

NIH
HEAL
INITIATIVE

# Non-addictive Analgesic Therapeutics Development [Small Molecules and Biologics] to Treat Pain (UG3/UH3 Clinical Trial Optional)

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**Charles Cywin, Michael Oshinsky & Ann Marie Broome**


***#NIHhealInitiative***

National Institutes of Health
*HEAL Initiative*

# NIH Helping to End Addiction Long-term (HEAL) Initiative: Pain Research Priorities

## Enhance Pain Management

- Understand the biological underpinnings of chronic pain
- Accelerate the discovery and pre-clinical development of non-addictive pain treatments
- Advance new non-addictive pain treatments through the clinical pipeline
- Inform best practices for effective pain management while minimizing risk of addiction


Read about the research plan:

www.nih.gov/heal-initiative


JAMA June 12, 2018 Opinion

VIEWPOINT

Helping to End Addiction Over the Long-term
The Research Plan for the NIH HEAL Initiative

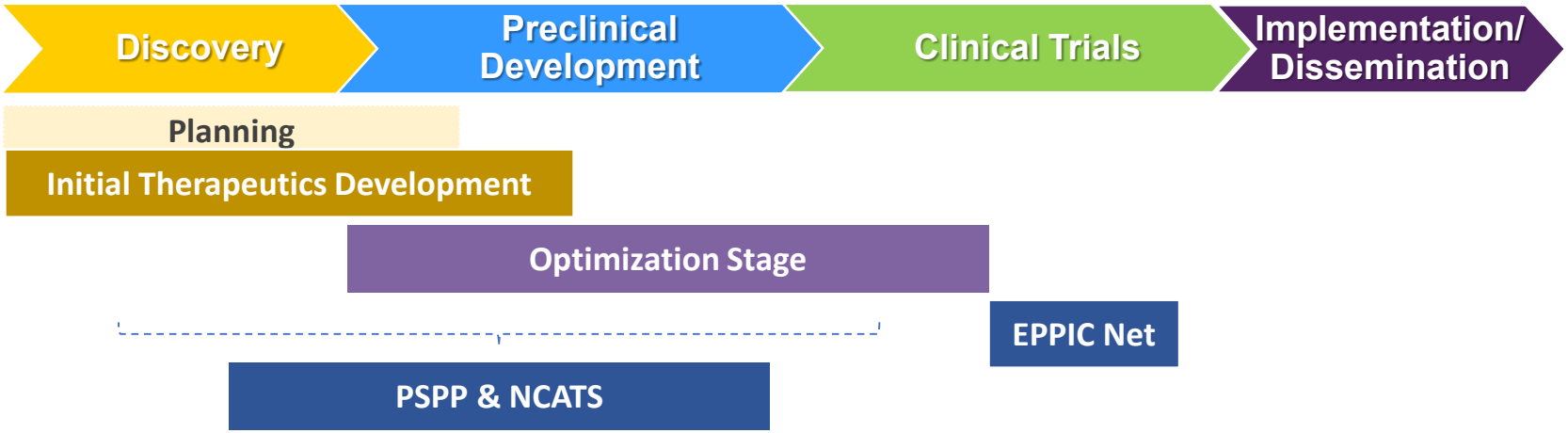
Collins, Koroshetz, Volkow; JAMA, 2018

# Scientific Challenges – Analgesics Development

***Specific Challenges:***

1. Complexity of biology/pharmacology
2. Lack of validated targets
3. Lack of translatable pain measures
4. Lack of predictable preclinical models
5. Rigorous proof of concept studies
6. **Robust therapeutic tools**
7. **Early indication for safety and efficacy**
    a. **Target engagement biomarkers**
8. **Lack of resources and expertise at academic centers**

# Proposed HEAL Analgesic Development Program

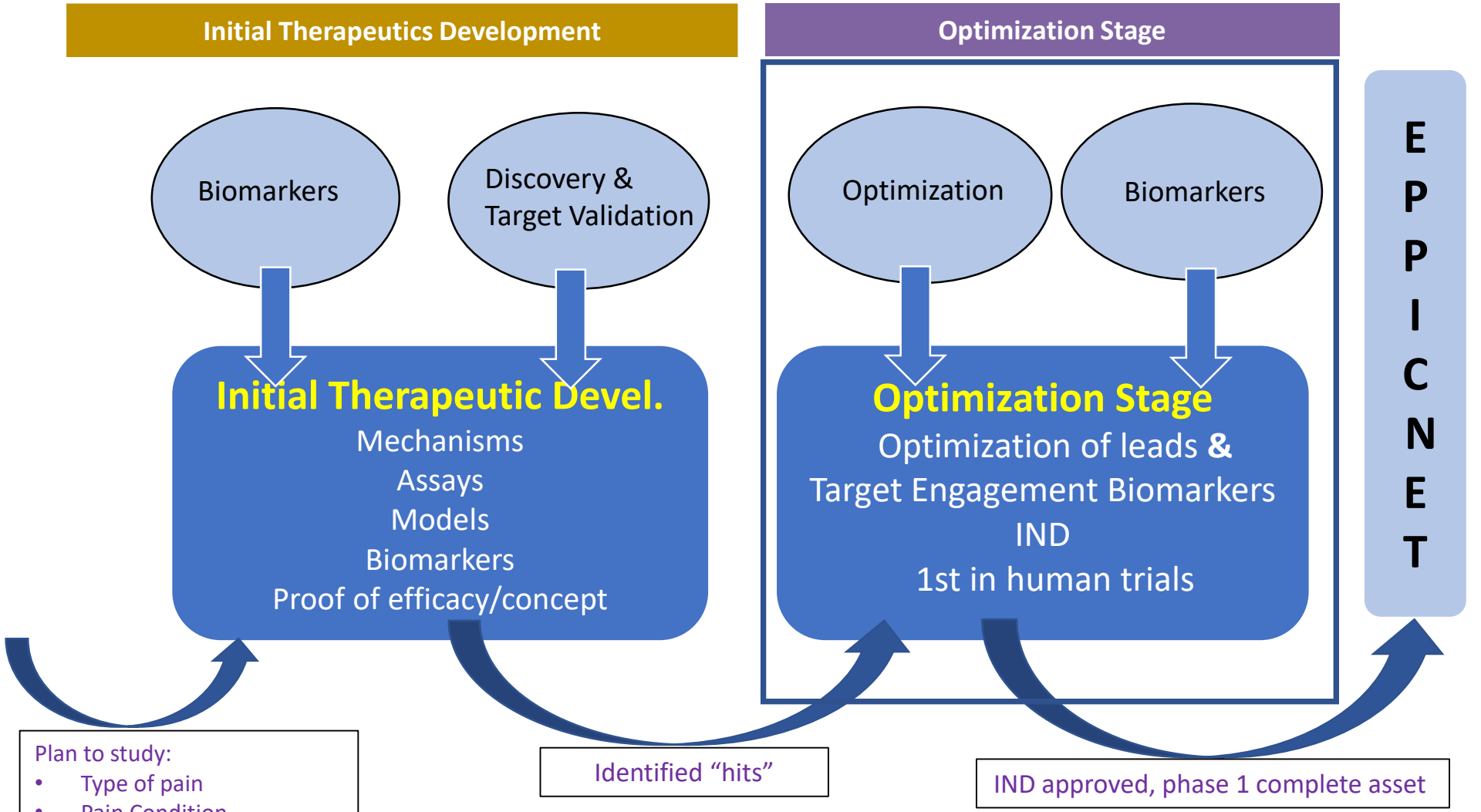



Realign Programs for Analgesics Development:

- ✓ Focus on deliverables
- ✓ Focus on scientific challenges
- ✓ Minimize program complexity
- ✓ Incentivize industry to reinvest

Grants | Grants & Contracts | Grants, Contracts & Intramural Resources

# Realignment: HEAL Analgesic Development Program



# Non-addictive Analgesic Therapeutics Development [Small Molecules and Biologics] to Treat Pain

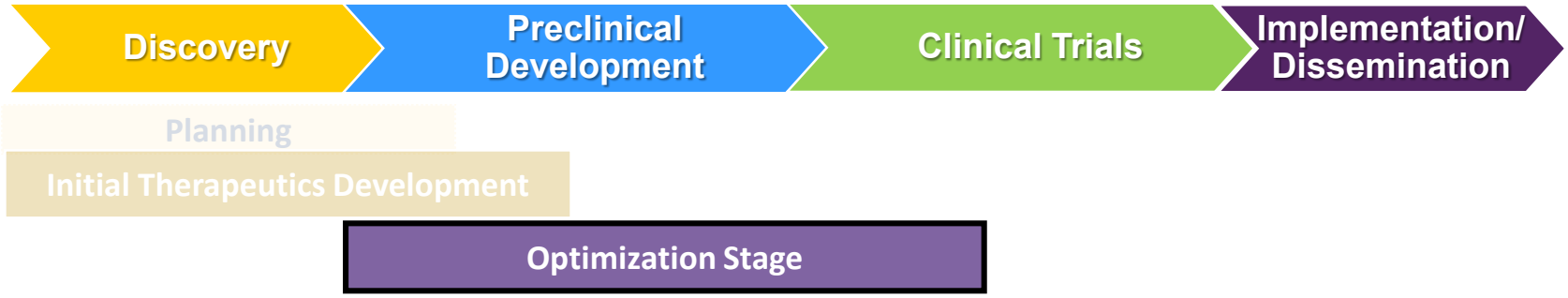
## Goal

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

## Five-year Benchmarks

- ✓ At least 5 promising projects with appropriate assay(s), model(s), and tools - ready for preclinical lead optimization.
- ✓ At least 3 novel analgesics with an IND and human safety data – ready for clinical efficacy studies through EPPIC-Net or equivalent phase II trial.

# Non-addictive Analgesic Therapeutics Development [Small Molecules and Biologics] to Treat Pain (UG3/UH3) (RFA-NS-21-010)

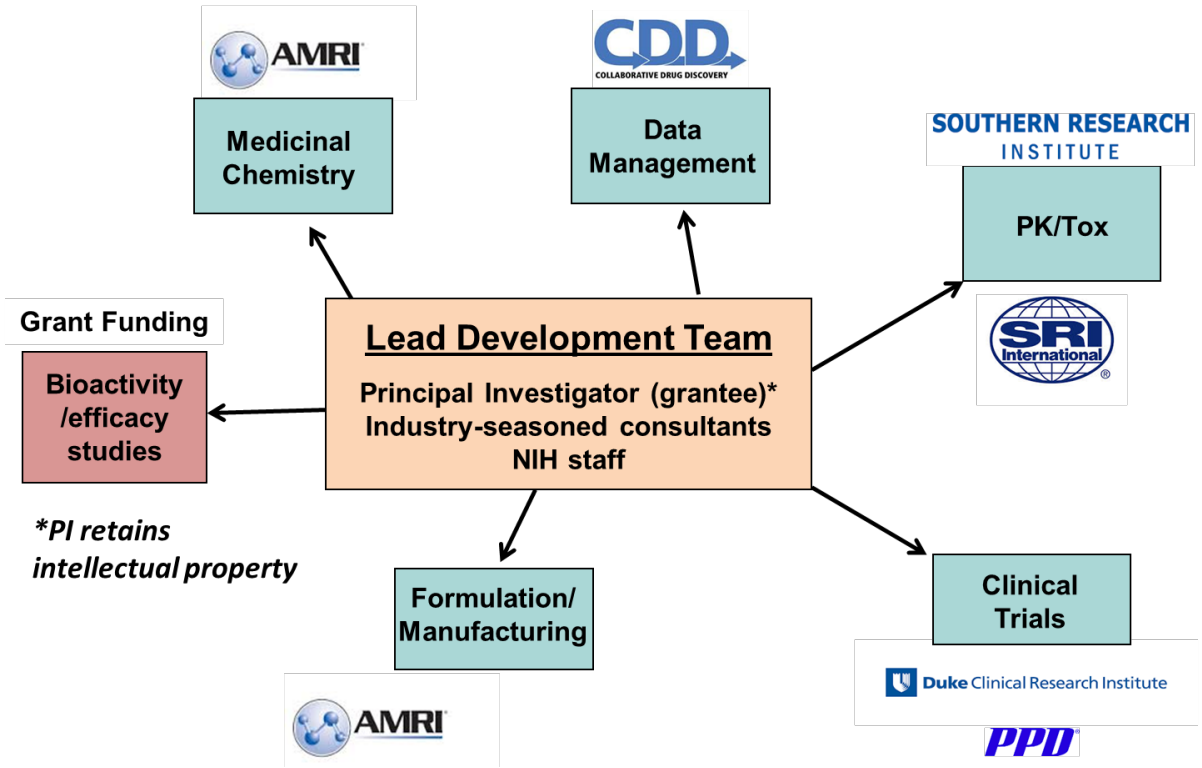



- Milestone driven Cooperative agreements
- Identify and conduct the studies necessary to meet the requirements for initiating optimization or IND-enabling studies
- Lead optimization to identify a development candidate
- Support IND-enabling studies and Phase I trials
- Expert scientific consultants, CROs, PSPP, and NCATS

**End Goals and Milestones:**

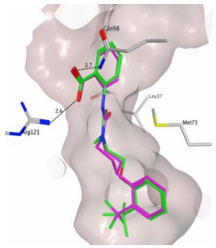
- ✓ Identify clinical candidate
- ✓ Optimization and IND-enabling studies
- ✓ File IND
- ✓ Complete Phase I trial(s)
- ✓ Identify companion target engagement biomarker
- ✓ Seek partnerships
- ✓ Ready for Phase II clinical trial

# Provide Resources Not Readily Available in Academia

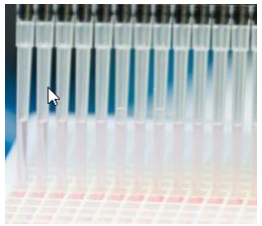



* Contract resources are tailor-made to support PI teams
*(Other contracts may be implemented)*

# Non-addictive Analgesic Therapeutics Development [Small Molecules and Biologics] to Treat Pain (UG3/UH3 Clinical Trial Optional)



In vitro testing



In vivo efficacy testing

Structure Activity

AMRI

PK/Tox

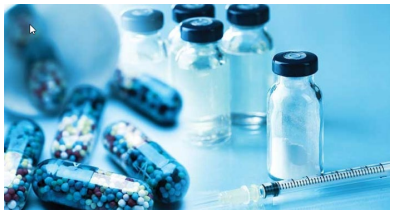
SRI International

SOUTHERN RESEARCH INSTITUTE

Pharmacokinetics
Toxicology

FDA

IND Assembly



Manufacturing/ Formulation

Clinical Trials

Duke

PPD

**UG3 Phase (Optimization)**
**Anticipate to launch up to 17 projects during first 3 years**

**UH3 Phase (Final Optimization/Development)**
**Anticipate ~5 projects to advance to UH3**

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***Receipt Dates: March 24, 2021 with dates continuing until June 2022***

# Focus on Markers to Support Target Engagement and Pharmacodynamics for Early Clinical work

- **PD/response (target engagement) biomarkers**
- **Safety biomarkers**

✓ Interpret IND Toxicology
✓ Project Phase I human dosing

# Non-addictive Analgesic Therapeutics Development [Small Molecules and Biologics] to Treat Pain (UG3/UH3)

***The overall goal of this initiative is to support preclinical optimization and early Phase I testing to develop of safe, effective, and non-addictive small molecule and biologic therapies to treat pain.***

- Accelerate the optimization and development of promising small molecule and biologic hits/leads into therapeutic agents
- Entry Criteria:
  - A rigorous biological rationale for the intended approach
  - A promising small molecule or biologic starting point for optimization
  - Scientifically sound assays to optimize and test the agent

# 9 Participating IC's plus ORWH


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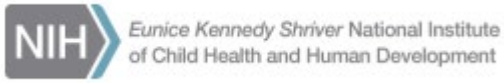


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# Key Resources Available

- NIH Contracts, medicinal chemistry, PK, drug manufacturing and formulation and Toxicology,
  - Available for small molecules and coming for some aspects of biologics
- Access to NIH Contracted Subject Matter Expert Consultants (Optimization and Development)
- NCATS intramural scientists and programs
  - Need to reach out to establish CRADA with NCATS prior to submission on application.
- Additional IC resources as available

# Anticipate Most Projects Will Enter at the Discovery Stage

***All Projects Begin with UG3 Phase***


**Eligible Organizations**

- Academic Institutions
- Small Businesses
- Foreign Institutions and Components*

| Discovery | | | Development |
|---|---|---|---|
| Exploratory | Hit to Lead | Lead Optimization | IND Enabling/Phase I |

Duration of UG3/UH3 combined is 5 yrs maximum

**General (UG3/UH3) RFA-NS-21-010**
UG3: 2 yrs max
UH3: 3 yrs

# NOT-NS-21-016

- **Release Date:** November 25, 2020

- The purpose of this notice is to inform potential applicants of the removal of the Cost Matching Requirement Instructions for RFA-NS-21-010 "HEAL Initiative: Non-addictive Analgesic Therapeutics Development [Small Molecules and Biologics] to Treat Pain (UG3/UH3 Clinical Trial Optional)". This information was erroneously published in the FOA. NINDS has removed the Cost Matching Requirement instructions from the R&R Budget and the letters of support, under the PHS 398 Research Plan, as shown below. This notice is effective for the March 24, 2021 receipt date and subsequent due dates.

# Activities that are nonresponsive

- Screening to identify hit compounds
- Basic research and studies of disease mechanism
- Animal model development
- Development of diagnostics and diagnostic devices
- Studies directed beyond Phase I clinical testing
- Opioid sparing projects and projects targeting mu-opioid

# Two Phase Grant Mechanism

1. Exploratory/Hit to Lead period (UG3):
   - Expect to start up 17 projects under this RFA in the first 3 years.
   - Identify and conduct the studies necessary to meet the entry for Lead Optimization
   - Design execution plans and go/no go milestones for all subsequent UH3 award
   - Progression from the UG3 award to the UH3 award will be based on **administrative review**
   - Each project can receive only one UG3 award

2. Lead Optimization/IND assembly period/Clinical (UH3):
   - Up to 5 projects expected to advance to this phase in first 5 years.
   - These projects will proceed through to the Phase I Clinical trial

# First Phase-UG3 (1-2 years)

- All projects must enter the UG3 phase of the program.

- For entry, projects must have:
  - A promising small molecule or biologic starting point for optimization
  - A rigorous biological rationale for the intended approach, and scientifically sound assays to test the agent.
  - Discuss options for target engagement biomarkers if available.

- FOA encourages projects proposing the following optimization activities:
  - Optimization using potency and efficacy screens
  - Preliminary efficacy testing in appropriate pain animal models
  - Characterization and testing for ADME (absorption, distribution, metabolism, and excretion)

- Goal:  Select a characterized lead candidate
  - Ready for in vivo efficacy testing, (additional optimization may be necessary.

# Second Phase-UH3

Administrative Review to determine which projects enter UH3.

- Any further optimization activities if needed
- Biomarker development
- Non-GLP toxicology studies (e.g. dose range finding toxicology)
- Pharmacokinetics (PK)
- Formulation and stability studies
- Cell bank development and testing
- Gene expression level
- Biodistribution, tumorigenicity, and immunogenicity
- Process development
- Manufacturing of candidate therapeutics for IND
- IND-enabling safety pharmacology, genotoxicity, hERG and toxicology studies.

# Administrative Review

- NIH program staff and leadership will conduct an annual administrative review.

- At the end of the UG3 phase, NIH program staff and leadership will determine if the project will advance to the UH3 phase.

- The reviews will be based on:
  - Successful achievement of milestones
  - The overall feasibility of project advancement including biomarker work and considering data that may not have been captured in milestones
  - Competitive landscape for the disease indication and drug target
  - Program priorities
  - Availability of funds

# Some things to do

- **Read the Funding Opportunity Announcement carefully**
- **Include budget sheets for all years of the grant (both phases) by year (e.g. 5-year grant should have 5 sets of budget sheets).**
- **Clearly indicate what will be done as part of the grant and what is expected by NIH contractors. (TABLE)**
- **Address Biomarker Component**
- Do discuss your proposal with NIH
  - Program Directors
- Stick to page limit
- Put forth a solid scientific premise and address rigor
- Address obvious criticisms of the starting points
  - Suggest contacting a colleagues and NIH staff.

# Some things to do

- Scientific premise
  - *Explicitly discuss the quality of the data presented in prior publications in a detailed manner.*
- 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.*

# Some additional things to do

- Complete your required registrations at least 6-8 weeks in advance of receipt dates
- Consider submitting your application early
  - Gives you a chance to react to issues that might result in your application being withdrawn.
- Discuss your budget with NIH Staff if you have questions.
- Talk with your tech transfer/BD group.
  - Need to plan for funding patents and licensing activities

# Things NOT to do

- Please do not plan for this to be sole funding for your lab
  - Milestone driven programs can end abruptly.
- Forget to address use of NIH contract resources
  - Please do not plan for NIH contracts for disease biology.
  - Please do not include NIH contracts in application budget
  - Do not reach out to planned NIH contractors for letters of support

# Questions and Discussions

1. Application process
2. Review process
3. Proposals and budgets
4. Contracts
5. Intellectual property

## Webinar Questions?

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Small Molecule: charles.cywin@nih.gov
General Pain Portfolio: michael.oshinsky@nih.gov