NINDS IGNITE

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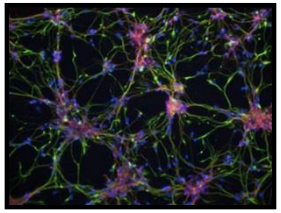
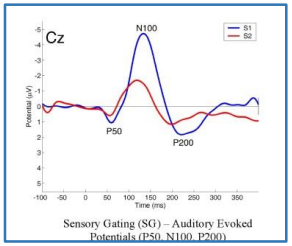
IGNITE Program Goal- Get to BPN/CREATE

IGNITE is meant to serve a feeder program to the later-stage therapy development programs such as the Cooperate Research to Enable and Advance Translational Enterprises (CREATE) for Biologics and Blueprint Neurotherapeutics (BPN) Program for Small Molecules

IGNITE: A Suite of Early Translational Funding Opportunities

1. PAR-18-761: Neurotherapeutic Agent Characterization and In vivo Efficacy Studies
2. PAR-18-762: Assay Development and Therapeutic Agent Identification
3. PAR-18-763: Development and Validation of Model Systems and/or Pharmacodynamic Markers to Facilitate Neurotherapeutic Discovery





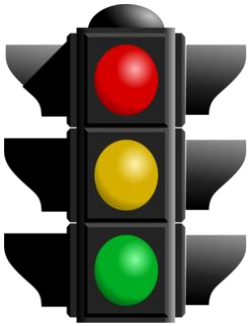
Budget: ≤$499,000/Year; ≤$750,000 for Project

Upcoming Application Due Dates: Feb 20, 2019; June 19, 2019

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

The R61/R33 Mechanism

R61: Demonstrate Feasibility and Prepare for R33 (≤2 Years for R61; ≤3 Years for the Project)



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

PAR-18-761
Pharmacodynamics 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 rational
- Relevance for therapy development

https://grants.nih.gov/grants/guide/pa-files/PAR-18-761.html

PAR-18-761: 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.)
- Focused 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 inform design, refinement, and validation of the PD measure and/or in vivo efficacy models and testing procedures

PAR-18-761: 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)
- Validation and replication studies

Out of Scope Activities for PAR-18-761

Including but not limited to:

- Development of de novo animal models and pharmacodynamics measures (see PAR-18-763)
- Assay development/identification of novel therapeutic agents (see PAR-18-762)
- GLP toxicology studies/Investigational New Drug (IND) enabling studies
- Discovery/development of devices, surgical procedures, diagnostics, or rehabilitation strategies
- Discovery/development of biomarkers, although use of existing biomarkers is appropriate
- Studies of disease mechanism
- Target identification
- Manufacture of therapeutics
- Clinical research and clinical trials

PAR-18-762
Assay Development and Therapeutic Agent 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

https://grants.nih.gov/grants/guide/pa-files/PAR-18-762.html

PAR-18-762: 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 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-18-762: 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 R33 Activities

- Preparation and screening of select series of therapeutic agents, including HTS
- Preparation of therapeutic agent(s) and confirmation of structure, sequence or biological characteristics
- Development and selection of cell lines/vectors to produce bioactive agents
- 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)

PAR-18-762 Out of Scope Activities

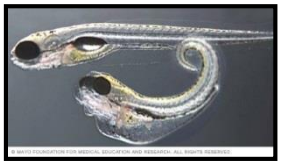
Including but not limited to:

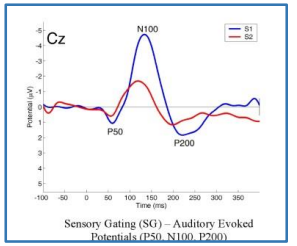
- Target identification
- Development of assays or probes to support basic understanding of disease or other basic research
- Pharmacodynamics and in vivo efficacy studies (see PAR-18-761)
- Development of devices, surgical procedures, diagnostics, and rehabilitation strategies
- Development of biomarkers
- IND-enabling studies
- Studies of disease mechanisms
- Clinical compound manufacture
- Clinical trials except for E4 exemption

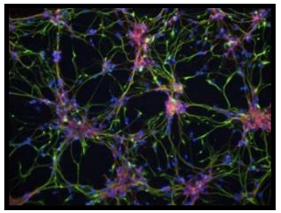
PAR-18-763
Development and Validation of Model Systems and/or Pharmacodynamic Markers

Goals:

- to promote a significant improvement in the translational relevance of animal models, ex vivo systems, and pharmacodynamic markers that will be utilized to facilitate the development of neurotherapeutics
- These model systems and PD markers should translate to the clinical setting to the degree that they can inform the decision to advance a therapeutic candidate to clinical testing and can inform clinical study design







*Note: Applicants can propose to develop either a model system or a PD marker; they do not need to propose both

PAR-18-763: Definitions

- Pharmacodynamic (PD) Marker
  - Component of the molecular pathway mediating the biological effects of therapeutic target modulation (direct or indirect)
  - Component of disease etiology that is involved in drug target modulation
- Internal Validation
  - Precision, reliability, analytical sensitivity, accuracy and dynamic range of endpoints utilized in the model system or PD marker measurements
- 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-18-763
Development and Validation of Model Systems and/or Pharmacodynamic Markers

Entry Criteria

- Strong translational rationale
- Relevance for therapy development
- Plans to collaborate with clinician experienced in conduct of clinical trials

Examples of activities for the R61 Phase

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

PAR-18-763: R61 Transition and R33 Phase

- **End of R61 Phase/Basis for Milestones**
  - Model system or PD marker is feasible for external validation activities in R33 phase
  - Internal validation completed
  - Model system or PD marker reflects the functional or physiological pathway of the disease or therapeutic target as intended
- **Examples of Activities in 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

Out of Scope Activities for PAR-18-763

Including but not limited to:

- Development of animal and ex vivo cellular models for the purpose of understanding disease etiology
- Cell line development
- Identification of CNS drug targets
- Discovery of disease initiation, remission, relapse, or progression biomarkers
- In vitro primary assay development and test agent screening (see PAR-18-762)
- Test agent screening and optimization (see PAR-18-762)
- Studies aimed at testing a potential therapeutic agent for efficacy or safety in an existing and validated model system (see PAR-18-761)
- Studies aimed at identifying, optimizing or developing a potential therapeutic agent in an existing and validated model system (see PAR-18-761)
- Device discovery and/or development
- Clinical Research or Clinical Studies with the exception of research that meets the E4 human subjects exemption criteria

General Tips for all 3 FOAs

- Contact us in advance
- Have clear milestones
- Include a rigorous study design and supporting data (see NOT-NS-11-023)
- Have a multidisciplinary team
- Discuss intellectual property (for therapeutics)
- Have a therapy development plan
- Small Businesses are encouraged to consider the SBIR/STTR program. Contact: Stephanie Fertig (fertigs@ninds.nih.gov)

Questions after webinar is completed?

timothy.lyden@nih.gov

Thank You for Your Interest!

https://www.ninds.nih.gov/Current-Research/Research-Funded-NINDS/Translational-Research/Funding-Programs-Researchers/IGNITE