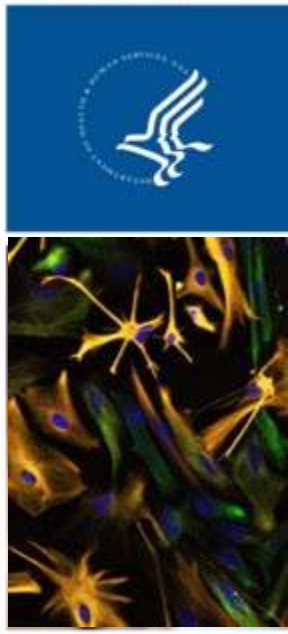
National Institute of Neurological Disorders and Stroke

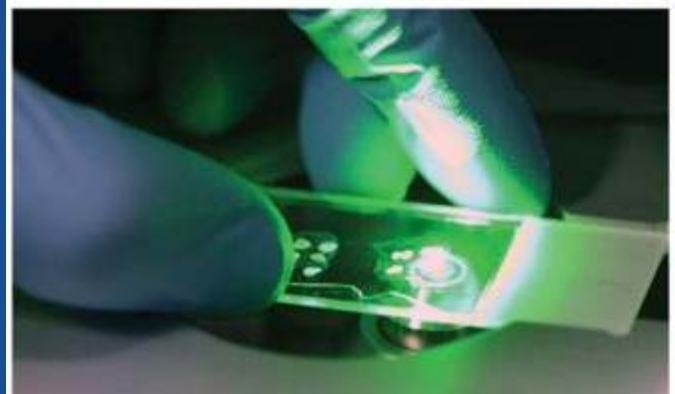
NIH Funding for Translational Neurotherapeutic Research and Development

The 19th Annual Non-Dilutive Funding Summit

Charles L Cywin, PhD
Director, Small Molecule Neurotherapeutic Development

January 10, 2024





BPN Program

BPN Staff

Director, Small Molecule Neurotherapeutic Development
Charles Cywin, PhD

Health Program Specialist
Carolyn Bondar, PhD

Operations Coordinator
Rakonda Medley, BS

Scientific Program Managers
Mohamed Hachicha, PhD
Pascal Laeng, PhD
Enrique Michelotti, PhD
Mary Ann Pelleymounter, PhD
Shamsi Raeissi, PhD
Matthew Rice, PhD

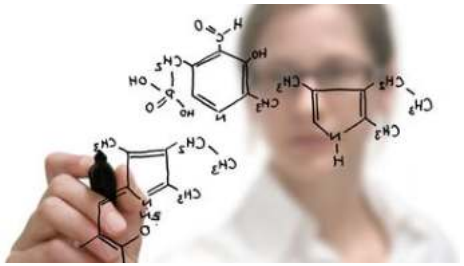
SPM-BPN Administration
Oreisa O'Neil Mathurin, MPH-EOC
Ranga Rangarajan, PhD-Contracts

BPN Program Vision

Combine Strengths of NIH and Industry Expertise for Small Molecule Neuroscience Drug Discovery & Development

NIH investigator-initiated ideas

- Novel drug targets
- Strong disease assays and models



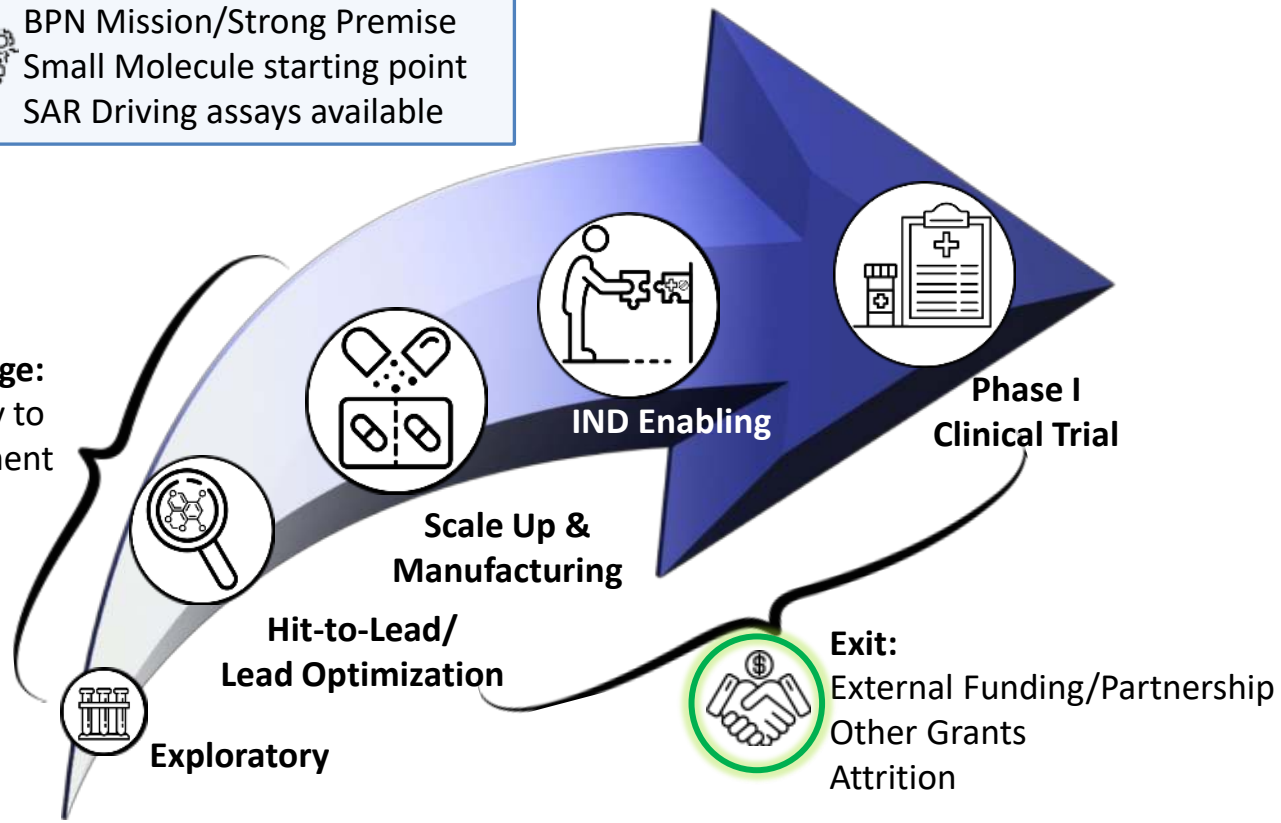
Industry expertise

- Advisors with extensive pharma experience
- Industry-standard contract services

BPN Goals

"Grand Challenge to Provide Grant Funding and Resources to Facilitate Small Molecule Drug Discovery and Development to Treat Nervous System Disorders"

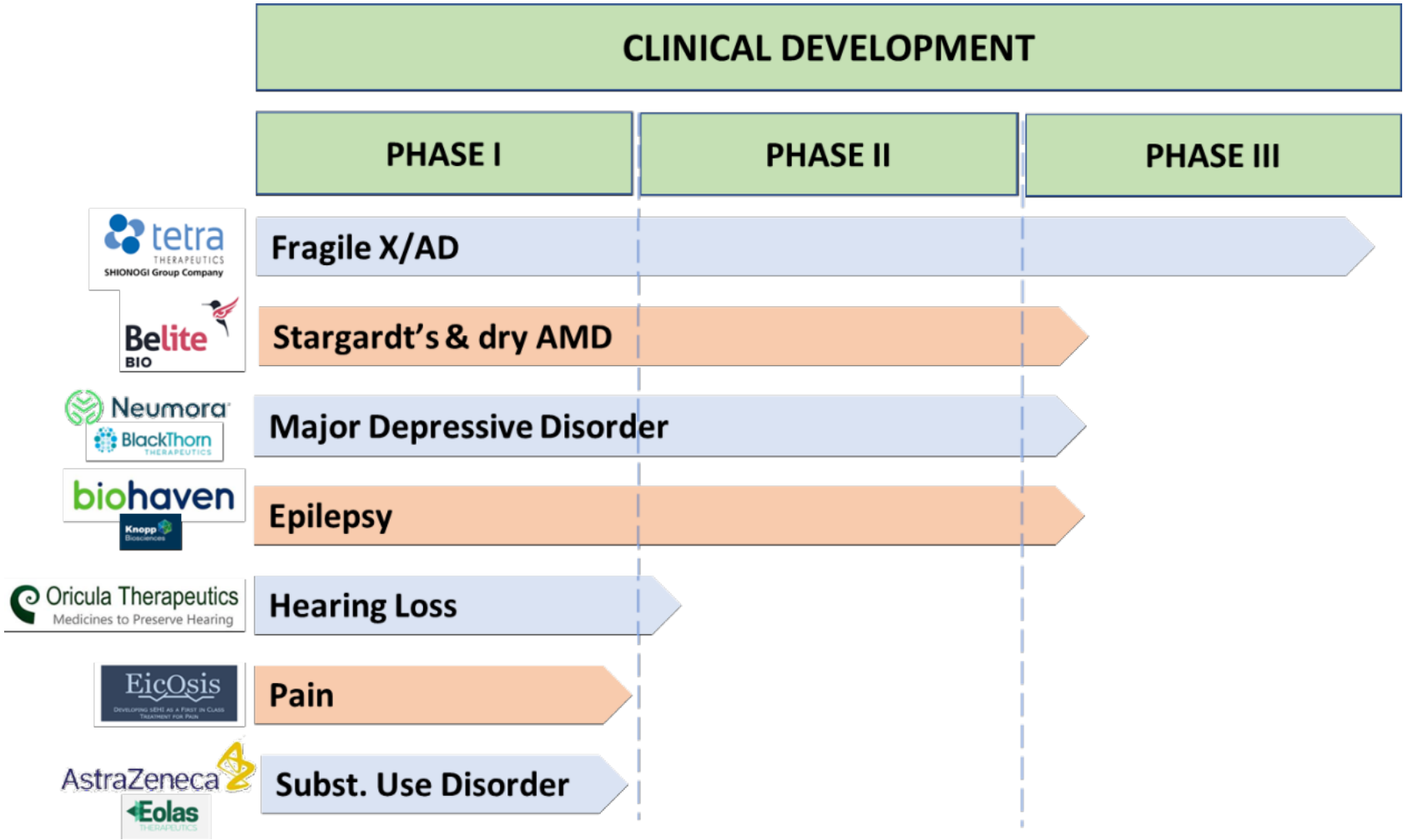
Minimum Entry Criteria:
BPN Mission/Strong Premise
Small Molecule starting point
SAR Driving assays available



Program Goals:

- To de-risk potential therapeutics to the point that industry will invest in them, allowing potential new drugs to reach patients efficiently.
- To identify the best ideas for translation in the NIH research community through this funding opportunity and associated infrastructure.
- To provide non-dilutive grant (PAR) funding and necessary resources (contracts, consultants, etc.) that are typically lacking in our research community.
- **Preserve PI/Institution's Intellectual Property (IP) to facilitate licensing**

Progression of Successful BPN Projects



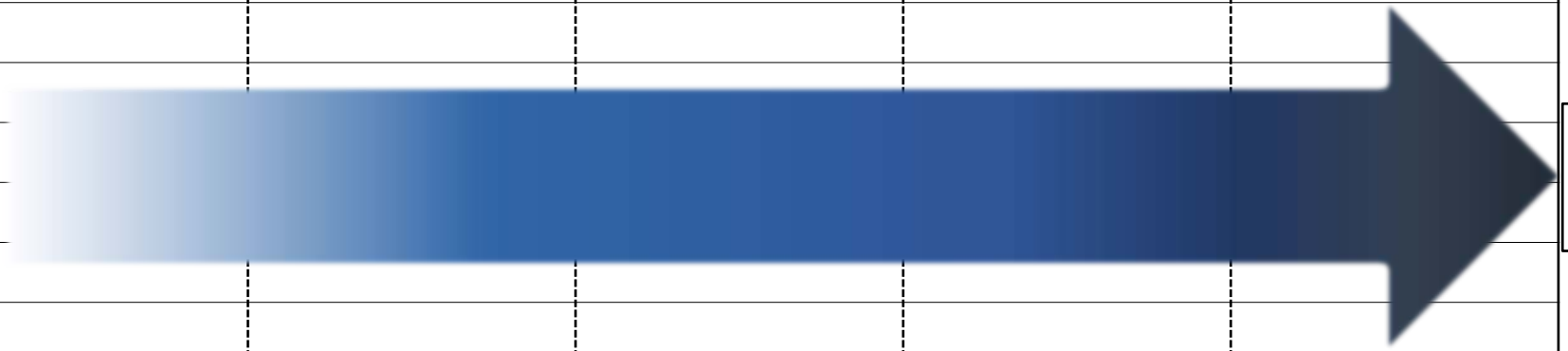
>10 projects have announced additional industry funding since utilizing the BPN

Valued at close to ***$2B*** *in potential investments*

3 additional INDs and trials supported ad hoc

Current BPN Portfolio

Asset	Exploratory	Hit to Lead	Lead Optimization	Predevelopment	IND Enabling
KOR, Stimulant Use Disorder					
Unspecified kinase, Spinal Cord Injury					
CB2R, Stimulant Use Disorder					
EP2, Epilepsy					
nNOS-PSD95, Neuropathic Pain					
AT2, Neuropathic Pain					
ELP1, Familial Dysautonomia					
NMII, Stimulant Use Disorder					



***40** Projects funded to date covering **8** ICs*

BPN Network: *Offering Infrastructure, Expertise, and Grant Funding*

up to ~$12M/project (if all milestones are met)

Lead/Product Development Team

Principal Investigator
Industry-seasoned consultants
NIH Staff

- Medicinal Chemistry
- Assay Development
- Pharmacokinetics & Drug Metabolism
- Chemistry, Manufacturing & Control
- Pharmaceutical Development
- Toxicology
- Regulatory

NIH Grant

Bioactivity/ Efficacy Studies

NIH Contracts

Medicinal Chemistry

curia

PK/Tox

SRI International
IITRI
TOXICOLOGY RESEARCH LABORATORY
TRL

Data Management

CDD
COLLABORATIVE DRUG DISCOVERY

Manufacturing & Formulation

curia
MRIGlobal

Clinical Trials

Duke
PPD

Highlights

- Contract Resources are tailor-made to support project
- Non-dilutive funding
- PI team's intellectual property is retained by PI's institution

Program progression is milestone driven

Participating Institutes: NCCIH, NEI, NIA, NIAAA, NICHD, NIDA, NIDCR, NIMH, and NINDS

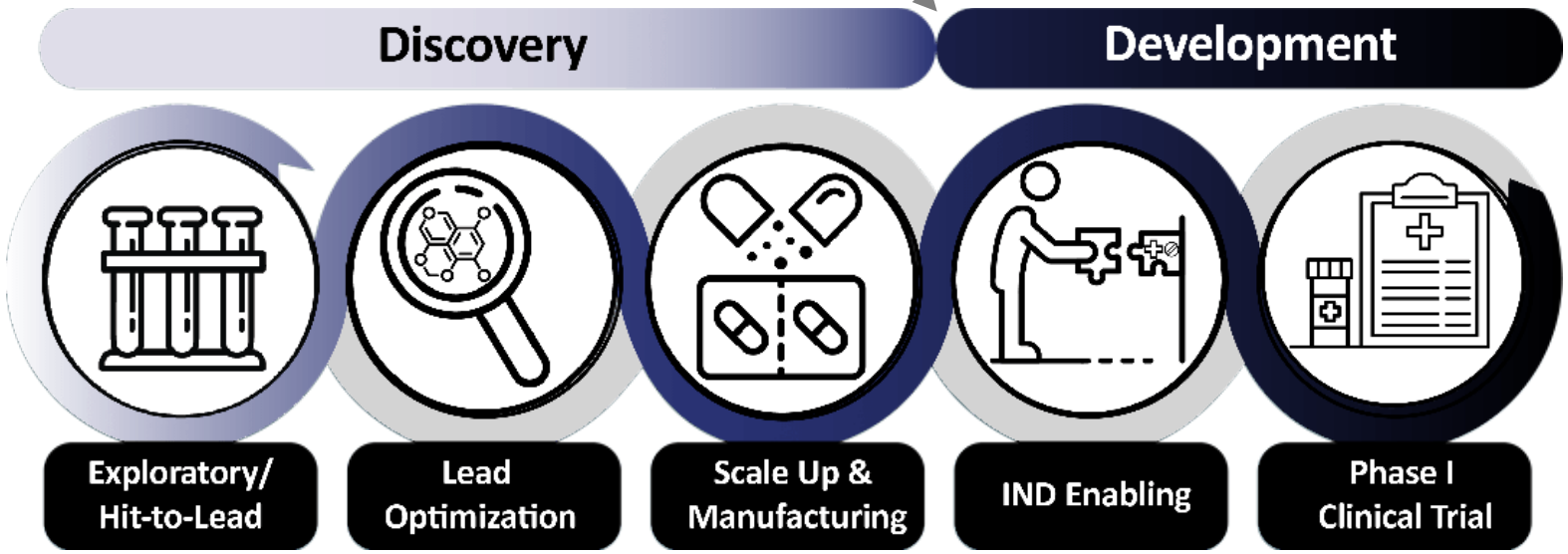
BPN Projects Can Enter at Any Preclinical Stage

All Projects Begin with Preparatory Phase

Preparatory Phase
UG3 or U44 Phase I

- Complete entry criteria for SAR or IND-enabling studies
- Conduct due diligence

Not all ICs accept Development Projects



General (UG3/UH3) PAR-24-043
UG3: Up to $300K direct costs x 1 yr*
UH3: Up to $1.5M/yr direct costs x 4 yrs*

*If any proposed budget year exceeds $500K in direct costs then you need permission to submit

SBIR (U44-I/II) PAR-24-063
Phase I: Up to $500K/yr*($700K total across ≤2 yrs)
Phase II: Up to $1.5M/yr ($3M total across ≤3 yrs)

*NINDS rules check specific IC rules if no vertebrate animal work $225K/yr

NIH Blueprint | Neurotherapeutics Network for Biologics

BPN-Biologics

A Customized Combination of Infrastructure, Expertise, and Funding

- Cooperative agreement and SBIR Fast-Track award programs support biologics discovery and development
- Access to consultants and contracts that provide discovery, preclinical development, and clinical trial support

Lead Product Development Team
Principal Investigator
Industry-seasoned consultants
NIH staff

PAR-21-163 (UG3/UH3); PAR-21-233 (SBIR - U44)
Next Application Due Date: February 9, 2024

Chris Boshoff, PhD
christoffel.boshoff@nih.gov

NIH Grant

Bioactivity/ Efficacy Studies

NIH Contracts

cGMP Manufacturing | **PK/Tox** | **Clinical Trials** | **Data Management**

Up to ~$10M/project
(if all milestones are met)

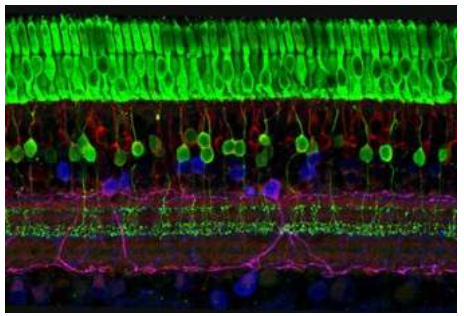


Image Credit: Wei Li, NEI

Projects can enter at either the:

- Discovery stage: for lead characterization and optimization to improve the potency and/or suitability for clinical testing
- Development stage: to advance a development candidate through IND-enabling toxicology studies and Phase I clinical testing

Modalities: antibodies, peptides, proteins, gene-based therapies, cell therapies, other emerging biotechnologies

https://neuroscienceblueprint.nih.gov/neurotherapeutics/bpn-biologics

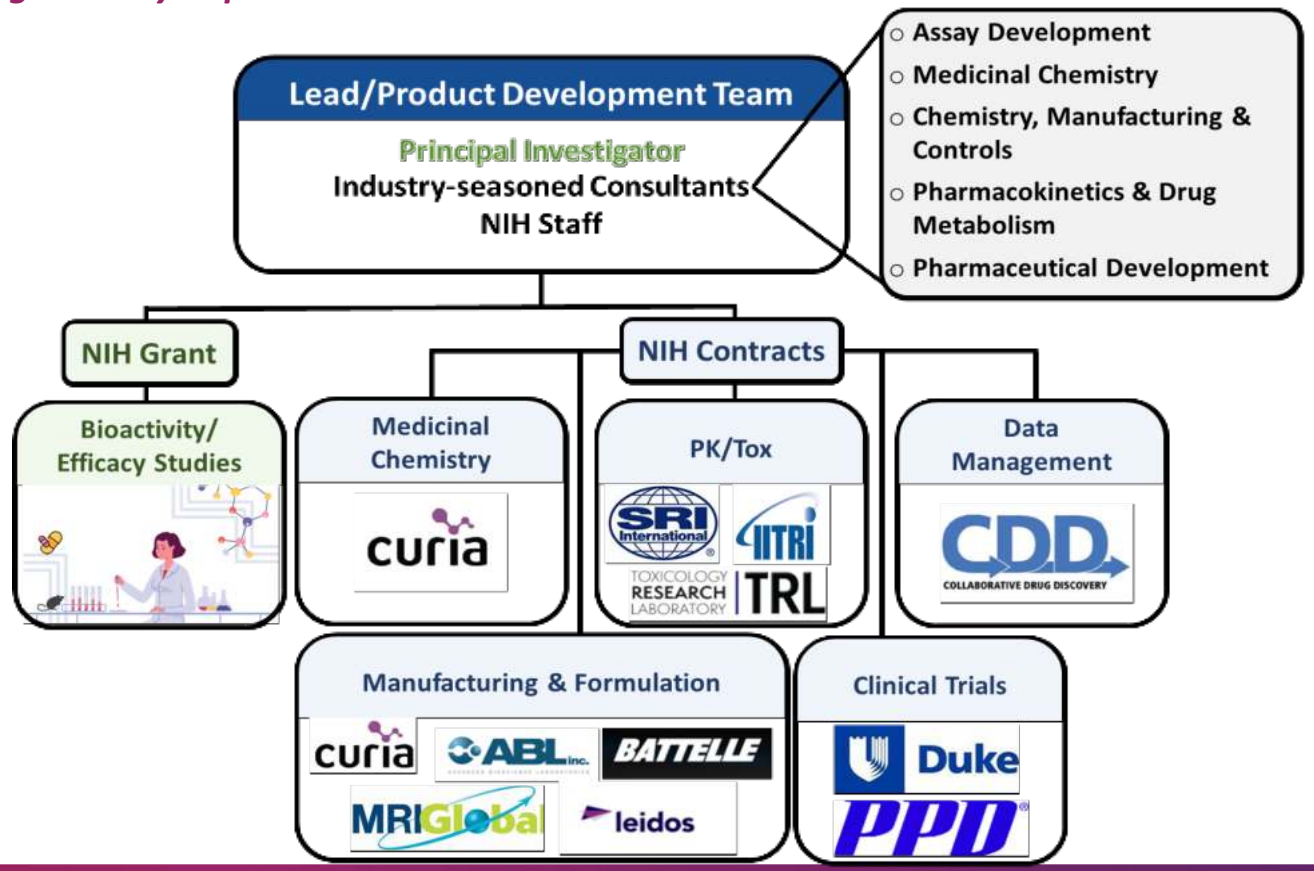
HEAL Pain Therapeutics Development Program (PTDP)

UG3/UH3 Phased Award Cooperative Agreement: RFA:NS-24-019

Hit/Lead Optimization → **Lead Selection/Lead Characterization** → **IND Enabling Studies** → **Phase I Clinical Trial**

Virtual Pharma Approach Featuring Industry-Experienced Consultants and NIH Contract Resources

- Supports biologic and small molecule therapeutic development
- NIH Consultants are assigned and tailored to each project based on needed expertise
- NIH Contract resources are tailored to stage of each project
- Awardee can choose which NIH contracts to use or opt to budget their own contracts in grant proposal
- *PI team's Intellectual Property Retained by PI's Institution*



NIH HEAL INITIATIVE

Features of the HEAL PTDP Grant: RFA-NS-24-019

Goal: Accelerate development of novel, non-opioid, non-addictive analgesics

Grant Features:

- Phased, milestone driven cooperative agreement grant with maximum 5 years of funding
- Supports the early therapeutic development process, including:
  - Hit to Lead activities
  - Lead optimization, selection and characterization
  - Biomarker optimization and PK/PD development
  - IND-enabling studies and Phase I trials

End Goals & Milestones

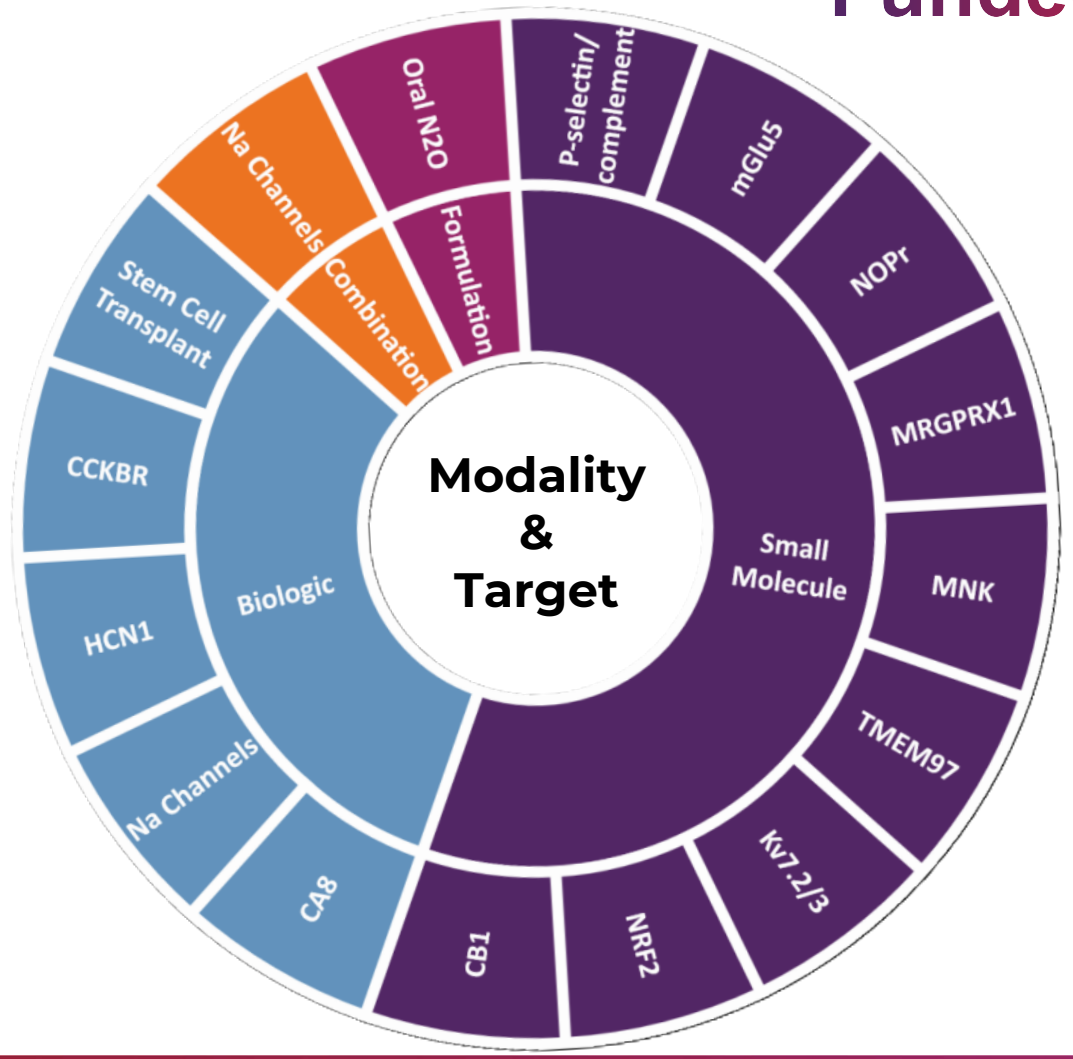
- ✓ Identify and fully characterize a lead candidate
- ✓ Identify target engagement biomarker if possible
- ✓ Seek partnerships
- ✓ Complete IND enabling studies
- ✓ File IND
- ✓ Complete Phase I trial(s)
- ✓ Ready for Phase II clinical trial

NIH HEAL INITIATIVE

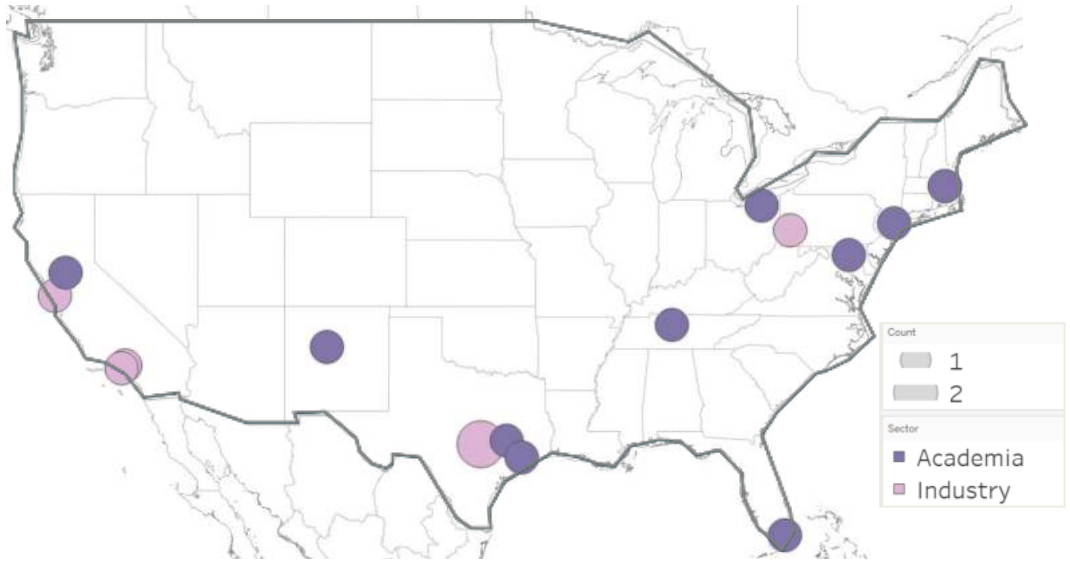
2024 Receipt Dates (same date for re-submission):

January 24th | May 24th | September 24th

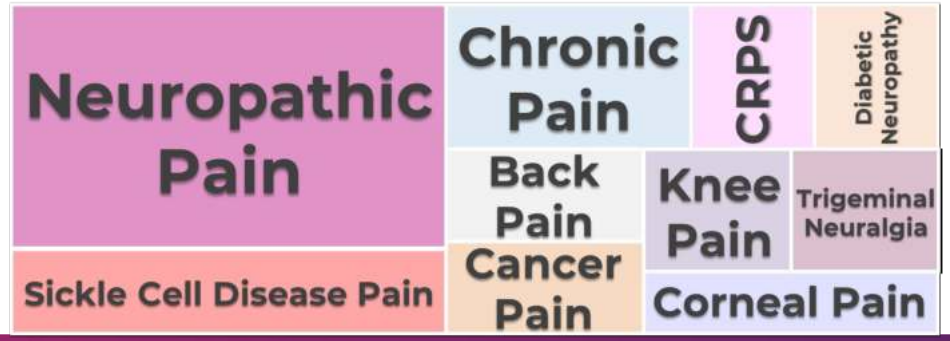
A Snapshot of HEAL Pain Therapeutics Development Program Funded Research



Location & Sector



Pain Condition



NIH HEAL INITIATIVE

Contact: Mary Ann Pelleymounter, Program Director
mary.pelleymounter@nih.gov

NINDS IGNITE Program

IGNITE Team:

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Ms. Shruthi Thomas
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Ms. Ashley Givens
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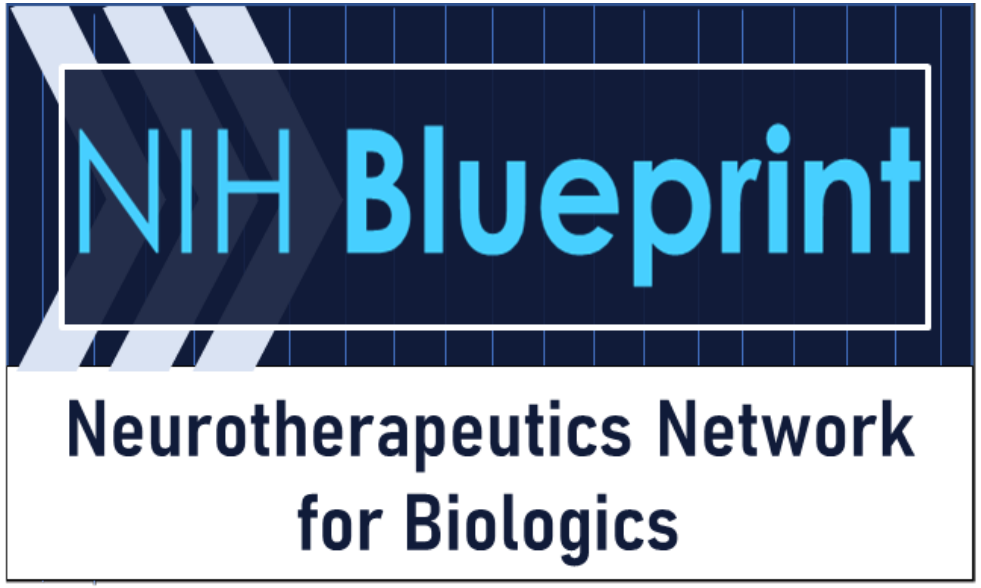
IGNITE Goal: Prepare Applicants for Later-Stage Programs

IGNITE is meant to serve a feeder program to later-stage therapy development programs such as the Blueprint Neurotherapeutics Network for Small Molecules or for Biologics

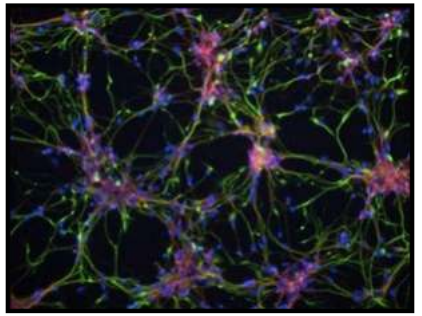


IGNITE Funding Opportunites

PAR-21-124: Assay Development and Therapeutic Agent Identification

PAR-21-123: Development and Validation of Model Systems to Facilitate Neurotherapeutic Discovery

PAR-21-122: Neurotherapeutic Agent Characterization and In vivo Efficacy Studies



Budget: ≤$499,000/Year; ≤$750,000 for Project

Upcoming Application Due Date: Feb 20, 2024

See NOT-OD-15-039 for info on late submissions

NIH National Institute of Neurological Disorders and Stroke

IGNITE

Milestoned Mechanisms Allow for Dependent Aims

R61 Phase 1: Demonstrate Feasibility and Prepare

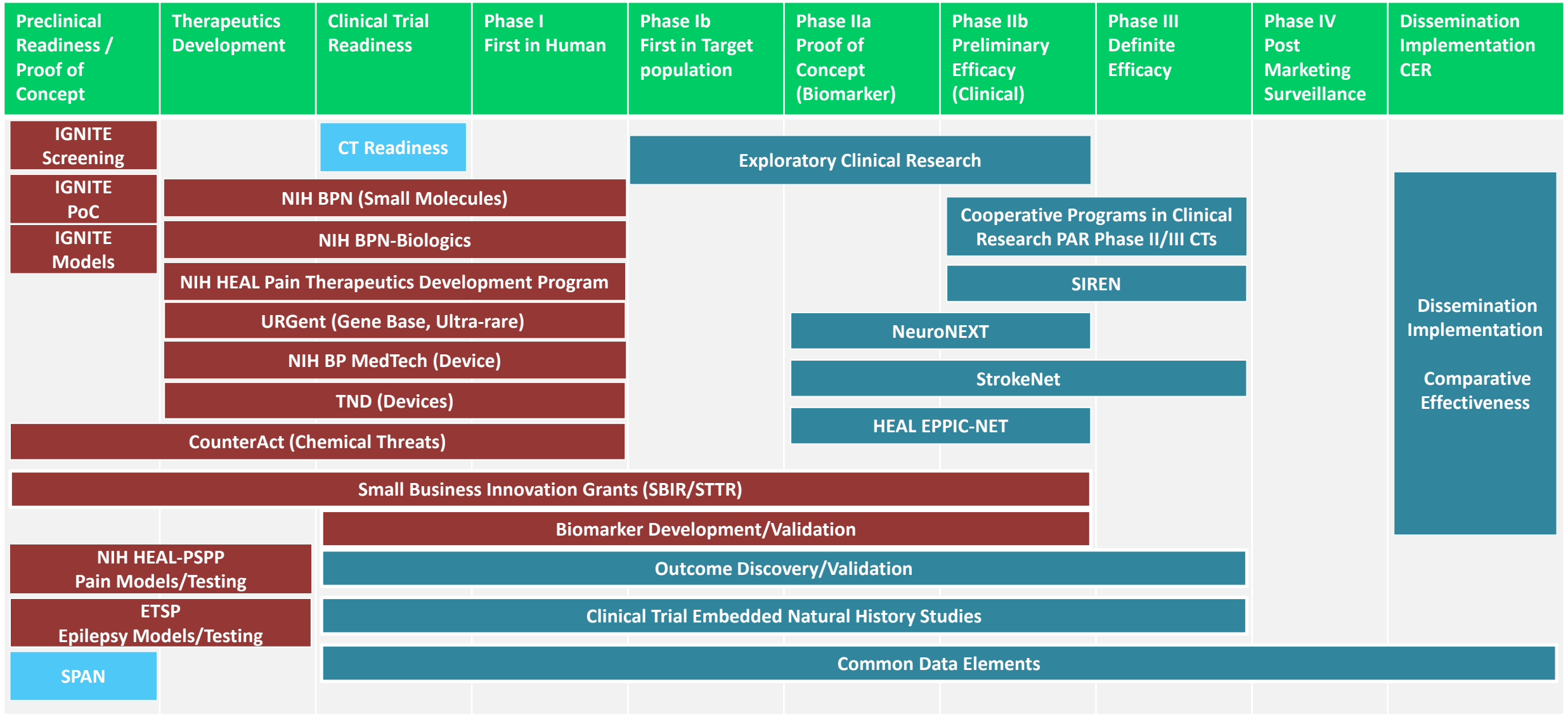
Go/No-Go Milestones

R33 Phase 2: The Key Experiment

Extremely Clear, Quantitative and Definitive Milestones are *Essential*

Transition to Phase 2 via Administrative Review

NINDS Offers Programs Across the Translational and Clinical Spectrum



National Institute of Neurological Disorders and Stroke

Division of Neuroscience

Division of Translational Research

Division of Clinical Research

General Tips

- Contact us in advance
- Read NOFO's carefully
- Pay attention to non-responsive activities*
- Include a rigorous designs and supporting data (see NOT-NS-11-023)
- Have a multidisciplinary team; note the multidisciplinary reviews
- Strive to increase the diversity of your team (see NOT-OD-20-031)
- Discuss intellectual property (for therapeutics) as requested
- Have a therapy development plan
- Small Businesses are encouraged to consider the SBIR/STTR program. Contact: Emily Caporello (emily.caporello@nih.gov)

*** Non-responsive applications will be withdrawn**

More on NOFO's

- Notice of Funding Opportunity Announcements (NOFOs)
  - Read the each NOFO carefully
    - PA vs PAR vs RFA: Each one can have different requirements, review criteria, eligibility etc.
    - Is it a Cooperative Agreement (U-grant vs. R-grant)?
    - Is it milestone based?
    - Is it an SBIR mechanism?
  - Follow the instructions in the NOFO
    - Failure to do so may result in your application being withdrawn from consideration prior to review.

Hit Compound ≠ Clinical Candidate

- Is there a sufficient therapeutic window between activity at desired and undesired targets?
  - hERG inhibition?
  - Other off-target effects?
  - Inhibitor of common CYPs?

- Is PK/PD consistent with the dosing strategy in the Target Product Profile?

Profile your compound early on

Incorporate IP into Your Strategy

- Consider future licensing strategy
- Don’t develop someone else’s compound
- Avoid encumbering your own future work

Contact your Tech Transfer/Business Development official early on

Development Plan-Plan with the End in Mind

- **Target population**
  - Pediatric vs. adult patients?
  - Early vs. advanced disease?
- **Dosing regimen**
  - Chronic or acute treatment?
  - Frequency?
- **Route of administration**
  - Oral? IV? Eye drops? Transdermal? etc.
- **Desired outcome**
  - Comparison to standard of care?

Engage clinicians in developing a Target Product Profile

Rigor is Important

- Preliminary and supporting data
  - *Explicitly discuss the quality of the data presented in prior publications in a detailed manner. Were they done in a rigorous manner, utilizing randomization, blinding, inclusion/exclusion criteria and the appropriate power analysis*

- Rigor
  - *Detail the controls being used for each type of experiment and appropriately highlight potential confounds like surgery exposure, genotype, culture-to-culture variability, and human placebo effects.*
  - *Include details within the experimental design about the reduction of potential bias, including blinding, randomization, and inclusion/exclusion criteria.*
  - *Describe the source of the data on which the sample size estimation (power analysis) is based **and** details about the analysis itself.*

Questions?

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https://www.ninds.nih.gov/current-research/research-funded-ninds/translational-research