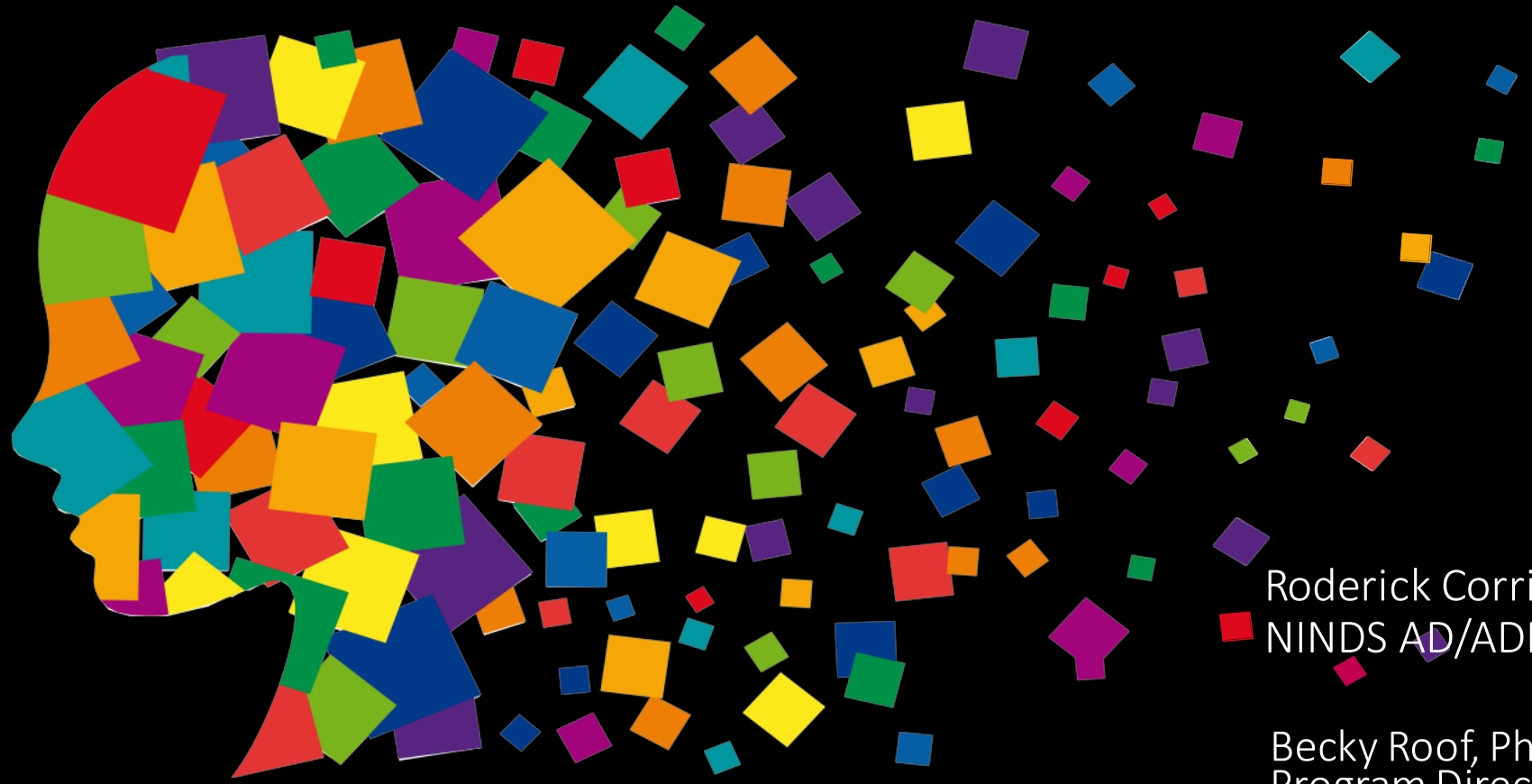
NINDS AD/ADRD Programs Overview and Current Funding Opportunities that Focus on Drug Development



Roderick Corriveau, PhD
NINDS AD/ADRD Program Lead

Becky Roof, PhD
Program Director within Division of Translational Research, NINDS

September 14, 2022

Addressing AD/ADRD is a National Priority

- Irreversible, progressive brain diseases that affect more than 5.8 million people in U.S.
- Slowly destroy brain function leading to cognitive decline, behavioral and psychiatric disorders, declines in activities of daily living and self-care
- Major public health issue affecting health and finances individuals, families, and the overall population

The NAPA law (2011) offers a historic opportunity to address AD/ADRD

Goal 1 of the National Plan is to Prevent or Treat AD/ADRD by 2025

Patient and Caregiver *Voices of AD/ADRD*

https://youtu.be/FQEsQIBBPC8

Created By: NINDS ONCE Office

National Plan to Address AD Definition of ADRD

ADRD:

Types of dementias sharing cognitive & pathological features with Alzheimer's Disease and/or commonly co-occur with typical Alzheimer's Disease pathology

Vascular Contributions (VCID)

- Vascular contributions to cognitive impairment and dementia (VCID)
- Frequently a part of typical clinical Alzheimer's disease
- Diverse spectrum of disorders **caused by cerebrovascular & cardiovascular disease**
- **Reducing vascular risk factors** may decrease dementia risk

Lewy Body Dementia (LBD)

- Lewy bodies, **pathological hallmark of Parkinson's disease**, are also present in brains of people with Lewy Body Dementia (LBD, PDD)
- Dementia occurs with problems with **movement**, **sleep**, **mood**, & **hallucinations**

Fronto-temporal Degeneration (FTD)

- Onset often occurs **in a person's 50s or 60s**
- Progressive decline in **social behavior and/or language** (memory can be spared)
- Can be associated with **amyotrophic lateral sclerosis (ALS)**

Mixed Dementias (MED)

- Majority of all dementia cases (age 65+) are **mixed or multiple etiology dementias**, mainly Alzheimer's pathology (beta-amyloid plaques and tau tangles) with cerebrovascular disease and/or Lewy bodies

Paradigm Shift: Multiple Potential Pathways to Dementia

LIFESTYLE FACTORS
- Physical Activity
- Diet
- Drug/Alcohol Abuse

ENVIRONMENTAL FACTORS
- Education
- Head Trauma
- Toxins/Other

PSYCHOSOCIAL FACTORS
- Depression/Anxiety

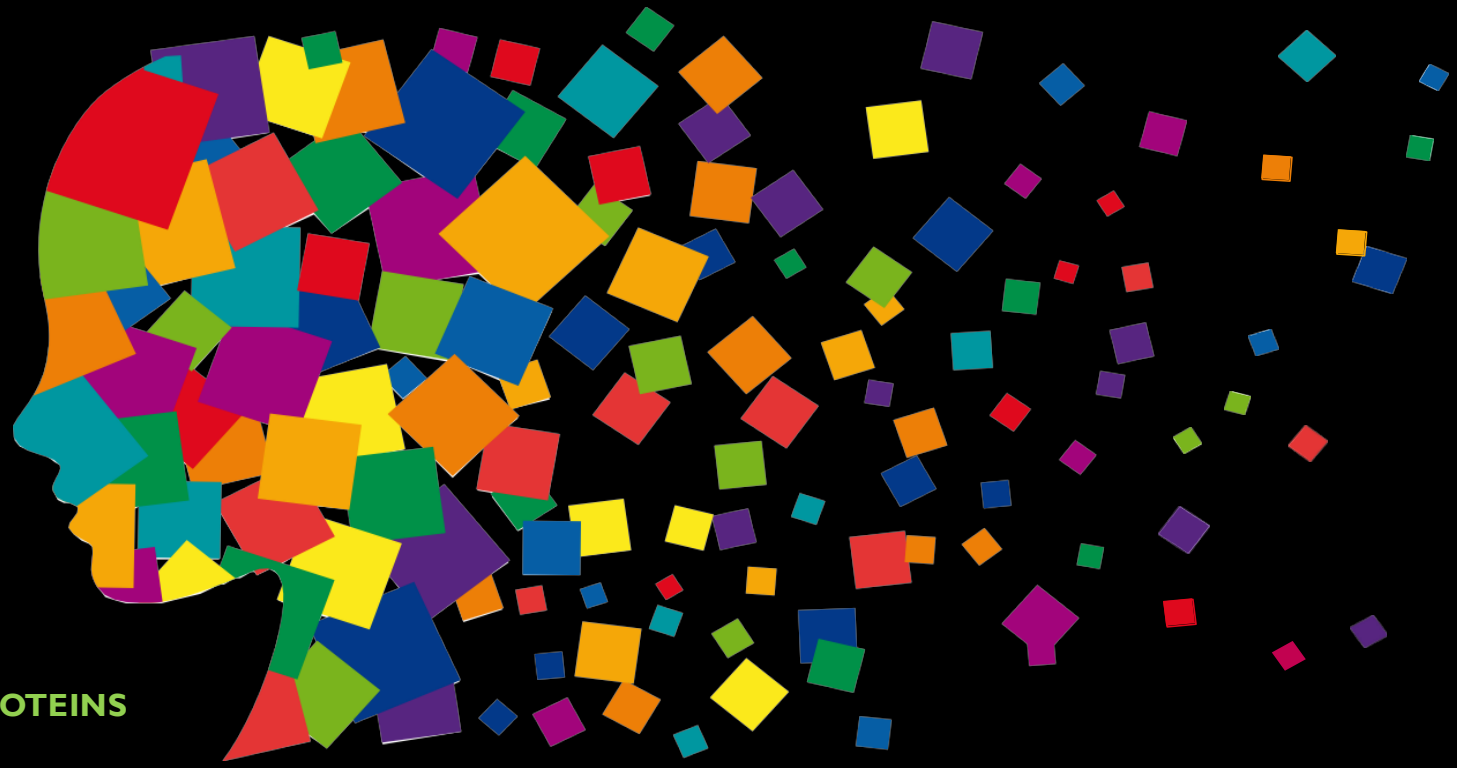
OTHER MEDICAL RISKS
- Metabolic / Obesity / Diabetes
- Hypertension / Heart Disease / Stroke
- Inflammation
- Certain Infectious Diseases
- Certain Medications

HEALTH DISPARITIES FACTORS

AGING

GENETIC FACTORS

SEX F>M



***MISFOLDED PROTEINS**
- Amyloid
- Tau
- Alpha Synuclein
- TDP-43

***VASCULAR DISORDERS**
- Injury, Infarct (Stroke)
- White Matter Disease
- Other Vessel Disease

***OTHER DISORDERS**

COGNITIVE IMPAIRMENT and DEMENTIA DIAGNOSES

Alzheimer's Dementia
Lewy Body Dementias
Vascular Dementias
Frontotemporal Dementias
Limbic Predominant TDP
Mixed Dementias
Other Cognitive Impairment
Other Dementias

NIH National Institute of Neurological Disorders and Stroke

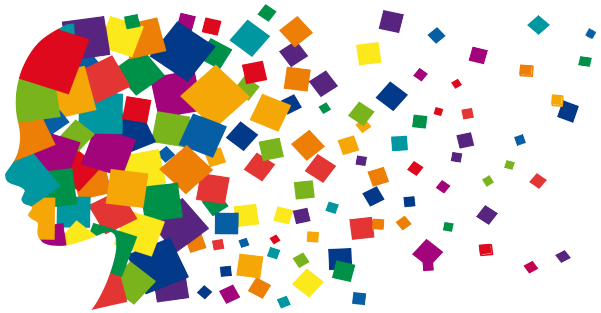
NIH ADRD Summits Shape ADRD Research Priorities

2011 NAPA Law, Goal 1: Prevent and Effectively Treat AD/ADRD by 2025

Triennial AD, ADRD & Care Summits → **Research Recommendations** → **Milestones** → **Scientific Advances Toward Goal 1**

ADRD Summits: 2013, 2016, 2019, 2022

- ❑ **NIA leads NIH response to the National Plan* to Address AD/ADRD**
- ❑ **NINDS leads, across the NIH, LBD, FTD, VCID & ADRD Summits**
- ❑ **NINDS and NIA collaborate closely**
  - ➢ Funding opportunities
  - ➢ Supplement program to expand the field
  - ➢ Paylines
  - ➢ Triennial Summits



NIH National Institute on Aging

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*https://aspe.hhs.gov/reports/national-plan-2021-update

NINDS ADRD Funding Initiatives for FY2022 and FY2023

FY 2022: 14 AD/ADRD Funding Announcements
FY 2023: 14 AD/ADRD Funding Announcements

WORKFORCE

Diversity
Training
Career

RESEARCH – Multiple Potential Pathways to Dementia in Populations and Individuals

- **Social Determinants**
- **Modifiable Risk(s)**
- **Mechanisms & Pathology**
- **Microbiome**
- **Covid-19 & Dementia**
- **Translational**
- **Biomarkers & Diagnosis**
- **Clinical Trials:**
  - Exploratory - Treatments for LBD & FTD
  - Pragmatic - Decrease or Prevent VCID

Visit the NINDS *Focus on Alzheimer's Disease & Related Dementias* page for AD/ADRD Funding Announcement details:

https://www.ninds.nih.gov/current-research/focus-disorders/alzheimers-related-dementias

NIH National Institute of Neurological Disorders and Stroke

NIH National Institute on Aging

NINDS AD/ADRD Current and Planned Funding Announcements:
Disease Mechanisms and Training

ANNOUNCEMENT	TITLE
NOT-AG-22-025	NOSI: Alzheimer's-Focused Administrative Supplements for NIH Grants that are Not Focused on AD; **Due Date: October 1, 2022**
PAR-22-211	Impact of the Microbiome-Gut-Brain Axis on AD/ADRD (R01); **Due Date: October 5, 2022**
PAR-22-208	Structural Biology of ADRD Proteinopathies (R01); (reissue of RFA-NS-18-015); **Due Date: October 7, 2022**
PAR-23-023	Cellular and Molecular Mechanisms of Prion-Like Aggregate Seeding, Propagation, and Neurotoxicity in AD/ADRD (R01); **Due Date: October 24, 2022**
RFA-NS-22-061	Training Award to Promote Cross-Training in the Fields of TBI as a Risk Factor for (AD/ADRD) (K18); **Due Date: November 4, 2022**
RFA-NS-22-062	Connecting Machine Readable Digital Human ADRD Neuropathological Library Platforms for Advanced Analytics (U24); **Due Date: November 4, 2022**
PAR-22-235	Blood Brain Barrier Response to Antibodies Targeting Beta-Amyloid (R01); **Due Date: November 10, 2022**
RFA-NS-23-017	Optimization of Genome Editing Therapeutics for ADRD (U01); **Due Date: November 30, 2022**
PAR-22-093	Research on Current Topics in ADRD (R01); **March 11, July 8, Nov 14, 2022-2024 due dates** (NIA leads)
NOT-NS-21-047	Administrative Supplements to Promote Diversity for NINDS AD/ADRD Awardees; **Multiple due dates, through March 2024**
PAR-22-021	NINDS Institutional AD/ADRD Research Training Program (T32); **Standard dues dates, Expiration: May 26, 2024**
PAR-22-022	NINDS AD/ADRD Advanced Postdoctoral Career Transition Award to Promote Diversity (K99/R00); **Standard dues dates, Expiration: July 13, 2024**
NOT-AG-21-051	NOSI: Sleep Disorders and Circadian Clock Disruption in AD/ADRD of Aging; **Expiration: November 13, 2024**

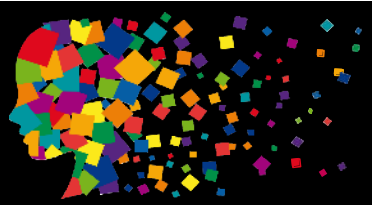
NINDS AD/ADRD Current and Planned Funding Announcements:
Clinical Trials, Clinical Research and Translation

ANNOUNCEMENT	TITLE
RFA-NS-23-001	Pragmatic Clinical Trials in Community Settings to Decrease or Prevent VCID Outcomes, Including in Populations that Experience Health Disparities (U01); **Due Date: September 15, 2022**
PAR-22-221	AD/ADRD, Adverse Childhood Experiences, and Social Determinants of Health Ancillary Studies of Existing Longitudinal Cohorts (R01); **Due Date: October 5, 2022**
RFA-NS-22-059	Early-Stage Therapy Development for ADRD (R61/R33); **Due Date: October 31, 2022**
RFA-NS-22-055	Functional Target Validation for Alzheimer's Disease-Related Dementias (ADRDs) (R61/R33)(Re-issue RFA-NS-19-015); **Due Date: November 8, 2022**
RFA-NS-22-056	Treatments for Lewy Body Dementias & Frontotemporal Degeneration - Exploratory Clinical Trial (Related to RFA-NS-21-008) (U01); **Due Date: November 21, 2022**
PAS-22-196	Advancing Research on AD/ADRD SBIR/STTR Programs(R43/R44) ***(Clinical Trial Optional);*** **Standard due dates, Expiration: September 06, 2025** (NIA leads)
PAS-22-197	Advancing Research on AD/ADRD SBIR/STTR Programs(R41/R42) ***(Clinical Trial Optional);*** **Standard due dates, Expiration: September 06, 2025** (NIA leads)
Concept Approved	Postmortem Neuropathology, Cellular, and Molecular Analyses, Including Ex-Vivo Imaging, to Assess the Significance of Human TBI and VCID AD/ADRD-Relevant Imaging and Clinical Findings During Life

14 NINDS ADRD funding initiatives are planned for FY 2023, for more information see:
https://www.ninds.nih.gov/Current-Research/Focus-Disorders/Alzheimers-Related-Dementias

No RFA is needed to apply!! NINDS special AD/ADRD payline for investigator-initiated research applications to NIH Parent R01 and NINDS R21 (PA-21-219)

NINDS AD/ADRD Program - Thank You to *NINDS and NIA Leadership and Staff*



Walter Koroshetz (NINDS)

Richard Hodes (NIA)

Roderick Corriveau (NINDS)
Kiara Bates (NINDS)
Erin Bryant (ONCE)
Roger Campbell (NINDS)
Chi Chang (NINDS)
Sara Dodson (NINDS)
Amber McCartney (NINDS)
Nia Pree (NINDS)
Arvind Shukla (NINDS)
Keith Whitaker (NINDS)

Hibah Awwad (NINDS)
Debra Babcock (NINDS)
Patrick Bellgowan (NINDS)
Karrah Benson (NINDS)
Dawn Beraud (NIA)
Francesca Bosetti (NINDS)
Bo-Shiun Chen (NINDS)
Tom Cheever (NINDS)
Jue Chen (NHLBI)
Jessica Corley (NINDS)
Will Daley (NINDS)
Damali Martin (NIA)
Cerise Elliott (NIA)
Carlos Faraco (NINDS)
Susan Fowler (NINDS)
Jordan Gladman (NINDS)
Amelie Gubitz (NINDS)
Jane Hettinger (NINDS)
Brandon Hartsell (NINDS)
Rebecca Hommer (NINDS)
Mir Ahamed Hossain (NINDS)
John Hsiao (NIA)
Sophia Jeon (NINDS)
David Jett (NINDS)
Michelle Jones-London (NINDS)
Melinda Kelly (NIA)
Jim Koenig (NINDS)
Stephen Korn (NINDS)
Lyn Jakeman (NINDS)
Tim Lavaute (NINDS)
Pascal Laeng (NINDS)
Quynh Ly (NINDS)
Ernie Lyons (NINDS)
Mack Mackiewicz (NIA)
Gary Marlowe (NINDS)
Eliezer Masliah (NIA)
Marguerite Matthews (NINDS)
Linda McGavern (NINDS)
Barbara McMakin (NINDS)
Daniel Miller (NINDS)
Marilyn Moore-Hoon (NINDS)
Ana Olariu (NINDS)
Lisa Opanashuk (NIA)
Suzana Petanceska (NIA)
Rebecca Price (NINDS)
Shanta Rajaram (NINDS)
Becky Roof (NINDS)
Toya Rogers (NINDS)
Paul Scott (NINDS)
Beth-Anne Sieber (NINDS)
Nina Silverberg (NIA)
Natalia Strunnikova (NINDS)
Christine Swanson-Fischer (NINDS)
Amir Tamiz (NINDS)
Anna Taylor (NINDS)
Carol Taylor-Burds (NINDS)
Natalie Trzcinski (NINDS)
Nsini Umoh (NINDS)
Andrea Varea (NINDS)
Margo Warren (NINDS)
Samantha White (NINDS)
Kyle Whitehead (NINDS)
Shellie Wilburn (NINDS)
Carl Wonders (NINDS)
Clinton Wright (NINDS)
Xiling Yin (NINDS)

Review Branch
Karrah Benson
Bo-Shiun Chen
Gary Marlowe
Marilyn Moore-Hoon

ADRD Summit Session Leads
FTD: Tom Cheever
Health Equity: Richard Benson
LBD: Debra Babcock
MED-Overall, -TBI, -LATE: Linda McGavern
MED-COVID-19: Keith Whitaker
VCID: Roderick Corriveau

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AD/ADRD Translational Pipeline of FOAs

Target Validation R61/R33
RFA-NS-22-055

Early Therapy Development R61/R33
RFA-NS-22-059

Blueprint Neurotherapeutics (BPN) Small Molecule OR Biologics UG3/UH3 or U44

NIH Blueprint
Neurotherapeutics Network

Functional Target Validation for ADRD

RFA-NS-22-055

Goals:

- De-risk subsequent translational research and accelerate the advancement of novel therapies for ADRD
- Increase confidence in the efficacy and safety of novel target.
- Built on target ID to address druggability and knowledge gaps:

- Functional evidences in disease-relevant *in vitro* assays & *in vivo* models?

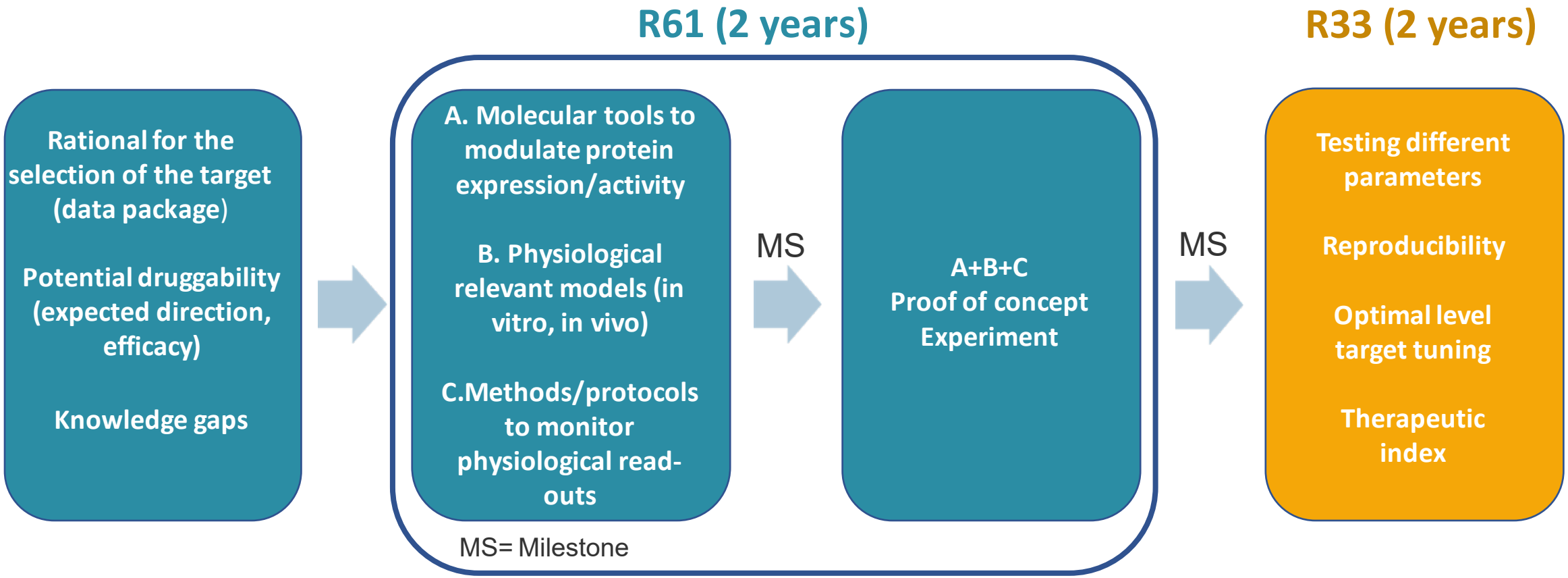
- Druggable target?
- Direction, duration, timing & efficacy of target modulation?

- Disease-relevant target isoforms?
- Difference human vs rodent?

- Incomplete knowledge about the biology
- Therapeutic index? (efficacy vs. toxicity)

Functional Target Validation for ADRD

RFA-NS-22-055



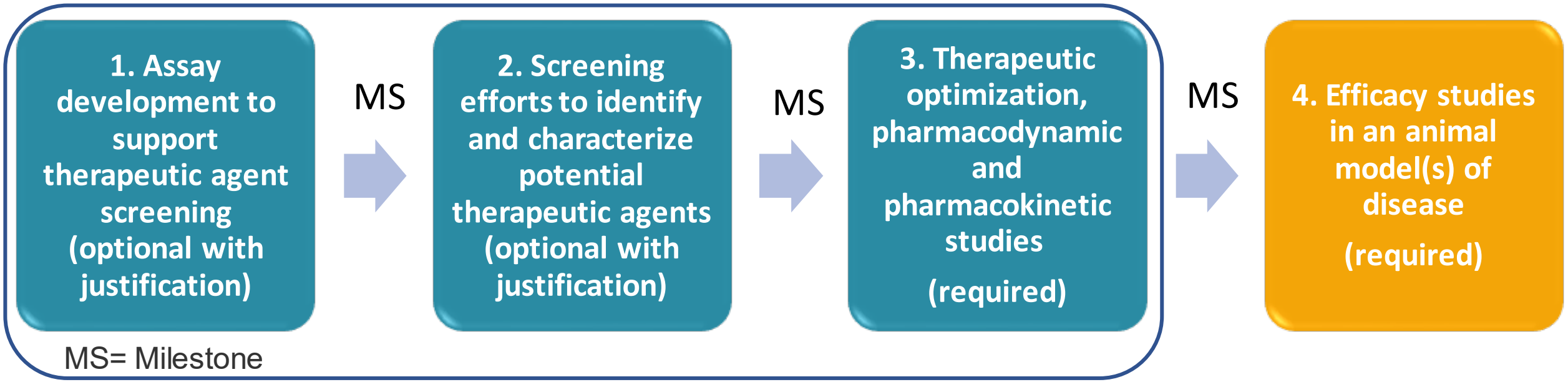
Collaborative interactions between interdisciplinary teams are a critical aspect of this FOA. Successful target validation applications will require extensive collaboration among experts in respective technical and disease areas

Functional Target Validation for ADRD

Key information	RFA-NS-22-055
Due Date (**only 1!**)	November 08, 2022
Budget	R61: No more than $600,000 DC/year R33: No more than $1,000,000 DC/year
Project period	Up to 4 years, 2 years for the R61 phase with 2 additional years for the R33 phase may be requested. Actual duration depends on achievement of milestones
Other attachments	Additional supporting data can be included in the Appendix "Supportive Data for Target Identification Selection" and must not be longer than 6 pages.
Special instructions	Milestones, rigor, proof of concept, collaboration plan between multidisciplinary teams
Point of Contact	Dr. Pascal Laeng (Pascal.Laeng@nih.gov)

Early-Stage Therapy Development for ADRD

RFA-NS-22-059



- Target should be novel but validated
- Therapeutic agent could be a small molecule or biologic. Therapeutic devices are not supported in this RFA
- Include a multidisciplinary team
- It is anticipated that successful applicants will be able to meet the entry criteria for the Blueprint Neurotherapeutics Network, Blueprint for Biologics or other similar later-stage translational programs at the end of the R61/R33 grant period.

Early-Stage Therapy Development for ADRD

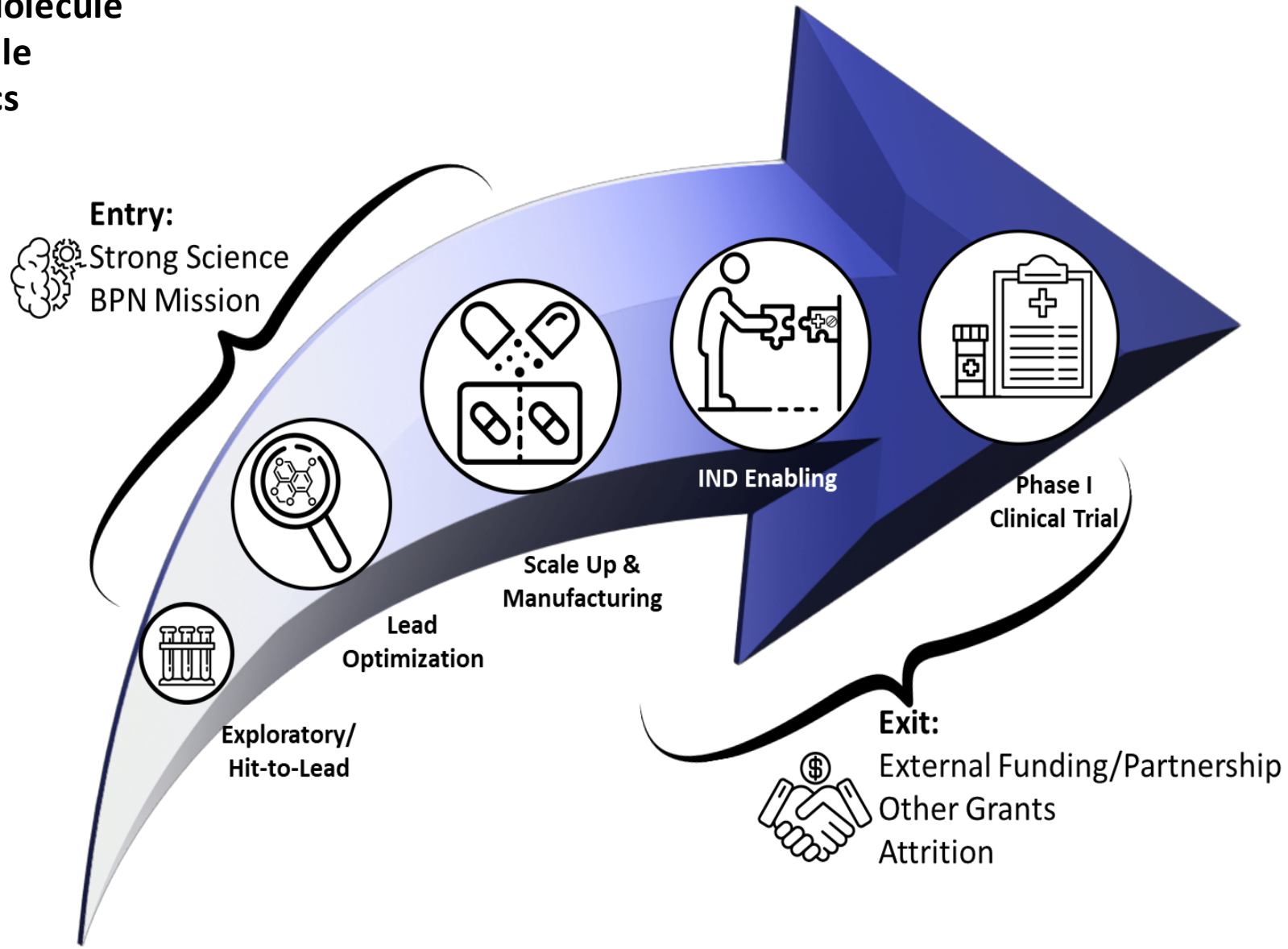
Key information	
Due Date (**only 1!**)	October 31, 2022
Budget	No more than $500,000 DC/year
Project period	Up to 5 years*, with no more than 4 years for the R61 phase and no more than 3 years for the R33 phase may be requested. **Timeline for each stage must be clear in the application.** Actual duration depends on achievement of milestones
Other attachments	Intellectual Property (IP) strategy should be included
Special instructions	Milestones, rigor, therapy development plan, multidisciplinary diverse teams
Point of Contact	Becky Roof (Rebecca.Roof@nih.gov)

*Applications proposing less than 4 stages of work are expected to request less time.

Blueprint Neurotherapeutics Program

NIH Blueprint Neurotherapeutics Network

PAR-20-122 (UG3/UH3) Small Molecule
PAR-20-111 (U44) Small Molecule
PAR-21-163 (UG3/UH3) Biologics
PAR-21-233 (U44) Biologics

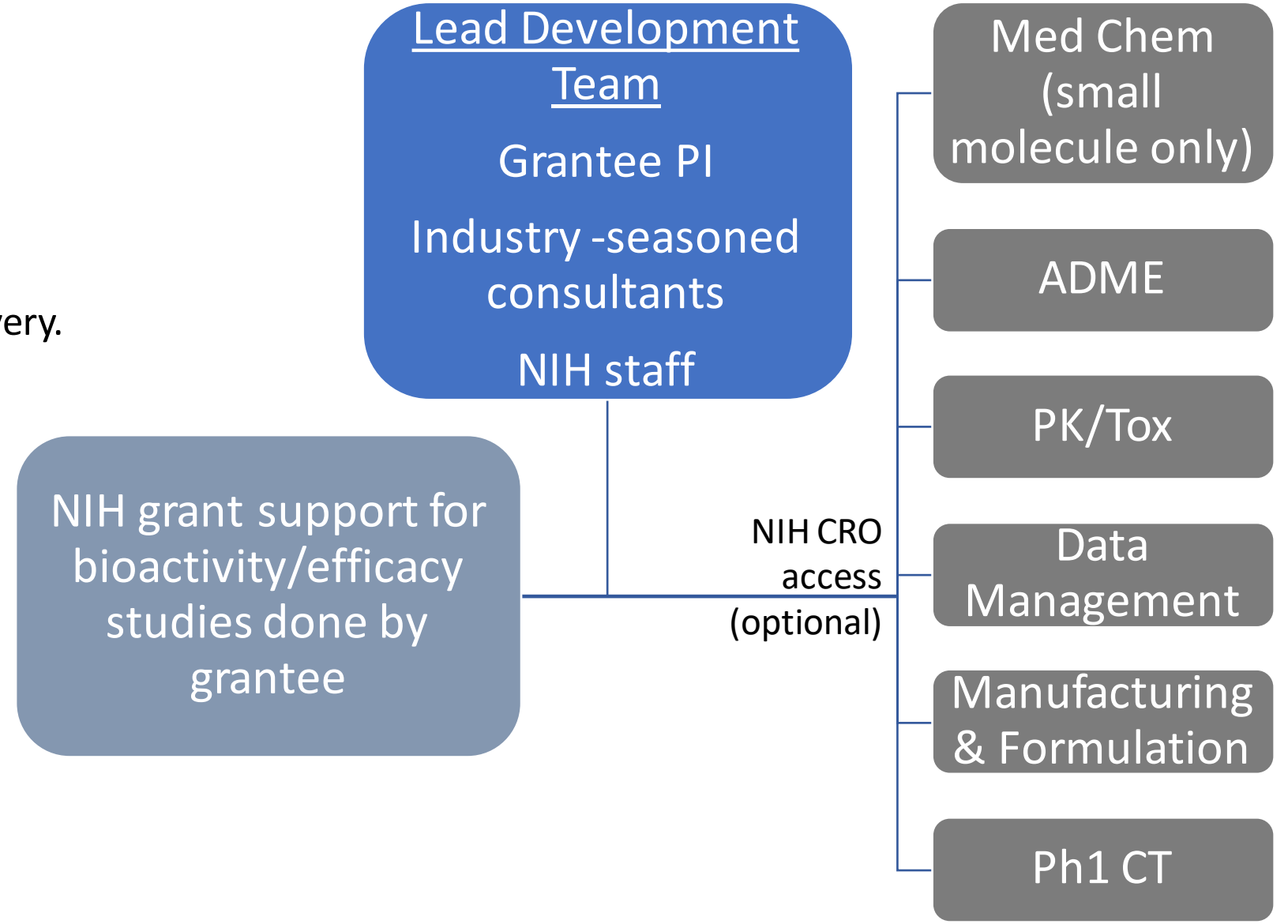


Blueprint Neurotherapeutics Program

NIH Blueprint Neurotherapeutics Network

Program Goals

- To provide funding and necessary resources (CRO access and drug discovery expertise) for drug discovery.
- To maintain the IP of the grantee
- To de-risk potential therapeutics to the point that industry invests and advances the new drugs towards patients efficiently.



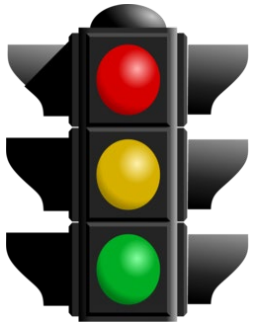
Blueprint Neurotherapeutics Program

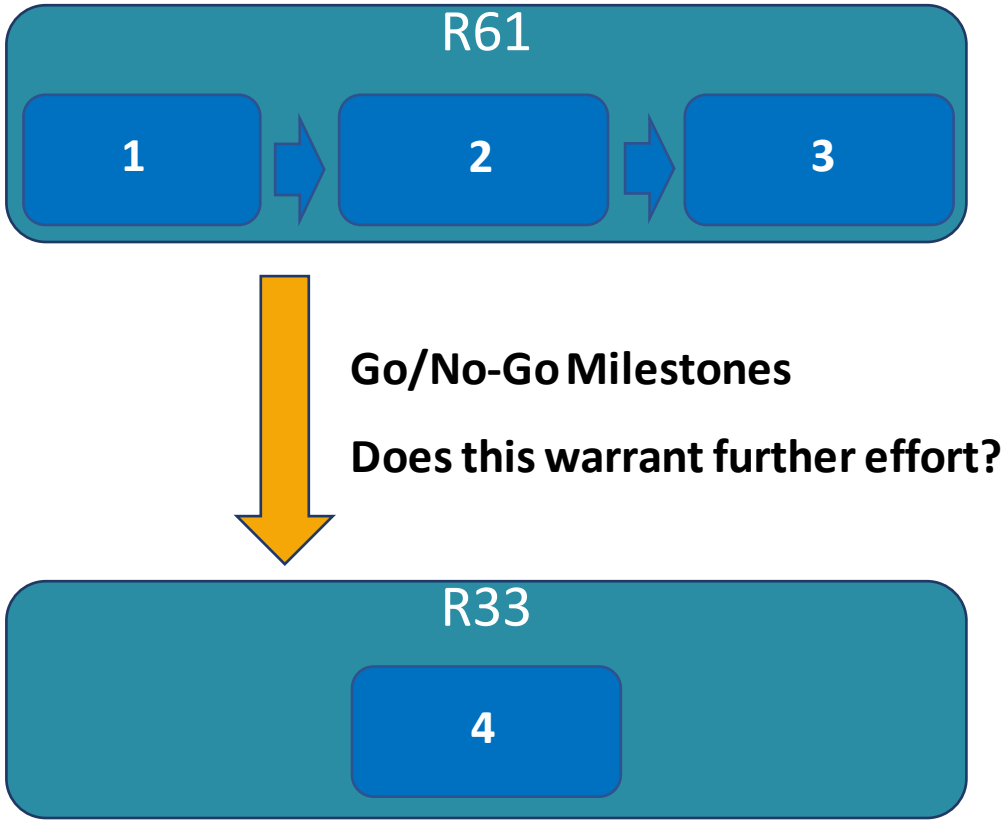
NIH Blueprint Neurotherapeutics Network

Key information	Small Molecule PAR-20-122 (UG3/UH3)*	Biologics PAR-21-163 (UG3/UH3)*
Next due dates	August 9, 2022, February 9, 2023	Same as small molecule
Budget	not limited but need to reflect the actual needs of the proposed project ($500K or more DC require 6-weeks prior approval)	Same as small molecule
Project period	Up to 1 year UG3; up to 4 years UH3 may be requested. Actual duration depends on achievement of milestones	Same as small molecule except UG3 can be 2 years (still 5 years total)
Other attachments	Intellectual Property (IP) strategy **must** be included	Same as small molecule
Special instructions	Applications can come in at discovery or development phase. Please be clear which NIH resources you are utilizing	Same as small molecule
Point of Contact	Chuck Cywin (Charles.Cywin@nih.gov)	Mario Skiadopoulos (Mario.Skiadopoulos@nih.gov)

* SBIR U44 FOAs also available- please see PAR-20-111 and PAR-21-233 for details

Translational FOAs- Milestones and Mechanism



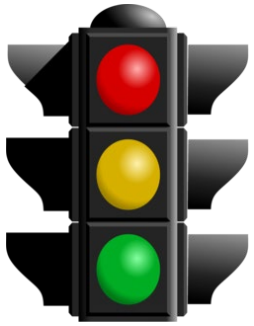


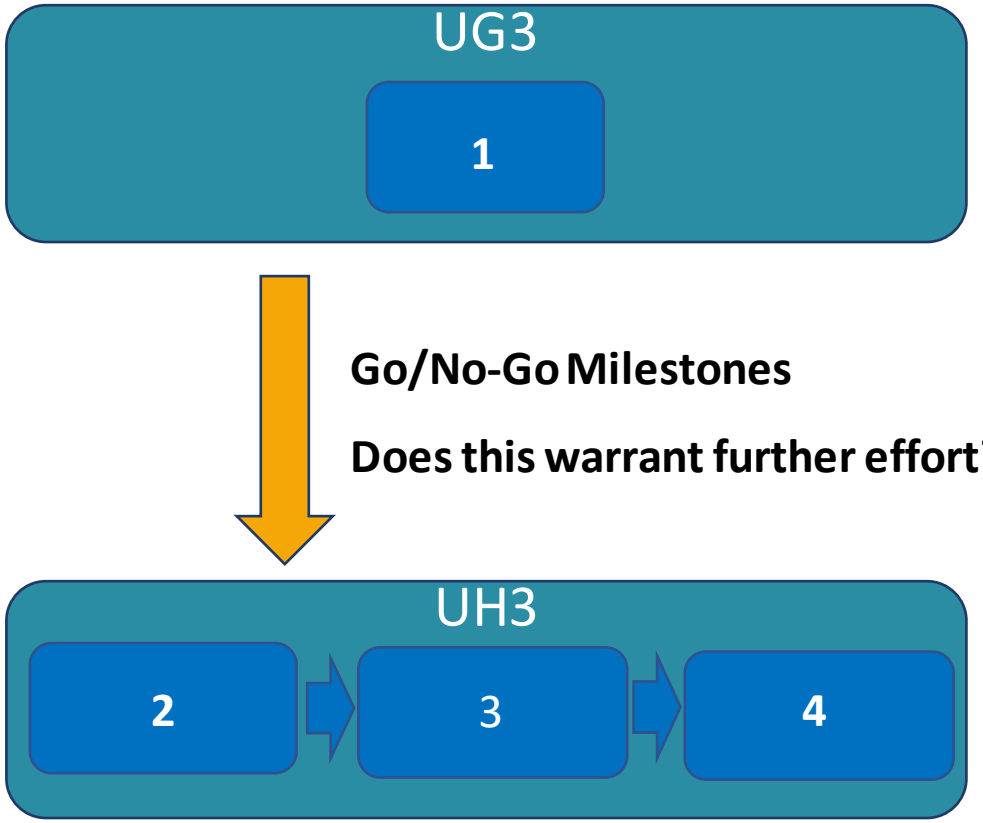
Benefit of this mechanism: Milestones allow for dependent aims!

Extremely clear, quantitative and strong milestones are *Essential*

Milestone transitions via administrative review (faster than peer review)

Translational FOAs- Milestones and Mechanism





Benefit of this mechanism: Milestones allow for dependent aims!

Extremely clear, quantitative and strong milestones are *Essential*

Milestone transitions via administrative review (faster than peer review)

Translational FOAs- Words of Advice

- Contact a Program Officer before applying
- Have a multidisciplinary team; note the multidisciplinary, translationally-focused review
- Milestones need to be clear and quantitative. They also need to be strong and well-supported
- Include a rigorous study design and supporting data (see NOT-NS-11-023)
- Strive to increase the diversity of your team (see NOT-OD-20-031)
- Discuss intellectual property (letters of support for target validation FOA; other attachment for Early Therapy and BPN)
- Clearly demarcate R61 v R33 or UG3 v UH3 activities (also different stages in RFA-NS-22-059) and timeline. For BPN, be clear on which NIH contracts you are using
- Pay attention to non-responsive activities

Questions and Answers

Rod Corriveau: Roderick.Corriveau@nih.gov

Becky Roof: Rebecca.Roof@nih.gov

Pascal Laeng: Pascal.Laeng@nih.gov