

NINDS IGNITE



Dr. Becky Roof
rebecca.roof@nih.gov

Dr. Shardell Spriggs
shardell.spriggs@nih.gov

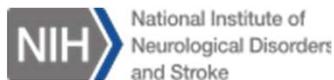
Dr. Julia Bachman
julia.bachman@nih.gov

Mr. Tim Lyden
timothy.lyden@nih.gov

Ms. Ashley Givens
ashley.givens2@nih.gov

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

PAR-18-761: Neurotherapeutic Agent Characterization and In vivo Efficacy Studies



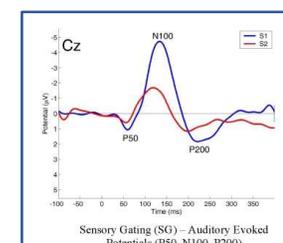
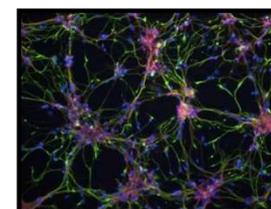
PAR-18-762: Assay Development and Therapeutic Agent Identification



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

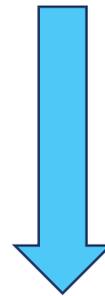


Upcoming Application Due Dates: Oct 20, 2020; Feb 17, 2021

See [NOT-OD-15-039](#) and [NOT-OD-20-082](#) for info on late submissions

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

- X Scale up of compound A*
- ✓ Generate X grams of compound A with a purity $\geq X\%$ as determined by method K

- X We will perform PK studies and select compounds with the best characteristics to test in animal models*
- ✓ Compounds must exhibit the following properties: $t_{1/2} \geq X$, brain:plasma ratio $\geq X$, microsomal stability $> X\%$ after 1 hour at 37°C, etc.

- X Fully optimized and validated assay*
- ✓ $Z' > 0.5$, signal-to-noise ratio $\geq X$, DMSO tolerance up to $X\%$

- 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-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 rationale
- Relevance for therapy development

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 with 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

PAR-18-761: Out of Scope Activities

Including but not limited to:

- Target identification
- Studies of disease mechanism
- 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
- Manufacture of therapeutics
- Clinical research* and clinical trials

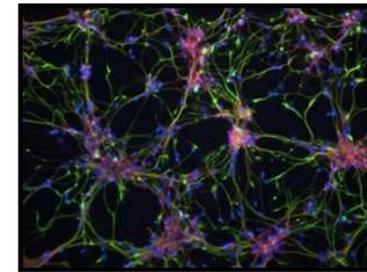
**with the exception of research that meets the exemption 4 criteria*



PAR-18-762: 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-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 develop 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)

PAR-18-762: Out of Scope Activities

Including but not limited to:

- 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
- Target identification
- Development of biomarkers
- IND-enabling studies
- Studies of disease mechanisms
- Clinical compound manufacture
- Clinical research* and clinical trials



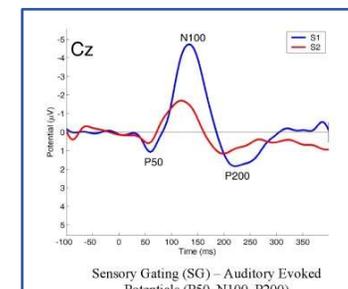
**with the exception of research that meets the exemption 4 criteria*

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
- 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*



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 biomarker measurement(s)

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: R61/R33 Example Activities

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

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

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 (PAR-18-762)
- Studies aimed at testing a potential therapeutic agent for efficacy or safety in an existing and validated model system (PAR-18-761)
- Studies aimed at identifying, optimizing or developing a potential therapeutic agent in an existing and validated model system (PAR-18-761)
- Device discovery and/or development ([Translational Devices](#) program)
- Clinical research* and clinical trials

**with the exception of research that meets the exemption 4 criteria*



General Tips for all 3 FOAs

- Contact us in advance
- Have clear milestones- see examples [here](#)
- Include a rigorous study design and supporting data (see [NOT-NS-11-023](#))
- Have a multidisciplinary team; note the multidisciplinary review
- 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)
- Pay attention to clinical research rules...

NIH Human Subjects Research

NIH Definition of human subjects research: Research involving a living individual about whom data or biospecimens are obtained/used/studied/analyzed through interaction/intervention, or identifiable, private information is used/studied/analyzed/generated.

Clinical research: Research conducted with human subjects (or on material of human origin such as tissues and specimens) *unless the studies fall under 45 CFR 46.101(b) (4) (i.e. Exemption 4).*

Exemption 4: Collection/study of data/specimens if the sources are publicly available or the information is recorded such that subjects cannot be identified.
Secondary research for which consent is not required.

For more information: [NIH OER Human Subjects Research](#)

Not sure?

Reach out to your institute's IRB or human subjects officer

Email: OER-HS@nih.gov

NIH Human Subjects Research



Home » Policy & Compliance » Human Subjects » Definition of Human Subjects Research

POLICY & COMPLIANCE

Policy Topics

Human Subjects Research

Definition of Human Subjects Research

Pre and Post Award Process

Certificates of Confidentiality

Single IRB Policy

Policies & Regulations

Training & Resources

Definition of Human Subjects Research

According to 45 CFR 46.40, a human subject is "a living individual about whom an investigator (whether professional or student) conducting research:

- Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
- Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens."

Are you planning on conducting human subjects research? Learn more about research that meets the definition human subjects research, Federal regulation requirements, and whether your project may be considered exempt. Also, learn about NIH specific considerations and become more familiar with NIH policies, and other regulations as it relates to human subjects research protections.

DECISION TOOL

Am I doing Human Subjects Research?

FIND OUT HERE

Decision Tool: Am I Doing Human Subjects Research?

The questionnaire is a tool to assist you with determining whether your project involves non-exempt human subjects research, meets the criteria for exempt human subjects research, or does not involve human subjects research.



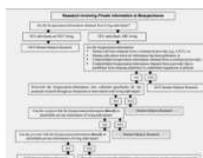
Human Subjects Research Infographic

This resource summarizes the definition of human subjects research and provides examples of human subjects research projects. It also describes what you will need when you are preparing your NIH application and what is required if you are funded.



Exempt Human Subjects Research Infographic

This resource is a guide to simplify the understanding of the exemptions from the federal regulations for the protection of human subjects research. It summarizes Exemptions 1, 2, 3, 4, 5, 6, 7 and 8, providing basic definitions, examples of studies that meet and do not meet the criteria of the exemption, and aspects one must consider when engaged in exempt or non-exempt human subjects research.



Research Involving Private Information or Biospecimens Flowchart

Studies involving the use of human specimens or data may or may not be considered to be research involving human subjects, depending on the details of the materials to be used. Use this flowchart to help determine if studies involving private information or biospecimens may meet the definition of human subjects research.

NINDS IGNITE

Questions after the webinar is completed?

timothy.lyden@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](#)

