

NINDS CREATE BIO PROGRAM



Cooperative Research to Enable and Advance Translational Enterprises

http://www.ninds.nih.gov/funding/areas/translational_research/CREATE-Bio.htm

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CREATE Bio Program Supports

- Disorders that fall under NINDS mission
- Biotechnology products and biologics
 - Peptides, proteins, oligonucleotides, gene therapies, cell therapies
- Lead optimization to early clinical trials

Why the Webinar?

CREATE Bio Program is new

- Published in July 2014
- NINDS translational U01 program is replaced with
 - CREATE Bio
 - CREATE Devices
 - BNP 2.0 small molecules

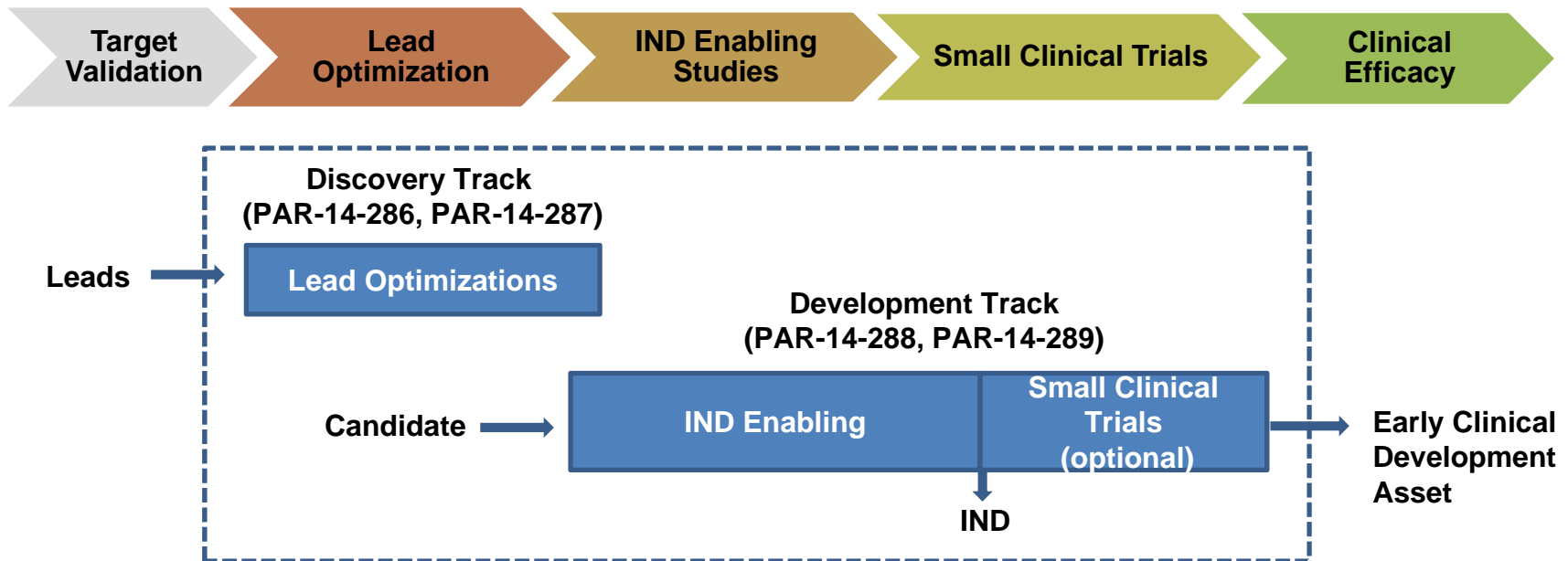
Not a typical NIH grant

- Cooperative agreement mechanism
 - Milestone-driven
 - NINDS program staff provide input on project plans, milestones and go/no-go decisions

Focus of the Webinar

- Overview of CREATE Bio program
- Application and funding process
- Key expectations for applications
- Helpful tips and common pitfalls
- Budget guidance

CREATE Bio Program Overview



- How to choose the Discovery Track or the Development Track?
 - Use [Decision Tree at the website](#)
 - Complete background questionnaire and e-mail us wangh16@ninds.nih.gov

Discovery vs Development

	Discovery Track	Development Track
Purpose	Optimization of therapeutic lead(s)	IND-enabling studies and early-phase clinical trials
End goals	Characterize and select a candidate, which has bioactivity, stability, bioavailability, in vivo efficacy and/or target engagement, etc., that are consistent with the desired clinical application	An IND application submitted to the FDA, at a minimum. The program also supports early-phase clinical trials, but these are not required components of proposed projects
Grant mechanism	Funded up to 4 years through the U01 or SBIR U44 cooperative agreement mechanism	Funded up to 5 years through UH2-UH3 or SBIR U44 cooperative agreement mechanism

Discovery Track

- **Entry**

- Leads show in vivo efficacy and/or target engagement
- The leads have been sufficiently characterized so that key parameters to be optimized can be quantitatively specified
- Well characterized in vitro and in vivo assays

- **Required end goals**

- Optimization is complete: structure, selectivity, stability, manufacturability, etc.
- Candidate characterization is complete: dose, time and duration of treatment, pharmacokinetics/bioavailability at the relevant site of action, and pharmacokinetics-pharmacodynamics relationship etc.
- Feasibility for production and reproducible production of the candidate

Discovery Track Example Activities

- Optimization of the leads
- Further in vivo pharmacology
- Evaluation of metabolism, if applicable
- Optimization of production (e.g., expression levels, yield)
- Process development for scale-up manufacturing
- Stage-appropriate bioanalytical assay development
- Optimization of delivery systems and special formulations
- Optimization and validation of the target engagement assays
- Pre-IND meeting
- Limited initial work for the Development Track preparatory Phase (No IND-enabling toxicology studies)

Discovery Track Out of Scope Activities

- Developing animal models
- Basic research of disease mechanisms
- Early activities such as target identification and validation
- Development of risk, detection, diagnostic, prognostic, efficacy prediction biomarkers
- Manufacture of therapeutics for clinical trials
- Clinical research and clinical trials involving human subjects except those described in scope to develop and validate target engagement assays
- Stand-alone studies to identify, validate, or qualify a target engagement marker and other bioanalytical assays
- Activities already performed utilizing other private or public funds to advance the agent
- Activities that are supported through the CREATE Bio Development Track, with the exception of the transitioning activities designed to enable easy transition from the Discovery to the Development Track

Development Track

- **Entry**
 - Same as Discovery end goal
 - Comprehensive data package to justify big investment
 - Rigorous preclinical testing
 - Competitive for the disease of interest
- **End goal**
 - IND application with a clinical-ready asset
 - Complete small clinical trials (optional)

Development Track Example Activities

UH2: Preparatory for UH3 Preclinical development

- Chemistry, Manufacturing, and Control (CMC) activities for IND-enabling pharmacology/toxicology
- Pharmacokinetic evaluations in species relevant for toxicology or human dose-prediction
- Preliminary safety such as dose-range finding toxicology
- Optimizing and/or validation of appropriate assays to be used in humans

UH3: Preclinical Development and optional small clinical trials

- IND-enabling toxicology
- Tumorigenicity, immunogenicity, biodistribution studies
- Large animal study to assess biocompatibility for delivery devices
- Validation of appropriate assays such as for target engagement markers to enable human use
- IND and other regulatory submissions

Development Track

Out of Scope Activities

- Animal model development
- Basic research and studies of disease mechanisms
- Early research such as identifying and validating targets and generation of preliminary agents that are not suitable for human testing
- Development of risk, detection, diagnostic, prognostic, efficacy prediction biomarkers. (NINDS recognizes that target engagement markers developed under the UH2 phase may evolve into predictive markers for treatment trials, but it is not the intent of this FOA to develop predictive biomarkers.)
- Activities to obtain a candidate that are covered under CREATE Bio Discovery Track
- Activities already performed utilizing other private or public funds to advance the agent
- Performance of a clinical trial with the objective of demonstrating clinical efficacy

Early Small Early Clinical Trials (optional)

- Population: patients with indicated disease, or healthy volunteers
- Total subjects ≤ 50
- Design is single dose or single ascending dose treatment, and may be placebo-controlled or open-label studies; multiple ascending dose may be requested only if agent has a short half-life
- Outcomes are safety, pharmacokinetics and pharmacodynamics/target engagement/target modulation. Note that clinical efficacy outcome data may be collected to prepare for Phase 2 studies, but efficacy cannot be the primary objective of the study
- The duration of the clinical trial, from initiation at first informed consent signature to the completion of data analysis, should rarely exceed 2 years
- Stand alone clinical trial applications are not accepted

Application and Funding Process for All CREATE Bio PARs

Future receipt dates:

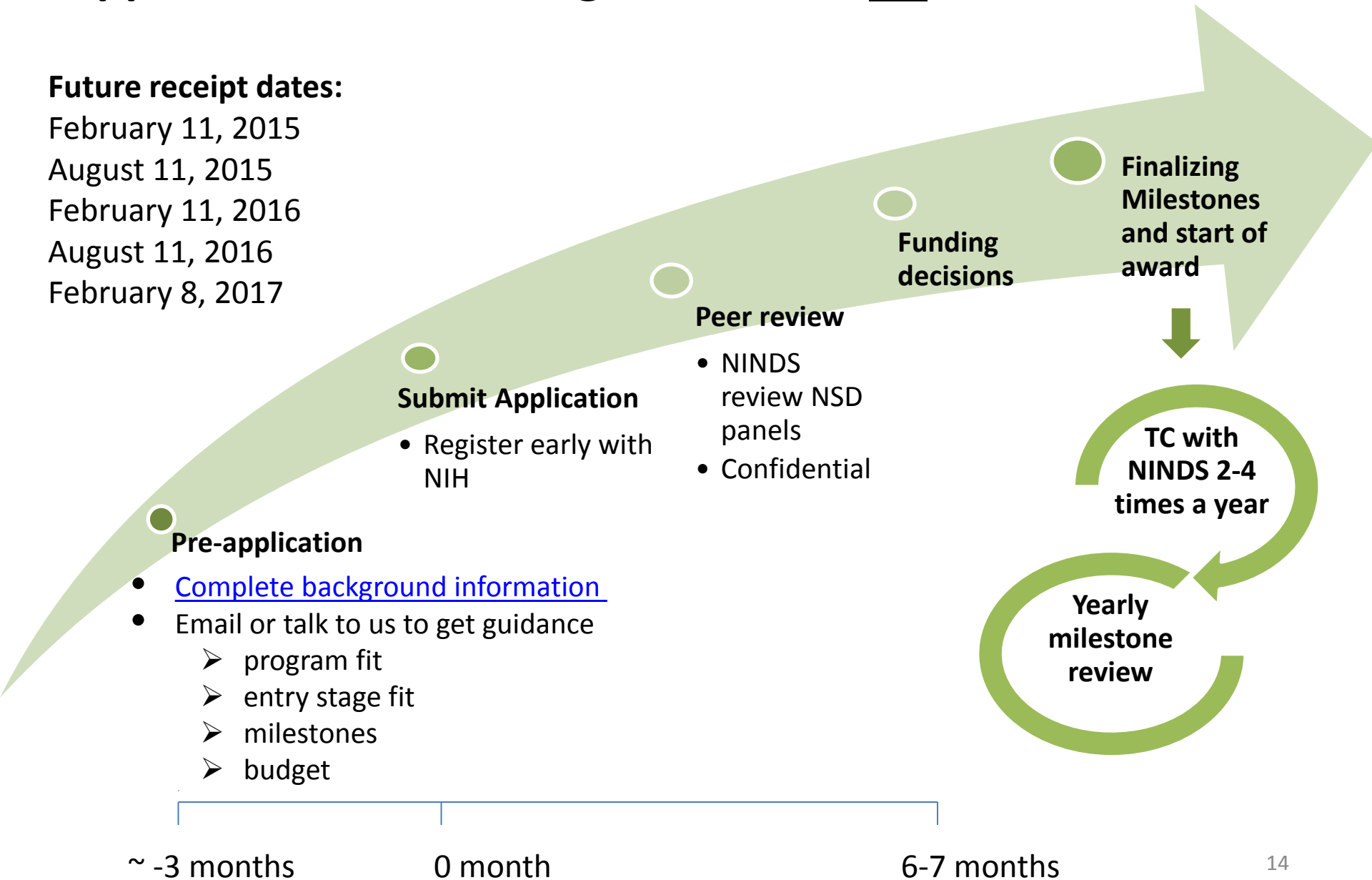
February 11, 2015

August 11, 2015

February 11, 2016

August 11, 2016

February 8, 2017



Key Expectations for Applications for All CREATE Bio PARs

- Comprehensive background and data package
 - Sufficient information for evaluation
 - Confidential (only abstract is publicly available if funded)
- A clear target product profile (TPP) and plans for clinical proof-of-concept study
- Milestones
- Multidisciplinary team
- Emphasis on rigorous study design and reporting
- Intellectual property plans

A Clear TPP and Plans for Clinical Proof-of-Concept Study

- Patient population
 - Diagnosis with details such as treating vs. preventing symptoms
 - What standard of care the patient population will be on
- Route of administration
 - SC and IV are hugely different in feasibility for chronic dosing
- Efficacy
 - Endpoints to be evaluated and how much effect is targeted
- Reviewer will keep the TPP and the plans for clinical proof-of-concept study in mind when reviewing the data package and the proposal
- Examples on the CREATE Bio website

http://www.ninds.nih.gov/funding/areas/translational_research/CREATE-Bio-Example-TPP.htm

Milestones

- Milestones to be used for measuring success in achieving each objective in Research Plans
 - Provide details on methods, assumptions, experimental designs, and data analysis plans
 - Quantitative criteria should be robust
- Milestones will be reviewed and impact the overall score
- Examples on CREATE Bio website

http://www.ninds.nih.gov/funding/areas/translational_research/CREATE-Bio-Example-Milestone.htm

Multidisciplinary Team

- The formation of the multidisciplinary team is a requirement prior to entry
 - Preclinical and clinical scientists
 - CMC experts
 - Regulatory experts
 - Statisticians
 - Other academic/industry experts relevant to the therapeutic modality

Rigorous Study Design and Reporting (both data package and proposal)

- Explain the choice of model(s) or assay(s), primary, secondary and exploratory endpoints, and why they are clinically relevant
- Describe power analyses and associated assumptions for the determination of sample size, statistical handling of the data such as criteria for data inclusion or exclusion, and describe the procedures of blinding and randomization
- Explain what key data have been reproduced, by the applicants or by independent investigators
- Figures should have associated text on the number of animals per group, how many times the experiments were repeated, and whether the data are representative or aggregated

Intellectual Property Strategy

- IP landscape surrounding the therapy
- Constraints and freedom to operate
- Details if patents have been filed
- Future IP filing and execution plans

Planning Essentials

Keep the end in mind
... Target Product
Profile (TPP) and plans
for clinical POC trial

Have multidisciplinary
team to formulate the
plans

Engage regulatory
agency when
appropriate

Talk to NINDS Program
Staff early

Read the FOA including
the review criteria (not
your typical NIH
application)

Propose rigorous and
clear milestones for
success and go/no-go

Check out examples, and
resources on the CREATE
Bio program website

Rigorous Study
Design and Reporting
and comprehensive
data package

Address IP Strategy

Register with NIH
> 6 weeks if new to
NIH grants

Common Pitfalls – for Both Tracks in vivo Data Package or Proposal

- Inappropriate statistical analysis or lack of explanation of the choice of endpoints, expected effect size, and statistical assumptions or methods
- No specification of the purity or selectivity of the agent for in vivo testing
- Lack of replication externally or minimally by the PI (can be proposed in the proposal if necessary)
- Lack of demonstration of a meaningful relationships of efficacy with dose, exposure, or level of target engagement
- In vivo studies (efficacy or target engagement) have not been done with the proposed lead/candidate

Common Pitfalls for the Leads (Discovery Track)

- Not knowing or describing all the gaps to optimize the leads
- Ignoring pharmaceutical properties needed to develop a therapeutic agent; e.g., stability, manufacturability, selectivity, purity, etc.
- No indication or justification of quantitatively desired profile after optimization
- Too many aspects of the leads need to be optimized that it is not feasible to complete during the grant period

Common Pitfalls for Assays (in vivo or in vitro for both Tracks)

- No description of dynamic range and whether the assay can discriminate different levels of treatment (e.g., doses)
- Lack of justification for new endpoints
- Assays are not established and characterized by the PI or collaborator's labs where the work is proposed
- Preliminary assay data does not support what is proposed
 - Short-term vs. long-term
 - Different endpoints
 - Pre-symptomatic or symptomatic
 - Adult vs. juvenile

Budget Guidance (Non-SBIR)

- \geq \$500K in any year: must contact NINDS program at least 6 weeks before submission to get NINDS senior leadership permission to submit
- For both tracks: Budget not limited but must reflect the actual needs of the proposed project. Suggestions below:

	Discovery Track (U01)	Development Track (UH2/UH3)
Non-SBIR	< \$500 K/year in direct cost for up to 4 yrs	< \$1 M/year in direct cost for UH2 for up to 2 yrs < \$1.5 M/year in direct cost for UH3 Combined UH2+UH3 for up to 5 yrs

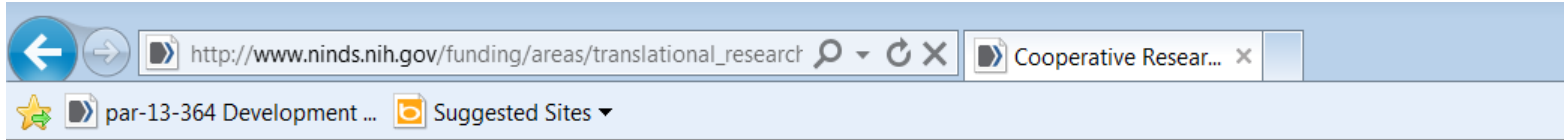
Budget Guidance (SBIR)

- Set aside budget
- SBIR eligible applicants should apply through SBIR PARs

	Discovery Track (U44)	Development Track (U44)
SBIR	<p>< \$500K in total cost in Phase I for up to 1 yr</p> <p><\$2 M total cost in Phase II for up to 3 yrs</p>	<p>< \$1 M/year in total cost for Phase I for up to 2 yrs</p> <p>< \$1.5 M/year in total cost for Phase II for up to 3 yrs</p>

CREATE Bio Website

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Small Business
Office of Clinical
Research

Research Programs

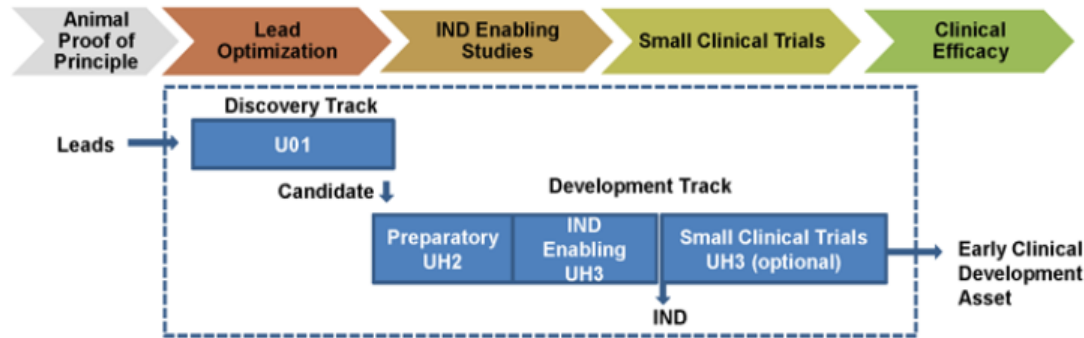
Find People

About NINDS

CREATE Bio

- ▶ [Funding Opportunity Announcements](#)
- ▶ [CREATE Bio Program Overview Presentation\(pdf, 460 KB\)](#)
- ▶ [CREATE Bio pre-application process](#)
- ▶ [Comparison of Discovery and Development Tracks](#)
- ▶ [Definitions](#)
- ▶ [Examples](#)
- ▶ [Biologic Decision Tree\(pdf, 203 KB\)](#)
- ▶ [CREATE FAQ](#)
- ▶ [Staff Contacts](#)

CREATE Bio Program Overview



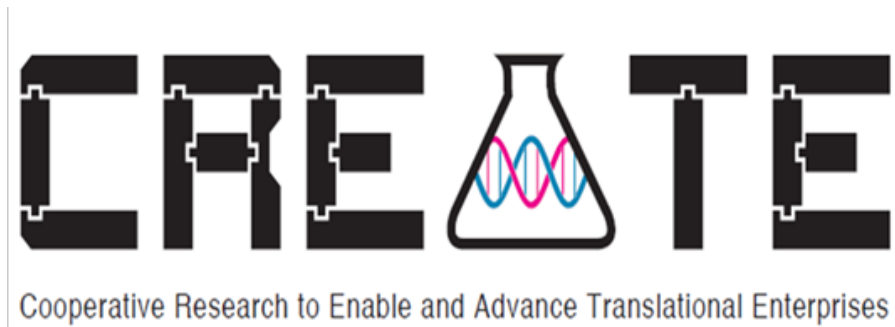
The NINDS Cooperative Research to Enable and Advance Translational Enterprises for Biotechnology Products and Biologics (CREATE Bio) program is dedicated to biotechnology product- and biologics-based therapies, which broadly include modalities such as peptides, proteins, oligonucleotides, gene therapies, and cell therapies. The program includes two tracks: the Discovery Track supports lead optimization in order to obtain a candidate appropriate for entering the Development Track, and the Development Track supports IND-enabling studies for the candidate, as well as early-phase clinical trials.

- ▶ Funding Opportunity Announcements:
 - ▶ NINDS CREATE Bio Discovery Track: Optimization in Preparation for Development of Biotechnology Products and Biologics (U01) ([PAR-14-286](#))
 - ▶ NINDS CREATE Bio Discovery Track: Optimization in Preparation for Development of Biotechnology Products and Biologics (SBIR) ([PAR-14-287](#))
 - ▶ NINDS CREATE Bio Development Track: Preclinical and Early-phase Clinical Development for Biotechnology Products and Biologics (UH2/UH3) ([PAR-14-288](#))
 - ▶ NINDS CREATE Bio Development Track: Preclinical and Early-phase Clinical Development for Biotechnology

We welcome
and appreciate
your comments
and suggestions

Questions?

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http://www.ninds.nih.gov/funding/areas/translational_research/CREATE-Bio.htm

ADDITIONAL SLIDES

SBIR Application Types Allowed

- Discovery Track
 - New (Fast-Track)
 - Renewal (Phase II)
 - Resubmission (Fast-Track and Phase II)
 - Revision (Fast-Track and Phase II)
- Development Track
 - New (Fast-Track)
 - Resubmission (Fast-Track)
 - Revision (Fast-Track)

Coming Soon: IGNITE

- Replace translation R21:
 - Pharmacodynamics and/or In vivo Efficacy Studies for Small Molecules & Biologics/Biotechnology Products
 - Assay Development & Therapeutic Agent Identification & Characterization to Support Therapeutic Discovery
 - Development of Translational Animal Models & Pharmacodynamic Measures Relevant to the Discovery of Therapeutics to Treat Neurological Disease

Entry Criteria for CREATE Bio Discovery Track

(1) There must be a clear and convincing demonstration of preclinical proof-of-concept (e.g., clear dose-response relationship). The therapeutic leads should show either in vivo efficacy using clinically relevant outcome measures (e.g., anatomical, and functional when possible), and/or in vivo target engagement (measurement of target binding or proximal downstream effects) at the clinically intended site of action, using sufficient experimental and statistical rigor. If an established animal model exists for the disease, demonstration of in vivo efficacy is the minimal requirement.

(2) Applicants must have one or more therapeutic leads from which a candidate can potentially be derived. For a therapeutic lead, a few final design characteristics may still need to be optimized. The leads must have been sufficiently profiled so that all the essential key parameters to be optimized to fulfill criteria for a candidate can be quantitatively specified and prioritized.

(3) For key in vitro and in vivo assays proposed to optimize the leads, applicants must have pre-existing data demonstrating that the assays are suitable for the proposed purpose and available in either the applicant's or collaborator's laboratories. Appropriate controls should be employed and efforts should be taken to demonstrate dynamic detection range and acceptable variability so the feasibility of conducting the proposed studies can be adequately assessed.

End Goals of CREATE Bio Discovery Track

- (1) Optimization is finished and final characterization of the candidate, such as structure/identity, selectivity, stability, manufacturability, and other modality-specific characteristics are complete.
- (2) For a candidate with sufficient purity, its minimal effective dose, optimal effective dose, time and duration of treatment, have been determined in relevant in vivo assays using clinically relevant functional and/or anatomical outcome measures, and/or in vivo target engagement assays. The in vivo study results should also include assessment of pharmacokinetics, bioavailability at the relevant site of action, and pharmacokinetics-pharmacodynamics relationship. In particular for CNS disorders, there needs to be rigorous evidence that the agent is blood-brain-barrier penetrant (unless the agent is proposed to be delivered directly to the CNS) and available at an effective dose or evidence that the agent can act in the periphery. *Key studies should be sufficiently powered and controlled with experimental and statistical rigor to lend a high degree of confidence in the results, with sufficient information available about study design, execution, analysis, and interpretation.*
- (3) Feasibility for production and reproducible production of the candidate.

Entry Criteria for Development Track

Only the most promising agents that have undergone rigorous preclinical testing and are considered state-of-the-art for the disease of interest will be considered for advancement to IND-enabling studies in the Development Track and at a minimum the following is required:

- (1) Optimization is finished and final characterization of the candidate, such as structure/identity, selectivity, stability, manufacturability, and other modality-specific characteristics are complete.
- (2) For a candidate with sufficient purity, its minimal effective dose, optimal effective dose, time and duration of treatment, have been determined in relevant in vivo assays using clinically relevant functional and/or anatomical outcome measures, and/or in vivo target engagement assays. The in vivo study results should also include assessment of pharmacokinetics, bioavailability at the relevant site of action, and pharmacokinetics-pharmacodynamics relationship. In particular for CNS disorders, there needs to be rigorous evidence that the agent is blood-brain-barrier *Key studies should be sufficiently powered and controlled with experimental and statistical rigor to lend a high degree of confidence in the results, with sufficient information available about study design, execution, analysis, and interpretation.*
- (3) Feasibility for production and reproducible production of the candidate.