Expanding Therapeutic Options for Opioid Addiction and Overdose

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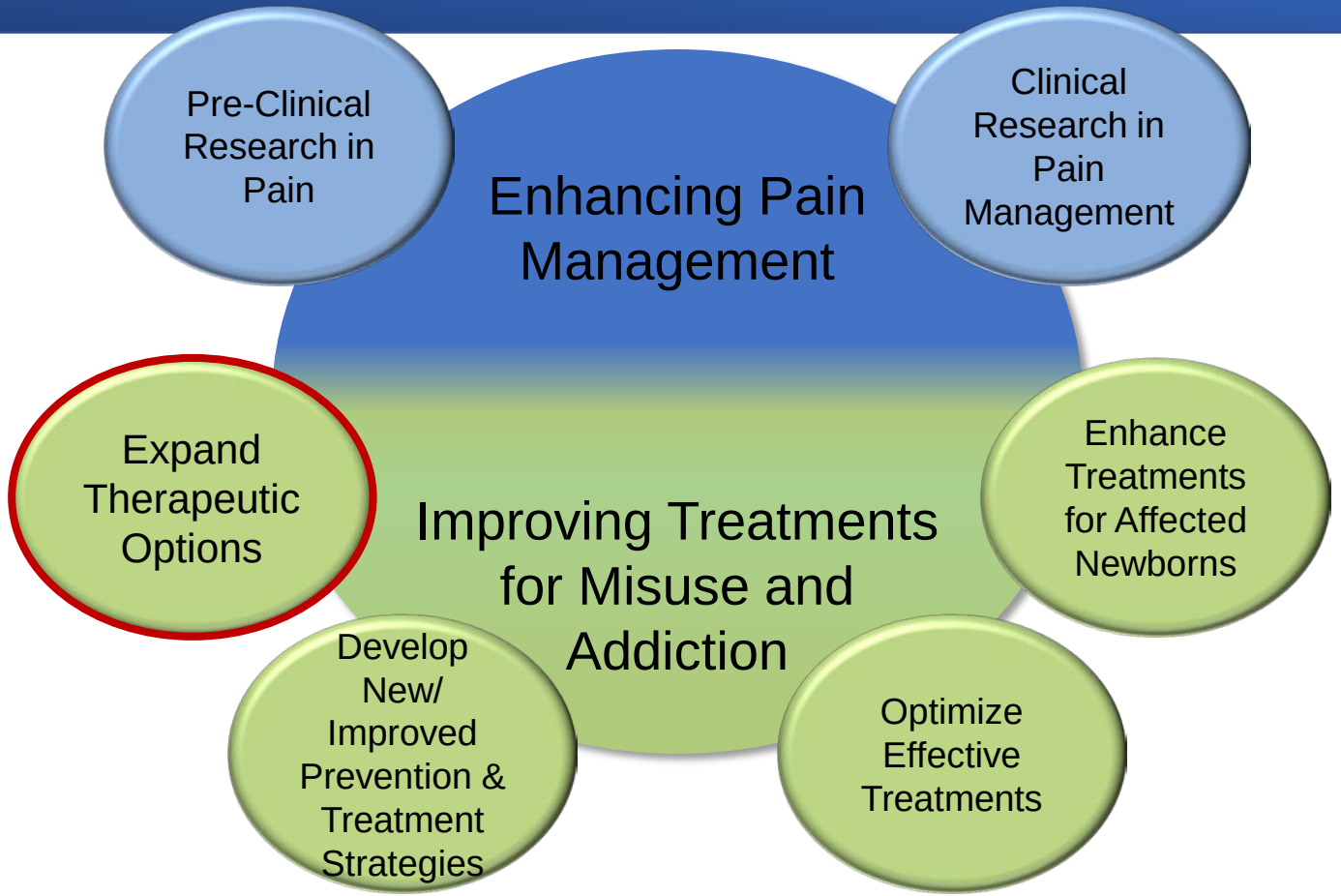
National Institute on Drug Abuse

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

Drugs of Abuse

- Commonly Abused Drugs Charts
- Emerging Trends and Alerts
- Alcohol
- Club Drugs
- Cocaine
- Fentanyl
- Hallucinogens
- Inhalants
- Heroin
- Marijuana
- MDMA (Ecstasy/Molly)

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 μ-opioid antagonist
- Nafamostat (PF614): Opioid delivery in combination with the Bio-Activated Molecular Delivery (Bio-MD™) 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

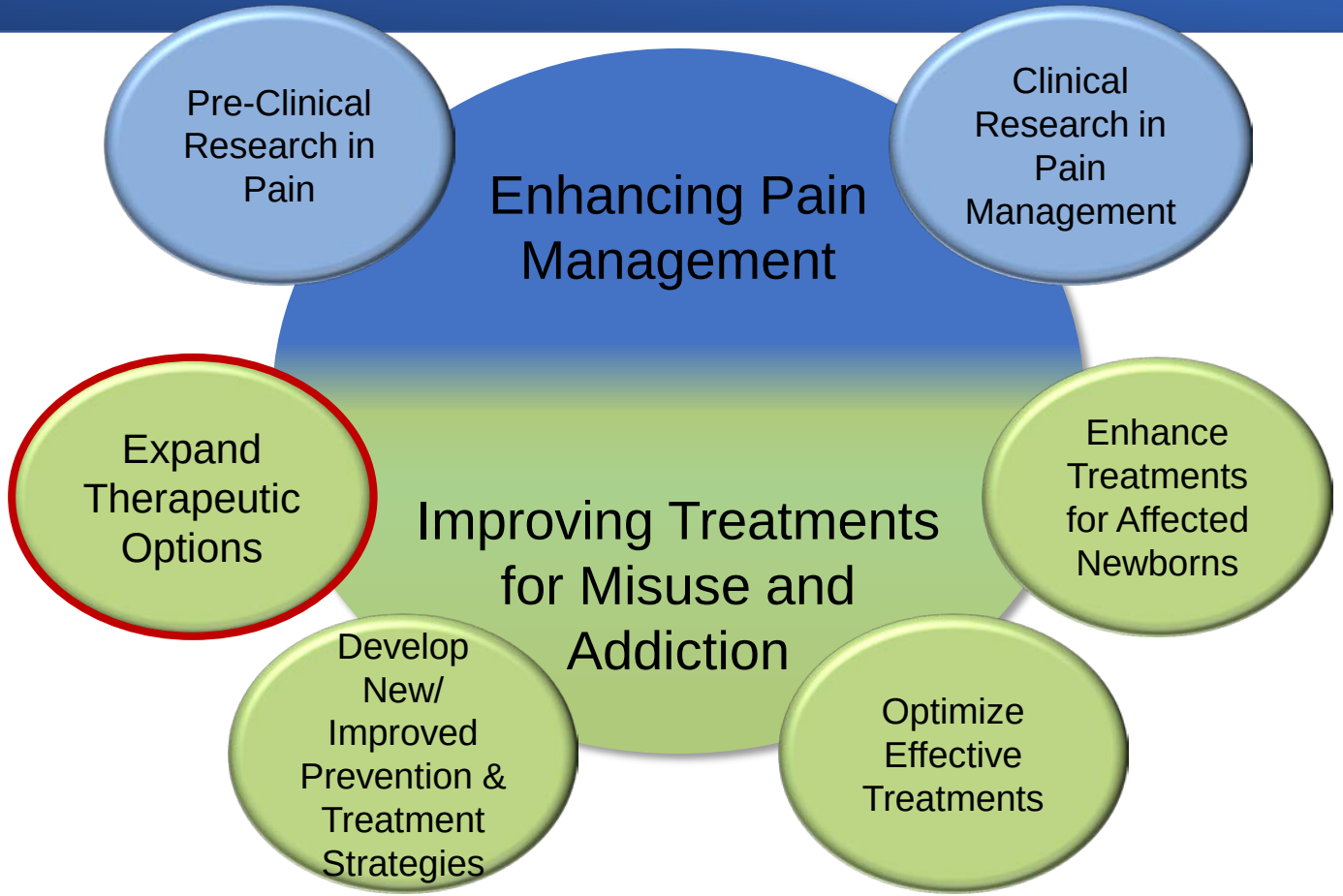
- NIAID: Immunotherapies
- NIAAA: Respiratory stimulants
- NINDS: Pain and OUD
- NCATS: *In vivo* assessment of promising probes, Developments of annotated screening library
- NIH Clinical Center: Anti-craving therapies (ANS-6637)
- NICHD: Treatment of NAS/NOWS
- NHLBI: Sleep and respiratory distress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

Immunotherapies to Treat Opioid Use Disorder

Kentner Singleton, Ph.D.

National Institute of Allergy and Infectious Diseases

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

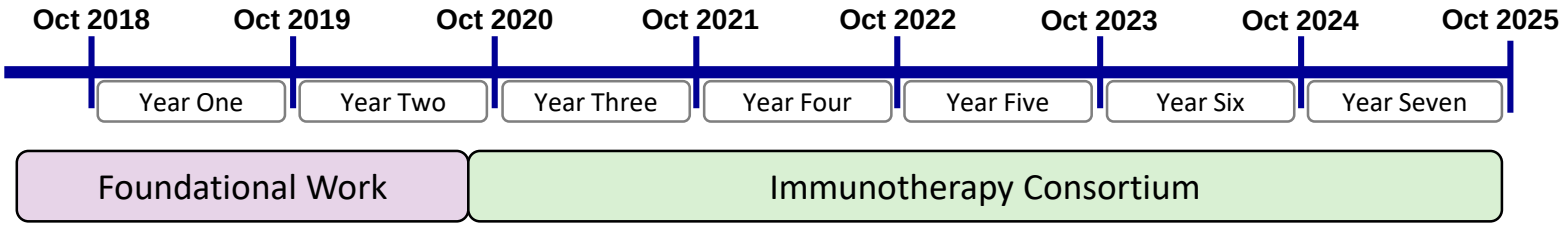
NIAID Activities to Address Challenges in Vaccine Development

- 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

Immunotherapy Program Activities



- 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

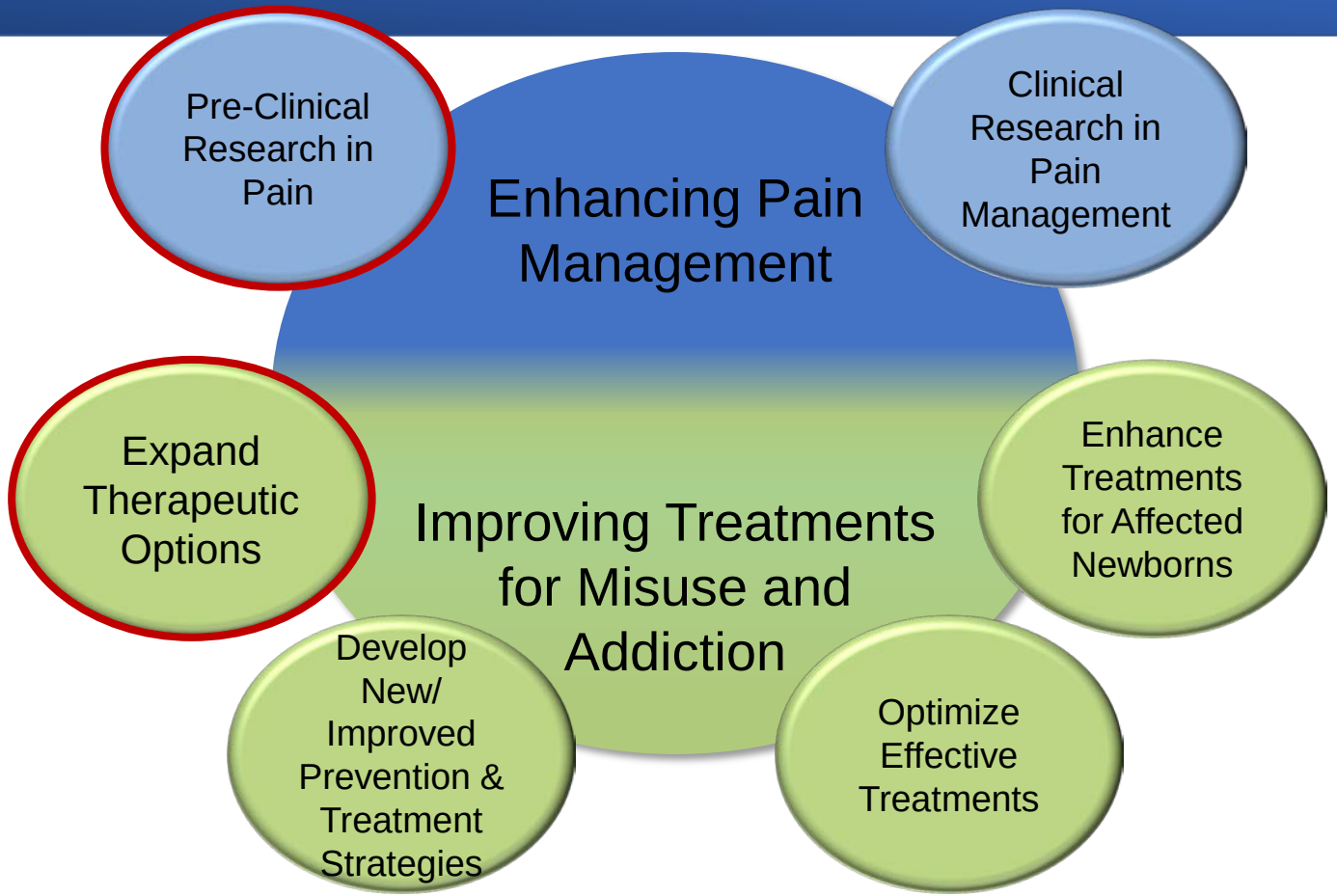
Collaborations for Developing Drugs and Testing Platforms for Pain, Addiction, and Opioid Use Disorder

Christine Colvis, Ph.D.

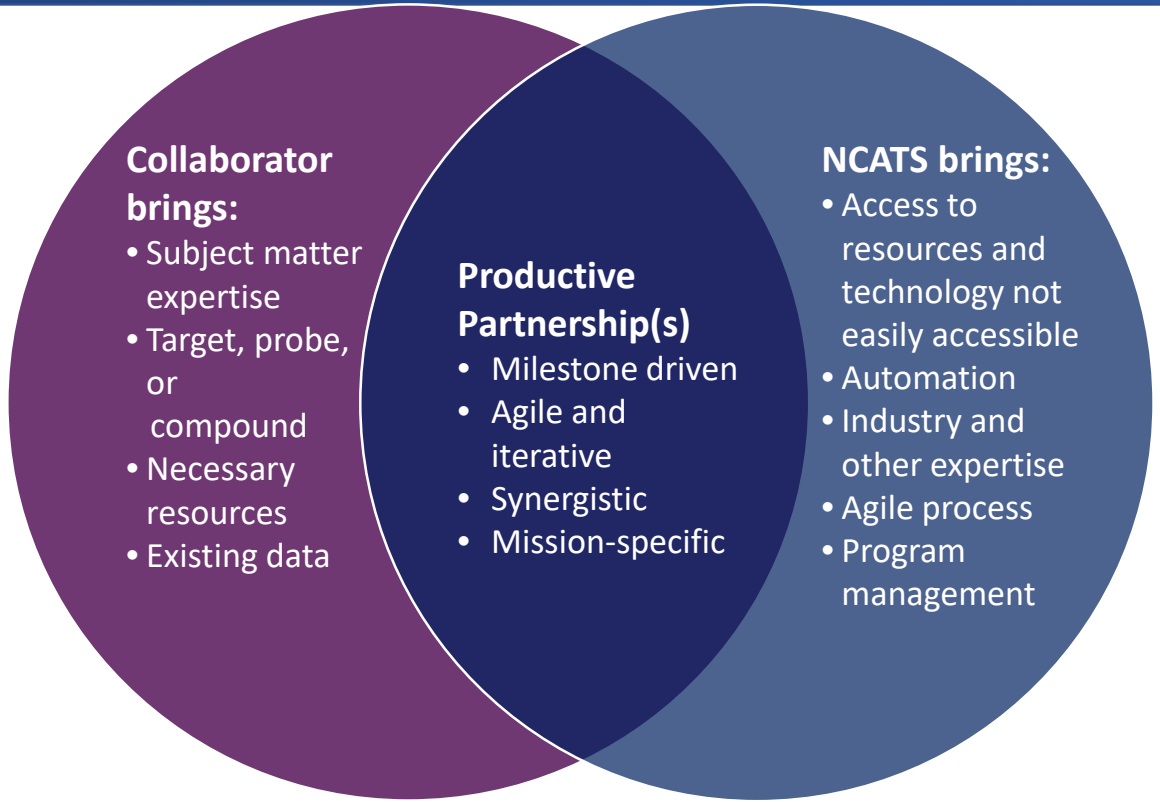
Director, Drug Development Partnership Programs

National Center for Advancing Translational Sciences

HEAL Initiative Research



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

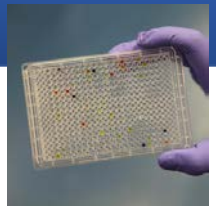


HEAL
NIH · Helping to End Addiction Long-term

Drug Development Capabilities

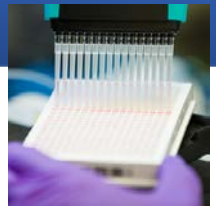
HTS assay adaptation, development

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

Cheminformatics platforms

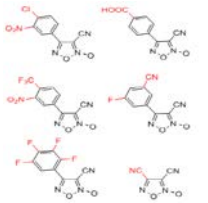
Molecular modeling and docking, Machine learning, High content image analysis

Hit to lead medicinal chemistry

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

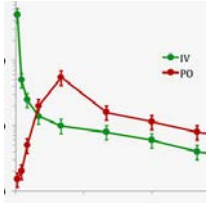
ADMET assays

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



Late Stage Optimization/ Target validation

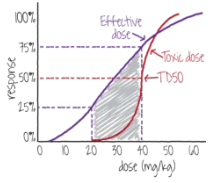
To finalize declaration of clinical candidates



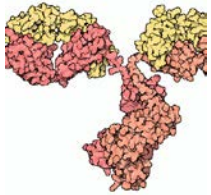
Pharmacokinetics/ pharmacodynamics

GMP manufacturing and formulation

To scale up the production of the compound for clinical testing



GLP safety evaluation and toxicology

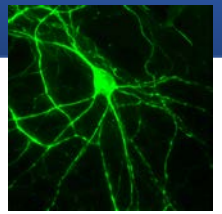


Therapeutic modality expertise

Including small molecules, biologics and gene and cell therapies

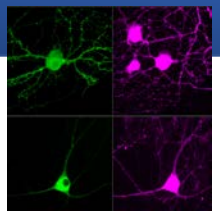
Repurposing of approved therapies

Human Cell-based Models



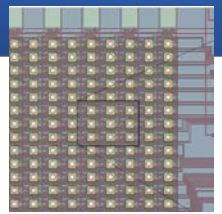
Access to relevant human cell types

Sensory neurons (nociceptors) and other neuronal subtypes



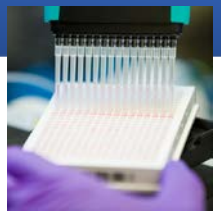
Advanced imaging technologies for functional cell characterization

High-content confocal, calcium imaging, optogenetics



High-throughput electrophysiology methods

High-density multi-electrode arrays 26,400 electrodes/well

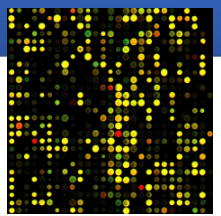


Measurement of signaling pathways, metabolism & specific targets

Cyclic AMP, PKA activity, CREB phosphorylation, energy metabolism

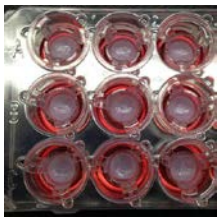
Longitudinal tracking of cell behavior

Multiple measurements over days, weeks or months



Combined single-cell transcriptomic & proteomic analyses

Drug response in individual nociceptors and other neuronal phenotypes



Tissue engineering technologies

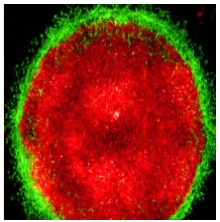
Development of tissues-in-a-well

Automated production of iPS cell-derived cells

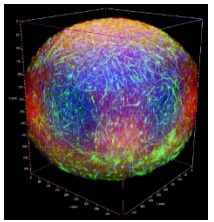
To reproducibly scale up production of human tissue relevant cells

3D bioprinters

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

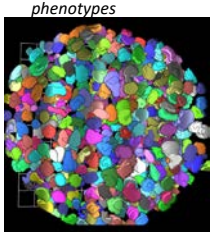


Spatially defined and physiologically relevant tissue models



Validation of 3D organoid cultures

Neural spheroids for compound screening



Assays using 3D tissue models

High-content confocal, calcium imaging, optogenetics, multielectrode,arrays, neurotransmiters biosensors

Opportunity for Collaborations

HEAL Initiative: Announcement of Collaboration Opportunities for Developing Drugs and Human Cell-Based Testing Platforms for Pain, Addiction and Overdose

Notice Number: NOT-TR-19-018

Key Dates

Release Date: March 6, 2019

Related Announcements

None

Issued by

National Center for Advancing Translational Sciences (NCATS)

Purpose

KEY DATES

Pre-proposals and proposals will be accepted and reviewed on a rolling basis. The dates in the table below are the last dates the pre-proposals and proposals will be accepted for that cycle. Pre-proposals and proposals submitted after those dates will be considered for the next cycle.

	*Cycle I	Cycle II	Cycle III
Pre-proposal	March 18, 2019	July 18, 2019	November 18, 2019
Full proposal	April 22, 2019	August 22, 2019	December 23, 2019
**Notification from NCATS	June 1, 2019	October 1, 2019	February 1, 2020

*Proposals submitted within the first cycle will be considered for implementation on a rolling basis.

**Notification whether the full proposal will enter into discussions with NCATS scientists to make a final determination of feasibility, alignment of goals, and project plan with milestones and go-no go decisions.

PURPOSE

NIH's Helping to End Addiction Long-termSM (HEAL) Initiative seeks to speed scientific solutions to the national opioid public health crisis. The NIH HEAL Initiative will bolster research across NIH to (1) improve treatment for opioid misuse and addiction and (2) enhance pain management. More information about the HEAL Initiative is available at: https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative.

BACKGROUND

As part of the NIH HEAL initiative, the NCATS continues its efforts for developing drugs and human cell-based testing platforms for pain, addiction and overdose complements the target identification, animal model efficacy testing, and human clinical network expertise of other laboratories to enable the development of new experimental therapeutics through drug screening in human-based, physiologically relevant in vitro systems, high efficiency chemical synthesis of new compounds, and IND enabling studies. Given the limitations of current treatments and failures in the development efforts for new therapies, drugs that modulate novel targets and have different and better structure-activity profiles are needed.

The NCATS intramural research program, Division of Preclinical Innovation (DPI) can provide exceptional expertise and resources for efficient translation of promising therapeutic development projects that address questions relevant to pain, addiction and overdose. Depending on the nature of the proposed collaboration, expertise in more than one laboratory may be applied. Specifically, collaboration opportunities are available with or among the following NCATS laboratories/programs:

- Stem Cell Translation Laboratory
- 3-Dimensional Tissue Bioprinting Laboratory
- Pharmacological Probe Development Program
- Enabling Investigational New Drug (IND) Applications

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