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

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Scientific Director
NCATS pre-clinical HEAL initiatives involve both extramural opportunities and intramural collaborations

- 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
  - See https://ncats.nih.gov/heal for a full list of NCATS HEAL-Related Funding Opportunities

- 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
The Preclinical Translation Process
(using small molecule drugs as an example)

Identify disease mechanism → Create testing system → Test chemicals in system → Modify (chemistry) for human use → Test in animals → Test in humans

Basic Research → Assay Development → Screening → Medicinal Chemistry → Preclinical Development → Clinical Development

NCATS Division of Preclinical Innovation
Collaborators can work with the SCTL to develop iPSC-derived cellular platforms for improved prediction of *in vivo* human effects of lead compounds.

**Capabilities**

- **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
3-D Tissue Biofabrication Laboratory

Collaborators can work with the 3-D Laboratory to biofabricate multicellular functional tissues using human primary or iPSC-derived cells that are better models of human disease state and response to new drugs.

Capabilities

- **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, e.g., 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
Pharmacological Probe Development

Use assay development and quantitative high-throughput screening to identify promising compounds to modulate novel targets; optimize compound properties to probe novel targets.

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

- **Counterscreen & confirmatory assays**

- **Cheminformatics platforms**
  - Molecular modeling and docking, Machine learning, High content image analysis

- **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
Enabling Investigational New Drug Applications

Joint project teams develop prototype therapeutics into IND-enabled small molecules, biologics, and gene and cell therapies ready for clinical testing

Capabilities

Target validation and lead optimization

To finalize declaration of clinical candidates

Pharmacokinetics/pharmacodynamics

GLP safety evaluation and toxicology

Therapeutic modality expertise

Including small molecules, biologics and gene and cell therapies

GMP manufacturing and formulation

To scale up the production of the compound for clinical testing

Repurposing of approved therapies
Collaboration Proposal Process

https://ncats.nih.gov/heal/intramural-capabilities

Responsibility
- Potential Collaborator/Applicant
- NCATS
- Technical Experts

Options:
- Reproducible
- Not Reproducible
Collaboration Proposal Process

https://ncats.nih.gov/heal/intramural-capabilities

• Pre-proposal submission
  - Rolling submission
  - 2-Page limit
  - High-level overview
    - Hypothesis and Goals
    - Background and prior art
    - Summary of proposed scientific approach
    - Alignment with NIH HEAL HCBS goals
    - Potential public health impact

Responsibility
- Potential Collaborator/Applicant*
- NCATS
- Technical Experts

If yes, invite collaborator to submit full proposal
- Collaborator submits full proposal*
- Input from Technical Experts
- Determine Selection
  - Explore Possible Implementation: Request Additional Information, if needed
  - Develop Provisional Milestone-Driven Collaboration Plan
- Test of Concept
  - Reproducible
  - Not Reproducible
  - Proceed with Collaboration
  - Stop
Collaboration Proposal Process

https://ncats.nih.gov/heal/intramural-capabilities

- Determine alignment with HCBS goals
  - If yes, potential collaborators will be invited to submit a full proposal

Responsibility
- Potential Collaborator/Applicant
- NCATS
- Technical Experts
Collaboration Proposal Process
https://ncats.nih.gov/heal/intramural-capabilities

- Full proposal submission
  - 7-Page limit
  - Provide specific details regarding
    - Premise of the study and effect on the opioid crisis if the goals are achieved
    - Hypothesis and goals
    - Background and prior art
    - Description of unique resources (models, reagents, etc.) you will bring to the collaboration
    - Summary of scientific approach taken to date, including preliminary data
    - Proposed milestones, assignment of responsibilities and timeline
    - Proposed go/no-go decision points
    - Current roadblocks to advancing the science
    - Alignment with NCATS intramural program’s
    - Potential translational science and public health impact
    - Next steps if the project is successful

Responsibility
- Potential Collaborator/Applicant*
- NCATS
- Technical Experts

* Rolling PreProposal Submission*

If yes, invite collaborator to submit full proposal

Collaborator submits full proposal*

If no, notify collaborator of no selection

Determine Alignment with HCBS Goals

Determine Selection

Explore Possible Implementation; Request Additional Information, if needed

Send Regrets Letter

Develop Provisional Milestone-Driven Collaboration Plan

Test of Concept

Reproducible
- Proceed with Collaboration
- Stop

Not Reproducible

Send Regrets Letter
Collaboration Proposal Process
https://ncats.nih.gov/heal/intramural-capabilities

- Input from technical experts
  - Collaboration proposals evaluated by ad hoc technical experts
  - Experts from the extramural community with expertise in the fields of pain, addiction, and overdose will provide input
  - Identify strengths and weakness

Responsibility
- Potential Collaborator/Applicant*
- NCATS
- Technical Experts▲

[Diagram showing the process Flowchart]
Collaboration Proposal Process

https://ncats.nih.gov/heal/intramural-capabilities

- Selection of collaborations for considerations
  - 3 Potential outcomes
    - Selected for consideration- move forward with tentative collaboration implementation
    - Not selected for consideration
    - Not selected at present, but may be reconsidered if resources become available

Responsibility
- Potential Collaborator/Applicant*
- NCATS
- Technical Experts

[*] Indicates required action
Collaboration Proposal Process

https://ncats.nih.gov/heal/intramural-capabilities

- **Collaboration Plan- If selected for consideration**
  - The DPI collaborating lab will discuss with the selected collaborators what the needs are, what the collaborator will contribute to the collaboration, and determine whether to proceed with developing a detailed collaboration plan and further refine the milestones that define the go/no-go decision points
  - NCATS will notify the collaborator of decision to proceed or stop
  - NCATS Office of Strategic Alliances will engage with the collaborator and the DPI lab to execute the appropriate agreements such as CRADAs and RCAs.
Collaboration Proposal Process
https://ncats.nih.gov/heal/intramural-capabilities

- Proof of concept/Model System Validation
  - The first Go/No Go decision will be reproducibility of the proof of concept/model system
    - Successful reproducibility will result in full study implementation.
    - Unsuccessful reproducibility will serve as the first no-go decision point. Trouble-shooting options will be discussed.

Responsibility
- Potential Collaborator/Applicant
- NCATS
- Technical Experts

Rolling PreProposal Submission

Determine Alignment with HCBS Goals

If no, notify collaborator of no selection

If yes, invite collaborator to submit full proposal

Collaborator submits full proposal

Input from Technical Experts

Determine Selection

Explore Possible Implementation; Request Additional Information, if needed

Develop Provisional Milestone-Driven Collaboration Plan

Send Regrets Letter

Test of Concept

Reproducible
- Proceed with Collaboration

Not Reproducible
- Stop

Send Regrets Letter
Collaboration Proposal Process
https://ncats.nih.gov/heal/intramural-capabilities

- Milestone driven
- Go/no go decisions tracked
- Milestones drive project decision making
- Data and resources generated are shared

Responsibility:
- Potential Collaborator/Applicant
- NCATS
- Technical Experts

If yes, invite collaborator to submit full proposal
If no, notify collaborator of no selection

Collaborator submits full proposal

Input from Technical Experts

Determine Alignment with HCBS Goals

Determine Selection

Explore Possible Implementation; Request Additional Information, if needed

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Reproducible
Not Reproducible

Proceed with Collaboration
Stop

Send Regrets Letter

Send Regrets Letter
Summary

**Human Cell-Based Platforms for testing new treatments**

- iPSC-Derived Neurons for Pain and Reward Pathways
- 3-D Bioprinted Tissue Models

**Accelerating Translation of Novel Compounds for Clinical Testing**

- Development of Pharmacological Probes for Novel Targets
- Development of Investigational New Drugs for Clinical Testing

**Model Complexity**

- Cells
- Multi-organ

**Preclinical Development**

- Early
- Late

**Clinical Testing and Trials**

**More Information:**

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https://ncats.nih.gov/heal/intramural-capabilities