

IGNITE Q&A Webinar

Tuesday, April 13, 2021



NINDS Team:

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NCCIH Special Guest:

Dr. Craig Hopp *hopfdc@nih.gov*

- This webinar will be recorded
- The webinar recording and slides will be posted on the IGNITE website
- PDF of slides with embedded links will be emailed to registered attendees
- Please use Q&A box to post all questions
- Questions can be entered at any time and will be read by a presenter during the Q&A session following the presentation (*some may be answered online*)
- 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:

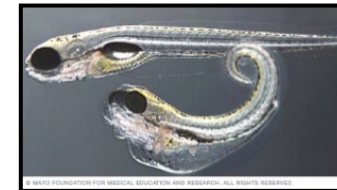
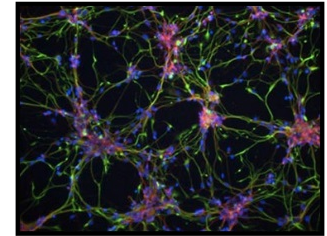
A Suite of Early Translational Funding Opportunities

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

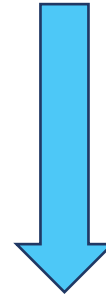
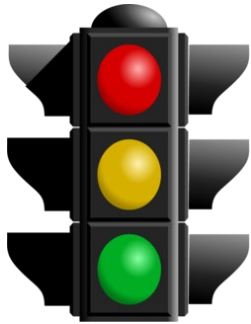


Upcoming Application Due Dates: June 17, 2021; Oct. 19, 2021

See [NOT-OD-15-039](#) 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 $X\%$

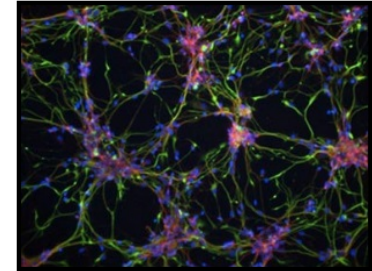
- X Treatment with protein B decreases seizures compared to control*
- ✓ Daily i.p. injection of protein B for 2 weeks decreases seizure frequency by $X\%$ and duration by $Y\%$ compared to vehicle-treated controls ($n = Z$ animals per group, $p < 0.5$)

More detailed [IGNITE milestone examples](#)
can be found on our website!

PAR-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



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**

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.

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

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
Federal Regulation (45 CFR 46.40) defines a human subject as a living individual about whom an investigator (whether professional or student) conducting research:

Examples of human subjects research include:

- Collecting data
- Interviewing and/or
- Observing behavior
- Conducting a survey
- Administering a questionnaire
- Conducting a focus group
- Changing computer records
- Interviewing a patient
- Analyzing biological specimens

Included in the NIH application:

- ✓ Protection of Human Subjects attachment

Funded grants also need:

- ✓ An Institutional Review Board (IRB) certificate (IRB) with OHRP
- ✓ IRB approval or determination of exemption

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

This infographic details the criteria for various exemptions from the federal regulations for the protection of human subjects research. It includes categories such as 'Research on Educational Settings, Practices, and Policies', 'Research on Public Health Activities', 'Research on Biological Specimens', and 'Research on Certain Types of Surveys and Interviews'. Each exemption is accompanied by a brief description and a list of key criteria.

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

This flowchart outlines the steps for conducting research involving private information or biospecimens. It starts with 'Research Planning' and 'IRB Review' (Exempt or Not Exempt). If not exempt, it details the 'IRB Review Process' including 'IRB Application', 'IRB Review', and 'IRB Approval'. It also covers 'Data Management' and 'Data Access' requirements.

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?

ashley.givens2@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](#)

