Department of Health and Human Services
Part 1. Overview Information

Participating Organization(s)

National Institutes of Health (NIH (http://www.nih.gov))

Components of Participating Organizations

NIH Blueprint for Neuroscience Research (http://neuroscienceblueprint.nih.gov (http://neuroscienceblueprint.nih.gov/))

National Institute of Neurological Disorders and Stroke (NINDS (http://www.ninds.nih.gov))
National Eye Institute (NEI (http://www.nei.nih.gov))
National Institute on Aging (NIA (http://www.nia.nih.gov))
National Institute on Alcohol Abuse and Alcoholism (NIAAA (http://www.niaaa.nih.gov))
Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD (http://www.nichd.nih.gov))
National Institute of Dental and Craniofacial Research (NIDCR (http://www.nidcr.nih.gov))
National Institute on Drug Abuse (NIDA (http://www.nida.nih.gov))
National Institute of Mental Health (NIMH (http://www.nimh.nih.gov))
National Center for Complementary and Integrative Health (NCCIH (http://www.nccam.nih.gov))

Funding Opportunity Title

Blueprint Neurotherapeutics Network (BPN): Small Molecule Drug Discovery and Development of Disorders of the Nervous System (UG3/UH3 Clinical Trial Optional)

Activity Code

UG3 (//grants.nih.gov/grants/funding/ac_search_results.htm?text_curr=ug3&Search.x=0&Search.y=0&Search_Type=Activity)/UH3 (//grants.nih.gov/grants/funding/ac_search_results.htm?text_curr=uh3&Search.x=0&Search.y=0&Search_Type=Activity) Exploratory/Developmental Phased Award Cooperative Agreement

Announcement Type

Reissue of PAR-17-205 (https://grants.nih.gov/grants/guide/pa-files/PAR-17-205.html)

Related Notices

None

Funding Opportunity Announcement (FOA) Number

PAR-18-546

Companion Funding Opportunity

PAR-18-541 (https://grants.nih.gov/grants/guide/pa-files/PAR-18-541.html), U44 Small Business Innovation Research (SBIR) Cooperative Agreement - Fast-Track

Number of Applications

See Section III. 3. Additional Information on Eligibility.

Catalog of Federal Domestic Assistance (CFDA) Number(s)

93.853; 93.866; 93.867; 93.279; 93.273; 93.865; 93.121; 93.242; 93.213

Funding Opportunity Purpose

The Blueprint Neurotherapeutics Network (BPN) invites applications from neuroscience investigators seeking support to advance their small molecule drug discovery and development projects into the clinic. Participants in the BPN are responsible for conducting all studies that involve disease- or target-specific assays, models, and other research tools and receive funding for all activities to be conducted in their own laboratories. In addition, applicants will collaborate with NIH-funded consultants and can augment their project with NIH contract research organizations (CROs) that specialize in medicinal chemistry, pharmacokinetics, toxicology, formulations development, chemical synthesis including under Good Manufacturing Practices (GMP), and Phase I clinical testing. Projects can enter either at the Discovery stage, to optimize promising hit compounds through medicinal chemistry, or at the Development stage, to advance a development candidate through Investigational New Drug (IND)-enabling toxicology studies and phase I clinical testing. Projects that enter at the Discovery stage and meet their milestones may continue on through Development. BPN awardee Institutions retain their assignment of IP rights and gain assignment of IP rights from the BPN contractors (and thereby control the patent prosecution and licensing negotiations) for drug candidates developed in this program.

Key Dates

Posted Date

December 21, 2017

Open Date (Earliest Submission Date)

January 7, 2018

Letter of Intent Due Date(s)

30 days prior to the application due date

Application Due Date(s)

February 7, 2018, August 9, 2018, February 9, 2019, August 9, 2019, February 11, 2020, by 5:00 PM local time of applicant organization. All types of non-AIDS applications allowed for this funding opportunity announcement are due on these dates.

Applicants are encouraged to apply early to allow adequate time to make any corrections to errors found in the application during the submission process by the due date.

AIDS Application Due Date(s)

May 7, 2018, September 7, 2018, May 7, 2019, September 7, 2019, May 7, 2020 by 5:00 PM local time of applicant organization. All types of AIDS and AIDS-related applications allowed for this funding opportunity announcement are due on these dates.

Applicants are encouraged to apply early to allow adequate time to make any corrections to errors found in the application during the submission process by the due date.

Scientific Merit Review

June 2018, November 2018, June 2019, November 2019, June 2020

Advisory Council Review

October 2018, January 2019, October 2019, January 2020, October 2020

Earliest Start Date

November 2018

Expiration Date

May 8, 2020

Due Dates for E.O. 12372

Not Applicable

Required Application Instructions

It is critical that applicants follow the Research (R) Instructions in the SF424 (R&R) Application Guide (//grants.nih.gov/grants/guide/url_redirect.htm?id=12000), except where instructed to do otherwise (in this FOA or in a Notice from the *NIH Guide for Grants and Contracts* (//grants.nih.gov/grants/guide/)). Conformance to all requirements (both in the Application Guide and the FOA) is required and strictly enforced. Applicants must read and follow all application instructions in the Application Guide as well as any program-specific instructions noted in Section IV. When the program-specific instructions deviate from those in the Application Guide, follow the program-specific instructions. **Applications that do not comply with these instructions may be delayed or not accepted for review.**

There are several options available to submit your application through Grants.gov to NIH and Department of Health and Human Services partners. You **must** use one of these submission options to access the application forms for this opportunity.

1. Use the NIH ASSIST system to prepare, submit and track your application online.

   Apply Online Using ASSIST

2. Use an institutional system-to-system (S2S) solution to prepare and submit your application to Grants.gov and eRA Commons (http://public.era.nih.gov/commons/) to track your application. Check with your institutional officials regarding availability.

3. Use Grants.gov (../ApplyButtonSplash.cfm?oppNum=PAR-18-546) Workspace to prepare and submit your application and eRA Commons (http://public.era.nih.gov/commons/) to track your application.

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Part 2. Full Text of Announcement

Section I. Funding Opportunity Description

A. Overview

Recent advances in neuroscience offer unprecedented opportunities to discover new treatments for nervous system disorders. However, before a new chemical entity can be tested in a clinical setting, it must undergo a process of chemical optimization to improve potency, selectivity, and drug-like properties, followed by pre-clinical safety testing to meet the standards set by the Food and Drug Administration (FDA) for clinical testing. All of the necessary expertise and resources are not commonly available to small companies as these activities are largely the domain of large pharmaceutical and biotechnology companies and contract research organizations.

To facilitate drug discovery and development by the neuroscience community, the NIH Blueprint for Neuroscience Research (https://neuroscienceblueprint.nih.gov/ (https://neuroscienceblueprint.nih.gov/)) established the Blueprint Neurotherapeutics Network (BPN), which offers neuroscience researchers funding for drug discovery and development activities that can be conducted in their own laboratories. Researchers have the opportunity to collaborate with NIH-funded consultants and contract research organizations (CROs) that specialize in medicinal chemistry, pharmacokinetics, toxicology, formulations development, chemical synthesis under Good Manufacturing Practices (GMP), and Phase I clinical testing. A current list of BPN contractors and consultants is available at https://neuroscienceblueprint.nih.gov/bpdrugs/bpn_resources.htm (https://neuroscienceblueprint.nih.gov/bpdrugs/bpn_resources.htm).

This Funding Opportunity Announcement (FOA) invites applications for new BPN projects. Applicants may propose to conduct all drug discovery and development activities themselves or collaborate with BPN contractors on activities of their choice. The PD/PI will be responsible for conducting all studies that involve disease- or target-specific assays, models, and other research tools. A Program Director/Principal Investigator

(PD/PI) with- for example medicinal chemistry expertise and resources may additionally request funding to conduct structure-activity relationship (SAR) studies in his or her own lab but collaborate with BPN contractors on in vitro ADMET, in vivo PK, drug manufacturing and IND-enabling toxicology studies. By contrast, a PD/PI with limited experience in drug discovery and development may opt to collaborate with all available BPN contractors.

For each project funded under this FOA, the NIH will assemble a customized Lead Development Team (LDT). The LDT will be co-chaired by the PD/PI and a BPN consultant and will include members of the PD/PI's team, additional BPN consultants, and NIH staff. The LDT will establish an overall strategy for the project, including milestones proposals, plan studies to be conducted by BPN contractors, and coordinate activities across different research sites.

Potential applicants are strongly encouraged to read Frequently Asked Questions (FAQs) on the BPN website (http://neuroscienceblueprint.nih.gov/bpdrugs/faqs.htm (http://neuroscienceblueprint.nih.gov/bpdrugs/faqs.htm)) and contact NIH Scientific/Research staff and participating NIH Institutes/Centers prior to preparing an application to discuss how they may best utilize BPN resources and whether their application fits the mission of a particular NIH IC.

B. Scope

The BPN is dedicated to the discovery and development of small molecule compounds, of a size and structure that can be readily synthesized and chemically modified (if optimization is required). This program is not designed to support development of biologics or biotechnology products, including oligonucleotides and proteins, or devices. Applicants should contact NIH Scientific/Research staff regarding small peptides (typically less than 6 amino acids) and other complex chemical structures, as well as combination therapies, to determine suitability for optimization and development within the BPN.

To be supported by this FOA, a project must focus on a nervous system condition that falls within the mission of one of the participating Institutes or Centers. Please see Section C below for more information on the interests of the participating Institutes and Centers and alternative programs to consider.

Projects can enter the BPN either at the Discovery stage, to optimize promising hit and lead compounds through medicinal chemistry, or at the Development stage, to advance a single development candidate through Investigational New Drug (IND)-enabling toxicology studies and Phase I clinical testing. Applications that propose entry at the Discovery stage can include Development work as well.

Past experience with BPN suggests that many otherwise excellent awarded projects often require additional data or the generation of tools in the first year in order to meet the program's requirements for initiating medicinal chemistry or IND-enabling studies. For this reason, all BPN projects will begin with a preparatory phase of up to a year, funded by the UG3 award mechanism, to allow projects to complete any work needed before launching medicinal chemistry (if entering at the Discovery stage) or IND-enabling studies (if entering at the Development stage). During this preparatory period, the NIH will form the LDT, which will identify and oversee the studies necessary to meet the BPN requirements for initiating medicinal chemistry or IND-enabling studies. The LDT will also design plans and go/no-go milestones for all subsequent Discovery and/or Development work, which will be funded by the UH3 award. Progression from the UG3 award to the UH3 award will be based on administrative review (see Section D., Milestones). After successful completion of the UG3 phase, a project may proceed either to the UH3 phase in either hit-to-lead/lead optimization (SAR) (the discovery phase) or to IND-enabling studies (the development phase). A schematic of this project structure is available on the BPN website at https://neuroscienceblueprint.nih.gov/bpdrugs/bpn_resources.htm (https://neuroscienceblueprint.nih.gov/bpdrugs/bpn_resources.htm).

The following sections describe the Discovery and Development stages in more detail, including the program entry criteria, the program requirements for initiating medicinal chemistry and IND-enabling studies, and examples of activities that can be conducted during the UG3 preparatory phase.

Potential applicants are strongly encouraged to contact NIH Scientific/Research staff prior to preparing an application to clarify which entry stage is most appropriate for their project and what to include in their plans for the UG3 preparatory phase.

Discovery

Projects that require medicinal chemistry to improve the potency and drug-like properties of promising bioactive compounds will enter the BPN at the Discovery stage. The process of understanding the structure-activity relationship (SAR) for desired drug properties typically requires dozens of rounds of compound synthesis and testing. Initially, medicinal chemistry will focus heavily on optimizing activity and potency of compounds in primary and secondary in vitro assays. Subsequently, SAR will increase emphasis on ADMET (absorption, distribution, metabolism, excretion, toxicity) properties of the compounds, with continued monitoring and optimization of bioactivity. The ultimate goal of the SAR effort is selection of a development candidate with sufficient bioactivity and drug-like properties to proceed to IND-directed pre-clinical safety assessment with reasonable projected human doses.

Entry Criteria for Discovery Stage

Projects must meet the following requirements prior to entering Discovery:

- Rigorous data supporting the hypothesis that modulating the putative drug target/affected pathway will produce a desirable outcome for the intended disease indication (it is not necessary to know the precise drug target or mechanism of action)
- A bioactive compound, in hand, that will serve as a starting point for optimization with:
    - Proof of identity and purity (typically >95%, as determined by, e.g., NMR, melting point, or LC/MS, with no single impurity > 0.5%)
    - in vitro biological activity (typically < 1μM in biochemical assays and <10μM in cell-based assays relevant to the drug target), confirmed by repeat dose-response testing, with more than one batch of compound
    - Selectivity for the intended target over closely related targets, if desired (and when the target is known)
- Availability of primary and secondary in vitro bioactivity assays that can be used or optimized for driving SAR studies
- Availability of preclinical animal model(s) that can be used to assess in vivo efficacy or target engagement (measurement of target binding or proximal downstream effects).
- Availability of selectivity and counter-screening assays to address potential activity at related targets and other undesirable activities or artifacts
- No obvious legal (e.g., intellectual property) constraints to pursuing the proposed chemical scaffold(s) and using the proposed assays and models for research purposes and/or commercial development

Preparatory Activities for Discovery Stage (UG3)

All Discovery projects will begin with a UG3 preparatory phase of up to one year to prepare for SAR studies, which will be supported during the UH3 phase. The PD/PI will be responsible for conducting all studies that involve disease- or target-specific assays, models, and other research tools. The following are general expectations for a BPN project to initiate SAR studies:

- Completion of an in vitro ADME and physicochemical profile for the starting compound that includes measures of aqueous solubility, microsome stability, CYP inhibition, and permeability (e.g., MDCK or Caco-2)
- Demonstration that the primary assay meets the following validation criteria to reliably rank compounds with similar activities:
    - A statistical demonstration of reliability, e.g., a Z-factor (Z') ≥0.5 and a coefficient of variation (CV) ≤20%

        - Concentration response testing over at least 10 concentrations generates reproducible EC50 values within a 3-fold range for at least 4 compounds
        - Blinded test-retest reliability with r2 of at least 0.75 on at least 8 compounds exhibiting EC50 values across a 100-fold range of potencies
        - Throughput of at least 10 compounds per week, run with sufficient replicates to produce robust and reproducible 10-point dose-response curves
    - Demonstration that the proposed secondary bioactivity assays and counter-screening and selectivity assays have sufficient reliability and throughput for their proposed use in the project
    - Demonstration of a clear correlation between activity in the primary assay and activity in confirmatory assays and models, sufficient to justify advancement criteria in a testing funnel

Examples of activities that can be supported during the Discovery preparatory phase include:

- Establishment of a project milestone plan, including milestones that must be met to initiate SAR studies and desired compound profiles (including prospective criteria) at completion of lead optimization
- Refinement of a compound testing funnel, including studies to correlate activity across different bioactivity assays to justify advancement criteria
- In vivo pharmacology studies to demonstrate target engagement
- Studies to develop or validate target engagement markers that will be used in critical-path experiments
- Optimization and validation of bioactivity, selectivity, and counter-screening assays
- Critical-path pharmacology studies to clarify the compound mechanism of action (e.g., agonist vs. positive allosteric modulator)
- ADMET profiling of starting compound(s) to identify liabilities to address through medicinal chemistry
- Limited exploratory medicinal chemistry (approximately 2 chemists for 6 months) to enable demonstration/confirmation of synthetic route and bioactivity of proposed hit compounds
- Procurement of commercially available analogs ("SAR by catalog")

Applicants may propose to use BPN contractors for chemical synthesis and ADMET profiling or request funds to conduct this work themselves.

Discovery Activities after Preparatory Phase (UH3)

The BPN typically supports up to two years of medicinal chemistry in the UH3 phase. By the end of the first year of the UH3 phase, the PD/PI is expected to demonstrate in vivo activity for a representative compound from the lead series, delivered by any route of administration. By the end of the second year of chemistry, the PD/PI should identify a development candidate that meets the entry criteria for Development (below).

The Discovery UH3 phase typically includes the following activities:

- Design and synthesis of analogs for SAR studies
- Compound scale up for in vivo testing, dose ranging finding toxicity (DRF) evaluation
- Testing of analogs in bioactivity assays and animal models
- Testing of analogs in selectivity and counter-screening assays
- Testing of analogs in ADMET assays (e.g., microsome stability, CYP induction and inhibition, solubility, permeability in MDCK or Caco-2 cells, plasma protein binding, brain/plasma ratio, pharmacokinetics [PK] in multiple species)

The PD/PI will be responsible for conducting primary in vitro biological assessment of compounds on a one-to-two week schedule to inform the design of subsequent iterations of compound synthesis. In addition to a regular testing schedule in the primary assay, the PD/PI will provide confirmation of the activity of select compounds in secondary and counter-screening assays and animal models relevant to the drug target and therapeutic indication.

BPN contractors can produce compound analogs for SAR testing, scale up compounds as needed for in vivo testing, and provide standard screening services to assess in vitro and in vivo ADMET characteristics of the compounds. Typically, in the UH3 phase the BPN contractors will assign approximately 4 medicinal chemist

FTEs to a project, generating approximately 4-8 compounds per week, plus additional staff to support computational chemistry modeling and in vitro ADMET studies as appropriate.

Compounds that meet the BPN's criteria for a development candidate can continue seamlessly on into Development.

Development

The Development stage includes IND-directed preclinical safety studies, GMP synthesis of clinical trial material, formulation development, and phase I clinical testing. Projects that have completed medicinal chemistry optimization and identified a development candidate may initiate Development activities within BPN. The BPN does not support SAR studies during Development.

Entry Criteria for Development Stage

Applications for entry into the Development stage must have identified the candidate compound and cannot request additional medicinal chemistry resources. It may be acceptable to have 2 candidates that will be narrowed to a single candidate as part of the UG3 activities (time and budget permitting).

Applications must meet the following requirements prior to entering the Development portion of the UH3 phase:

- A strong package of data linking the putative drug target/affected pathway to the proposed disease indication and supporting the hypothesis that altering the target activity as proposed will produce desirable outcomes for the disease.
- Proposed compound must have in vitro and in vivo biological activity and ADMET properties appropriate for the intended clinical use (i.e., the disease indication, patient population, delivery mode, treatment duration, and treatment regimen) and outcomes.
- Applicants should show that their proposed compounds are efficacious when delivered by the clinically intended route of administration, at exposure levels that can likely be achieved clinically with the proposed human dosing regimen.
- Proposed compounds should give defensible results in tests for Ames mutagenicity, hERG activity, microsome stability, CYP inhibition, plasma protein binding, and aqueous solubility.
- In cases where the molecular target of compound action is known, the applicant should demonstrate the degree of selectivity for the intended target over closely related targets.
- Counter-screening to determine selectivity across a broad panel of unrelated pharmacological targets (e.g., G protein-coupled receptors, kinases, etc.) is also required.
- Demonstration that the ability of the PD/PI's institution to develop and commercialize the proposed compound(s) is unlikely to be blocked or impeded by legal (e.g., intellectual property) constraints and that there is support from the institution to file and maintain the patents estate and necessary regulatory documents along with associated cost (see Other Attachments below).

Preparatory Activities for Development

All applications proposing to enter Development at the start of UH3 stage will begin with a UG3-funded preparatory phase of up to one year, to prepare for IND-enabling studies, which will be supported during the UH3 phase. (Projects that began in Discovery will conduct this preparatory work during their UH3 phase.) The following are general expectations for a project to initiate IND-enabling studies within BPN:

- Dose-range finding toxicology studies (rodent and non-rodent) show an acceptable safety margin (e.g., 5x if toxicity can be monitored, reversible, and has premonitory signs; 10x if toxicity is more severe but controllable/reversible; 30x if toxicity is unlikely to be easily monitored, controllable, reversible, or have premonitory signs)
- Viable synthetic route for manufacturing (acceptable cost, number of steps and purification techniques needed)

- Viable API (active pharmaceutical ingredient; salt and polymorph selection complete, acceptable stability to support initial clinical trial)

Examples of activities that can be supported during the Development preparatory phase include:

- Establishment of a preclinical development plan, including milestones for advancement into IND-enabling studies and the desired profile for a development candidate
- Design and planning for the Phase I clinical trials (if applicable)
- Validation of ADMET data
- Replication/confirmation of key in vivo pharmacology data
- Scale-up synthesis
- Salt and polymorph screening
- Compound stability studies
- Pre-formulation studies
- Multiple-dose rodent PK testing, with pharmacodynamic (PD) correlations if applicable
- Dose-range finding toxicology
- Metabolite identification

The PD/PI is responsible for conducting all studies that involve disease- or target-specific assays, models, and other research tools. BPN contractors can perform all other work.

Development Activities after Preparatory Phase (UH3)

The Development UH3 phase may include the following:

- GMP manufacturing of material for phase I clinical testing
- IND-enabling toxicology studies
- IND document preparation
- Phase I clinical trial (a single and/or multiple ascending dose study to characterize safety, PK, and PD)

The PD/PI's Institution will be responsible for assembly and Submission of the IND application and scheduling meetings with the FDA. NIH staff and consultants on the LDT must be included in all meetings with the FDA

The development of the protocol and management of the phase I trial will be performed by a Clinical Development Team (CDT), which will evolve from the LDT and include the PD/PI, clinical consultants identified by the PD/PI and NIH, and NIH staff. The protocol, selected supporting trial documents, and regulatory documents will be submitted to NIH for administrative review (including internal and external experts) prior to commencement of the clinical trial (defined as signing of first informed consent).

BPN contractors can conduct the preclinical safety studies, GMP synthesis, formulation and other activities required to prepare for human testing. BPN contractors will provide data and reports in a format suitable for inclusion in an IND application and will assist in the development of the application. The phase I clinical trial can also be conducted through BPN contractors.

Activities considered out of scope of this Announcement

The following activities are considered out of scope of the BPN:

- Screening to identify hit compounds
- Basic research and studies of disease mechanism
- Animal model development
- Development of risk, detection, diagnostic, prognostic, predictive, and prevention biomarkers as well as PET ligands
- Development of diagnostics and diagnostic devices
- Development of biologics and biotechnology products
- Studies directed beyond Phase I clinical testing

C. NIH Institute and Center Interests and Guidance

National Institute on Aging (NIA)

NIA is interested in studies that will provide drug development expertise and infrastructure support to researchers interested in developing new small molecules aimed at modifying the behavioral symptoms in Alzheimer's disease (AD), delaying the onset or slowing the progression of AD, mild cognitive impairment (MCI), other dementias of aging and age-related cognitive decline. Ideally, this initiative is aimed at researchers who have promising small molecule compounds, but lack the necessary outside expertise and infrastructure to advance these compounds to the clinic.

Researchers who may have the necessary drug development expertise and access to infrastructure to advance small molecules to the clinic should consider submitting an application to the Alzheimer's

Drug Development Program (PAR-15-174 (https://grants.nih.gov/grants/guide/pa-files/PAR-15-174.html)). This program is also available to researchers who are interested in the preclinical development of biologics or repurposed drugs.

NIA and the AD scientific community recognize that one of the major challenges to the successful development of drugs for AD is the poor translation of preclinical efficacy from AD animal models to the clinic. Meta analyses of preclinical studies indicate that a key factor contributing to the poor predictive power of AD animal models is the lack of standards in the design, conduct, and data analyses. Therefore, to improve the quality and predictive value of animal model studies NIA urges applicants, describing supporting data or proposed animal model studies, to follow best practices guidelines as summarized at: http://alzres.com/content/3/5/28 (http://alzres.com/content/3/5/28)).

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

Without a specific "receptor", alcohol has numerous molecular targets in the brain, and alcohol-seeking behavior and alcoholism are influenced by multiple neurotransmitter systems, neuromodulators, hormones, and signal transduction pathways. Many potential target sites for which new pharmaceuticals may be developed have, therefore, been identified. These include neurotransmitter systems related to opioids, serotonin, dopamine, glutamate, γ-aminobutyric acid (GABA), endocannabinoids, the hypothalamic-pituitary-adrenal (HPA) axis, adenosine, neuropeptide systems (for example, neuropeptide Y, corticotropin releasing factor), signal transduction pathways (such as protein kinase A and protein kinase C); and gene transcription factors (such as delta Fos B and cAMP response element-binding protein [CREB]). NIAAA is interested in research aimed to develop pharmaceuticals targeting new molecular sites to provide effective therapy to a broader spectrum of alcoholic individuals. Recent research has discovered specific genetic variants that may contribute to the risk for alcoholism and/or render alcohol dependent individuals responsive to specific therapeutic agent. NIAAA is interested in supporting research to develop pharmaceuticals targeting individuals with identified genotypic and phenotypic characteristics to improve efficacy and safety.

National Eye Institute (NEI)

The National Eye Institute (NEI) interest in BP neuro-therapeutics is to develop novel therapies to treat diseases and disorders of the visual system, especially blinding eye diseases such as cataracts, glaucoma, age-related macular degeneration, retinitis pigmentosa and other conditions.The NEI is also interested in other visual system disorders such as strabismus and amblyopia that could be treated with pharmacological interventions. Each project should have a well-defined end-point, achievable within a five-year time frame, for developing a treatment for a specific disease or disorder of the visual system. The steps towards this goal should be clearly delineated in a series of milestones that support the development of a novel therapeutic that can then be tested in a clinical trial. If successful, a project funded under this program may lead to filing an IND-directed pharmacological and toxicological study, and Phase I clinical testing. Investigators are encouraged to contact NEI program staff to discuss potential research projects prior to application submission to determine alignment of the planned studies with priorities of the Institute.

National Institute of Dental and Craniofacial Research (NIDCR)

NIDCR is interested in neurotherapeutics development for painful disorders of the orofacial region including temporomandibular joint disorder, trigeminal neuropathies, burning mouth syndrome, and other conditions. Recent advances in genomics and phenotyping of subjects with orofacial pain conditions have expanded the scope of potential targets to treat these conditions. Receptor systems, ion channels, and pro- and anti-inflammatory molecules have been implicated in chronic pain. NIDCR is interested in supporting research that will lead to highly efficacious and specific pharmacological treatments of subjects with orofacial pain disorders.

Investigators are encouraged to contact NIDCR program staff to discuss potential research projects prior to application submission to determine alignment of the planned studies with priorities of the Institute mission and strategic plan.

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

The NICHD is interested in supporting research aimed to develop novel pharmacotherapies for the treatment of developmental disorders, diseases and conditions in pediatric population. Investigators are strongly encouraged to discuss their research plans with NICHD Scientific/Research contact prior to submitting their application.

National Institute of Mental Health (NIMH)

NIMH supports neuroscience research to discover the causes of mental illness and to develop more effective and safer treatments. The NIMH is interested in applications proposing development of therapies aimed at novel molecular and clinical targets for the treatment of mental disorders, especially treatment-resistant depression, bipolar disorder, schizophrenia, PTSD, and autism spectrum disorder. Studies aimed at the development of new ligands for targets where a probe or therapeutic already exists are generally of lower priority.

NIMH will only support projects entering the BPN at the Discovery (optimization of validated small molecule hits and promising lead compounds through medicinal chemistry) stage. NIMH will not support projects entering the BPN at the Development (IND enabling/GMP synthesis or Phase I trials) stage. Projects at the Development stage should consider applying to the NIMH SBIR/STTR Programs https://www.nimh.nih.gov/funding/small-business-research-programs.shtml. Projects at the early clinical trials phase should consider the NIMH SBIR Program or the First in Human and Early Stage Clinical Trials of Novel Investigational Drugs or Devices for Psychiatric Disorders (U01) https://grants.nih.gov/grants/guide/pa-files/PAR-17-327.htmlhttps://grants.nih.gov/grants/guide/pa-files/PAR-14-107.html (or its reissue). Investigators are strongly encouraged to discuss their research plans with NIMH Scientific/Research contact prior to submission to determine alignment of the planned studies with NIMH priorities and to assess whether this or other NIMH funding opportunities are most appropriate. Please see the following NIMH drug discovery FOAs: Drug Discovery for Nervous System Disorders PAR-16-041 (R01) and PAR-16-042 (R21), Discovery of in vivo Chemical Probes PAR-17-336 PAR-14-279 (R01), National Cooperative Drug Discovery/Development Groups (NCDDG) for the Treatment of Mental Disorders, Drug or Alcohol Addiction PAR-17-186 PAR-14-234 (U19) and PAR-18-230 PAR-14-184(U01) or the reissues of these FOAs.

Consistent with NIMH's Research Domain Criteria (RDoC) initiative, research projects directed towards ameliorating pathophysiology that is potentially more proximal to specific functional deficits (domains) than DSM diagnostic entities are encouraged. Additional information about the RDoC approach can be found at the RDoC website (http://www.nimh.nih.gov/research-priorities/rdoc/index.shtml). The testing of functional domains not included specifically in RDoC may also be considered, if well justified.

High-quality and reproducible studies that are reported to the scientific community in a transparent manner are an essential cornerstone of the research enterprise. Attention to principles of study design and transparency are essential to enable reviewers, the scientific community, and NIH to assess the quality of scientific findings. In support of this important goal, investigators must follow instructions to address Rigor and Reproducibility (http://grants.nih.gov/reproducibility/index.htm (//grants.nih.gov/reproducibility/index.htm))

Further information on NIMH research priorities can be found in the NIMH Strategic Plan, (http://www.nimh.nih.gov/about/strategic-planning-reports/index.shtml) Strategic Research Priorities (http://www.nimh.nih.gov/about/strategic-planning-reports/strategic-research-priorities/index.shtml), and Interventions Workgroup Report (http://www.nimh.nih.gov/about/advisory-boards-and-groups/namhc/reports/fromdiscoverytocure_103739.pdf). Applicants are strongly encouraged to discuss applications with NIMH staff listed in Section VII - Agency Contact(s) Scientific/Research Contacts.

National Institute of Neurological Disorders and Stroke (NINDS)

A list of diseases that is relevant to the research mission of the NINDS can be found at https://www.ninds.nih.gov/Disorders/All-Disorders (https://www.ninds.nih.gov/Disorders/All-Disorders) ; applicants are encouraged to contact the NINDS to discuss disease areas of interest.

This FOA serves as the primary support mechanism at NINDS for the discovery and development of small molecule drugs. Researchers focused on the development of biologics and biotechnology products should consider the CREATE-Bio program (https://www.ninds.nih.gov/Current-Research/Research-Funded-NINDS/Translational-Research/CREATE-BIO). Applicants seeking support only to conduct early stage clinical trials should consider applying for an NINDS Exploratory Clinical Trials R01, through PAR-17-122 (https://grants.nih.gov/grants/guide/pa-files/PAR-17-122.html), which provides additional flexibility in budget and time, as well as the option of including a phase II trial.

There is growing recognition that the quality and reproducibility of both preclinical and clinical research depend on the rigor with which researchers conduct studies, control for potential bias, and report essential methodological details. Examples of critical elements of a well-designed study are summarized on the NINDS website http://www.ninds.nih.gov/funding/transparency_in_reporting_guidance.pdf (http://www.ninds.nih.gov/funding/transparency_in_reporting_guidance.pdf). NINDS urges applicants to this program to consider these elements when describing supporting data and proposed studies.

National Center for Complementary and Integrative Health (NCCIH)

NCCIH is interested in supporting research aimed at compounds and small molecules from natural products (e.g., cannabinoids, venoms, conotoxins, melatonin, prebiotics, probiotics, herbs, etc.) that may be used or developed to modulate CNS-based symptoms with priority given to pain and pain related symptoms including sleep, stress, and mood disorders. Investigators are strongly encouraged to discuss their research plans with the NCCIH Scientific/Research contact prior to submitting their applications.

National Institute on Drug Abuse (NIDA)

Through participating in this FOA, NIDA aims to provide drug development expertise and infrastructure to support the addiction researchers interested in developing new molecular entities for the treatment of substance use disorders (SUD). Projects focused on cocaine, methamphetamine and marijuana use disorders are of high priority for NIDA because there are currently no FDA-approved treatments for these indications.

NIDA will only support the projects to develop the innovative pharmacological approaches entering the BPN at the Discovery stage. Specifically, NIDA is interested in using the BPN mechanism to support the (academic) addiction researchers in the "hit to lead optimization" stages with a well-justified proposal for the development stage as well.

NIDA applicants are strongly encouraged to take full advantage of the opportunities the BPN affords, including collaboration with BPN consultants and NIH-supported contract research organizations (CROs) that specialize in medicinal chemistry, pharmacokinetics, toxicology, formulations development, chemical synthesis under Good Manufacturing Practices (GMP). Researchers, who possess the drug development expertise and access to the necessary infrastructure to advance small molecules to the clinic, should consider submitting their applications to specialized NIDA-administered programs.

Investigators are strongly encouraged to discuss their research plans with NIDA program staff prior to submission to determine alignment of the planned studies with NIDA's interest and priorities. NIDA staff will also provide help in assessing whether this or other NIDA funding opportunities would be the most appropriate.

D. Milestones

Because drug discovery and development are inherently high risk, it is expected that there will be significant attrition as projects progress. Go/No-Go milestones (typically every six months) will be established by the LDT at the start of each project and updated as needed.

An administrative review will be conducted by NIH program staff, with technical input from an External Oversight Committee (composed of senior non-federal scientists who are not directly involved in BPN projects), to decide which projects will advance from the UG3 phase to the UH3 phase and progress after each subsequent milestone based on:

- Successful achievement of milestones
- The overall feasibility of project advancement, considering data that may not have been captured in milestones
- Competitive landscape for the disease indication and drug target
- Program priorities
- Availability of funds

Approval for commencement of a clinical trial (defined as signing of informed consent by first prospective subject) will include the following:

- Successful achievement of the defined preclinical development milestones;
- Submission of an IND with documentation for one of the following: 1) acceptance of clinical protocol by FDA; 2) elapse of the 30 day post filing waiting period without comment from the FDA; 3) completion of protocol changes or amendments requested by FDA.
- Submission of the clinical protocol and supporting documents to NIH for administrative review and notification of NIH approval;
- Agreement on updated timeline and milestones for the clinical trial.

PLEASE NOTE: If a funded project does not make sufficient progress toward the agreed upon milestones at any stage, funding for the project and access to BPN contract resources may be discontinued (see section VI.2.).

E. Quality and Compliance Requirements

Since the goal of this program is to generate therapeutics which will be eligible for FDA approval, adherence to compliance and quality criteria is required.

- It is expected that all IND enabling nonclinical studies will be performed in a manner consistent with Good Laboratory Practices (GLP).
- All clinical trials must be performed following Good Clinical Practices (GCP) and in accord with NIH Policy for Data and Safety Monitoring (http://grants.nih.gov/grants/guide/notice-files/not98-084.html (//grants.nih.gov/grants/guide/notice-files/not98-084.html)).

Investigational products for use in clinical trials must be produced under current Good Manufacturing Practice (cGMP) practices.

F. Intellectual Property (IP)

Since the ultimate goal of this program is to bring new drugs to the market, the creation and protection of intellectual property (IP) that will make drug candidates attractive to potential licensing and commercialization partners are a significant consideration in designing research strategies and prioritizing projects for funding. This program is structured so that the awardee institution retains their assignment of IP rights and gains assignment of IP rights from the BPN contractors (and thereby control the patent prosecution and licensing

negotiations) for drug candidates developed in this program. It is expected that the awardee institution will take responsibility for patent filings, maintenance and licensing efforts toward eventual commercialization. The PD/PI is expected to work closely with technology transfer/business development officials at his or her institution to ensure that royalty agreements, patent filings, and all other necessary IP arrangements are completed in a timely manner and that commercialization plans are developed and updated over the course of the project. Award recipients will be encouraged to identify and foster relationships with potential licensing and commercialization partners early in the drug development process, consistent with the goals of the BPN.

See Section VIII. Other Information for award authorities and regulations.

Section II. Award Information

Funding Instrument

Cooperative Agreement: A support mechanism used when there will be substantial Federal scientific or programmatic involvement. Substantial involvement means that, after award, NIH scientific or program staff will assist, guide, coordinate, or participate in project activities. See Section VI.2 for additional information about the substantial involvement for this FOA.

Application Types Allowed

New
Resubmission
Revision

The OER Glossary (//grants.nih.gov/grants/guide/url_redirect.htm?id=11116) and the SF424 (R&R) Application Guide provide details on these application types.

Clinical Trial?

Optional: Accepting applications that either propose or do not propose clinical trial(s)

Need help determining whether you are doing a clinical trial? (https://grants.nih.gov/grants/guide/url_redirect.htm?id=82370)

Funds Available and Anticipated Number of Awards

The number of awards is contingent upon NIH appropriations and the submission of a sufficient number of meritorious applications.

Award Budget

Application budgets are not limited but need to reflect the actual needs of the proposed project.

Award Project Period

Applicants may seek up to one year of UG3 funding. The UH3 phase cannot exceed four years. The actual duration of individual projects will depend on successful achievement of milestones and conditions as described in Milestones Section of the program overview.

NIH grants policies as described in the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11120) will apply to the applications submitted and awards

made from this FOA.

Section III. Eligibility Information

1. Eligible Applicants

Eligible Organizations

Higher Education Institutions

- Public/State Controlled Institutions of Higher Education
- Private Institutions of Higher Education

The following types of Higher Education Institutions are always encouraged to apply for NIH support as Public or Private Institutions of Higher Education:

o Hispanic-serving Institutions

o Historically Black Colleges and Universities (HBCUs)

o Tribally Controlled Colleges and Universities (TCCUs)

o Alaska Native and Native Hawaiian Serving Institutions

o Asian American Native American Pacific Islander Serving Institutions (AANAPISIs)

Nonprofits Other Than Institutions of Higher Education

- Nonprofits with 501(c)(3) IRS Status (Other than Institutions of Higher Education)
- Nonprofits without 501(c)(3) IRS Status (Other than Institutions of Higher Education)

For-Profit Organizations

- Small Businesses
- For-Profit Organizations (Other than Small Businesses)

Governments

- State Governments
- County Governments
- City or Township Governments
- Special District Governments
- Indian/Native American Tribal Governments (Federally Recognized)
- Indian/Native American Tribal Governments (Other than Federally Recognized)
- Eligible Agencies of the Federal Government
- U.S. Territory or Possession

Other

- Independent School Districts
- Public Housing Authorities/Indian Housing Authorities
- Native American Tribal Organizations (other than Federally recognized tribal governments)
- Faith-based or Community-based Organizations
- Regional Organizations
- Non-domestic (non-U.S.) Entities (Foreign Institutions)

Foreign Institutions

Non-domestic (non-U.S.) Entities (Foreign Institutions) **are** eligible to apply.
Non-domestic (non-U.S.) components of U.S. Organizations **are** eligible to apply.
Foreign components, as defined in the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11118), **are** allowed.

Required Registrations

Applicant Organizations

Applicant organizations must complete and maintain the following registrations as described in the SF 424 (R&R) Application Guide to be eligible to apply for or receive an award. All registrations must be completed prior to the application being submitted. Registration can take 6 weeks or more, so applicants should begin the registration process as soon as possible. The NIH Policy on Late Submission of Grant Applications (//grants.nih.gov/grants/guide/notice-files/NOT-OD-15-039.html) states that failure to complete registrations in advance of a due date is not a valid reason for a late submission.

- Dun and Bradstreet Universal Numbering System (DUNS) (http://fedgov.dnb.com/webform) - All registrations require that applicants be issued a DUNS number. After obtaining a DUNS number, applicants can begin both SAM and eRA Commons registrations. The same DUNS number must be used for all registrations, as well as on the grant application.
- System for Award Management (SAM) (https://www.sam.gov/portal/public/SAM/) (formerly CCR) – Applicants must complete and maintain an active registration, **which requires renewal at least annually**. The renewal process may require as much time as the initial registration. SAM registration includes the assignment of a Commercial and Government Entity (CAGE) Code for domestic organizations which have not already been assigned a CAGE Code.
- o NATO Commercial and Government Entity (NCAGE) Code (//grants.nih.gov/grants/guide/url_redirect.htm?id=11176) – Foreign organizations must obtain an NCAGE code (in lieu of a CAGE code) in order to register in SAM.
- eRA Commons (//grants.nih.gov/grants/guide/url_redirect.htm?id=11123) - Applicants must have an active DUNS number and SAM registration in order to complete the eRA Commons registration. Organizations can register with the eRA Commons as they are working through their SAM or Grants.gov registration. eRA Commons requires organizations to identify at least one Signing Official (SO) and at least one Program Director/Principal Investigator (PD/PI) account in order to submit an application.
- Grants.gov (//grants.nih.gov/grants/guide/url_redirect.htm?id=82300) – Applicants must have an active DUNS number and SAM registration in order to complete the Grants.gov registration.

Program Directors/Principal Investigators (PD(s)/PI(s))

All PD(s)/PI(s) must have an eRA Commons account. PD(s)/PI(s) should work with their organizational officials to either create a new account or to affiliate their existing account with the applicant organization in eRA Commons. If the PD/PI is also the organizational Signing Official, they must have two distinct eRA Commons accounts, one for each role. Obtaining an eRA Commons account can take up to 2 weeks.

Eligible Individuals (Program Director/Principal Investigator)

Any individual(s) with the skills, knowledge, and resources necessary to carry out the proposed research as the Program Director(s)/Principal Investigator(s) (PD(s)/PI(s)) is invited to work with his/her organization to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH support.

For institutions/organizations proposing multiple PDs/PIs, visit the Multiple Program Director/Principal Investigator Policy and submission details in the Senior/Key Person Profile (Expanded) Component of the SF424 (R&R) Application Guide.

2. Cost Sharing

This FOA does not require cost sharing as defined in the *NIH Grants Policy Statement*. (//grants.nih.gov/grants/guide/url_redirect.htm?id=11126)

3. Additional Information on Eligibility

Number of Applications

Applicant organizations may submit more than one application, provided that each application is scientifically distinct.

The NIH will not accept duplicate or highly overlapping applications under review at the same time. This means that the NIH will not accept:

- A new (A0) application that is submitted before issuance of the summary statement from the review of an overlapping new (A0) or resubmission (A1) application.
- A resubmission (A1) application that is submitted before issuance of the summary statement from the review of the previous new (A0) application.
- An application that has substantial overlap with another application pending appeal of initial peer review (see NOT-OD-11-101 (//grants.nih.gov/grants/guide/notice-files/NOT-OD-11-101.html)).

Section IV. Application and Submission Information

1. Requesting an Application Package

Buttons to access the online ASSIST system or to download application forms are available in Part 1 of this FOA. See your administrative office for instructions if you plan to use an institutional system-to-system solution.

2. Content and Form of Application Submission

It is critical that applicants follow the Research (R) Instructions in the SF424 (R&R) Application Guide (//grants.nih.gov/grants/guide/url_redirect.htm?id=12000), except where instructed in this funding opportunity announcement to do otherwise. Conformance to the requirements in the Application Guide is required and strictly enforced. Applications that are out of compliance with these instructions may be delayed or not accepted for review.

For information on Application Submission and Receipt, visit Frequently Asked Questions – Application Guide, Electronic Submission of Grant Applications (//grants.nih.gov/grants/guide/url_redirect.htm?id=41137).

Letter of Intent

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows IC staff to estimate the potential review workload and plan the review.

By the date listed in Part 1. Overview Information, prospective applicants are asked to submit a letter of intent that includes the following information:

- Descriptive title of proposed activity
- Name(s), address(es), and telephone number(s) of the PD(s)/PI(s)
- Names of other key personnel
- Participating institution(s)
- Number and title of this funding opportunity

The letter of intent should be sent to:

Charles Cywin, Ph.D.
National Institute of Neurological Disorders and Stroke (NINDS)
Telephone: 301-496-1779
Email: charles.cywin@nih.gov (mailto:charles.cywin@nih.gov)

Page Limitations

All page limitations described in the SF424 Application Guide and the Table of Page Limits (//grants.nih.gov/grants/guide/url_redirect.htm?id=11133) must be followed.

Instructions for Application Submission

The following section supplements the instructions found in the SF424 (R&R) Application Guide and should be used for preparing an application to this FOA.

SF424(R&R) Cover

All instructions in the SF424 (R&R) Application Guide must be followed.

SF424(R&R) Project/Performance Site Locations

All instructions in the SF424 (R&R) Application Guide must be followed.

SF424(R&R) Other Project Information

All instructions in the SF424 (R&R) Application Guide must be followed.

Note that applications in which all human subject work is proposed to be conducted by BPN CROs (i.e. not part of the grant budget) should not indicate that their applications involve human.

Facilities & Other Resources:

All applicants should describe their institutions' existing or planned infrastructure for bringing the compounds to practical application (e.g., licensing for further drug development, managing IP, commercializing discoveries) consistent with achieving the program goals. For a multiple-PD/PI, multiple-institution application, applicants should describe the infrastructure of each institution for bringing the technologies to practical application and for coordinating these efforts (e.g., licensing, managing intellectual property) among the institutions consistent with achieving the goals of the program. Applicants should clarify how IP will be shared or otherwise managed if there are multiple PD/PIs and institutions involved in the UG3/UH3-supported work, to ensure that IP remains unencumbered.

Other Attachments: Applications must include an *Intellectual property (IP) strategy.*

Applicants are encouraged to prepare this section in consultation with their institutions' technology transfer officials.

For Discovery stage projects, applicants should describe any constraints of which they are aware that could impede their use of compounds, assays, or models for research purposes and/or commercial development (e.g., certain restrictions under transfer or sharing agreements, applicants' previous or present intellectual property filings and publications, compounds with similar structures that are under patent and/or on the market, etc.) and how these issues would be addressed. If the applicant's institution has filed pertinent patents, the applicant should indicate filing dates, the type of patent, and application status.

For Development stage projects, applicants should describe their efforts to confirm that there are unlikely to be IP or other legal constraints that could block or impede development or commercialization of the proposed compounds. If the applicant's institution has filed pertinent patents, the applicant should indicate filing dates, the type of patent, and application status.

SF424(R&R) Senior/Key Person Profile

All instructions in the SF424 (R&R) Application Guide must be followed.

R&R Budget

All instructions in the SF424 (R&R) Application Guide must be followed.

The UG3/UH3 award is intended to support studies to be conducted by the PD/PIs and associated personnel. The UG3/UH3 budget may not support drug development activities that the applicant proposes to conduct through BPN contracts. Equipment requests are allowed but not encouraged. Equipment requests should be considered only if the equipment is absolutely necessary to the success of the project and cannot be supported by any other means. This is likely to be a subject of negotiation before an award is made. Some budget requests may be made for the PD/PI's Institution to assemble and file the IND.

The UG3/UH3 budget may include travel costs for one or two trips per year to attend meetings of the BPN External Oversight Committee or hold face-to-face meetings of the LDT/CDT.

It is expected that the PD/PI will dedicate at least 20% level of effort (2.4 person months) to managing a BPN project. It is strongly recommended that potential applicants consult NIH staff about their anticipated budget in the early stages of preparing an application.

R&R Subaward Budget

All instructions in the SF424 (R&R) Application Guide must be followed.

PHS 398 Cover Page Supplement

All instructions in the SF424 (R&R) Application Guide must be followed.

PHS 398 Research Plan

All instructions in the SF424 (R&R) Application Guide must be followed, with the following additional instructions:

Specific Aims: The Specific Aims section should include Aims delineated for the UG3 (preparatory) and UH3 phases. If a clinical study is proposed, define the aims of the clinical study.

Research Strategy: The Research Strategy section should include the entire project scope including plans for both the UG3 and UH3 phases and should include the following subsections:

- Clinical Impact (Significance)
- Biological Rationale and Compound Profile (Significance)
- Testing strategy (Approach)
- Innovation
- Table of proposed activities that provides the following information: Activity (medicinal chemistry, assays, PK, etc.), throughput (e.g. samples per month), source (PD/PI lab, sub awardee, BPN Contractor), advancement criteria.

Clinical Impact (Significance): Each application generally should focus on only one disorder or disease, even if the compound proposed for the project shows activity in models for more than one disorder. This is because the target patient population and intended use guide the design of the drug and of the preclinical studies, such as toxicology and formulation.

- Briefly describe the current state of knowledge of the etiology, clinical characteristics, and current and projected prevalence of the proposed disease indication.
- Briefly discuss available treatments, including all treatment modalities, and their limitations.
- Discuss how the proposed project relates to therapeutics development efforts underway in academia and industry.
- Provide a *Target Product Profile (TPP)*, a table based on an FDA template that summarizes the minimal/ideal profile of the final marketed product and shows the ultimate goals of the proposed drug development effort, such as disease indication, patient population, delivery mode, treatment duration, treatment regimen, and standards for clinical efficacy (see guidance and example of suggested format at http://neuroscienceblueprint.nih.gov/resources/target-product-profile.htm (http://neuroscienceblueprint.nih.gov/resources/target-product-profile.htm)). Explain why the minimally acceptable and ideal parameters offer advantages over currently available treatments and how they relate to other therapeutics under development.
- Briefly comment on the feasibility of conducting clinical trials toward the goals in the TPP (e.g., availability of patients for clinical trials).
- Describe the group clinical expertise used to determine the goals of the drug development program and the clinical trial.

Biological Rationale and Compound Profile (Significance): Justify the choice of drug target/pathway and proposed strategy to alter the target/pathway activity.

- Describe the intended biological target/pathway.
- Provide the evidence that links this target to the proposed disease indication.
- Provide the evidence that altering target activity as proposed will give desirable outcomes for the proposed disease indication.
- Present the chemical structure of the compound(s) proposed for optimization or as the development candidate.
- Describe how the compound(s) were identified. For Discovery projects, present structure-activity relationship (SAR) data, if available.
- Provide a *Compound Profile Table* (see guidance and example of suggested format at http://neuroscienceblueprint.nih.gov/resources/example_compound_profile_table.htm (http://neuroscienceblueprint.nih.gov/resources/example_compound_profile_table.htm)) that summarizes the pharmacological and ADMET activities of the compound(s) proposed for optimization or as the development candidate. Note any potential liabilities.
- For Discovery projects, show that the compound proposed as the starting point for optimization alters the activity of the putative target as intended and/or produces desired outcomes in disease models, with sufficient detail to allow reviewers to evaluate the rigor of the experimental design. Explain the choice of models, assays, and endpoints for these studies.
- For Development projects, show that the proposed development candidate has clinically relevant in vivo activity, when delivered by the clinically intended route of administration, at exposure levels that can likely be achieved clinically with the proposed human dosing regimen.
- Describe the supporting in vivo biology study design in detail, including the power analysis and associated assumptions for the determination of sample size, statistical handling of the data (such as criteria for data inclusion or exclusion), procedures used for blinding and randomization, and whether studies were replicated.
- Discuss the clinical relevance of the preclinical outcome measures and observed effect size.
- Show the data that demonstrate the relationship between compound exposure and activity and explain how these data support the clinical dosing regimen proposed in the TPP.

Testing Strategy (Approach): Specify whether the project is proposed for entry at the Discovery or Development stage. Clearly indicate within a table which activities will be conducted by the PD/PI and associated personnel (i.e., funded by the UG3/UH3 award) and which activities will be conducted by BPN contractors. Include experimental designs and justification for all studies that will be conducted by the PD/PI and associated personnel. Activities that will be conducted by BPN contractors need not be described in detail in the application, since these will be planned after award by the LDT.

- For Discovery-stage projects:
    - Present a table that lists all of the in vitro and in vivo assays that will be run by the PD/PI and associated personnel. The table should include descriptive names of the assays, the assay throughput, and the proposed advancement criteria for each assay.
    - Explain the rationale for the choice of assays, assay design, and advancement criteria, and clarify how these relate to the desired drug properties presented in the Target Product Profile.
    - Show assay validation data or present plans to optimize and validate assays.
    - If requesting funding to conduct all of the assays for SAR studies, including ADMET, provide a testing funnel that shows how these assays will be ordered and grouped into testing tiers.
    - If requesting funding for medicinal chemistry within the PD/PI's laboratory, describe the SAR strategy that will be used.
    - For the in vivo bioactivity study required to declare a development candidate, provide details on the study design, including power analysis and associated assumptions for sample size estimation, the process for blinding and randomization, and data handling rules, such as criteria for inclusion and exclusion of data. Describe plans for data analysis and interpretation, including what effect size would be considered minimally acceptable and clinically relevant (i.e., what constitutes a go/no-go decision for advancement into Development).

- Indicate how target engagement and/or pharmacodynamic markers will be used to detect activity at the putative target in preclinical models and in patients, if available or proposed for development.
- If requesting funding to conduct preclinical Development activities, include a Gantt chart that lays out each step (e.g., GMP synthesis, formulations development, and IND-enabling studies).
- For projects entering at the Development phase, present a synthetic scheme and experimental details (yields, conditions, reagents) for the development candidate. If requesting funding for process development, describe the strategy for adapting the synthesis for scale up to levels sufficient to run a Phase I trial.
- Provide a brief description of the clinical trial strategy. We anticipate that details of the trial are likely to change during therapeutic development. As appropriate, applicants are encouraged to make use of NIH resources for clinical research (https://www.ninds.nih.gov/Current-Research/Research-Funded-NINDS/Clinical-Research (https://www.ninds.nih.gov/Current-Research/Research-Funded-NINDS/Clinical-Research)).

Innovation: Explain how the project offers a novel approach to treating the proposed disease indication.

- If therapeutics that target the same molecule, pathway, or cellular process have been tested in clinical trials for the proposed disease indication, explain why the proposed approach would be expected to provide a benefit over those therapeutics.
- If drugs with similar structures have been tested in clinical trials for the proposed disease indication, explain why the proposed drug would be expected to give significantly better clinical outcomes.
- Comment on the novelty of proposed approach, target, pathway, assays or models.

Letters of Support: If applying from an academic institution, include a letter of support from the technology transfer official who will be managing intellectual property and licensing associated with this project and agreement to share confidentially with NIH details of any licensing agreements related to the proposed program relevant to determining feasibility of commercialization for the proposed disease area.

If research will be performed at more than one institution, include a letter of support from each institution clarifying how intellectual property (IP) will be shared or otherwise managed across the institutions, to ensure that the IP remains unencumbered, consistent with achieving the goals of the program.

Resource Sharing Plan: Individuals are required to comply with the instructions for the Resource Sharing Plans as provided in the SF424 (R&R) Application Guide, with the following modification:

- All applications, regardless of the amount of direct costs requested for any one year, should address a Data Sharing Plan.
- . If patent protection is being sought, investigators should explain how data will be shared after filing for patent protection to allow for both further research and the development of commercial products to advance forward, consistent with achieving the goals of the program

Appendix:

Only limited Appendix materials are allowed. Follow all instructions for the Appendix as described in the SF424 (R&R) Application Guide.

PHS Human Subjects and Clinical Trials Information

When involving NIH-defined human subjects research, clinical research, and/or clinical trials follow all instructions for the PHS Human Subjects and Clinical Trials Information form in the SF424 (R&R) Application Guide, with the following additional instructions:

Note that applications in which all clinical trial work is proposed to be conducted by BPN CROs (i.e. not part of the grant budget) should not indicate that their applications involve include a clinical trial.

If you answered "Yes" to the question "Are Human Subjects Involved?" on the R&R Other Project Information form, you must include at least one human subjects study record using the Study Record: PHS Human Subjects and Clinical Trials Information form or a Delayed Onset Study record.

Study Record: PHS Human Subjects and Clinical Trials Information

All instructions in the SF424 (R&R) Application Guide must be followed with the following additional instructions:

Section 4 - Protocol Synopsis

4.2 Study Design

4.2 a. Narrative Study Description: Include determination of dose levels.

4.2c. Interventions. For "Intervention Description", include route of administration

4.3. Outcome Measures: At least one outcome measure should include PK assessments, with attention to demonstration of CNS penetration (if appropriate) and target engagement or modulation.

Delayed Onset Study

All instructions in the SF424 (R&R) Application Guide must be followed.

PHS Assignment Request Form

All instructions in the SF424 (R&R) Application Guide must be followed.

Foreign Institutions

Foreign (non-U.S.) institutions must follow policies described in the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11137), and procedures for foreign institutions.

3. Unique Entity Identifier and System for Award Management (SAM)

See Part 1. Section III.1 for information regarding the requirement for obtaining a unique entity identifier and for completing and maintaining active registrations in System for Award Management (SAM), NATO Commercial and Government Entity (NCAGE) Code (if applicable), eRA Commons, and Grants.gov

4. Submission Dates and Times

Part I. Overview Information contains information about Key Dates and times. Applicants are encouraged to submit applications before the due date to ensure they have time to make any application corrections that might be necessary for successful submission. When a submission date falls on a weekend or Federal holiday (https://grants.nih.gov/grants/guide/url_redirect.htm?id=82380), the application deadline is automatically extended to the next business day.

Organizations must submit applications to Grants.gov (//grants.nih.gov/grants/guide/url_redirect.htm?id=11128) (the online portal to find and apply for grants across all Federal agencies). Applicants must then complete the submission process by tracking the status of the application in the eRA Commons (//grants.nih.gov/grants/guide/url_redirect.htm?id=11123), NIH's electronic system for grants administration. NIH and Grants.gov systems check the application against many of the application instructions upon submission. Errors must be corrected and a changed/corrected application must be submitted to Grants.gov on or before the application due date and time. If a Changed/Corrected application is submitted after the deadline, the application will be considered late. Applications that miss the due date and time are subjected to the NIH Policy on Late Application Submission.

Applicants are responsible for viewing their application before the due date in the eRA Commons to ensure accurate and successful submission.

Information on the submission process and a definition of on-time submission are provided in the SF424 (R&R) Application Guide.

5. Intergovernmental Review (E.O. 12372)

This initiative is not subject to intergovernmental review. (//grants.nih.gov/grants/guide/url_redirect.htm?id=11142)

6. Funding Restrictions

All NIH awards are subject to the terms and conditions, cost principles, and other considerations described in the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11120).

Pre-award costs are allowable only as described in the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11143).

7. Other Submission Requirements and Information

Applications must be submitted electronically following the instructions described in the SF424 (R&R) Application Guide. Paper applications will not be accepted.

Applicants must complete all required registrations before the application due date. Section III. Eligibility Information contains information about registration.

For assistance with your electronic application or for more information on the electronic submission process, visit Applying Electronically (//grants.nih.gov/grants/guide/url_redirect.htm?id=11144). If you encounter a system issue beyond your control that threatens your ability to complete the submission process on-time, you must follow the Guidelines for Applicants Experiencing System Issues (//grants.nih.gov/grants/ElectronicReceipt/support.htm#guidelines). For assistance with application submission, contact the Application Submission Contacts in Section VII.

Important reminders:

All PD(s)/PI(s) must include their eRA Commons ID in the Credential field of the Senior/Key Person Profile Component of the SF424(R&R) Application Package**.** Failure to register in the Commons and to include a valid PD/PI Commons ID in the credential field will prevent the successful submission of an electronic application to NIH. See Section III of this FOA for information on registration requirements.

The applicant organization must ensure that the DUNS number it provides on the application is the same number used in the organization's profile in the eRA Commons and for the System for Award Management. Additional information may be found in the SF424 (R&R) Application Guide.

See more tips (//grants.nih.gov/grants/guide/url_redirect.htm?id=11146) for avoiding common errors.

Upon receipt, applications will be evaluated for completeness and compliance with application instructions by the Center for Scientific Review, NIH. Applications that are incomplete or non-compliant will not be reviewed.

Requests of $500,000 or more for direct costs in any year

Applicants requesting $500,000 or more in direct costs in any year (excluding consortium F&A) must contact a Scientific/ Research Contact at least 6 weeks before submitting the application and follow the Policy on the Acceptance for Review of Unsolicited Applications that Request $500,000 or More in Direct Costs as described in the SF424 (R&R) Application Guide.

Post Submission Materials

Applicants are required to follow the instructions for post-submission materials, as described in the policy (//grants.nih.gov/grants/guide/url_redirect.htm?id=82299). Any instructions provided here are in addition to the instructions in the policy.

Section V. Application Review Information

1. Criteria

Only the review criteria described below will be considered in the review process. As part of the NIH mission (//grants.nih.gov/grants/guide/url_redirect.htm?id=11149), all applications submitted to the NIH in support of biomedical and behavioral research are evaluated for scientific and technical merit through the NIH peer review system.

For this particular announcement, note the following:

- Risks should be evaluated in a stage appropriate fashion and the ability for the BPN to mitigate those risks with milestones. Earlier-stage projects are inherently riskier than later-stage projects. Projects should be evaluated relative to expectations for their proposed entry stage, when assessing risk.
- The market size for the proposed drug should not be considered in assessing the significance of a project.
- Projects should not be penalized if the mechanism of action of the compound is unknown. While this may add to the risk, the increased risk may be counterbalanced by increased novelty.
- Evaluation of the approach should focus on the biological rationale, the potential for identifying a compound with drug-like properties, potential patient benefit, competitive landscape (novelty), and strengths/weaknesses of studies to be conducted by the PD/PI. Work to be conducted by BPN contractors (which may include medicinal chemistry, pharmacokinetics, toxicology, formulations development, chemical synthesis under Good Manufacturing Practices (GMP), and Phase I clinical testing) will be designed by NIH-provided consultants and contractors after award.
- Applications that propose entry at the Development stage but that reviewers consider better suited for the Discovery stage or vice versa should nevertheless be evaluated and scored based on the entry criteria and expectations for the proposed entry stage. Reviewers can note in their comments that the project may be more appropriate for entry at a different stage.

In addition, for applications involving clinical trials:

A proposed Clinical Trial application may include study design, methods, and intervention that are not by themselves innovative but address important questions or unmet needs. Additionally, the results of the clinical trial may indicate that further clinical development of the intervention is unwarranted or lead to new avenues of scientific investigation.

Overall Impact

Reviewers will provide an overall impact score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following review criteria and additional review criteria (as applicable for the project proposed).

Scored Review Criteria

Reviewers will consider each of the review criteria below in the determination of scientific merit, and give a separate score for each. An application does not need to be strong in all categories to be judged likely to have major scientific impact. For example, a project that by its nature is not innovative may be essential to advance a field.

Significance

Does the project address an important problem or a critical barrier to progress in the field? Is there a strong scientific premise for the project? If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Specific to this announcement:

- How significant an advantage does the proposed drug offer over other treatments under development (in any therapeutic class)?

- What is the likelihood that completion of the research objectives will lead to a therapy for the intended disease (i.e., is there a clear path into the clinic)?
- How strong are the data supporting the choice of drug target and compound for the proposed disease indication?
- For projects entering at the Discovery stage, are the proposed hit compounds sufficiently active in assays that are relevant to the proposed disease indication?
- For projects entering at the Development stage, does the applicant have a well profiled and fully-optimized compound with in vitro and in vivo biological activity and ADMET properties appropriate for the intended clinical use? Has the applicant provided convincing data that the compound is efficacious when delivered by the intended route of administration, at exposure levels that can likely be achieved clinically with the proposed human dosing regimen?

In addition, for applications proposing clinical trials

- Are the scientific rationale and need for a clinical trial to test the proposed hypothesis or intervention well supported by preliminary data, clinical and/or preclinical studies, or information in the literature or knowledge of biological mechanisms? For trials focusing on clinical or public health endpoints, is this clinical trial necessary for testing the safety, efficacy or effectiveness of an intervention that could lead to a change in clinical practice, community behaviors or health care policy? For trials focusing on mechanistic, behavioral, physiological, biochemical, or other biomedical endpoints, is this trial needed to advance scientific understanding?

Investigator(s)

- Are the PD(s)/PI(s), collaborators, and other researchers well suited to the project? If Early Stage Investigators or those in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? If the project is collaborative or multi-PD/PI, do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the project?
- **Specific to this announcement:**
- Are the expertise and experience of the PD(s)/PI(s), collaborators, and other proposed researchers appropriate for the work they intend to conduct themselves, including chemistry and clinical trials, if proposed?
- Is there adequate statistical support for experimental design and data analyses?
- Is there sufficient clinical expertise to define the goals of the drug development effort for the intended disease indication, even if the trial will be conducted by BPN contractors?

In addition, for applications proposing clinical trials

With regard to the proposed leadership for the project, do the PD/PI(s) and key personnel have the expertise, experience, and ability to organize, manage and implement the proposed clinical trial and meet milestones and timelines? Do they have appropriate expertise in study coordination, data management and statistics? For a multicenter trial, is the organizational structure appropriate and does the application identify a core of potential center investigators and staffing for a coordinating center?

Innovation

Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions? Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

Specific to this announcement:

Would the proposed drug be expected to give significantly better clinical outcomes than have been observed in previous efforts focused on the same target?

In addition, for applications proposing clinical trials

Does the design/research plan include innovative elements, as appropriate, that enhance its sensitivity, potential for information or potential to advance scientific knowledge or clinical practice?

Approach

Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed? Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed? Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects?

Specific to this announcement:

- Are the proposed studies appropriate, feasible, and consistent with the proposed Target Product Profile, and likely to advance the project to the desired endpoint within the proposed timeframe?
- Are proposed experimental designs and methodological approaches sufficiently rigorous to give meaningful results?
- For projects entering at the ***Discovery stage***:
    - Are the proposed compounds suitable for SAR studies and optimization into a drug candidate?
    - Are the proposed in vivo studies and go/no-go criteria appropriate for declaring a development candidate?
- For projects entering at the ***Development stage:***
    - Is it feasible to scale up the proposed development candidate to levels required for
    - IND-enabling studies and clinical trials?
    - For applicants that propose to conduct Development work themselves, does their Development plan include all of the appropriate studies for obtaining an IND? Are the timelines realistic?

If the project involves human subjects and/or NIH-defined clinical research, are the plans to address 1) the protection of human subjects from research risks, and 2) inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion or exclusion of children, justified in terms of the scientific goals and research strategy proposed?

In addition, for applications proposing clinical trials

Does the application adequately address the following, if applicable

Study Design

Is the study design justified and appropriate to address primary and secondary outcome variable(s)/endpoints that will be clear, informative and relevant to the hypothesis being tested? Is the scientific rationale/premise of the study based on previously well-designed preclinical and/or clinical research? Given the methods used to assign participants and deliver interventions, is the study design adequately powered to answer the research question(s), test the proposed hypothesis/hypotheses, and provide interpretable results? Is the trial appropriately designed to conduct the research efficiently? Are the study populations (size, gender, age, demographic group), proposed intervention arms/dose, and duration of the trial, appropriate and well justified?

Are potential ethical issues adequately addressed? Is the process for obtaining informed consent or assent appropriate? Is the eligible population available? Are the plans for recruitment outreach, enrollment, retention, handling dropouts, missed visits, and losses to follow-up appropriate to ensure robust data collection? Are the planned recruitment timelines feasible and is the plan to monitor accrual adequate? Has the need for randomization (or not), masking (if appropriate), controls, and inclusion/exclusion criteria

been addressed? Are differences addressed, if applicable, in the intervention effect due to sex/gender and race/ethnicity?

Are the plans to standardize, assure quality of, and monitor adherence to, the trial protocol and data collection or distribution guidelines appropriate? Is there a plan to obtain required study agent(s)? Does the application propose to use existing available resources, as applicable?

Data Management and Statistical Analysis

Are planned analyses and statistical approach appropriate for the proposed study design and methods used to assign participants and deliver interventions? Are the procedures for data management and quality control of data adequate at clinical site(s) or at center laboratories, as applicable? Have the methods for standardization of procedures for data management to assess the effect of the intervention and quality control been addressed? Is there a plan to complete data analysis within the proposed period of the award?

Specific to this announcement:

If the PD/PI is requesting funding to conduct a clinical trial, are the general quality and appropriateness of the proposed study design, including the study population, number of subjects, duration of the clinical study, and safety, pharmacokinetic, and pharmacodynamic endpoints appropriate?

Environment

Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?

In addition, for applications proposing clinical trials

If proposed, are the administrative, data coordinating, enrollment and laboratory/testing centers, appropriate for the trial proposed?

Does the application adequately address the capability and ability to conduct the trial at the proposed site(s) or centers? Are the plans to add or drop enrollment centers, as needed, appropriate?

If international site(s) is/are proposed, does the application adequately address the complexity of executing the clinical trial?

If multi-sites/centers, is there evidence of the ability of the individual site or center to: (1) enroll the proposed numbers; (2) adhere to the protocol; (3) collect and transmit data in an accurate and timely fashion; and, (4) operate within the proposed organizational structure?

Additional Review Criteria

As applicable for the project proposed, reviewers will evaluate the following additional items while determining scientific and technical merit, and in providing an overall impact score, but will not give separate scores for these items.

Study Timeline

Specific to applications proposing clinical trials

Is the study timeline described in detail, taking into account start-up activities, the anticipated rate of enrollment, and planned follow-up assessment? Is the projected timeline feasible and well justified? Does the project incorporate efficiencies and utilize existing resources (e.g., CTSAs, practice-based research networks, electronic medical records, administrative database, or patient registries) to increase the efficiency of participant enrollment and data collection, as appropriate?

Are potential challenges and corresponding solutions discussed (e.g., strategies that can be implemented in the event of enrollment shortfalls)?

Intellectual Property

For Development-stage projects, has the applicant demonstrated that the ability of his or her institution to develop and commercialize the proposed development candidate is unlikely to be blocked or impeded by intellectual property constraints?

If multiple institutions are proposed, is it clear how intellectual property will be shared or otherwise managed to avoid encumbering the IP, consistent with achieving the goals of the program? Are these plans acceptable?

Protections for Human Subjects

For research that involves human subjects but does not involve one of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate the justification for involvement of human subjects and the proposed protections from research risk relating to their participation according to the following five review criteria: 1) risk to subjects, 2) adequacy of protection against risks, 3) potential benefits to the subjects and others, 4) importance of the knowledge to be gained, and 5) data and safety monitoring for clinical trials.

For research that involves human subjects and meets the criteria for one or more of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate: 1) the justification for the exemption, 2) human subjects involvement and characteristics, and 3) sources of materials. For additional information on review of the Human Subjects section, please refer to the Guidelines for the Review of Human Subjects (//grants.nih.gov/grants/guide/url_redirect.htm?id=11175).

Inclusion of Women, Minorities, and Children

When the proposed project involves human subjects and/or NIH-defined clinical research, the committee will evaluate the proposed plans for the inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion (or exclusion) of children to determine if it is justified in terms of the scientific goals and research strategy proposed. For additional information on review of the Inclusion section, please refer to the Guidelines for the Review of Inclusion in Clinical Research (//grants.nih.gov/grants/guide/url_redirect.htm?id=11174).

Vertebrate Animals

The committee will evaluate the involvement of live vertebrate animals as part of the scientific assessment according to the following criteria: (1) description of proposed procedures involving animals, including species, strains, ages, sex, and total number to be used; (2) justifications for the use of animals versus alternative models and for the appropriateness of the species proposed; (3) interventions to minimize discomfort, distress, pain and injury; and (4) justification for euthanasia method if NOT consistent with the AVMA Guidelines for the Euthanasia of Animals. Reviewers will assess the use of chimpanzees as they would any other application proposing the use of vertebrate animals. For additional information on review of the Vertebrate Animals section, please refer to the Worksheet for Review of the Vertebrate Animal Section (//grants.nih.gov/grants/guide/url_redirect.htm?id=11150).

Biohazards

Reviewers will assess whether materials or procedures proposed are potentially hazardous to research personnel and/or the environment, and if needed, determine whether adequate protection is proposed.

Resubmissions

For Resubmissions, the committee will evaluate the application as now presented, taking into consideration the responses to comments from the previous scientific review group and changes made to the project.

Renewals

Not Applicable.

Revisions

For Revisions, the committee will consider the appropriateness of the proposed expansion of the scope of the project. If the Revision application relates to a specific line of investigation presented in the original application that was not recommended for approval by the committee, then the committee will consider whether the responses to comments from the previous scientific review group are adequate and whether substantial changes are clearly evident.

Additional Review Considerations

As applicable for the project proposed, reviewers will consider each of the following items, but will not give scores for these items, and should not consider them in providing an overall impact score.

Applications from Foreign Organizations

Reviewers will assess whether the project presents special opportunities for furthering research programs through the use of unusual talent, resources, populations, or environmental conditions that exist in other countries and either are not readily available in the United States or augment existing U.S. resources.

Select Agent Research

Reviewers will assess the information provided in this section of the application, including 1) the Select Agent(s) to be used in the proposed research, 2) the registration status of all entities where Select Agent(s) will be used, 3) the procedures that will be used to monitor possession use and transfer of Select Agent(s), and 4) plans for appropriate biosafety, biocontainment, and security of the Select Agent(s).

Resource Sharing Plans

Reviewers will comment on whether the following Resource Sharing Plans, or the rationale for not sharing the following types of resources, are reasonable: (1) Data Sharing Plan (//grants.nih.gov/grants/guide/url_redirect.htm?id=11151); (2) Sharing Model Organisms (//grants.nih.gov/grants/guide/url_redirect.htm?id=11152); and (3) Genomic Data Sharing Plan (GDS) (//grants.nih.gov/grants/guide/url_redirect.htm?id=11153).

Authentication of Key Biological and/or Chemical Resources:

For projects involving key biological and/or chemical resources, reviewers will comment on the brief plans proposed for identifying and ensuring the validity of those resources.

Budget and Period of Support

Reviewers will consider whether the budget and the requested period of support are fully justified and reasonable in relation to the proposed research.

2. Review and Selection Process

Applications will be evaluated for scientific and technical merit by (an) appropriate Scientific Review Group(s) convened by NINDS, in accordance with NIH peer review policy and procedures (//grants.nih.gov/grants/guide/url_redirect.htm?id=11154), using the stated review criteria. Assignment to a Scientific Review Group will be shown in the eRA Commons.

As part of the scientific peer review, all applications:

- May undergo a selection process in which only those applications deemed to have the highest scientific and technical merit (generally the top half of applications under review) will be discussed and assigned an overall impact score.
- Will receive a written critique.

Applications will be assigned on the basis of established PHS referral guidelines to the appropriate NIH Institute or Center. Applications will compete for available funds with all other recommended applications . Following initial peer review, recommended applications will receive a second level of review by the appropriate national Advisory Council or Board. The following will be considered in making funding decisions:

- Scientific and technical merit of the proposed project as determined by scientific peer review.
- Availability of funds.
- Relevance of the proposed project to program priorities.
- Feasibility of developing a strong intellectual property position for the project, consistent with achieving the goals of the program. The NIH will work with applicants to determine if intellectual property concerns raised by reviewers or by NIH staff can be addressed prior to program entry or within the program.
- Feasibility of conducting the work proposed within the BPN structure

3. Anticipated Announcement and Award Dates

After the peer review of the application is completed, the PD/PI will be able to access his or her Summary Statement (written critique) via the eRA Commons (//grants.nih.gov/grants/guide/url_redirect.htm?id=11123). Refer to Part 1 for dates for peer review, advisory council review, and earliest start date.

Information regarding the disposition of applications is available in the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11156).

Section VI. Award Administration Information

1. Award Notices

If the application is under consideration for funding, NIH will request "just-in-time" information from the applicant as described in the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11157).

A formal notification in the form of a Notice of Award (NoA) will be provided to the applicant organization for successful applications. The NoA signed by the grants management officer is the authorizing document and will be sent via email to the grantee's business official.

Awardees must comply with any funding restrictions described in Section IV.5. Funding Restrictions. Selection of an application for award is not an authorization to begin performance. Any costs incurred before receipt of the NoA are at the recipient's risk. These costs may be reimbursed only to the extent considered allowable pre-award costs.

Any application awarded in response to this FOA will be subject to terms and conditions found on the Award Conditions and Information for NIH Grants (//grants.nih.gov/grants/guide/url_redirect.htm?id=11158) website. This includes any recent legislation and policy applicable to awards that is highlighted on this website.

Additionally, ICs may specify any special reporting requirements for the proposed clinical trial to be included under IC-specific terms and conditions in the NoA. For example: If the proposed clinical trial has elevated risks, ICs may require closer programmatic monitoring and it may be necessary to require the awardee to provide more frequent information and data as a term of the award (e.g., to clarify issues, address and evaluate concerns, provide documentation). All additional communications and information related to programmatic monitoring must be documented and incorporated into the official project file. Individual awards are based on the application submitted to, and as approved by, the NIH and are subject to the IC-specific terms and conditions identified in the NoA. ClinicalTrials.gov: If an award provides for one or more clinical trials. By law (Title VIII, Section 801 of Public Law 110-85), the "responsible party" must register and submit results information for certain "applicable clinical trials" on the ClinicalTrials.gov Protocol Registration and Results System Information Website (https://register.clinicaltrials.gov). NIH expects registration of all trials whether required under the law or not. For more information, see http://grants.nih.gov/ClinicalTrials_fdaaa/

Institutional Review Board or Independent Ethics Committee Approval: Grantee institutions must ensure that the application as well as all protocols are reviewed by their IRB or IEC. To help ensure the safety of participants enrolled in NIH-funded studies, the awardee must provide NIH copies of documents related to all major changes in the status of ongoing protocols. Data and Safety Monitoring Requirements: The NIH policy for data and safety monitoring requires oversight and monitoring of all NIH-conducted or -supported human biomedical and behavioral intervention studies (clinical trials) to ensure the safety of participants and the validity and integrity of the data. Further information concerning these requirements is found at http://grants.nih.gov/grants/policy/hs/data_safety.htm and in the application instructions (SF424 (R&R) and PHS 398).

Investigational New Drug or Investigational Device Exemption Requirements: Consistent with federal regulations, clinical research projects involving the use of investigational therapeutics, vaccines, or other medical interventions (including licensed products and devices for a purpose other than that for which they were licensed) in humans under a research protocol must be performed under a Food and Drug Administration (FDA) investigational new drug (IND) or investigational device exemption (IDE).

2. Administrative and National Policy Requirements

All NIH grant and cooperative agreement awards include the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11120) as part of the NoA. For these terms of award, see the *NIH Grants Policy Statement* Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General (//grants.nih.gov/grants/guide/url_redirect.htm?id=11157) and Part II: Terms and Conditions of NIH Grant Awards, Subpart B: Terms and Conditions for Specific Types of Grants, Grantees, and Activities (//grants.nih.gov/grants/guide/url_redirect.htm?id=11159). More information is provided at Award Conditions and Information for NIH Grants (//grants.nih.gov/grants/guide/url_redirect.htm?id=11158).

Recipients of federal financial assistance (FFA) from HHS must administer their programs in compliance with federal civil rights law. This means that recipients of HHS funds must ensure equal access to their programs without regard to a person's race, color, national origin, disability, age and, in some circumstances, sex and religion. This includes ensuring your programs are accessible to persons with limited English proficiency. HHS recognizes that research projects are often limited in scope for many reasons that are nondiscriminatory, such as the principal investigator's scientific interest, funding limitations, recruitment requirements, and other considerations. Thus, criteria in research protocols that target or exclude certain populations are warranted where nondiscriminatory justifications establish that such criteria are appropriate with respect to the health or safety of the subjects, the scientific study design, or the purpose of the research.

For additional guidance regarding how the provisions apply to NIH grant programs, please contact the Scientific/Research Contact that is identified in Section VII under Agency Contacts of this FOA. HHS provides general guidance to recipients of FFA on meeting their legal obligation to take reasonable steps to provide meaningful access to their programs by persons with limited English proficiency. Please see http://www.hhs.gov/ocr/civilrights/resources/laws/revisedlep.html. The HHS Office for Civil Rights also provides guidance on complying with civil rights laws enforced by HHS. Please see http://www.hhs.gov/ocr/civilrights/understanding/section1557/index.html (http://www.hhs.gov/ocr/civilrights/understanding/section1557/index.html); and http://www.hhs.gov/ocr/civilrights/understanding/index.html (http://www.hhs.gov/ocr/civilrights/understanding/index.html). Recipients of FFA also have specific legal obligations for serving qualified individuals with disabilities. Please see http://www.hhs.gov/ocr/civilrights/understanding/disability/index.html (http://www.hhs.gov/ocr/civilrights/understanding/disability/index.html). Please contact the HHS Office for Civil Rights for more information about obligations and prohibitions under federal civil rights laws at http://www.hhs.gov/ocr/office/about/rgn-hqaddresses.html (http://www.hhs.gov/ocr/office/about/rgn-hqaddresses.html) or call 1-800-368-1019 or TDD 1-800-537-7697. Also note it is an HHS Departmental goal to ensure access to quality, culturally competent care, including long-term services and supports, for

vulnerable populations. For further guidance on providing culturally and linguistically appropriate services, recipients should review the National Standards for Culturally and Linguistically Appropriate Services in Health and Health Care at http://minorityhealth.hhs.gov/omh/browse.aspx?lvl=2&lvlid=53 (http://minorityhealth.hhs.gov/omh/browse.aspx?lvl=2&lvlid=53).

In accordance with the statutory provisions contained in Section 872 of the Duncan Hunter National Defense Authorization Act of Fiscal Year 2009 (Public Law 110-417), NIH awards will be subject to the Federal Awardee Performance and Integrity Information System (FAPIIS) requirements. FAPIIS requires Federal award making officials to review and consider information about an applicant in the designated integrity and performance system (currently FAPIIS) prior to making an award. An applicant, at its option, may review information in the designated integrity and performance systems accessible through FAPIIS and comment on any information about itself that a Federal agency previously entered and is currently in FAPIIS. The Federal awarding agency will consider any comments by the applicant, in addition to other information in FAPIIS, in making a judgement about the applicant's integrity, business ethics, and record of performance under Federal awards when completing the review of risk posed by applicants as described in 45 CFR Part 75.205 "Federal awarding agency review of risk posed by applicants." This provision will apply to all NIH grants and cooperative agreements except fellowships.

Cooperative Agreement Terms and Conditions of Award

The following special terms of award are in addition to, and not in lieu of, otherwise applicable U.S. Office of Management and Budget (OMB) administrative guidelines, U.S. Department of Health and Human Services (DHHS) grant administration regulations at 45 CFR Parts 75 (Part 92 is applicable when State and local Governments are eligible to apply), and other HHS, PHS, and NIH grant administration policies.

The administrative and funding instrument used for this program will be the cooperative agreement, an "assistance" mechanism (rather than an "acquisition" mechanism), in which substantial NIH programmatic involvement with the awardees is anticipated during the performance of the activities. Under the cooperative agreement, the NIH purpose is to support and stimulate the recipients' activities by involvement in and otherwise working jointly with the award recipients in a partnership role; it is not to assume direction, prime responsibility, or a dominant role in the activities. Consistent with this concept, the dominant role and prime responsibility resides with the awardees for the project as a whole, although specific tasks and activities may be shared among the awardees and the NIH as defined below.

The PD(s)/PI(s) will have primary responsibility for:

- Determining experimental approaches, designing protocols, conducting experiments, and analyzing and interpreting research data for studies funded through this UG3/UH3.
- Serving as co-chair of the project Lead/Clinical Development Team (LDT/CDT),
- Presenting project updates (including raw data, when requested) in conference calls and annual face-to-face meetings of the BPN External Oversight Committee in the Washington, DC area.
- With the LDT/CDT, assisting in the development of a project milestone plan at the outset of the project.
- Coordinating and participating with NIH staff and NIH-contracted consultants in all aspects of scientific and technical management of the project.
- Collaborating and communicating effectively with NIH service contractors to achieve project goals.
- Providing goals and strategies for assay validation, screening throughput, and quality control, to NIH Program staff as requested.
- Ensuring that primary and secondary screening data and assay protocols developed as a part of this project are deposited in a centralized BPN database according to the timeline agreed upon by the LDT/CDT and the NIH Program Official and according to BPN policies.
- Adhering to BPN policies, including those regarding data release, intellectual property, and publications.
- Implementing all scientific and policy decisions approved by the LDT/CDT and the BPN program.

- Submitting periodic milestone progress reports in a standard format, as agreed upon by the LDT/CDT and BPN program.
- Preparing for annual administrative site visits by NIH Program staff and consultants.
- Working closely with his/her institution's technology transfer officials to ensure that royalty agreements, patent filings, and all other necessary intellectual property arrangements are completed in a timely manner
- Submission of the IND application and scheduling meetings with the FDA.
- Ensuring NIH staff and consultants on the LDT are included in all meetings with the FDA.
- Providing protocol, supporting clinical documents and regulatory documents required for administrative review prior to clinical trial
- Production of publication for clinical trial

All data or materials generated under this UG3/UH3 award and through collaborations of the PD/PI with other components of the Blueprint Neurotherapeutics Network will be owned by the respective awardee and the data will be considered to be confidential and business privileged information of the awardee, which nevertheless does not affect its obligations to share or deliver the material or data with the government as set forth elsewhere in the grant agreement or regulations.

NIH staff have substantial scientific and programmatic involvement that is above and beyond the normal stewardship role in awards, as described below:

An NIH Project Collaborator will be assigned to the project, with substantial scientific and programmatic involvement that is above and beyond the normal stewardship role in awards:

- Providing the LDT/CDT with BPN consultants who can provide strategic and technical guidance.
- Coordinating and participating in LDT/CDT meetings to discuss project status, planning, and implementation.
- With the LDT/CDT, assisting in the development of a project milestone plan at the outset of the project.
- Approving the final milestone language for incorporation into the award notice.
- Providing a perspective on the priorities of the NIH Blueprint for Neuroscience Research and BPN.
- Facilitating collaboration and data exchange among the awardee, NIH-contracted consultants, and service providers.
- Enhancing the project progress by providing access to various NIH resources when appropriate.
- Providing technical assistance, advice, and coordination to the project, although the dominant role and responsibilities for the activities funded by the UG3/UH3 reside with the awardee.
- Coordinating reports and presentations of project progress to the BPN External Oversight Committee.
- Coordinating review of clinical trial by internal NIH clinical and safety experts.
- Serving as scientific liaison among the awardee and other NIH program staff.
- Reporting periodically on the progress of the project to NIH leadership.

Leadership of the Institute/Center funding the project will make decisions on project continuation with input from NIH staff and the External Oversight Committee, based on:

- Successful achievement of milestones
- The overall feasibility of project advancement, considering data that may not have been captured in milestones
- Based on emerging and published literature on competition for the disease indication and drug target
- Program priorities
- Availability of funds

Areas of Joint Responsibility include:

Project Lead Development Team (LDT): The LDT typically will be co-chaired by the PD/PI and an NIH-contracted drug development consultant and will include additional members from the PD/PI's group, consultants and NIH staff. This team will collaboratively set strategic direction and guide the work flow for the project on an ongoing basis. The LDT will meet approximately every two weeks via teleconference to analyze and interpret data from the PD/PI and contracted laboratories and to formulate the subsequent experimental

plan. The LDT will propose milestones and produce progress reports for evaluation by the External Oversight Committee and program staff as needed.

If a clinical trial is performed, the LDT will be replaced by a Clinical Development Team (CDT), which will include the PD/PI, clinical consultants and NIH staff. The role and activities of the CDT during clinical development will be comparable to that of the LDT in earlier stages of the project.

The members of this collaborative effort are all made aware of the requirement for confidentiality due to the intent of the awardee to pursue commercialization of any qualified outcomes. Contractors and consultants of NIH will be made aware of the confidential nature of work done under this collaborative effort. The handling and disposition of this confidential data and business privileged information may be covered by the Trade Secrets Act, 18 U.S.C. Section 1905.

Dispute Resolution

Any disagreements that may arise in scientific or programmatic matters (within the scope of the award) between award recipients and the NIH may be brought to Dispute Resolution. A Dispute Resolution Panel composed of three members will be convened. It will have three members: a designee of the External Oversight Committee chosen without NIH staff voting, one NIH designee, and a third designee with expertise in the relevant area who is chosen by the other two; in the case of individual disagreement, the first member may be chosen by the individual awardee. This special dispute resolution procedure does not alter the awardee's right to appeal an adverse action that is otherwise appealable in accordance with PHS regulation 42 CFR Part 50, Subpart D and DHHS regulation 45 CFR Part 16.

3. Reporting

When multiple years are involved, awardees will be required to submit the Research Performance Progress Report (RPPR) (//grants.nih.gov/grants/rppr/index.htm) annually and financial statements as required in the NIH Grants Policy Statement. (//grants.nih.gov/grants/guide/url_redirect.htm?id=11161)

A final RPPR, invention statement, and the expenditure data portion of the Federal Financial Report are required for closeout of an award, as described in the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11161).

The Federal Funding Accountability and Transparency Act of 2006 (Transparency Act), includes a requirement for awardees of Federal grants to report information about first-tier subawards and executive compensation under Federal assistance awards issued in FY2011 or later. All awardees of applicable NIH grants and cooperative agreements are required to report to the Federal Subaward Reporting System (FSRS) available at www.fsrs.gov (//grants.nih.gov/grants/guide/url_redirect.htm?id=11170) on all subawards over $25,000. See the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11171) for additional information on this reporting requirement.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts from all Federal awarding agencies with a cumulative total value greater than $10,000,000 for any period of time during the period of performance of a Federal award, must report and maintain the currency of information reported in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently FAPIIS). This is a statutory requirement under section 872 of Public Law 110-417, as amended (41 U.S.C. 2313). As required by section 3010 of Public Law 111-212, all information posted in the designated integrity and performance system on or after April 15, 2011, except past performance reviews required for Federal procurement contracts, will be publicly available. Full reporting requirements and

procedures are found in Appendix XII to 45 CFR Part 75 – Award Term and Conditions for Recipient Integrity and Performance Matters.

Section VII. Agency Contacts

We encourage inquiries concerning this funding opportunity and welcome the opportunity to answer questions from potential applicants.

Application Submission Contacts

eRA Service Desk (Questions regarding ASSIST, eRA Commons registration, submitting and tracking an application, documenting system problems that threaten submission by the due date, post submission issues)
Finding Help Online: http://grants.nih.gov/support/ (//grants.nih.gov/support/) (preferred method of contact)

Telephone: 301-402-7469 or 866-504-9552 (Toll Free)

Grants.gov Customer Support (//grants.nih.gov/grants/guide/url_redirect.htm?id=82301) (Questions regarding Grants.gov registration and submission, downloading forms and application packages)
Contact Center Telephone: 800-518-4726

Email: support@grants.gov (mailto:support@grants.gov)

GrantsInfo (Questions regarding application instructions and process, finding NIH grant resources)
Email: GrantsInfo@nih.gov (mailto:GrantsInfo@nih.gov) (preferred method of contact)

Telephone: 301-945-7573

Scientific/Research Contact(s)

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Section VIII. Other Information

Recently issued trans-NIH policy notices (//grants.nih.gov/grants/guide/url_redirect.htm?id=11163) may affect your application submission. A full list of policy notices published by NIH is provided in the *NIH Guide for Grants and Contracts* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11164). All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement (//grants.nih.gov/grants/guide/url_redirect.htm?id=11120).

Authority and Regulations

Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and under Federal Regulations 42 CFR Part 52 and 45 CFR Part 75.

Weekly TOC for this Announcement (/grants/guide/WeeklyIndex.cfm?12-22-17)
NIH Funding Opportunities and Notices (/grants/guide/index.html)