NIH HEAL (Helping to End Addiction Long-term^{SM}) Initiative
Call for Proposals for Collaboration
Intramural Program
National Center for Advancing Translational Sciences (NCATS)
National Institutes of Health

Developing Drugs and Human Cell-Based Testing Platforms for Pain, Addiction and Overdose

INTRODUCTION

Safe, effective, and non-addictive drugs (small molecules and biologics) to treat pain, mitigate addiction and reverse overdose are key to addressing the opioid crisis. Given the limitations of current treatments and failures in development efforts for new therapies, drugs with better activity profiles that modulate novel targets, as well as more predictive drug development platforms, are needed. The NIH HEAL (Helping to End Addiction Long-term^{SM}) Initiative is a trans-NIH effort launched in April 2018 to advance national priorities in addressing the opioid crisis through science. The NCATS-led NIH HEAL Human Cell-Based Screening Platforms and Novel Drugs to Treat Pain, Addiction and Overdose (HCBS) initiative is a multi-component collaborative program that will develop human-based, physiologically relevant *in vitro* screening and characterization systems; high-efficiency synthesis and testing of small molecule compounds to modulate novel pain, addiction, and overdose targets; and investigational new drug (IND)-enabling studies for drugs for these indications.

The NCATS Division of Pre-Clinical Innovation (DPI), the intramural component of NCATS, comprises industry-scale expertise in stem cell biology, assay development, biomolecular screening, automated biology, medicinal chemistry, cheminformatics, data science and pre-clinical drug development, with advanced equipment and resources not available in most laboratories, such as large compound libraries (e.g., diverse drug-like molecules, approved and investigational drugs, mechanism-based compounds, and natural products); quantitative high-throughput and high-content screening; robotic automated cell culture; multiscale assay development; 3-D bioprinting; next-generation DNA and RNA sequencing; and integrated platforms to profile gene and protein expression and measure functional endpoints in cell cultures and on single cells.

Every NCATS DPI project is a collaboration with an external partner in the academic, biopharmaceutical or nonprofit sector. DPI functions via a unique operational model, which takes advantage of the complementary nature of NCATS' translational expertise and collaborators' biology/target/disease expertise. Collaborators bring a wealth of background knowledge and a starting point for a particular translational project, and NCATS scientists bring an equivalent wealth of knowledge in translation and the expertise to transform those starting points into therapeutically useful tools, platforms or investigational drugs. Joint project teams design and follow milestone-driven project plans to achieve agreed-upon deliverables specific to the need and stage of the project. Projects are provided the needed resources as long as milestones and timelines continue to be met, until the deliverables are completed. At whatever stage the projects conclude, the joint teams publish results in scientific journals where appropriate and disseminate relevant data, protocols and materials.

COLLABORATION OPPORTUNITIES

NCATS is offering opportunities to apply our state-of-the-art technologies and extensive experience

in therapeutic development to ideas and expertise in pain, addiction and overdose through collaboration. The opportunities for collaboration fall into two general categories: novel human cell-based screening platforms, and pharmacological probe and pre-clinical drug development (described below).

A. **Novel human cell-based screening platforms:** Traditionally, discovery of small molecule probes and drugs has begun with screens in cell-free systems or cell lines with heterologously expressed genes, often of non-human origin. While these platforms have value, they may identify compounds that do not reflect native human cellular physiology or disease, which have a high likelihood of failure at later stages of the translational process. The advent of induced pluripotent stem cell (iPSC) and 3-dimensional tissue printing technologies offers the opportunity to develop screening platforms that more accurately reflect human disease physiology and will allow the discovery of more robust and ultimately successful probe compounds and drugs for pain, addiction and overdose.

1. *iPSC-derived cell-based model development*: Investigators with a desire to develop and characterize iPSC-derived cell types relevant to nociception (e.g., primary and associative pain pathways), addiction (e.g., reward pathways), and overdose should apply. Proposals in this space should focus on development, in-depth characterization and rigorous utilization of human iPSC-based assays related to modeling and reversing pain, addiction and opioid overdose. The NCATS Stem Cell Translation Laboratory has specialized expertise in development of robust, reproducible and scalable automated iPSC differentiation protocols and comprehensive cell characterization. Among the lab's capabilities are:
    - Advanced imaging technologies (e.g., high-content confocal, calcium imaging, optogenetics) and data analysis for functional cell characterization, including longitudinal tracking of cell behaviors with multiple measurements over days, weeks or months
    - High-throughput electrophysiology methods (e.g., high-density multi-electrode arrays [26,400 electrodes/well]) to streamline monitoring of electrical activity at high spatiotemporal resolution
    - Measurement of cell signaling pathways, metabolism and specific targets (e.g., cyclic AMP, PKA activity, CREB phosphorylation, energy metabolism)
    - Combined single-cell transcriptomic and proteomic analyses that provide information on drug response in individual cells
    - Access to large numbers of iPSC-derived sensory neurons (nociceptors), neuronal subtypes (e.g., GABAergic, glutamatergic, dopaminergic), and astrocytes in chemically defined conditions already extant in the lab

2. *Development of 3-dimensional biofabricated tissue models*: Investigators with a desire to develop multicellular constructs that mimic the structure and function of tissues involved in pain (e.g., DRG, PAG, thalamus), addiction (e.g., ventral tegmentum, nucleus accumbens), or overdose (e.g., medulla) using relevant human primary or iPSC-derived cells should apply. The expertise of the NCATS 3-D Tissue Bioprinting Laboratory is the biofabrication of architecturally and physiologically accurate normal and disease-relevant tissue models in multi-well plate format, to increase the throughput of drug testing and to create models that are better predictors of human response to new drugs. This laboratory integrates advances in tissue engineering technologies, 3-D bioprinters, biocompatible polymers and hydrogels to validate the morphology and physiology of the biofabricated human tissues. The laboratory is also

developing disease-relevant assay readouts in 3-D tissues that are compatible with the screening capabilities available at NCATS. Specifically, the 3-D Tissue Bioprinting Laboratory offers:

- Collaborative biofabrication of 3-D tissues in multi-well plate format for drug screening
- Architectural, physiological and pharmacological validation of biofabricated 3-D tissue models
- Development of high-throughput quantitative endpoint measurements on 3-D tissue models
- Screening of drugs using the biofabricated 3-D tissue-in-a-dish relevant models, including stem cell-derived organoids
- Development and testing of compounds in 3-D blood-brain barrier models
- Joint development of engineering and 3-D tissue technology platforms

B. **Pharmacological probe and pre-clinical drug development:** The first step in qualifying a novel molecular target as potentially useful in therapeutic applications is the creation of a small molecule "probe" compound that can test the therapeutic hypothesis in cell-based or animal model systems. If those studies are promising, then development of a "drug" compound can begin, involving the multi-step recursive process to impart the properties required for submission of an IND application to the FDA or other regulatory agency.

1. *Pharmacological probe development:* Investigators who have identified potential pain, addiction or overdose targets can collaborate with this program to generate an optimized probe that will enable the testing of a therapeutic hypothesis. The laboratory encompasses assay development; quantitative high-throughput screening (qHTS) to identify promising compounds to modulate novel targets; and optimization by medicinal chemists to optimize potency, selectivity and pharmacokinetic properties required of an *in vitro*/*in vivo* pharmacological probe of the novel target. Assays of target activity adaptable for HTS, secondary assays to guide medicinal chemistry optimization and biological validation, and animal efficacy models, when applicable, should be available in the applicant's laboratory. Probes can also be tested using the iPSC or 3-D bioprinting platforms described above. Sharing probes with the scientific community will be a priority. Capabilities include:
    - Adaptation/miniaturization of assays for HTS and new assay development
    - Large diversity screening chemical libraries and specialty libraries for mechanistic dissection and drug repurposing
    - Counterscreening/confirmatory assays, including for common artifactual activities
    - Chemical informatics
    - Medicinal chemistry
    - *In vitro* ADMET and *in vivo* DMPK characterization

2. *Pre-clinical drug development*: Investigators/companies/nonprofit research institutions that have identified promising lead small molecule compounds or prototype biologic, gene or cell therapies for indications in pain, addiction or overdose can form joint project teams with the NCATS Therapeutic Development Branch (TDB) to develop IND-ready therapies for consideration by the FDA for clinical testing. Capabilities available through the TDB include:
    - Lead-to-clinical-candidate medicinal chemistry optimization
    - Repurposing of approved therapies
    - Formulation for optimal bioavailability

- *In vitro* ADMET and *in vivo* DMPK characterization
- Toxicological characterization, including *in vitro* and non-GMP and GMP toxicity studies
- CMC studies
- GMP scale-up and manufacturing of drug agent and drug product for clinical testing
- Project management

PROPOSAL TO COLLABORATE INSTRUCTIONS

Overview

This is not a grant application — if successful, funds will not be transferred to your institution to support your project. Rather, this is an application to collaborate with and gain access to the scientific capabilities, expertise and resources of the NCATS DPI, with the goal of developing novel testing platforms or developing promising probes of therapeutic candidates for pain, addiction or overdose indications. If successful, you will partner with DPI staff in developing a collaborative project plan. DPI will provide translational and drug development expertise and operations, and the applicant investigator collaborator(s) will provide starting points for the project and biological/disease expertise.

General Information

Pre-proposals and proposals will be accepted and reviewed on a rolling basis. The dates in the table below are the last dates when the pre-proposals and proposals will be accepted for the cycle under which they are listed. 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 of whether the full proposal will enter into discussions with NCATS scientists for a final determination of feasibility, alignment of goals, and collaboration plan with milestones and go/no-go decisions.

- Pre-proposals are requested to maximize efficiency of effort from collaborators and NCATS, ensuring candidate projects are within the scope of the NIH HEAL Initiative[SM] and the capacities of the NCATS DPI. Successful pre-proposal applicants will be asked to submit a full proposal.
- Pre-proposals can be submitted at any time to NCATSDPIHEALCollab@nih.gov.
- No full proposals will be accepted if they were not invited in response to a pre-proposal.
- Applicants whose full proposals are accepted will enter into discussions with NCATS scientists to explore possible implementation and make a final determination of whether to develop a collaboration plan. Factors that will be considered in this decision include feasibility, alignment of goals, potential milestones and go/no-go decisions. Only after a collaboration plan is agreed to by both partners will the project officially begin.
- Organizations eligible to submit collaboration proposals include:
    - Public/State-Controlled Institution of Higher Education
    - Private Institution of Higher Education
    - Nonprofit with 501(c)(3) IRS Status (Other than Institution of Higher Education)
    - Nonprofit without 501(c)(3) IRS Status (Other than Institution of Higher Education)

    - Small Business
    - Eligible Agencies of the Federal Government, including NIH intramural laboratories
- Submission requirements:
    - Potential collaborators are advised to submit only one proposal per submission cycle.
    - Resubmissions are allowed only if substantially improved.

Pre-Proposal Submission Process

- Pre-proposals are limited to two pages, 11-point Calibri font; material beyond the two-page limit will not be considered.
- Pre-proposals must be submitted by email to NCATSDPIHEALcollab@nih.gov.
- Pre-proposals must use the following structure:
    - Proposal title
    - Name, affiliation and expertise of lead collaborator
    - Primary component of the HCBS program being applied to (choose one):
        - iPSC-Derived Cell-Based Model Development
        - Development of 3-Dimensional Biofabricated Tissue Models
        - Pharmacological Probe Development
        - Pre-Clinical Drug Development
    - Current state/starting point for proposed collaboration
    - Goal/desired deliverable from proposed collaboration
    - Novelty of approach/desired deliverable. If similar models, probes or drugs currently exist or are in development, explain why your approach is different and better.
    - Statement of how success on the proposed project would impact the opioid crisis and advance the goals of the HCBS initiative
    - NOTE: Any intellectual property (IP) generated before initiation of the NCATS collaboration will be retained by the investigator/institution as background IP. The potential for development of new IP will depend on the stage at which the project enters into collaboration with NCATS. However, all collaborators should anticipate that there may be joint IP development with NCATS employees. Inventorship of any new, multi-party IP created from this collaboration will be determined according to U.S. patent law and governed under an agreement that will be executed at the outset of the formal research partnership, such as a Cooperative Research and Development Agreement (CRADA) or a Research Collaboration Agreement (RCA). Applicants are encouraged to review the templates for CRADAs and RCAs and talk with their respective technology transfer office prior to submitting a collaboration proposal, to ensure that they will have the freedom to enter into an agreement with NCATS. The templates can be found at https://ncats.nih.gov/alliances/forms. Questions regarding these NCATS agreement templates can be sent to the NCATS Office of Strategic Alliances via email at NCATSPartnerships@mail.nih.gov.

Full Proposal Submission Process

Potential collaborators will use the following process to submit a full proposal.

- Full proposals are limited to seven pages, 11-point Calibri font, inclusive of data tables and figures. The proposal should incorporate information from the two-page pre-proposal.
- Full proposals must be submitted to the email address provided with the notification to submit.
- Full proposals must use the following structure:
    - Proposal title

- Name, affiliation and expertise of the lead collaborator and other key personnel
- Primary component of the HCBS program being applied to (choose one):
  - iPSC-Derived Cell-Based Model Development
  - Development of 3-Dimensional Biofabricated Tissue Models
  - Pharmacological Probe Development
  - Pre-Clinical Drug Development
- Current support for the project and resources available
  - Description of any unique resources (models, reagents, etc.) you will bring to the collaboration
- Detailed description of the starting point and desired deliverable from the proposed collaboration, including accomplishments to date, prototypes and current roadblocks to reaching the deliverable
- Detail on the novelty of the approach/desired deliverable, including prior art. If similar models, probes or drugs currently exist or are in development, explain why your approach is different and better.
- Proposer's conception of best scientific approach to reaching deliverable
  - Proposed milestones, assignment of responsibilities — NCATS vs. potential collaborator — and proposed timeline (note: Collaborations that can be completed within 2–3 years are anticipated)
  - Proposed go/no-go decision points
  - Next steps if the project is successful
- Indication of how the desired deliverable would impact the opioid crisis and advance the goals of the NIH HEAL Initiative

- Supplemental Information
  - Support Letters (not to exceed one page each) should be a commitment of support, not merely an endorsement
    - From additional collaborators who will be contributing to the project
    - From the collaborators' institution(s)
  - Description of Intellectual Property (not to exceed four pages): To ensure freedom to operate on the proposed project, a clear description of the relevant patent space and status of IP is required (where relevant). This includes a list of any patents issued or pending with respect to either the agent to be developed or any non-commercially available technology or material required for the proposed project. Should a project require the use of non-commercially available technology or equipment that is patented by a third party, the collaborator should be prepared to explain how these materials will be accessed for this proposed collaboration. The following information is REQUIRED for the full proposal. If any of the following are not applicable to the project, state that explicitly (e.g., "There is no IP filed for the technology to be used for this project.").
    - Details of any existing IP at the collaborating institution that will be used in the project
      - Patents and patent applications
      - Significant know-how
    - Details of any third-party obligations regarding the relevant IP
  - Reference List
    - No more than 15 references relating directly to the proposal
  - Key Papers
    - PDFs of no more than two key papers to ensure all readers have access to critical data that may be cited

- Biosketches for All Key Personnel
    - Each biosketch should be no more than three pages and include the qualifications of key personnel, how they will contribute to the collaboration, verification of their ability to commit the time anticipated to complete the proposed work, and track record of collaboration.
- Protection of Human Subjects (if applicable)

Input from Technical Experts

Projects will be evaluated by ad hoc technical experts with the necessary technical and subject matter expertise. Input from technical experts is a privileged communication with the National Institutes of Health and may involve trade secrets, as well as commercial and financial information that is considered business confidential information.

- Areas for Input: Technical experts will not provide a score but rather will provide input on the strengths and weaknesses of the proposal, using the questions below to structure their review. Because this is a proposal for collaboration, the collaboration plan and much of the scientific approach will be determined after the project is selected. The technical review should focus on the research that has been done to date on the project, the areas proposed for collaboration, and the impact on the opioid crisis if the goals/end point of the collaboration are achieved, as well as the potential for the project to progress after the collaboration has ended. In general, collaborations that can be completed in 2 to 3 years are anticipated.
    - Technical Review Criteria
        - Scientific merits of the proposed collaboration
            - Is the premise of the project strong?
            - If the goals are accomplished, how will the opioid crisis be affected?
            - Will the work shift paradigms?
            - Is the work novel?
            - If human material is being used, is the description of human subjects protection consistent with NIH policies?
            - Are potential pitfalls/issues described?
        - Investigator(s)
            - Do the collaborators have the appropriate training and experience to advance the project once the collaboration has come to a close?
            - What is the record of accomplishment and collaboration?
        - Environment
            - If collaborators are proposed to conduct parts of the project themselves, do they have the necessary resources to accomplish their aims?
            - Is there evidence of institutional support?
        - Feasibility of completing goals
            - Will the milestones serve as strategic and objective benchmarks of progress?
            - Are the milestones realistic?
        - Synergy with HCBS goals
        - Translational sciences and public health impact
    - Experts will also note:
        - Specific strengths of the project
        - Specific weaknesses/recommendations for project improvement

- Decisions about which projects to explore with the potential collaborator for possible implementation will be made by the Scientific Director and NCATS Director, based on the input of the technical experts, portfolio balance and availability of NCATS resources.
- Decision Notification
    - The program manager will send the prospective collaborator a letter informing him/her whether the project has been accepted for consideration.

The initial notification of selection for possible implementation is to inform you that NCATS would like to explore the possibility of collaborating. Depending on the completeness of the information provided in your proposal, NCATS may request additional information before making a decision about the development of the provisional milestone-driven collaboration plan.

Collaboration Plan

- If the proposal is selected for possible implementation, the program manager will arrange an in-depth meeting with the collaborators. If the meeting is to be face-to-face, funding will be provided for the lead collaborator to travel to NCATS as needed.
- The DPI collaborating lab will discuss with the selected collaborators what the needs are, discuss 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 potential collaborator of the decision to proceed to collaboration plan development or stop.
- The NCATS Office of Strategic Alliances will engage with the collaborator and the DPI lab to execute the appropriate agreements, such as CRADAs and RCAs.

Test of Concept/Model System Validation

- The first implementation go/no-go decision — NCATS will determine the reproducibility of the concept and/or the model system.
    - Successful reproducibility will result in full study implementation.
    - Unsuccessful reproducibility will serve as the first no-go decision point. The program manager will set up a meeting with relevant personnel to discuss troubleshooting options. If no options are viable, the project will be closed.

Project Progression

- Lead collaborators and NCATS project leads will provide progress reports when milestone dates occur **AND** when prompted by NCATS leadership.
    - Go/no-go decision points will prompt project review. The HEAL lab leads will determine whether the milestones have been met and whether the project should proceed.
        - Missed milestones will trigger project review. The program manager will arrange a meeting with the team lead, project lead and lead collaborator to determine why the milestone was missed and possible remedial approaches or project termination.
        - If the recommendation is to terminate the project, the NCATS Director and Scientific Director will be consulted prior to termination.

Publication of Results

If a proposal is accepted for collaboration, the collaborator will agree that data (positive and negative results) and resources generated under the collaboration will be shared with the public through appropriate mechanisms that respect intellectual property, such as pre-print servers, peer-reviewed publications and data-sharing sites such as PubChem for HTS data.