



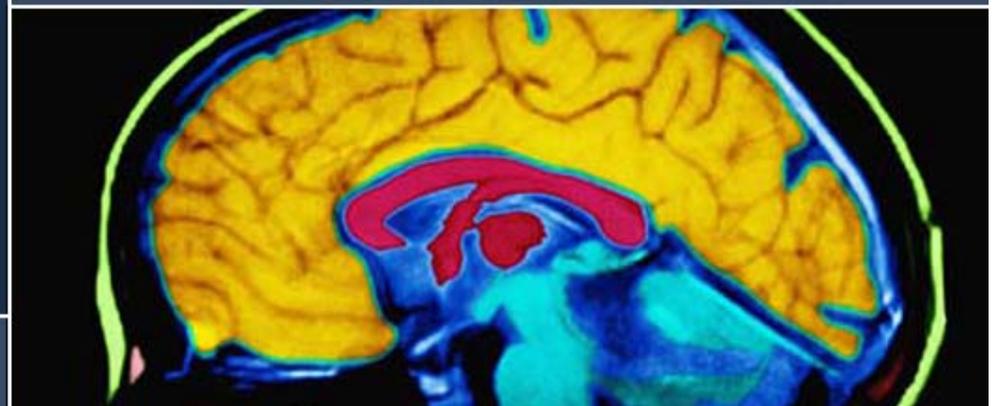
National Institute of
Neurological Disorders
and Stroke

Translational R21 (tR21) Revamp Concept Approval

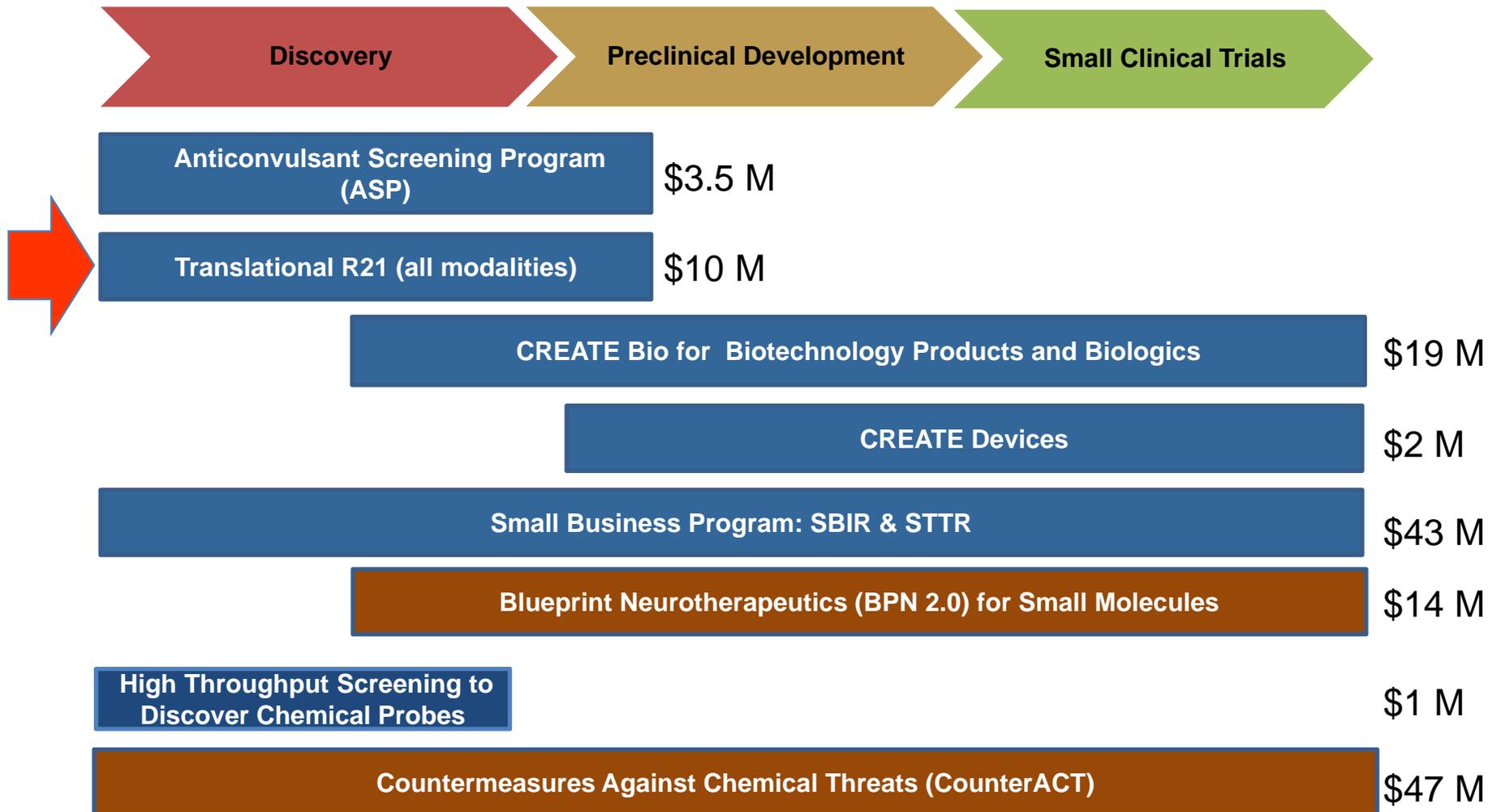
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Rajesh Ranganathan, PhD
Director, Office of Translational Research
NINDS
rajesh.ranganathan@nih.gov



NINDS Translational Funding Mechanisms



Current Translational R21 (tR21) PAR-13-023

- The current tR21 program (total direct costs of \$500,000 for the combined two-year award period) is intended to support research activities and lead directly to cooperative programs (BPN and CREATE) advancing projects towards clinical trials.
- The program has been in place for >10 years – Approximately 50 active projects and \$10M annual investment.
- There have been changes in scope and budget along the way, however, a comprehensive revamp is necessary to leverage lessons learned and ensure a more effective feeder into pipeline for recently launched BPN 2.0 & CREATE programs.
- The current announcement is expiring Jan. 2015 (last receipt date: Oct. 2014).

Program Revamp

Revamp mission:

“Replace the current tR21 program with a new program to seamlessly advance projects from early discovery (R01 & R21) into late-stage translational programs (BPN 2.0 & CREATE) in a manner that is scientifically rigorous, timely, and cost effective...”

Early Discovery
R01 & R21

Late-Stage Translation
BPN 2.0 & CREATE



Revamp Team

OTR

Chris Boshoff

Chuck Cywin

Rebecca Farkas

Stephanie Fertig

David Jett

Mary Ann Pelleymounter

Becky Roof

Amir Tamiz

Christina Vert

Pat Walicke

Hao Wang

Review

Bill Benzing

Ernie Lyons

Birgit Neuhuber

Natalia Strunnikova

OSPP

Bob Zalutsky

DER

Francesca Bosetti

Jane Fountain

Lyn Jakeman

Jim Koenig

Kip Ludwig

Laura Mamounas

Jill Morris

John Porter

Ursula Utz

Vicky Whittemore

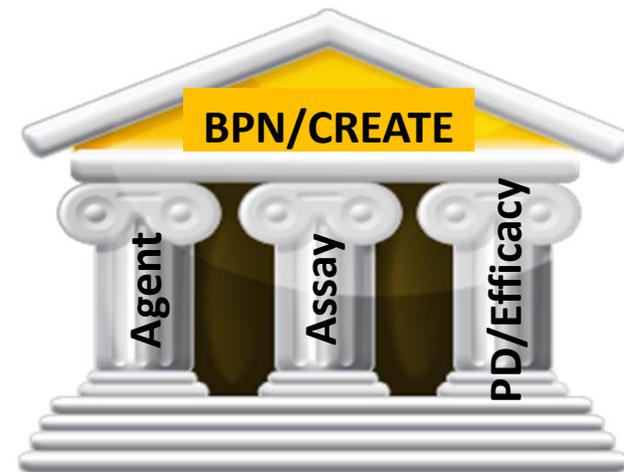
Leverage Lessons Learned and Address Key Challenges

- The new initiatives must be different from the existing parent R21/R01 programs
 - Goal is to feed CREATE/BPN 2.0 pipelines
 - Use milestone mechanism when appropriate
 - Provide more time for rigorous execution
- The new initiatives must encourage:
 - Characterization of therapeutic agents
 - Development, validation, and use of pharmacodynamic measures to strengthen efficacy end points
 - Development and validation of predictive and translatable animal models
 - Development of novel translational platform technologies



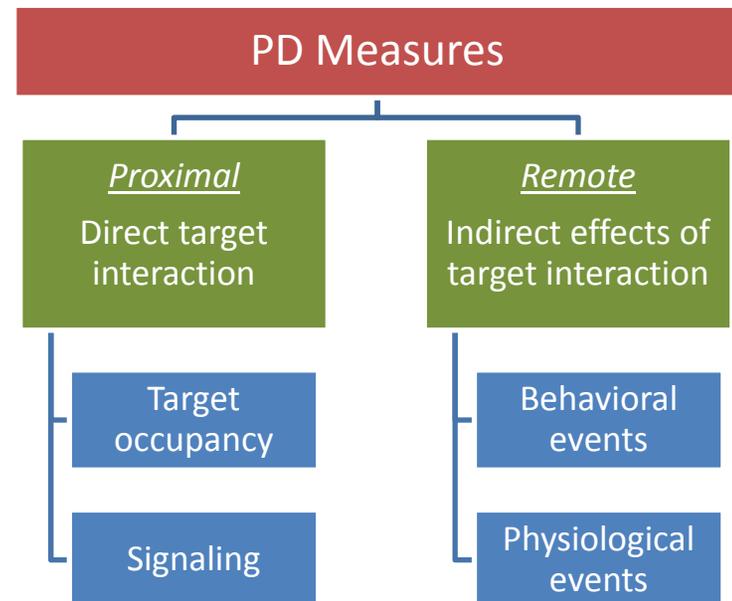
What is Required to Feed the BPN/CREATE Pipelines

1. Preliminary bioactive lead(s)
2. Essential assays (in vitro and in vivo) to enable optimization of the preliminary bioactive leads(s)
3. Either in vivo efficacy using clinically relevant outcome measures and/or in vivo target engagement and/or a path forward that clearly addresses efficacy studies



Pharmacodynamic (PD) Measures Desired to Build Confidence and De-risk Projects

- To provide evidence that the therapeutic agent has interacted with the intended molecular target, particularly when correlated with exposure
- If the drug target/pathway is related to the disease, PD measures should predict efficacy and can serve as cost-effective surrogates for efficacy in early/exploratory clinical trials



Proposed New Initiatives

Innovation Grants to Nurture Initial Translational Efforts (IGNITE)

Grant Program	Entry Criteria	End Goal
1) Assay development and therapeutic agent identification and profiling	Rationally selected assay(s) and therapeutic agents	Testing funnel to triage candidates, a battery of assays, and starting agents that are well profiled
2) Pharmacodynamics (PD) and/or in vivo efficacy studies	Evidence of validated/characterized animal model and PD measure, testing protocol and therapeutic agents	Well-characterized early-stage agents suitable for optimization
3) Neuroscience translational tools and models	Understanding of hypothesis regarding disease phenotype or mechanism(s) of action	Translatable animal models and quantifiable markers of target engagement applicable in humans
4) Neuroscience-focused translational platform technology development	Pilot evidence for proof of principle for platform technology	Validated approaches that enable and accelerate drug discovery for neurological disorders

1) Assay Development and Therapeutic Agent Identification and Characterization to Support Therapeutic Discovery

- This FOA encourages development of in vitro and ex vivo assays suitable for iterative screening efforts to identify and characterize potential therapeutic agents for neurological disorders.
- The goal is to support novel assay(s) necessary to support discovery and characterization of CNS therapeutic agents.
- R21/R33 Innovation Award mechanism. The R21 phase will support the initial development of in vitro and ex vivo assays. The R33 phase will support iterative screening efforts of potential CNS therapeutic agents; efforts to characterize promising therapeutic agents from the screen, and efforts to design, prepare, and further characterize additional agents.
- The total project period for a combined R21/R33 application may not exceed three years (direct costs are limited to \$250,000 per year), with no more than one year for the R21 phase and no more than two years for the R33 phase.

2) Pharmacodynamics and/or In vivo Efficacy Studies

- This FOA provides funding to prepare for and conduct pharmacodynamics and/or in vivo efficacy studies to demonstrate that a proposed therapeutic agent may have clinical utility to justify further development for a neurological disorder.
- The goal is to adapt state-of-the-art pharmacological, pharmacokinetic and biological measures to determine the feasibility of selected therapeutic agents to serve as a starting points for therapy development.
- R21/R33 Innovation Award mechanism. The R21 phase will support preparation and implementation of pharmacodynamics and/or in vivo efficacy animal studies. The R33 phase will support execution of the pharmacodynamics and/or in vivo animal studies.
- The total project period for a combined R21/R33 application may not exceed three years (direct costs are limited to \$250,000 per year), with no more than one year for the R21 phase and no more than two years for the R33 phase.

3) Neuroscience Translational Tools and Models

- This FOA encourages identification and development of:
 1. Novel animal models of neurological disease with clear phenotypic and/or genotypic similarities to the targeted human disorder and
 2. Validated measures of a therapeutic test agent's engagement with the intended molecular or cellular target (pharmacodynamics)
- The goal is to promote the development and preliminary validation of translational animal models and pharmacodynamics measurements that will facilitate the evaluation of new therapeutic agents.
- Research Project Grant Program (R01), awarded for 3 years, direct costs are limited to \$500,000 for three years.

4) Neuroscience-Focused Translational Platform Technology Development

- This FOA encourages neuroscience focused platform technology development to enable and accelerate drug discovery for therapeutics to treat neurological disorders.
- The goal is to promote the development and optimization of transformative technologies that will significantly improve any phase of drug discovery and development.
- Research Project Grant Program (R01), awarded for 3 years, direct costs are limited to \$500,000 for three years.

Key Advantages of the IGNITE Suite of Programs

The proposed suite of funding mechanisms:

- Will provide the early drug discovery data package required for entry into our late-stage drug discovery/development programs and/or external translational funding and partnering opportunities
- Is clearly differentiated and delineated from the parent R21 and R01 mechanisms
- Is specific and focused to allow investigators to pursue therapeutic discovery while providing enough time to deliver high-quality results
- Takes advantage of the R21/R33 mechanism:
 - ✓ Go/No-Go milestones defined by the applicant in their application
 - ✓ The proposed milestones are evaluated in the review criteria
 - ✓ Progress on milestones are assessed by program as part of the 2nd year progress report to determine whether the award will proceed to the R33 phase (administrative review)

Proposed Program to Support Research Activities and Lead Directly to Cooperative Programs



IGNITE (Assay Development)

IGNITE (PD & Efficacy)

IGNITE (Animal Model Dev.)

CREATE Bio for Biotechnology Products and Biologics

Blueprint Neurotherapeutics (BPN 2.0) for Small Molecules

IGNITE (Platform Technology)

Timelines to Publish IGNITE Announcements 1 & 2

Activity	2014												2015	
	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb
Conduct review	■	■	■	■	■									
Concept review with PDs					■									
Present Recommendation to NINDS ESC						6/16								
Draft FOA(s)							■	■						
Present at Council										9/11				
Present FOA(s) to ESC										9/29				
Notice of announcement										10/1				
Present at CSI										10/14				
Submit FOA to ENS											11/2			
Guide Corrections											11/16			
Publish announcement												12/16		
First receipt date														2/16

Announcements 3 & 4 will be published later in 2015