers complete with additional information

Objective Review Panel

Rolling review of dossiers complete with additional information

Dossiers

on assets judged highly meritorious based on initial templates generated by contractor

EPPIC-Net Process: Dossiers + Review #2

Asset Submission

Asset Review

Biologics

Devices

Drugs
Rolling review of templates, full dossiers, and clinical protocols

EPPIC-Net Process: Asset to Clinical Trial Protocol + Review #3

Objective Review Panel

Rolling review of templates, full dossiers, and clinical protocols
EPPIC-Net Process: NIH and Council Review

Asset Submission

Asset Review

Trial Design

Objective Review Panel

Rolling review of templates, full dossiers, and clinical protocols

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Clinical Trial Design and Execution

NIH HEAL Executive Committee

MDWG

IC Council
EPPIC-NET Resources for other HEAL Projects

- Back Pain Research Consortium BACPAC
  - Pain Management Effectiveness Research Network
  - Pain Biomarkers Initiatives
  - Common Fund: Acute to Chronic Pain Signatures
  - Pragmatic and Implementation Studies for the Management of Pain (PRISM)
- Integrated Approach to Pain & Opioid Use in Hemodialysis Patients
  - Other Pain Preclinical Programs

Data, Biosamples, Imaging
- Common Data Elements
- Repository

EPPIC-Net Infrastructure
- Clinical Coordinating Center
- Data Coordinating Center
- Clinical Sites
- Industry Data
EPPIC-Net Process and Timing

• Awards for CCC and DCC infrastructure
  • Receipt date: February 6, 2019 (passed)
  • Tentative Review date: April 15, 16
  • Tentative MDWG review: Mid-May
  • Tentative Council approval: May 23-24

• Awards for Clinical Centers (hubs and spokes)
  • Dates same as above, but considering additional receipt/review dates

• OTA awards for clinical trials
• Rolling submission; anticipate first trials in FY2020
Back Pain Research Consortium: BACPAC

Back Pain Consortium (BACPAC) Research Priorities
A patient-centric, translational research program

**BASIC**: Integrated model of Low Back Pain through improved understanding of mechanisms, leading to new therapies

**TRANSLATIONAL**: Clinical trails, integrating new therapies into multimodal interventions, combined with deep phenotyping and patient-reported symptoms and outcomes

**CLINICAL**: Algorithms to match patients to best treatments based on phenotype and psychosocial context
Pain Management Effectiveness and Implementation Research

• Pain Management ERN: To inform clinicians about the effectiveness of interventions or management strategies that will improve functional outcomes and reduce pain across the continuum of acute to chronic pain associated with many types of pain conditions

• Integrated care for hemodialysis patients: To develop tailored interventions for pain control and reduce reliance on opioids for hemodialysis patients

• Pragmatic and Implementation Studies for Management of Pain to Reduce Opioid Prescribing (PRISM): To integrate interventions with demonstrated efficacy into health care systems and implement health care system change toward evidence-based pain management
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Thank You!

NIH · Helping to End Addiction Long-term
Discover and Validate Novel Targets for Safe and Effective Pain Treatment

Basic biology target discovery projects

- Encourage collaboration from other fields
- Designed to reveal novel targets for small molecules, natural products, biologics, devices
- Devices: discovery of new sites for stimulation or electrophysiological signatures
- Open to all pain systems in CNS or periphery

Pain target validation

- Reproducibility and Robustness
  - Multi-site
  - Multiple strains/species
  - Sex
  - Age
- Generalizability of effect
  - Multiple pain models
- Test in animal model systems developed to better inform human studies
- Validation of pharmacodynamic and predictive biomarkers

Previously identified targets
Discover and Validate Novel Targets for Safe and Effective Pain Treatment

- To promote the basic science discovery and validation of novel targets for the treatment of pain that can be used to develop treatments that have minimal side effects and little to no abuse/addiction liability

Role of inflammatory cells and pathways in sensitization nerve and spinal cord.
Biomarkers: Modeling Pain Using fMRI

A Component Process Approach

B Stimulus Intensity Independent Pain Signature-1 (SIIPS1)

C Neurologic Pain Signature (NPS)

D NPS ‘Receptive Field’

E Benefits of a Combinatorial Model

Integrated Approach to Pain and Opioid Use in Hemodialysis Patients

*To develop tailored interventions for pain control and reduce reliance on opioids for hemodialysis patients*

Develop a multipronged and non-opioid approach to managing pain that uses precision treatment strategies based on individual needs

- Evaluate non-addictive analgesics to reduce pain
- Evaluate behavioral approaches for pain management
- Identify risk factors for opioid dependence
- Assess and treatment co-morbid conditions
- Enhance electronic health records to capture study outcome data

81% of hemodialysis patients suffer with pain, 62% received opioids, 23% high dose prescription. Headache, AV-fistula pain, musculoskeletal pain.
To inform clinicians about the effectiveness of interventions or management strategies that will improve functional outcomes and reduce pain across the continuum of acute to chronic pain associated with many types of pain conditions.

Evaluate the effectiveness of pharmacologic and nonpharmacologic therapies for a broad array of pain conditions.

- Comparative Effectiveness Research Network: leverage NCATS’ Trial Innovation Network
- Build pain expertise in coordinating centers and throughout CTSAs
- NIH will solicit proposals for Phase 3 clinical trials to inform best practices in pain management and minimize risk of addiction
- Coordinate data elements and storage with EPPIC-net and PRISM
Pragmatic and Implementation Studies for Management of Pain to Reduce Opioid Prescribing: PRISM

To integrate interventions with demonstrated efficacy into health care systems and implement health care system change toward evidence-based pain management

Conduct efficient, large-scale pragmatic trial or implementation science studies to improve pain management

- Embed the intervention under study into real world settings
- Collect data through the electronic records of the health care system
- Leverage the NIH Health Care Systems Collaboratory
- Focus on non-pharmacological approaches
- Collaboration with CMS for Medicare coverage consideration
Recent HEAL Pain Workshops

Jan. 30-31, 2019
State of the art in animal pain models and best practices

Feb. 7-8, 2019
Scientific challenges and opportunities from bench to bedside

Feb. 6, 2019
Discovery and development opportunities for natural products

Nov. 14-15, 2018
Discovery and Validation of Biomarkers to Develop Non-Addictive Therapeutics for Pain