Expanding Therapeutic Options for Opioid Addiction and Overdose

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Enhancing Pain Management

Improving Treatments for Misuse and Addiction

- Pre-Clinical Research in Pain
- Clinical Research in Pain Management
- Expand Therapeutic Options
- Develop New/Improved Prevention & Treatment Strategies
- Enhance Treatments for Affected Newborns
- Optimize Effective Treatments

HEAL Initiative Research: Overview
FDA-Approved Medications for Opioid Addiction and Overdose

- Methadone
- Buprenorphine
  - Sublingual
  - Monthly injection
  - Six month implant
- Naltrexone
  - Oral
  - Monthly
- Lofexidine
- Naloxone
  - Parenteral
  - Nasal

Close interaction with FDA
Improving Prevention and Treatment for Opioid Misuse and Addiction

• Expand therapeutic options for opioid addiction and overdose

1. New, more user-friendly formulations of existing medications
2. Longer duration, more powerful overdose-reversers
3. New approaches to reverse respiratory depression
4. Immunotherapies for opioids to prevent relapse and overdose
5. New targets and approaches for treating Opioid Use Disorder (OUD)
Focused Opioid Use Disorder Medications Development Research Project

**Goal**

Conduct a series of high-impact studies that will ideally lead to about 15 Investigational New Drugs (INDs), which would then produce around five New Drug Applications (NDAs) submitted to the Food and Drug Administration (FDA).

This project will focus on developing new addiction treatments and overdose-reversal tools. Three medications are currently FDA-approved to treat opioid addiction, and naloxone is available in both injectable and intranasal formulations to reverse overdose. But a wider range of options is needed in both areas. These may involve new formulations of existing drugs including longer-acting depot formulations of opioid agonists as well as stronger, longer-lasting naloxone formulations to more effectively reverse overdose from...
Expand therapeutic options for opioid addiction and overdose

- Goal: Fast-track the discovery and development of medications to prevent and treat OUDs or opioid overdose and to advance them in the FDA's drug development approval pipeline.

- RFA DA-19-002:
  - 5 cycles of reviews since May 2018;
  - 22 approved for funding, 16 others funded outside RFA
  - Rolling acceptance of applications

- Length of time between application receipt to approval for funding has been shortened from ~9 months to < 2 months

* Plus 16 outside the RFA
1. New formulations of existing medications

- Long-term opioid receptor antagonists
  - 6-month naltrexone (GO Medical Pharmaceuticals/Columbia U.)
  - 3-month naltrexone implant/BICX102 (BioCorX)
  - 6-month nalmefene (Titan Pharmaceuticals)

- Long-term opioid receptor agonists
  - Weekly Oral Buprenorphine
  - Weekly R-Methadone (Lyndra Pharmaceuticals)
2. Longer duration, more powerful overdose reversal

- Intranasal Nalmefene: OPNT003 (Opiant)
- Methocinnamox: Long acting, pseudo-irreversible \(\mu\)-opioid antagonist
- Nafamostat (PF614): Opioid delivery in combination with the Bio-Activated Molecular Delivery (Bio-MD\textsuperscript{TM} ) prodrugs, for oral overdose protection
- NRS-033: Nalmefene prodrug active for >28 days
3. New approaches to reverse respiratory depression

- Almitrine: Peripheral, stimulating chemoreceptors in the carotid bodies to enhance respiration
- Ampakines (e.g., CX717): Mediators of respiratory drive through AMPA glutamatergic receptor
- Repinoptan: full agonist of 5HT1a
4. Novel Medications for OUD

- **Preclinical**
  - Kindolor: Peripherally acting and targets receptors, Nav 1.7 and 1.8 voltage-sensitive sodium channels, NMDA receptor and glycine site antagonist
  - ITI-333: High affinity MOR partial agonist, 5-HT2A, and D1 receptors antagonist
  - D24M: MOR/DOR Heterodimer antagonist
  - MEB-1166 or MEB-1170: Highly ‘biased’ MOR agonists

- **Clinical**
  - Medications approved for treatment of conditions other than OUD:
    - Guanfacine, Suvorexant, Duloxetine, Ketamine, Dronabinol, Lorcaserin, Gabapentin

- **Immunotherapies** - more detail in next presentation
5. New targets and approaches

- Drugs to prevent opioid craving
  - ANS-6637 (Amygdala Pharmaceuticals): Selective ALDH2 Inhibitor that prevents pathophysiologic dopamine surge

- Safe non-addictive analgesics
  - MP1000 Arylepoxamide: Distinct from any of the traditional opioid receptors

- Protein Tyrosine Phosphatase Receptor D
  - Associated with dependence on opiates at the genetic level

- “Balanced” opioid biased agonists: PZM21
Trans-NIH Collaborations

- NIAID: Immunotherapies
- NIAAA: Respiratory stimulants
- NINDS: Pain and OUD
- NCATS: *In vivo* assessment of promising probes, Developments of annotated screening library
- NIH Clinical Center: Anti-craving therapies (ANS-6637)
- NICHD: Treatment of NAS/NOWS
- NHLBI: Sleep and respiratory distress
- NIDDK: Pain management in hemodialysis patients
- NIBIB: Devices
- NCCIH: Behavioral Interventions
Immunotherapies to Treat Opioid Use Disorder

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National Institute of Allergy and Infectious Diseases
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HEAL Initiative Research
Anti-Opioid Immunotherapies: Promising Complementary Therapeutic Approach

• Induce antibodies that bind specifically to the target opioid and decreases distribution to the brain, extinguishing reward and preventing overdose

• Animal studies have shown anti-opioid vaccines induce antibodies that prevent overdose and reduce opioid self-administration
  - Anti-opioid vaccines (oxycodone, morphine, heroin, fentanyl, carfentanil)
  - Monoclonal antibodies against fentanyl and analogs

• Encouraging results from nicotine vaccine clinical trials

• Individuals with high titers showed clinical benefits, including reduced nicotine usage
NIAID Activities to Address Challenges in Vaccine Development

• Improve vaccine safety and efficacy by:
  - Increasing antibody titers, duration, and affinity
  - Antigen and dose sparing with novel adjuvants
  - Optimizing for target populations
  - Identifying immune correlates of protection

• Product development
  - Collaborations with experts in formulation, scale-up, GMP
  - Established relationships with industry partners

• Communication across multiple government agencies
  - FDA, Drug Enforcement Administration (DEA)
Activities Supported by the Program

• Vaccine design and development
  - Immunogen design and optimization
  - Adjuvant screening
  - Define immune mechanisms required to induce protective anti-opioid antibodies
  - Preclinical immunogenicity and efficacy testing

• IND-enabling activities

• Vaccine manufacturing

• Phase I clinical trials
  - Includes mechanistic analyses of immunogenicity
• Oct 2018: Anti-opioid Immunotherapy Expert Meeting
• Oct 2018: Administrative supplements funded (NOT-AI-18-055)
  • 7 grants (1 NHLBI, 2 NIDA, 4 NIAID), 3 contracts (NIAID)
• Feb 2019: Established communication channel with DEA
• March 2019: Broad Agency Announcement published in FedBizOpps
• Sept 2019: Applications due; 3-4 awards planned by August 2020
• Late 2020: Kickoff meeting
Collaborations for Developing Drugs and Testing Platforms for Pain, Addiction, and Opioid Use Disorder

Christine Colvis, Ph.D.
Director, Drug Development Partnership Programs
National Center for Advancing Translational Sciences
HEAL Initiative Research

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Developing Drugs and Testing Platforms for Pain, Addiction and Overdose in Collaboration with NCATS

Collaborator brings:
- Subject matter expertise
- Target, probe, or compound
- Necessary resources
- Existing data

NCATS brings:
- Access to resources and technology not easily accessible
- Automation
- Industry and other expertise
- Agile process
- Program management

Productive Partnership(s)
- Milestone driven
- Agile and iterative
- Synergistic
- Mission-specific

Collaborator brings:  NCATS brings:
Drug Development Capabilities

HTS assay adaptation, development

GPCR and ion channel assays and high-content image-based assays

Drug repurposing libraries

All FDA approved compounds (>2,400), as well as >150,000 in annotated/diversity collections, HEAL-focused library

Counterscreen & confirmatory assays

Chemininformatic platforms

Molecular modeling and docking, Machine learning, High content image analysis

Hit to lead medicinal chemistry

Largest medicinal chemistry program at NIH, > 30 fume hoods, > 20,000 molecules made

ADMET assays

Aqueous kinetic solubility, rodent & human liver microsomal stability & PAMPA permeability

Late Stage Optimization/Target validation

To finalize declaration of clinical candidates

Pharmacokinetics/pharmacodynamics

To scale up the production of the compound for clinical testing

GMP manufacturing and formulation

GLP safety evaluation and toxicology

Therapeutic modality expertise

Including small molecules, biologics and gene and cell therapies

Repurposing of approved therapies
Human Cell-based Models

Tissue engineering technologies
Development of tissues-in-a-well

Access to relevant human cell types
Sensory neurons (nociceptors) and other neuronal subtypes

Automated production of IPS cell-derived cells
To reproducibly scale up production of human tissue relevant cells

Advanced imaging technologies for functional cell characterization
High-content confocal, calcium imaging, optogenetics

3D bioprinters
To create spatial cellular patterns in tissues such as neuronal circuits, neurovascular unit, innervated tissues

Spatially defined and physiologically relevant tissue models
High-density multi-electrode arrays 26,400 electrodes/well

Measurement of signaling pathways, metabolism & specific targets
Cyclic AMP, PKA activity, CREB phosphorylation, energy metabolism

3D bioprinters
To create spatial cellular patterns in tissues such as neuronal circuits, neurovascular unit, innervated tissues

Spatially defined and physiologically relevant tissue models
High-density multi-electrode arrays 26,400 electrodes/well

Validation of 3D organoid cultures
Neural spheroids for compound screening

Assays using 3D tissue models
High-content confocal, calcium imaging, optogenetics, multielectrode arrays, neurotransmitters biosensors

Longitudinal tracking of cell behavior
Multiple measurements over days, weeks or months

Combined single-cell transcriptomic & proteomic analyses
Drug response in individual nociceptors and other neuronal phenotypes
Opportunity for Collaborations

NOT-TR-19-018

- Guide Notice soliciting collaborations with NCATS Intramural research teams
- Not a funding solicitation
- Multiple opportunities to submit proposals
- Next pre-proposal due date: July 18
THANK YOU

NIH • Helping to End Addiction Long-term