

IGNITE 101



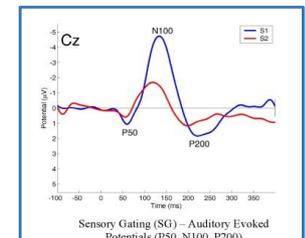
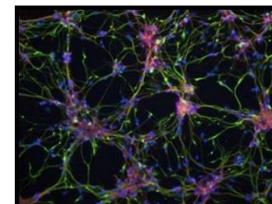
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IGNITE: A Suite of Early Translational Funding Opportunities

1. PAR-15-070: Assay Development and Therapeutic Agent Identification and Characterization[^]
2. PAR-15-071: Pharmacodynamics and In vivo Efficacy Studies[^]
3. RFA-NS-16-013: Development and Validation of Translational Model Systems for Drug Discovery*



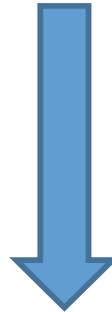
Budget: ≤\$250,000/Year; ≤\$750,000 for Project

[^]Next Application Due Date: June 16, 2016

***Next Application Due Date: June 21, 2016**

The R21/R33 Mechanism

R21: Demonstrate Feasibility and Prepare for R33. (≤ 2 Years for R21; ≤ 3 Years for the Project)



**Go/No-Go Milestones
Does This Warrant Further Investment?**

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-15-070

Assay Development and Therapeutic Agent Identification and Characterization

Goals

- To develop in vitro and/or ex vivo assays
- To conduct iterative screening efforts to identify and characterize potential neurotherapeutic agents



PAR-15-070: The R21 Phase

Examples of activities for R21 phase include, but are not limited to:

- Development of assay(s) to support a succinct testing funnel
- A combination of assays may be developed
- Development of in vitro or ex vivo potency/efficacy assay
- Development of assays to evaluate 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

PAR-15-070: The R33 Phase

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

- Preparation and screening of select series of therapeutic agents
- 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 measurements
- Assessment of initial pharmacokinetic parameters such as ADME.
- Assessment of potential off target activities.
- Optimization of therapeutic agent(s).

PAR-15-070 Out of Scope Activities

- Creation of assays or probes to better understand disease mechanisms
- Target identification
- Studies of disease biology
- Activities that are not part of translating an agent that has the potential to be clinically useful/relevant; Even if such activities are called 'translational'
- IND-enabling studies



PAR-15-071

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:

- Physicochemical/Biophysical characteristics
- Target engagement/pharmacodynamic studies
- Pharmacokinetic studies
- In vivo efficacy studies



PAR-15-071: The R21 Phase

Examples of activities for the R21 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.)
- Studies to develop dosage form(s)
- 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-15-071:R21 Transition and the R33 Phase

At the end of the R21 phase, investigators must exhibit successful completion of

- All necessary preparation and characterization of agent
- Pharmacokinetic studies
- Design, refinement, and validation of PD and/or efficacy animal studies using the appropriate controls and demonstrating feasibility
- 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 (exposure)-response activity with the intended route of administration.
- Studies correlating pharmacokinetic and pharmacodynamics measures (PK/PD)
- Studies to test the agent(s) along with or against positive and negative controls.

Out of Scope Activities for PAR-15-071

- Development of de novo animal models and pharmacodynamics measures
- Target identification
- Studies of disease biology
- Activities that are not part of translating an agent that has the potential to be clinically useful/relevant; Even if such activities are called 'translational'
- GLP toxicology studies with optimized therapeutic agents

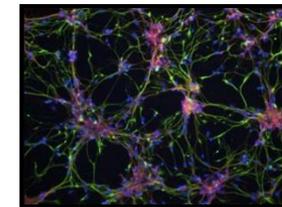
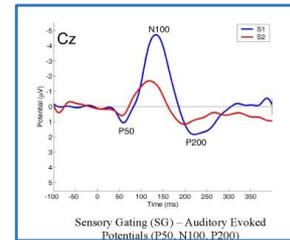
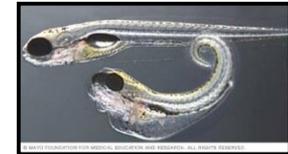


RFA-NS-16-013

Development and Validation of Model Systems and/or Pharmacodynamic Markers

Goals

- To promote a significant improvement in the translational relevance of preclinical models used in the discovery of neurotherapeutics
- To promote early development of pharmacodynamic markers (PD) used in the discovery of neurotherapeutics
- To provide translational tools for the drug discovery and development process
- To develop a fully validated model system, testing paradigm or PD marker that can be used in both preclinical and clinical settings to test the biological effects of a candidate neurotherapeutic agent



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

RFA-NS-16-013: The R21 Phase

Examples of activities for the R21 Phase

- Initial development of the model, testing paradigm or PD marker
- Any optimization related to feasibility, endpoint range, sensitivity, etc.
- Evaluation of the ability to scale up sufficiently for the R33 phase
- Evaluation of the specificity of the model system or PD marker as it relates to the disease or endpoint measures

RFA-NS-16-013: R21 Transition and R33 Phase

- End of R21 Phase/Basis for Milestones
 - Model system or PD marker is feasible for external validation activities in R33 phase
 - Internal validation activities are ongoing or have been 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
 - Complete internal validation for endpoints used in model system, testing paradigm of PD measure
 - Further scale-up for external validation studies, as needed
 - All external validation studies

Out of Scope Activities for RFA-NS-16-013



- Development of animal and ex vivo models for the purpose of understanding disease etiology
- Cell line development
- Identification of CNS drug targets
- Development of disease initiation, remission, relapse or progression biomarkers
- Human clinical validation of model systems or PD markers
- In vitro assay development and test agent screening (covered by PAR-15-070)
- Identification, optimization or development of a therapeutic agent in existing model systems (covered by PAR-15-070, PAR-15-071 and CREATE/BPN PARs)
- Pharmacokinetic studies of a potential therapeutic agent (covered by PAR-15-071)
- Device discovery and/or development (covered by PAR-14-300)

Questions?

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Meeting the Entry Criteria for BPN/CREATE

Entry criteria for BPN and CREATE:

- Essential assays (in vitro and in vivo) are in place to enable optimization of the preliminary bioactive leads(s)
- Preliminary bioactive lead(s)
- BPN:
 - Either in vivo efficacy using clinically relevant outcome measures and/or in vivo target engagement and/or a path forward that clearly addresses efficacy studies
- CREATE:
 - Convincing demonstration of proof of concept using clinically relevant outcome measures and/or in vivo target engagement

PAR-15-070 and PAR-15-071: Key Points to Address

- General, Stage-Appropriate Therapeutic Development Plan
- Strong biological rationale for the intended approach and supporting data from rigorously designed experiments
- Rigorous study design and reporting
- Multidisciplinary team (disease biology, clinical, statistical, drug development, etc.)
- Intellectual Property (i.e., freedom to operate)
- Goal should be to meet entry criteria for BPN/CREATE



RFA-NS-16-013: 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 of 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)

RFA-NS-16-013: Key Points to Address

- Strong Translational and Biological Rationale
 - Supported by rigorously obtained data
- Rigorous Study Design
 - Adequacy of controls, justification of sample size, statistical methods, blinding methods, strategies for randomization
 - Plans for internal validation appropriate for model system and proposed use in drug discovery
- Collaboration with Industry-Experienced Clinician
 - Provide collaboration plan
 - Letter of support from clinician
 - If clinician with industry experience is not available, a clinician experienced with the conduct of clinical trials is preferred
 - Clinician's role is advisory; clinical trials are out of scope
- Intellectual Property
 - Freedom to operate (model itself or agents used to create/test the model)

Innovation Grants to Nurture Initial Translational Efforts (IGNITE)

Purpose

To advance projects from early discovery (R01 & R21) into late-stage translational programs (BPN & CREATE) in a manner that is scientifically rigorous, timely, and cost effective



Important Points about Milestones

- NINDS uses milestones for measuring success in achieving the project objectives
- R21 milestones should include quantitative criteria
- Quantitative criteria should be robust and be consistent with the state-of-the-art in the field
- Timelines should be clear

