Session 3:
Presentation of Selected HEAL Program Areas to Enhance Pain Management
Discover and Validate Novel Targets for Safe and Effective Pain Treatment

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Discover and Validate Novel Targets for Safe and Effective Pain Treatment: Beginnings

- Consulted with experts from across government, industry, and academia to determine the pharmacological areas that could be best addressed through public-private partnerships.
- Concern that basic science proposals identify new targets, but do not contain rigorous validation studies.
  - Burden falls to industry to validate.
  - Increases the cost and risk of investment in new targets.
  - Examples of validation: multiple animal models of pain, knockout models, confirming that the target is present in human tissues.
- Goal: Align fundamental studies of pain pathways with the needs of companies and academics developing therapeutics to have well validated targets to work on.
Discover and Validate Novel Targets for Safe and Effective Pain Treatment

- **Purpose**: Promote the discovery and validation of novel therapeutic targets
- **Focus**: Link basic science discovery of targets that can be used to develop treatments with rigorous validation studies to demonstrate robustness as a pain treatment target
- **Goal**: Lower risk of adopting the target in translational projects to develop small molecules, biologics, natural substances, or devices that interact with this target for new pain treatments
  - Welcome projects to identify novel targets in specific populations such as women, children, older adults or other underrepresented groups
  - Not focused on translational research to develop new medical devices or any one or group of pain conditions
Discover and Validate Novel Targets for Safe and Effective Pain Treatment: Examples

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

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

RFA-NS-18-043 – R01
RFA-NS-18-042 – R21
NOT-NS-18-073 – Administrative Supplements
Preclinical Screening Platform for Pain (PPSP)

Amir Tamiz, PhD
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Preclinical Screening Platform for Pain (PSPP): Mission and Strategy

• Accelerate the Discovery and Pre-Clinical Development of Non-Addictive Treatments for Pain
• Establish a sophisticated preclinical testing program to help identify non-addictive pain treatments with ever increasing power to predict efficacy in human trials
• Acquire models for specific pain conditions and generate predictive endpoints
• Generate high quality data in pain models to support advancement of promising treatments towards clinical trials
A Proven Model to Spur Innovative Therapies

• Based on successful NINDS-funded Anticonvulsant Screening Program (ASP*)
• Contract mechanism to screen and profile submitted compounds/devices in a battery of preclinical models of acute and chronic pain
• Public database to publish best practices and high quality data

*Currently known as the Epilepsy Therapy Screening Program (ETSP)
Timelines (2018-2023)

2018
- Form advisory group
- Hold workshops
- Establish working funnel and protocols

2019
- Award platform contract
  - Start testing compounds
  - Start model development in-house
- Bring in new models
- Continue testing new targets and complete interrogating existing targets

2020-2022
- Convene workshop
- Evaluate initial goals and objectives and advances made

2023
-
Developing Drugs and Testing Platforms for Pain, Addiction and Overdose

Joni Rutter, PhD
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National Center for Advancing Translational Sciences
Developing Drugs and Testing Platforms for Pain, Addiction and Overdose

Model Complexity

Cells

- iPSC-derived neurons for pain and reward pathways
- Development of New Chemical Structures to Modulate Novel Targets
- Development of Pharmacological Probes for Novel Targets

Multi-organ

- 3-D Bioprinted Tissue Models
- Tissue Chips
- Development of Investigational Drugs Ready for Clinical Testing

Preclinical Development

- Early
- Late

Clinical Testing and Trials

Extramural and Intramural Collaborations
- Extramural Funding Opportunities
- Intramural Collaborations

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Extramural Opportunities and Intramural Collaborations through NCATS

**Intramural collaborations with NCATS** - to enable development of new experimental therapeutics
- Not an extramural grant - no funding provided to collaborator’s institution
- Team-based: You (who have existing data, disease knowledge and novel therapeutic hypothesis) + NCATS (preclinical drug development expertise and laboratory capabilities)
- Efficiency: state of the art technology and milestone-driven collaboration plans

**Extramural funding opportunities**
- RFA-TR-19-005: HEAL Initiative: Biofabricated 3D Tissue Models of Nociception, Opioid Use Disorder and Overdose for Drug Screening
- RFA-TR-19-003: HEAL Initiative: Tissue Chips to Model Nociception, Addiction, and Overdose
- NOT-TR-18-031: HEAL Initiative: Announcement of the NCATS ASPIRE Design Challenges to Develop Innovative and Catalytic Approaches Towards Solving the Opioid Crisis
Early Phase Pain Investigation Clinical Network (EPPIC-Net)

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National Institute of Neurological Disorders and Stroke
Early Phase Pain Investigation Clinical Network (EPPIC-Net)
Mission and Goals

**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 (DCC)
- Statistical expertise
- Trial expertise

Repositories:
Industry and HEAL biosamples, neuroimaging, and data

Clinical Coordination Center (CCC)
- 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, including 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 input from HEAL Partnership Committee
  - 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, NIH listservs, blogs, HEAL Partnership Committee

- The whole process will occur with use of Other Transaction Authority
EPPIC-Net Process: Asset to Clinical Trial Protocol

Asset Submission

Drugs

Biologics

Devices

Asset Review

Dossiers

Objective Review Panel

1. Rolling review of templates, full dossiers, and clinical protocols

Trial Design

Clinical Trial Design and Execution

Clinical Coordinating Center

Data Coordinating Center

Clinical Sites

Asset Owner
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

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EPPIC-Net Process and Timing

- Awards for CCC and DCC infrastructure
  - Tentative Council approval: May 23-24
- Awards for Clinical Centers (hubs and spokes)
  - Same as above, but considering additional receipt/review dates
- OTA awards for clinical trials
  - Rolling submission; anticipate first trials in FY2020
Questions/Discussion
Pain Management Effectiveness Research Network

Jane Atkinson DDS
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National Center for Advancing Translational Sciences
HEAL Pain Management Effectiveness Research Network (ERN) Goals

• Compare the effectiveness of existing therapies or novel approaches for delivering current therapies to prevent and manage pain while reducing risk of addiction

• Strengthen and inform current clinical guidelines for pharmacologic and non-pharmacologic treatments for numerous acute and chronic pain conditions

• Manage acute and chronic pain in people across diverse communities

• Provide patients & practitioners with a suite of effective strategies to alleviate pain and reduce reliance on opioids

• Improve the quality of life for patients and their families
Why establish the HEAL Pain Management ERN?

- There is insufficient high quality evidence for the effectiveness of strategies currently used to manage pain (see CDC Guideline for Prescribing Opioids for Chronic Pain, AHRQ Noninvasive, Nonpharmacological Treatment for Chronic Pain - A Systematic Review and Federal Pain Research Research Strategy).

- To rapidly respond to this national need, trials will be conducted in the HEAL Pain Management ERN, which will be established through existing infrastructure of the National Center for Advancing Translational Sciences (NCATS) Clinical and Translational Science Awards (CTSA) Program.

- This structure allows NIH to address pain management questions for multiple clinical conditions in one network.
Pain Management ERN Effectiveness Trials

Definition of Effectiveness Research for the ERN

The conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, treat and manage pain conditions in “real world” settings

Interventions of interest for the ERN

Medications, biologics, procedures, medical and assistive devices and technologies, diagnostic testing, behavioral change, complementary approaches, rehabilitation strategies, integrated approaches, and delivery system strategies tested in well controlled trials

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• Individual awards will support the trial study teams and costs for participants. The trials will address pain management questions across multiple NIH Institutes, Centers and Offices.

• Two additional trials will be incorporated into the ERN from existing clinical trial networks: Maternal-Fetal Medicine Units (MFMU) Network of NICHD and the NCI Community Oncology Research Program (NCORP).

• The NCATS Trial Innovation Network (TIN), an integral part of the CTSA Program, will provide clinical and biostatistical coordination and support for study recruitment. Pain experts will be included in the TIN.

• Trials will be conducted within the CTSA Program network and other clinical sites identified by the trial study teams. This allows recruitment from millions of patients with multiple pain conditions.
NCATS Trial Innovation Network will provide infrastructure including:

- Single IRB, Master Clinical Trial Agreements, study protocol development
- Recruitment and retention plans
- Study design, statistical analyses, data interpretation
- Manual of Procedures
- Training clinical site investigators
- Data management
- Additional site selection through the CTSA Program hubs
- Clinical operations, monitoring, project management, implementation
- DSMB reports
- Logistics for meetings
Trial study teams will work with the TIN and CTSA Hub sites

TIN:
- Clinical Coordination
- Data Coordination
- Single IRB
- Recruitment plans
- Identify additional CTSA clinical sites

- Individual study team with trial design
- CTSA clinical site
- CTSA clinical site
- CTSA clinical site
- CTSA clinical site
- non-CTSA clinical site
HEAL Pain Management ERN trial selection and Council review

Trial Applications

- RFA-NS-19-021
  - App
  - App
  - App
  - App

- Supplements
  - NCI
  - NICHD

Peer review

Trans-NIH Scientific Teams

Evaluate and Prioritize Applications

- MDWG
- IC Councils

NIH HEAL Executive Committee

Trials funded by the end of September 2019
HEAL Pain Management ERN Timeline

- RFA NS-19-021 UG3/UH3 Clinical Trial Planning and Implementation soliciting individual trials:
  - HEAL Multi-Disciplinary WG Input: August, 2019
  - Anticipated council and awards: September, 2019
- Begin planning year: October, 2019
- Kick off Meeting: November, 2019
Integration of HEAL Pain Management ERN with other HEAL clinical research networks

• Regular meetings of NIH staff overseeing HEAL trials
• Standardization across networks when possible and appropriate, including use of:
  • Validated Patient Reported Outcomes (PROs)
  • Common data elements
  • Common data standards, such as CDISC
  • Common adverse events coding
• Central data repository through EPPIC-Net for future public access
• Central biospecimen storage through EPPIC-Net for future public access