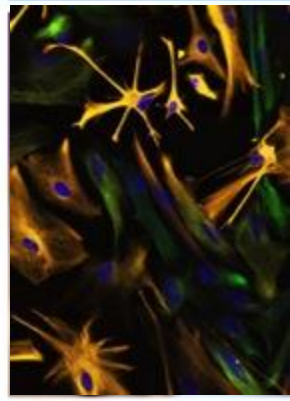
National Institute of Neurological Disorders and Stroke

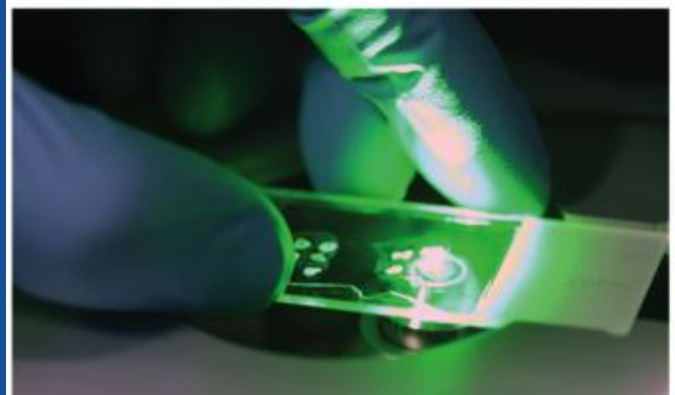
Translational Research, NINDS Programs

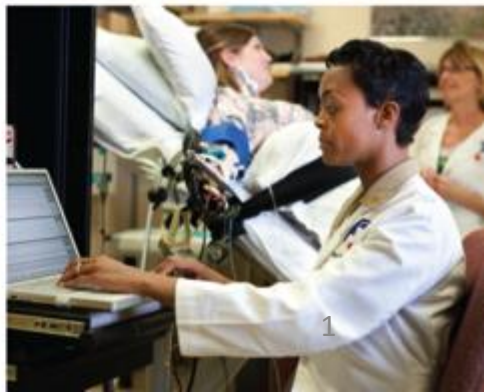
The 18th Annual Non-Dilutive Funding Summit

Charles L Cywin, PhD
Director, Small Molecule Neurotherapeutic Development

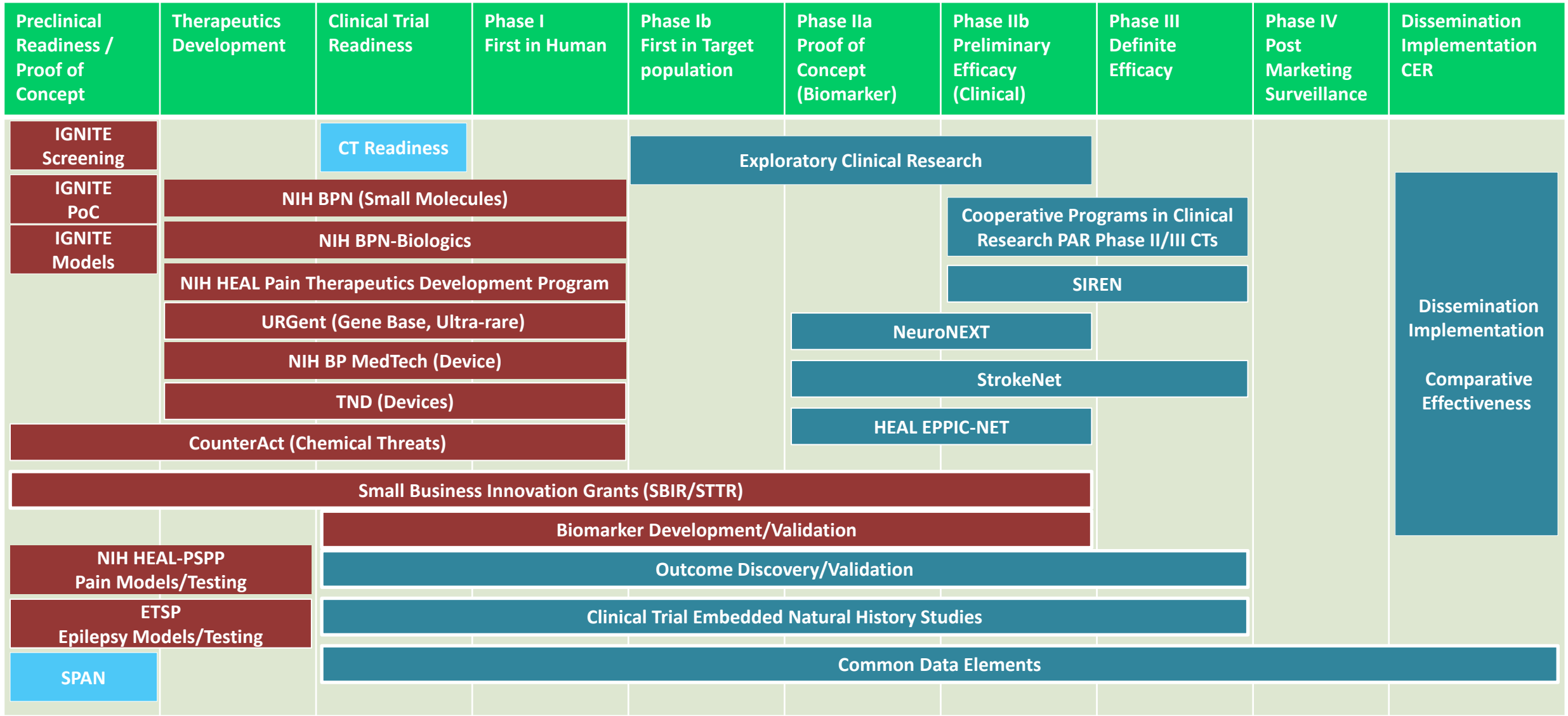
January 11, 2023







NINDS Offers Programs Across the Translational and Clinical Spectrum



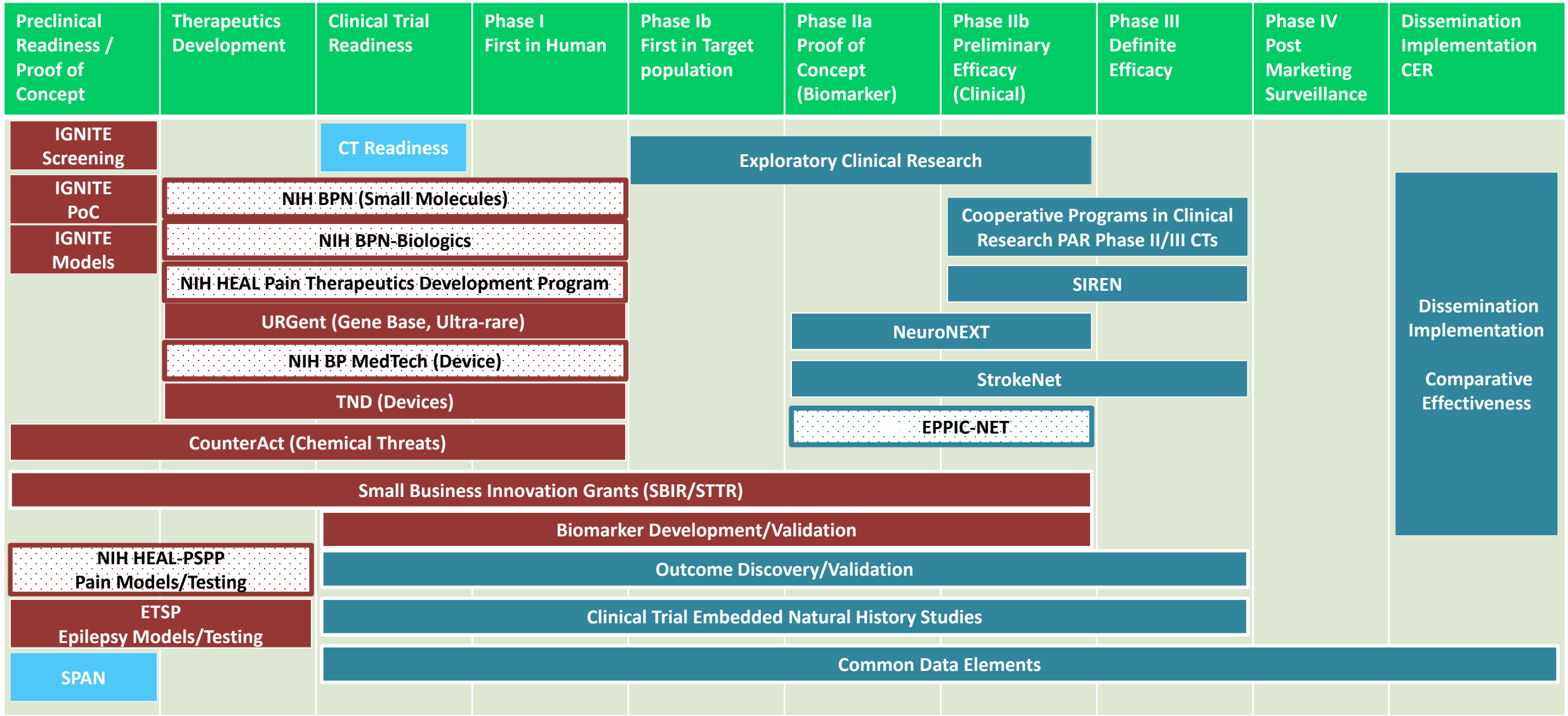
National Institute of Neurological Disorders and Stroke

Division of Neuroscience

Division of Translational Research

Division of Clinical Research

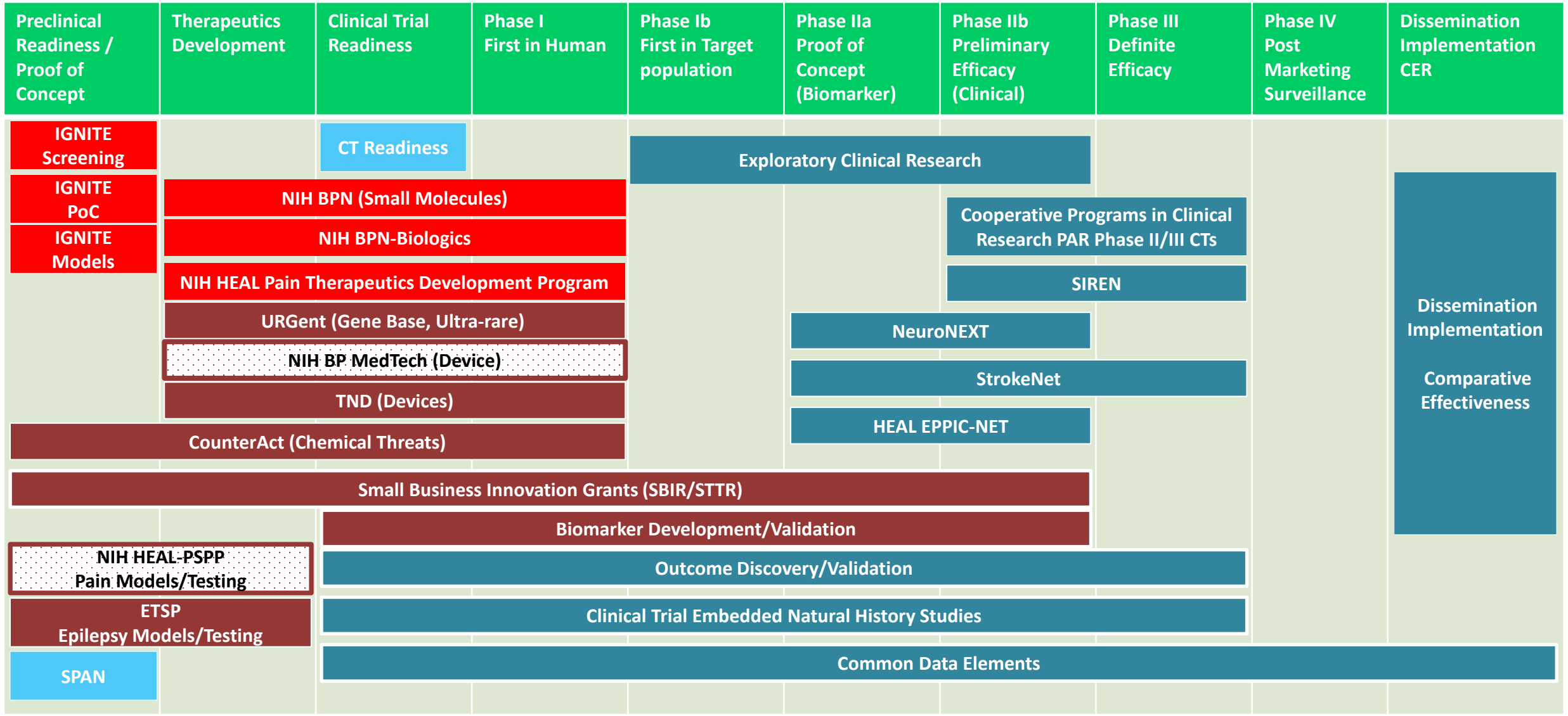
NINDS Offers Programs Across the Translational and Clinical Spectrum



National Institute of Neurological Disorders and Stroke

Division of Neuroscience | Division of Translational Research | Division of Clinical Research

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

NINDS IGNITE Program

IGNITE Team:

Dr. Becky Roof
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Dr. Shardell Spriggs
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Ms. Shruthi Thomas
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Ms. Ashley Givens
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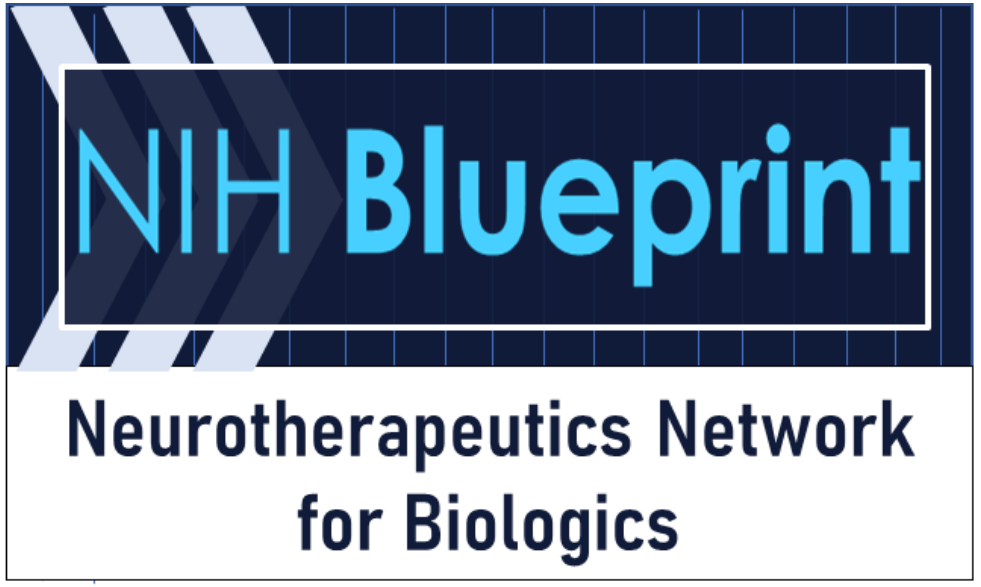
IGNITE Goal: Prepare Applicants for Later-Stage Programs

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

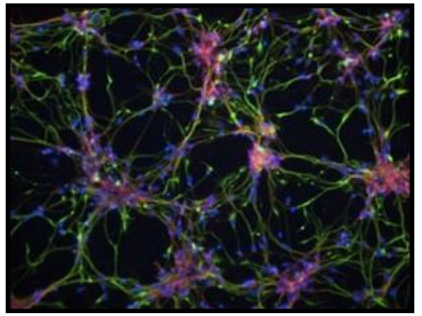


IGNITE Funding Opportunites

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 Dates: Feb 21, 2023; June 20, 2023

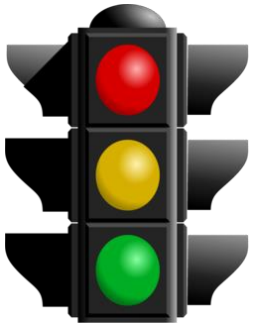
See NOT-OD-15-039 for info on late submissions

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

General Tips for IGNITE

- Contact us in advance
- Have quantitative go/no-go milestones*- see examples here
- Clearly demarcate R61 v R33 activities and timeline*
- Pay attention to non-responsive activities*
- Include a rigorous study design and supporting data (see NOT-NS-11-023)
- Have a multidisciplinary team; note the multidisciplinary review
- Strive to increase the diversity of your team (see NOT-OD-20-031)
- Discuss intellectual property (for therapeutics)
- Have a therapy development plan
- Small Businesses are encouraged to consider the SBIR/STTR program. Contact: Emily Caporello (emily.caporello@nih.gov)
- For a full IGNITE Q&A webinar, see here

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

BPN Program

NIH **Blueprint**
for Neuroscience Research

BPN Staff

Program Director

Charles Cywin, PhD

Health Program Specialist

Carolyn Bondar, PhD

Operations Coordinator

Rakonda Medley, BS

Scientific Project Managers

Pascal Laeng, PhD

Enrique Michelotti, PhD

Oreisa O'Neil-Mathurin, MPH (**EOC**)

Mary Ann Pelleymounter, PhD

Shamsi Raeissi, PhD

Ranga Rangarajan, PhD

Rebecca Roof, PhD

Carol Taylor-Burds, PhD

BPN Program Vision

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

NIH investigator-initiated ideas

- Solid scientific premise
- Expert disease biology
  - Assays and models

Industry expertise

- Consultants with extensive pharma experience across all R&D spectrum
- Pre-established industry-standard contract services available via BPN

End Goals

- Maintain IP
- Decreased risk as projects advance
- Advance projects to clinic and hand-off

BPN Success Stories

- **38 Projects funded to date covering 8 ICs**

- **Seven BPN compounds have INDs and first in human trials complete**
  - Two projects are now in Phase III (Fragile X/AD (Tetra) & Stargardt's/AMD (Belite))
  - Three projects are in Phase II (MDD (BlackThorn) & Hearing Loss (Oricula), Pain (Eicosis))
  - Two projects completing Phase I (SUD (Eolas) & epilepsy (Knopp-(now BioHaven))

- **Two more INDs and Phase I studies expected to start in 2023 (SUD and pain)**

- **Three additional INDs and trials supported ad hoc**
  - **NCCIH:** Assisted in IND enabling activities for (now in Phase III (Nicotine addiction) (Achieve))

- **Ten projects have announced additional industry funding since utilizing the BPN**
  - Valued at close to 2-billion dollars in potential investments

tetra THERAPEUTICS SHIONOGI Group Company

Belite BIO

Eolas THERAPEUTICS

Oricula Therapeutics Medicines to Preserve Hearing

BlackThorn THERAPEUTICS

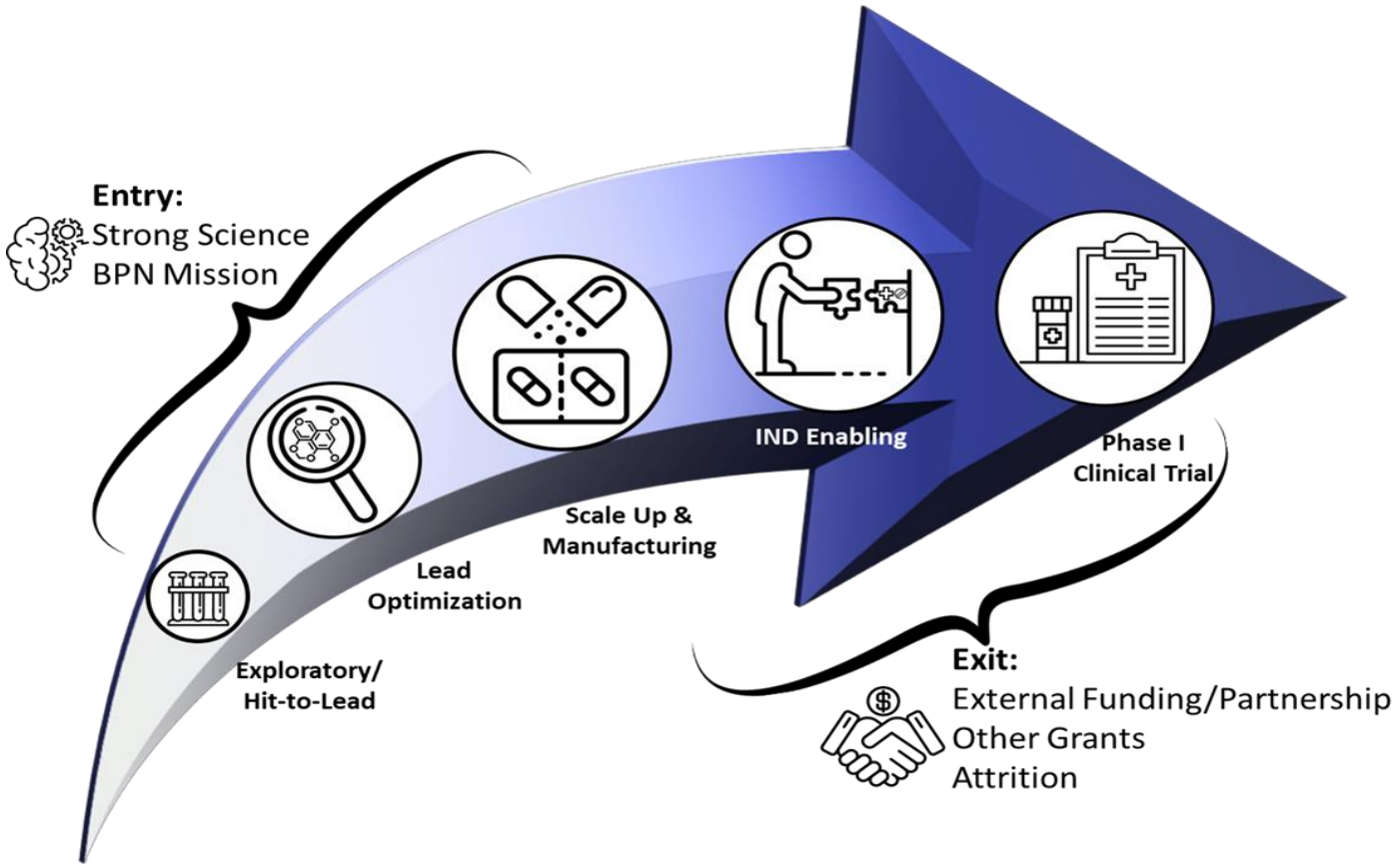
EicOsis Developing sEHI as a First in Class Treatment for Pain

Knopp Biosciences

ACHIEVE LIFE SCIENCES

Advance Projects for Hand-Off

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



Blueprint Neurotherapeutics Network (BPN)

Customized Combo of Infrastructure, Expertise, and Funds

Lead/Product Development Team

Principal Investigator
Industry-seasoned consultants
NIH staff

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

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

MRIGlobal National Solutions Worldwide Impact

curia

Clinical Trials

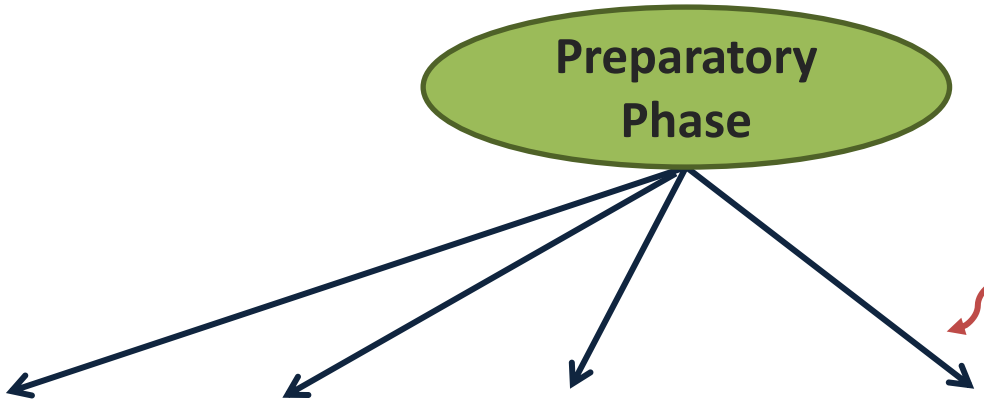
Duke

PPD

- Contract resources are tailor-made to support projects
- Program progression is milestone driven
- **PI team's Intellectual Property Retained by PI's Institution**

BPN – Projects Can Enter at Any Preclinical Stage

All Projects Begin with Preparatory Phase



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

Not all ICs accept Development Projects

Discovery			Development	
Exploratory	Hit to Lead	Lead Optimization	IND Enabling	Phase I Trial

General (UG3/UH3) PAR-20-122
UG3: Up to $300K direct costs x 1 yr
UH3: Up to $1.5M/yr direct costs x 4 yrs

SBIR (U44-I/II) PAR-20-111
Phase I: Up to $500K/yr*($700K total across ≤2 yrs)
Phase II: Up to $1.5M/yr ($3M total across ≤3 yrs)
*Limit varies by IC contact staff and if no vertebrate animal work $225K/yr

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Next Anticipated Application Date: February 9, 2023

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

NIH Grant

Bioactivity/ Efficacy Studies

NIH Contracts

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

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

PAR-21-163 (UG3/UH3); PAR-21-233 (SBIR - U44)

Chris Boshoff, PhD
christoffel.boshoff@nih.gov

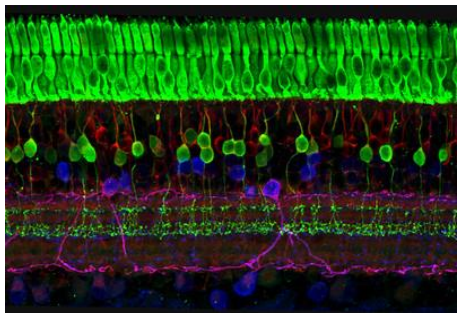


Image Credit: Wei Li, NEI

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

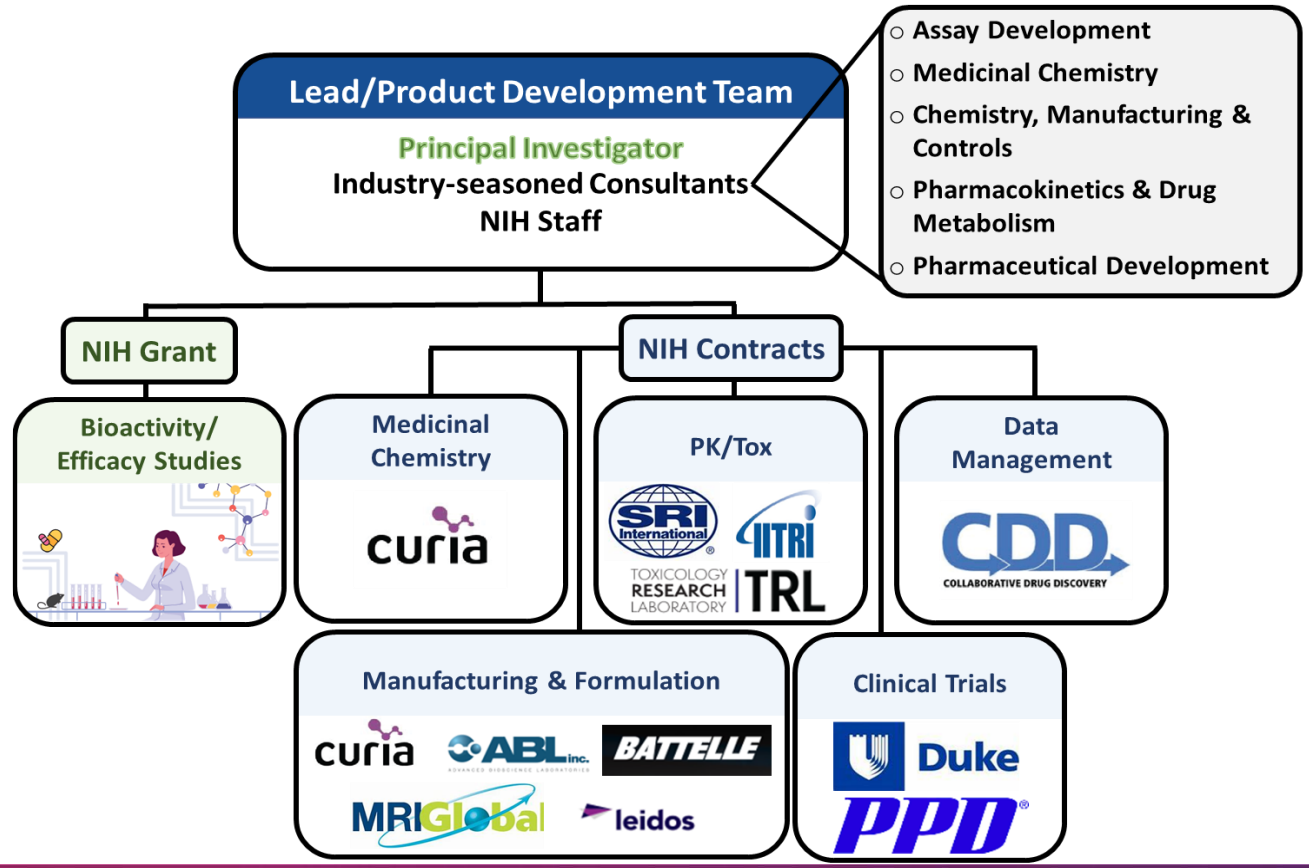
https://neurosciencebluepprint.nih.gov/neurotherapeutics/bpn-biologics

HEAL Pain Therapeutics Development Program (PTDP)

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*



Features of the PTDP Grant: RFA-NS-21-010

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

Grant Features:

- Phased, milestone driven cooperative agreement grant
- Supports Hit to Lead activities
- Supports lead optimization, selection and characterization
- Supports biomarker optimization and PK/PD development
- Supports 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

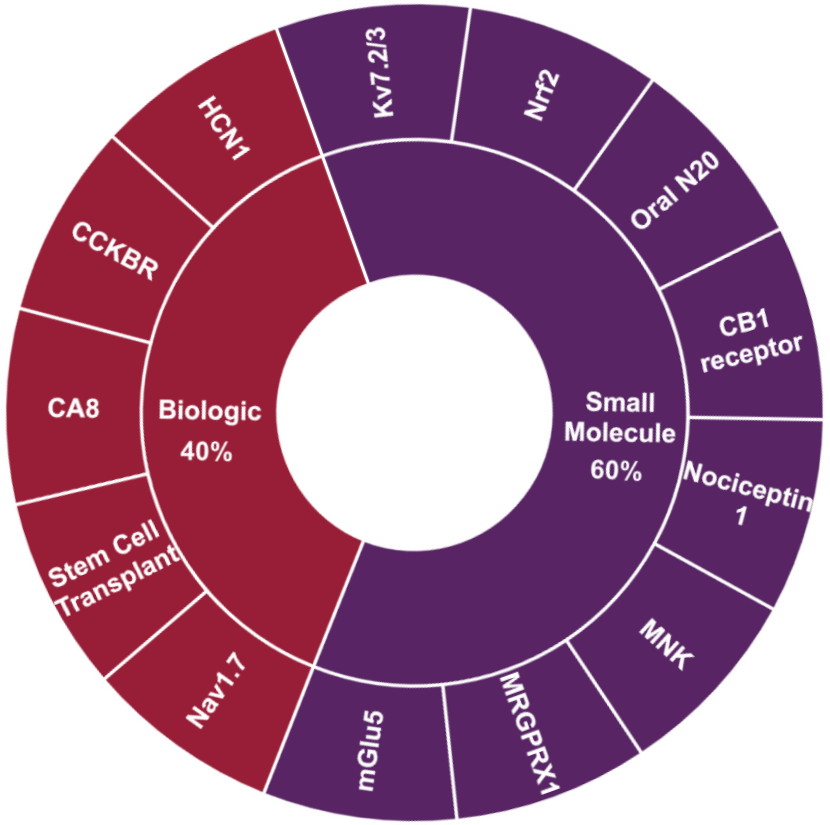
NIH HEAL INITIATIVE

Remaining receipt Dates: February 14, 2023, June 15, 2023 and October 17, 2023

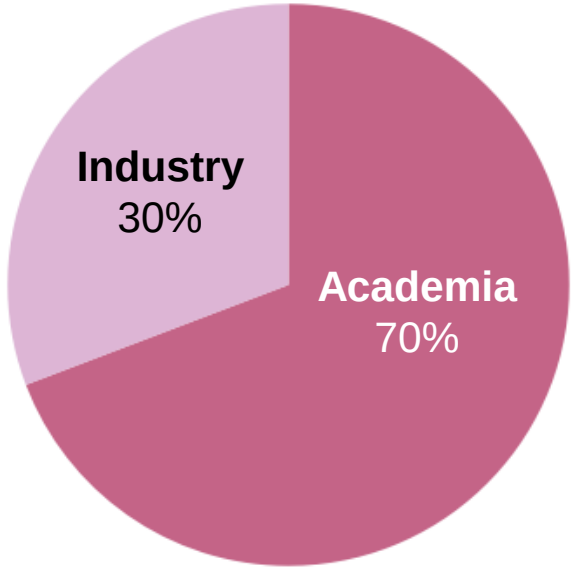
Contact : Mary Ann Pelleymounter (mary.pelleymounter@nih.gov)

A Snapshot of HEAL Pain Therapeutics Development Program Funded Research

Therapeutic Target and Modality

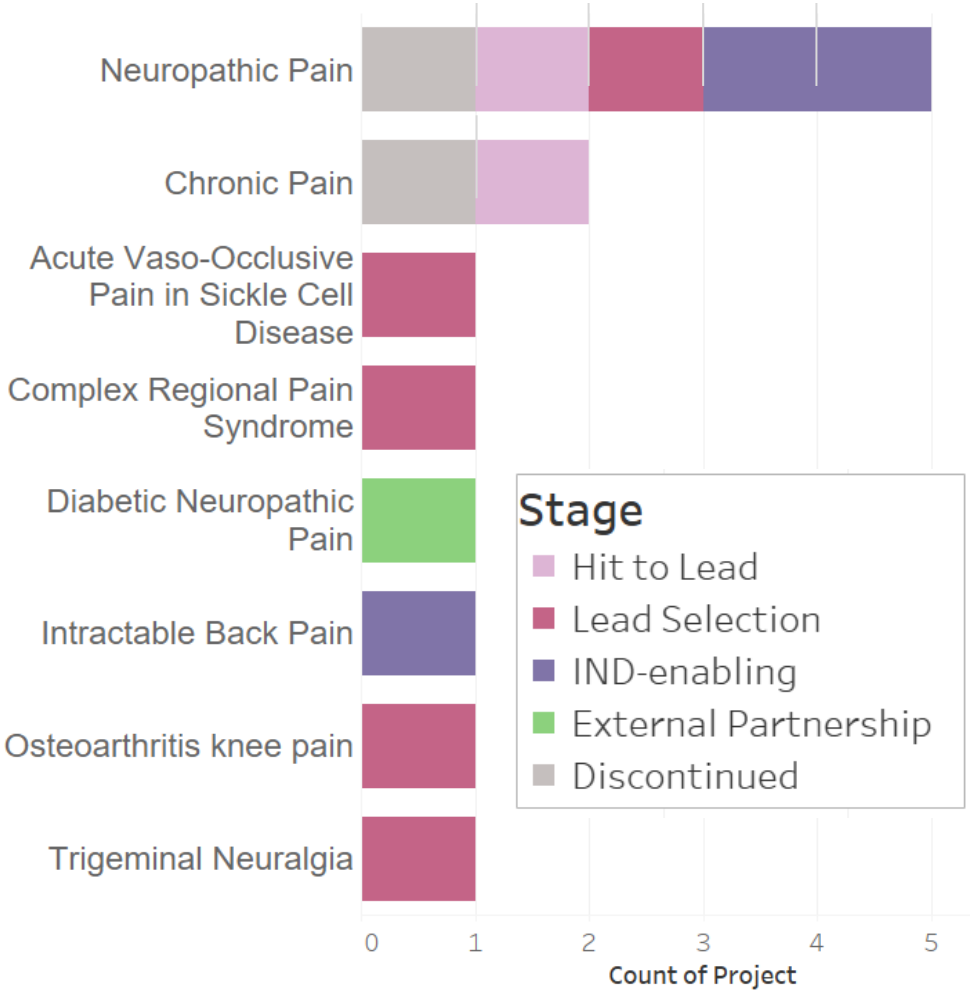


Sector



If all milestones are met, 2-3 IND Submissions are anticipated between FY23-24

Pain Condition and Stage



PTDP has a diverse mix of therapeutic targets and pain indications with roughly even proportions of biologic and small molecule modalities.

Types of Mechanisms

- Funding Opportunity Announcements (FOAs)
  - Read the each FOA 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 FOA
    - Failure to do so may result in your application being withdrawn from consideration prior to review.

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

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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

Some Things To Do

- 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