IGNITE Q&A Webinar

Wednesday, April 27, 2022

NINDS Team:

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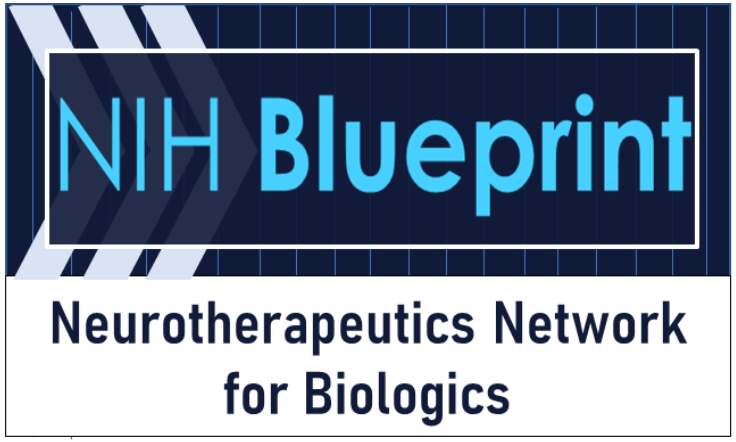
NCCIH Special Guest:

Dr. Craig Hopp *hoppdc@nih.gov*

- We will present the programs and then answer questions
- For project-specific questions, we'll be better able to help if you send us an aims page and we can set up a call.

IGNITE Program Goal- Get to BPN / BPN-Biologics

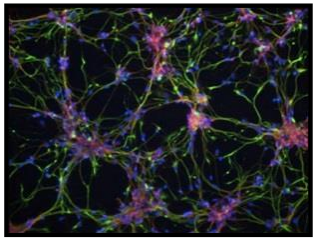
IGNITE is meant to serve a feeder program to later-stage therapy development programs such as the Blueprint Neurotherapeutics Network (BPN) for Small Molecules and the Blueprint Neurotherapeutics Network for Biologics (BPN-Biologics)



IGNITE:
A Suite of Early Translational Funding Opportunities

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: June 21, 2022; October 18, 2022

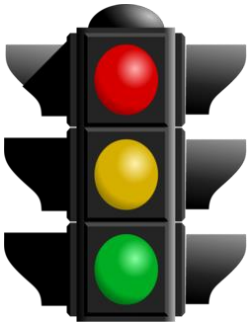
See NOT-OD-15-039 for info on late submissions

NIH National Institute of Neurological Disorders and Stroke

IGNITE

The R61/R33 Mechanism

R61: Demonstrate Feasibility and Prepare for the R33 (≤ 2 Years)



Go/No-Go Milestones

Does this warrant further effort?

R33: The Main Event

(≤ 2 Years R33; ≤ 3 Years for the Project)

Extremely Clear, Quantitative and Definitive Milestones are *Essential*.

Only 1 Go/No-Go Point

Transition to R33 via Administrative Review

Milestones: Clear and Quantitative

✗ *Scale up of compound A*

✓ Generate X grams of compound A with a purity ≥ X % as determined by method K

✗ *We will perform PK studies and select compounds with the best characteristics to test in animal models*

✓ Compounds must exhibit the following properties: $t_{1/2}$ ≥ X, brain:plasma ratio ≥ X, microsomal stability > X % after 1 hour at 37°C, etc.

✗ *Fully optimized and validated assay*

✓ *Z' > 0.5, signal-to-noise ratio ≥ X, DMSO tolerance up to X %*

✗ *Treatment with protein B decreases seizures compared to control*

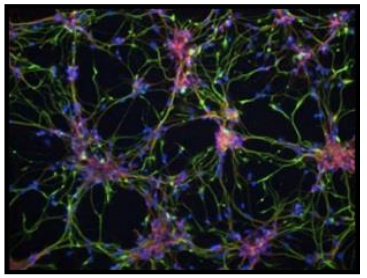
✓ Daily i.p. injection of protein B for 2 weeks decreases seizure frequency by X% and duration by Y% compared to vehicle-treated controls (n = Z animals per group, p <0.5)

More detailed IGNITE milestone examples
can be found on our website!

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

Goals

- Development of new translational assays
- Screening efforts to identify and characterize novel therapeutic agents



Entry Criteria

- Novelty
- Strong biological rationale and premise
- Relevance for therapy development
- Available test agent(s) or library

PAR-21-124: The R61 Phase

Examples of activities for R61 phase include, but are not limited to:

- Development and validation of assay(s) (including phenotypic assays) to support a succinct testing funnel
- Development of in vitro or ex vivo potency/efficacy assays
- Development of assays to evaluate properties (such as cellular uptake, engagement, infection, aggregation, downstream functional measures in vitro or ex vivo, purity and specificity)
- Development of assays to evaluate purity and identity of the therapeutic
- Assay development and optimization for High-Throughput Screening (HTS)
- A combination of assays may be developed to demonstrate relevant biological activity when a single assay may not provide adequate measurement of overall potency due to a complex mechanism of action or multiple activities of a preliminary therapeutic agent

PAR-21-124: R61 Transition and the R33 Phase

End of R61 Phase/Basis for Milestones - Examples

- Assay development and optimization completed
- Physicochemical or biophysical characterization of test compounds completed
- Development and selection of cell lines/vectors to produce bioactive agents to be used for assay validation or screening completed

Examples of activities for R33 phase include, but are not limited to:

- Preparation and screening of select series of therapeutic agents, including HTS
- Preparation of therapeutic agent(s) and confirmation of structure, sequence or biological characteristics
- Assessment of therapeutic agent's properties using computational analysis and early physicochemical/biophysical measurements
- Assessment of initial in vitro pharmacokinetic parameters such as ADME
- Assessment of potential off target activities
- Optimization of therapeutic agent(s)

NCCIH Interests

NCCIH is interested in supporting research geared toward development of robust, validated, analgesic assays suitable for medium to high throughput screening of natural product libraries through the NINDS IGNITE program. For the purposes of this PAR, natural products are defined as extracts, chromatographic fractions, or isolated secondary metabolites derived from herbal, botanical, marine, microbial, or animal sources. NCCIH is prioritizing analgesic targets relevant to musculoskeletal, neuropathic, and inflammatory pain conditions. NCCIH will not support applications related to chemotherapy or cancer related pain conditions.

The library must be limited to natural products only.

Point of Contact: Craig Hopp (hopdc@nih.gov)

PAR-21-124: Non-Responsive Studies

Non-responsive studies include those that involve any of the following activities**:**

- Applications focused on indications outside the mission of NINDS that do not meet NCCIH's above stated interests for screening natural products for non-cancer pain
- Development of risk, detection, diagnostic, prognostic, predictive, and prevention biomarkers
- Applications with the primary focus of developing PD biomarkers
- Development of devices, surgical procedures, diagnostics, and rehabilitation strategies
- Development of assays or probes to support basic understanding of disease or basic research; target identification; studies of disease mechanism
- In vivo efficacy studies (supported by companion FOA)
- Clinical compound manufacture or development of bioassays for clinical use
- IND-enabling studies
- Human subjects research except for research that meets the exemption 4 criteria

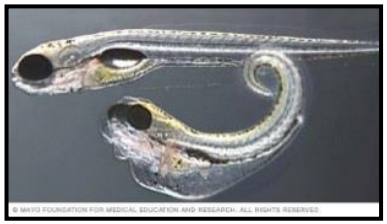
PAR-21-123:
Development and Validation of Model Systems

Goal:

- To promote a significant improvement in the translational relevance of animal models and ex vivo systems that will be utilized to facilitate the development of neurotherapeutics

Entry Criteria:

- Translational rationale for the proposed model system or ex vivo system and evidence of value for future drug discovery/development



PAR-21-123: Definitions

Internal Validation

- Precision, reliability, analytical sensitivity, accuracy and dynamic range characteristics of endpoints utilized to assess the animal model or model system

External Validation

- Similarity between model or model system and clinical manifestation of the disease (“face” validity)
- Similarity between model or model system and physiological basis of the disorder (“construct” validity)
- Similarity between the effect of a validated therapeutic intervention in the model or model system and in the clinical disease population (“predictive” validity)

PAR-21-123: R61/R33 Example Activities

Examples of activities for the R61 Phase

- Initial development of the model or ex vivo system
- Any optimization related to feasibility, endpoint range, sensitivity, etc.
- Internal validation for endpoints used
- Scale up for the R33 phase

Examples of activities for the R33 Phase

- All external validation studies, including comparisons of phenotype to human disease, comparisons of disease etiology in preclinical species to what is known about the human disease and efficacy of clinically validated therapeutic agents (if available) in the new model system

PAR-21-123: Non-Responsive Studies

Non-responsive studies include those that involve any of the following activities**:**

- Development of models for the purpose of understanding disease etiology
- Identification of CNS drug targets
- Discovery of disease initiation, remission, relapse, or progression biomarkers
- Applications with the primary focus of developing pharmacodynamic biomarkers
- Studies aimed at identifying, optimizing, evaluating, or developing a potential therapeutic agent:
  - In vitro primary assay development and test agent screening
  - Evaluating a potential therapeutic agent for efficacy or safety
  - Pharmacokinetic studies of a potential therapeutic agent
- Discovery or development of devices, device/drug combinations, surgical procedures, diagnostics, or rehabilitation strategies.
- Human subjects research except for research that meets the exemption 4 criteria

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

Goals

To demonstrate that early-stage neurotherapeutics have sufficient biological activity to warrant further investment using the following parameters:

- Target engagement/pharmacodynamic (PD) studies
- Pharmacokinetic (PK) studies
- In vivo efficacy studies

Entry Criteria

- Novelty- significant improvement over existing therapies
- Biological rationale
- Relevance for therapy development

PAR-21-122: The R61 Phase

Examples of activities for the R61 phase include, but are not limited to:

- Preparation of the therapeutic agent(s)
- Characterization of therapeutic agent(s) (purity, stability, biophysical characteristics, ADME, in vitro potency and selectivity, etc.)
- Limited SAR
- Studies to optimize dosing formulation
- Pharmacokinetics/biodistribution studies
- Studies to confirm that therapeutic agents reach and engage the target site (directly or indirectly)
- Studies to confirm selectivity
- Limited studies to identify potential PD markers
- Studies to inform design, refinement, and validation of the PD measure and/or in vivo efficacy models and testing procedures

PAR-21-122: R61 Transition and the R33 Phase

End of R61 Phase/Basis for Milestones

- All necessary preparation and characterization of agent
- Pharmacokinetic studies
- Design, refinement, and validation of PD markers
- A detailed in vivo study design that meets the NINDS RIGOR guidelines and will allow for demonstration of dose and exposure responses

Examples of activities for R33 phase include, but are not limited to:

- PD and/or in vivo efficacy studies with chemically and biologically characterized therapeutic agent(s)
- Dose-response activity with the intended route of administration
- Studies correlating pharmacokinetic and pharmacodynamics measures (PK/PD)
- Preliminary studies to assess early safety (not IND-enabling tox)
- Validation and replication studies

PAR-21-122: Non-Responsive Studies

Non-responsive studies include those that involve any of the following activities:

- Development of de novo animal models, assay development/discovery of novel therapeutic agents (covered by companion FOAs)
- Discovery and development of risk, detection, diagnostic, prognostic, predictive, or prevention biomarkers, although use of existing biomarkers is appropriate
- Applications with the primary focus of developing PD biomarkers
- GLP toxicology studies / IND-enabling studies, manufacture of therapeutics
- Discovery or development of devices, device/drug combinations, surgical procedures, diagnostics, or rehabilitation strategies
- Studies of disease mechanism or disease target identification
- Human subjects research except for research that meets the exemption 4 criteria

General Tips for all 3 FOAs

- Contact us in advance
- 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
- Notice that for NINDS analysis and tracking purposes, all no-cost extension requests will require prior NIH approval

More General Tips for all 3 FOAs

- Small Businesses are encouraged to consider the SBIR/STTR program. Contact: Emily Caporello (emily.caporello@nih.gov)
- Have quantitative go/no-go milestones*- see examples here
- Clearly demarcate R61 v R33 activities and timeline*
- Pay attention to non-responsive activities*
- Pay attention to human subjects research designations*

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

Resubmissions

- Most applications will not get funded
- We may encourage you to resubmit your application
- Resubmission/new applications have the same due date
  - June 21, 2022; October 18, 2022
- Resubmissions typically score better
- Respond to reviewer critiques

- *Reach out and contact us once you receive your Summary Statement*

NINDS IGNITE

Questions after the webinar is completed?

Rebecca.Roof@nih.gov

Thank You for Your Interest!

For project-specific questions, please contact us by email.

Additional information can be found on our IGNITE website

Coronavirus Disease 2019 (COVID-19):
Information for NIH Applicants and Recipients of NIH Funding