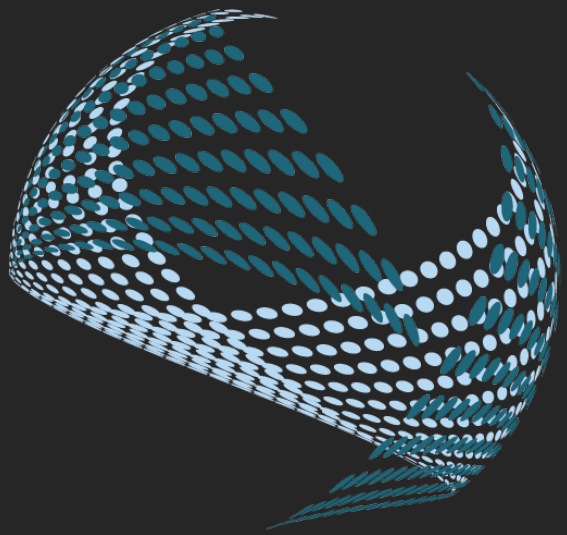


HANDS

Hydrocephalus Association Network for Discovery Science

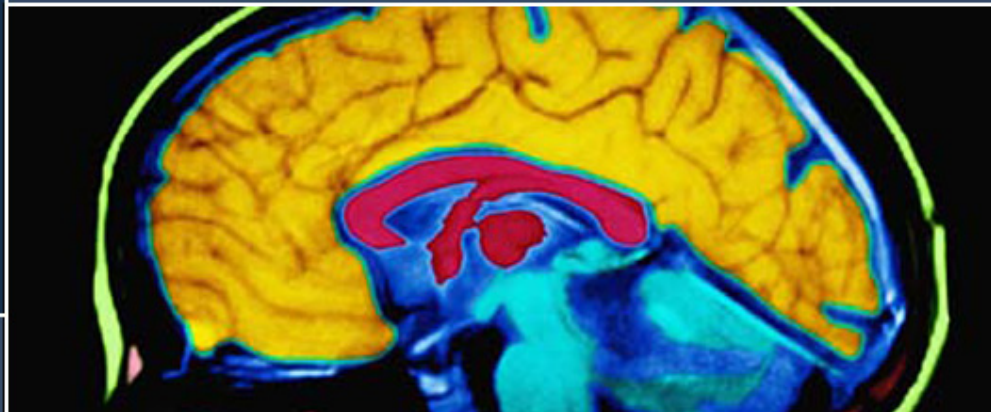
Collaboration • Innovation • Impact

National Institute of Neurological Disorders and Stroke

NINDS Funding Opportunities

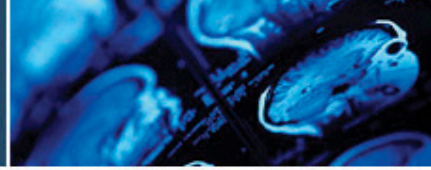
October 20, 2020

Jill Morris PhD
Program Director
Division of Neuroscience
jill.morris@nih.gov



National Institute of Neurological Disorders and Stroke

Noise Disclosure



AGENDA

- Role of a NINDS Program Director
- NINDS Funded Hydrocephalus Research
- NINDS Funding Opportunities
- Application Guidance

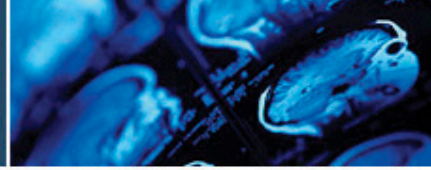
National Institute of Neurological Disorders and Stroke

NINDS' MISSION

- The mission of NINDS is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease.
- **NINDS News:** https://www.ninds.nih.gov/News-Events/News-and-Press-Releases

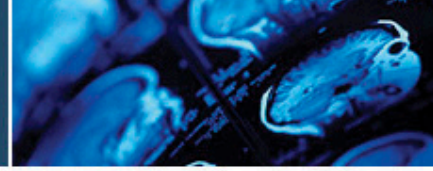
Walter J. Koroshetz, M.D.

The Role of a Program Director



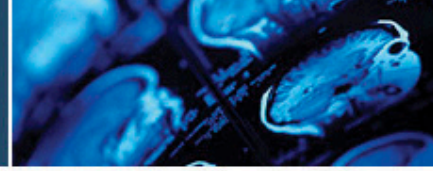
- **Act as a steward for a scientific area**
  - Interact with investigators and facilitate funding
- **** Interact with advocacy**
  - Information sharing including website information about the disease, new funding opportunities, awarded grants, etc.
  - Patient perspectives
  - Coordinating conference/workshop planning, strategic planning
  - Coordinated funding (formal co-funding, or patient organization picking up unfunded applications)
- Identify gaps in portfolio with insights from both advocacy and investigators
  - Hold workshops
  - Develop initiatives (across divisions)

The Role of a Program Director (cont'd)



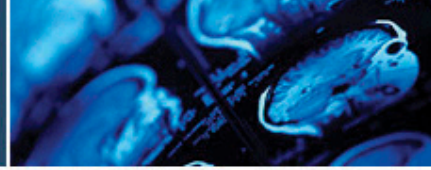
- **Oversee grant portfolios**
  - Responsible for trainee grants to clinical trials
  - Progress Reports
  - Administrative and Diversity Supplement Funding
  - Press Releases with Office of Communications and Public Liaison (OCPL)
  - Cooperative agreements (U grants)
    - Regularly scheduled calls
    - Milestones
    - Contracts

The Role of a Program Director (cont'd)



- **Respond to Congressional language and attend Congressional briefings with the Office of Science Policy and Planning (OSPP)**
  - Lobbying is prohibited
- **Participate in Trans-NINDS Activities**
  - e.g., Data Analysis Working Group, Diversity Working Group
- **Interact across the NIH**
  - Shared mission (e.g. NICHD, NIBIB)
    - For CDMRP, Member of Integration Panel and External Advisory Board
    - Blueprint Activities
  - Common Fund Activities – Metabolomics

Note: I play no role in review of applications.



AGENDA

- Role of a NINDS Program Director
- **NINDS Funded Hydrocephalus Research**
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Endoscopic versus Shunt Treatment of Hydrocephalus in Infants (U01 NS107486)

- PIs: John Kestle and the HCRN
- A multi-center randomized controlled trial (RCT) comparing ETV+CPC and shunt in infants with hydrocephalus in North America
- Primary outcome is the Bayley Scales of Infant and Toddler Development-third edition (BSID-3) Cognitive Scale at 12 months, with additional cognitive and Quality of Life measures to 5 years.

Hydrocephalus Research Funding

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-020-1090-2

Check for updates

Exome sequencing implicates genetic disruption of prenatal neuro-gliogenesis in sporadic congenital hydrocephalus

- PI: Kristopher Kahle, Yale School of Medicine
- R01 NS109358 and R01 NS111029
- “Modulation of choroid plexus immuno-secretory function to restore cerebrospinal fluid homeostasis in hydrocephalus”
- “Human genetics and molecular mechanisms of congenital hydrocephalus”

FY2020 New Award

Diffuse Optics for Pediatric Hydrocephalus Management

- R01 NS113945-01
- PI: Wesley Baker, Children's Hospital of Philadelphia
- ESI Award
- Validate the capabilities of a novel diffuse optical approach for non-invasive detection and prediction of elevated ICP and ischemia in children.

FY2020 New Award

Novel Ultrasound Indices of Intracranial Pressure and Brain Ischemia in Neonatal Hydrocephalus

- R01 NS119473-01
- PI: Misun Hwang, Children's Hospital of Philadelphia
- ESI Award
- Novel imaging approach using contrast-enhanced ultrasound to assess intracranial pressure and brain ischemia in the infant porcine model of hydrocephalus

FY2020 New Award

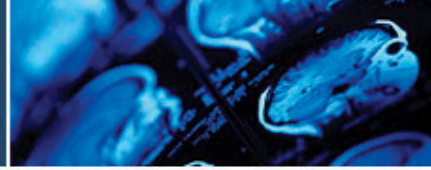
The Role of Complement in Cerebrospinal Fluid Shunt Infections

- K08 NS110923-01
- PI: Gwenn Skar, University of Nebraska Medical Center
- The role of complement in neurologic damage associated with cerebrospinal fluid shunt infection.
- Central hypothesis is that complement components induce microglial-mediated synaptic pruning and are responsible for late-stage cerebral edema.

FY2020 New Award

Xenopus as a Model System for Hydrocephaly and Ependymal Ciliogenesis

- R21 NS116484-01
- PI: Engin Deniz, Yale School of Medicine
- Seeks to further develop their Xenopus hydrocephalus model to evaluate congenital hydrocephalus candidate genes and distinguish ciliary vs. non-ciliary pathogenesis mechanisms.



AGENDA

- Role of a NINDS Program Director
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- **NINDS Funding Opportunities**
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NIH Funding Mechanisms

Basic Science and Early Translation Mechanisms

- Investigator Initiated Awards
- NINDS Program Project Awards
- Exploratory/Developmental Awards
- Training Awards

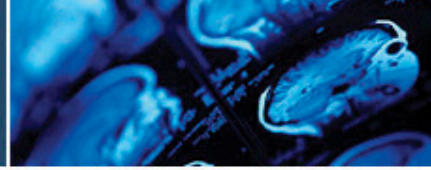
Translational Research Mechanisms

- NINDS Translational Program Awards
- Small Business Awards

Clinical Research Mechanisms

- NINDS Clinical Trial Awards

PA-18-622



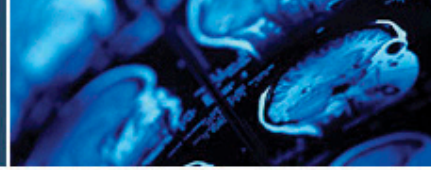
Disease Mechanisms of Prenatal and Pediatric Hydrocephalus (R01)

- Support hypothesis-driven research of prenatal and pediatric hydrocephalus.
- Developmental etiology (intrinsic factors including genetics) and acquired etiology (extrinsic factors including hemorrhage and infection) of prenatal and/or pediatric hydrocephalus.
- Focus on understanding the molecular, cellular and developmental mechanisms involved in the pathogenesis of prenatal and/or pediatric hydrocephalus.

Clinical trials – not allowed.
Standard due dates apply.

National Institute of Neurological Disorders and Stroke

PA-18-623



Tools to Enhance the Study of Prenatal and Pediatric Hydrocephalus (R21)

- Develop or substantially modify existing cutting-edge tools that will advance prenatal and/or pediatric hydrocephalus research.
- Objective: Remove barriers to hydrocephalus research that are due to scarcity of tools to investigate both the disease mechanisms and alternative therapies (non-shunt) in a rigorous manner.
- Should transform the field by generating tools including animal and cell models, novel methods and innovative technologies that will be widely used throughout the neuroscience community to understand disease mechanisms and/or developing therapeutics.

Clinical trials – not allowed.
Standard due dates apply.

NINDS Translational Programs

Early Discovery

R01 & R21

Late-Stage Translation

BPN 2.0 & CREATE

Clinical Trials

Validate assays

Fill gaps

Finalize protocols

Create plan

Scale

Develop tools

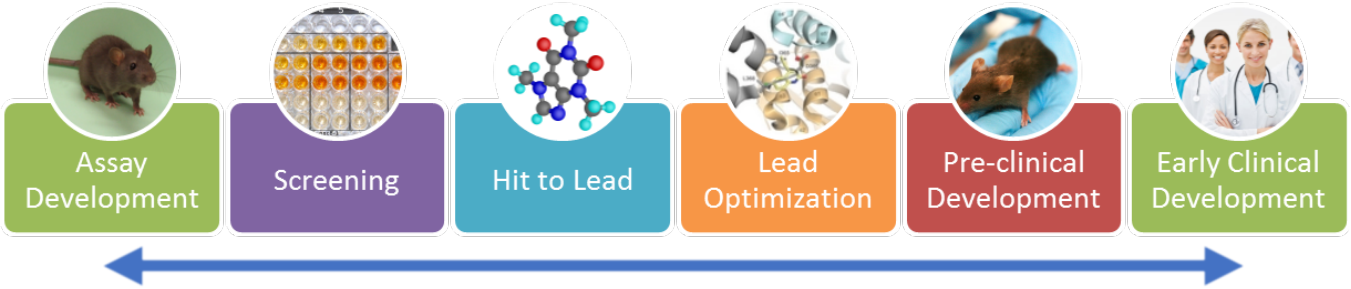
Team up with experts

Apply RIGOR

Confirm findings

Translation at NINDS: Bridging the Gap between Basic and Clinical Research

The mission of the NINDS Division of Translational Research (DTR) is to accelerate basic research findings towards patient use for neurological disorders and stroke by providing funding, expertise, and resources to the research community.



Supported: small molecule, biologic or device therapeutics; biomarkers; training

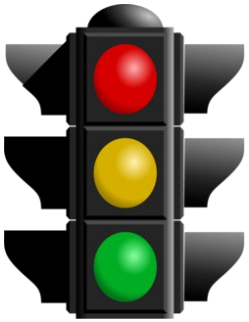
Provided: grants, access to contracts, access to consultants, training

How is Translational Science Different from Basic Science?

Basic Science	Translational Research
Hypothesis driven	Goal driven
Explore; go where the science takes you	Focus on a critical path
Need to plan for the next 3-5 years (grant to grant)	Need to plan for the next 10+ years (bench to bedside)
Expertise needed: disease, system, methods….	Expertise needed: disease, system, method, med chem, PK, toxicology, stats, regulatory, clinical, ...
Rigor and reproducibility are important	Rigor and reproducibility are **extremely** important

Milestoned Mechanisms Allow for Dependent Aims, Riskier Proposals

Phase 1: Demonstrate Feasibility and Prepare for Phase 2



Go/No-Go Milestones

Does this warrant further effort?

Phase 2: The Main Event

Examples: UG3/UH3, R61/R33, SBIR Fast Track

Extremely Clear, Quantitative and Definitive Milestones are *Essential*.

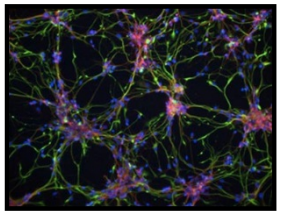
Transition to Phase 2 via Administrative Review

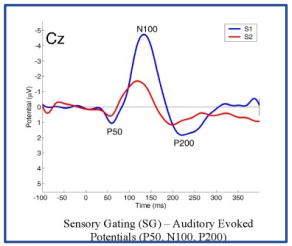
IGNITE:
A Suite of Early Translational Funding Opportunities

PAR-18-761: Neurotherapeutic Agent Characterization and In vivo Efficacy Studies

PAR-18-762: Assay Development and Therapeutic Agent Identification

PAR-18-763: Development and Validation of Model Systems and/or Pharmacodynamic Markers to Facilitate Neurotherapeutic Discovery





Budget: ≤$499,000/Year; ≤$750,000 for Project

Upcoming Application Due Dates: Oct 20, 2020; Feb 17, 2021

See NOT-OD-15-039 and NOT-OD-20-082 for info on late submissions

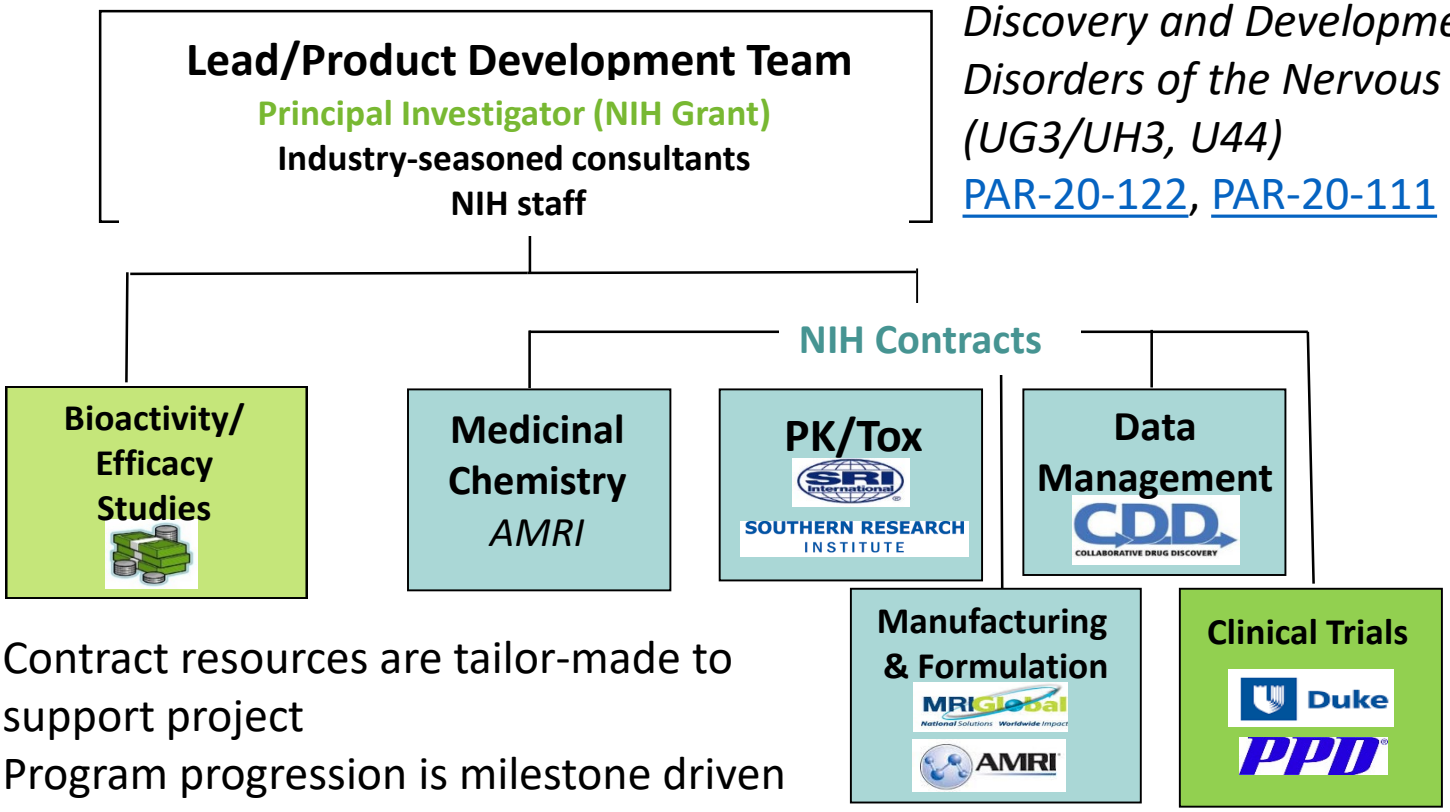
NIH National Institute of Neurological Disorders and Stroke

IGNITE

Therapeutic Development: NIH Blueprint Neurotherapeutics Network for Small Molecules

NIH Blueprint Neurotherapeutics Network

Grant Support: Small Molecule Drug Discovery and Development of Disorders of the Nervous System (UG3/UH3, U44)
PAR-20-122, PAR-20-111

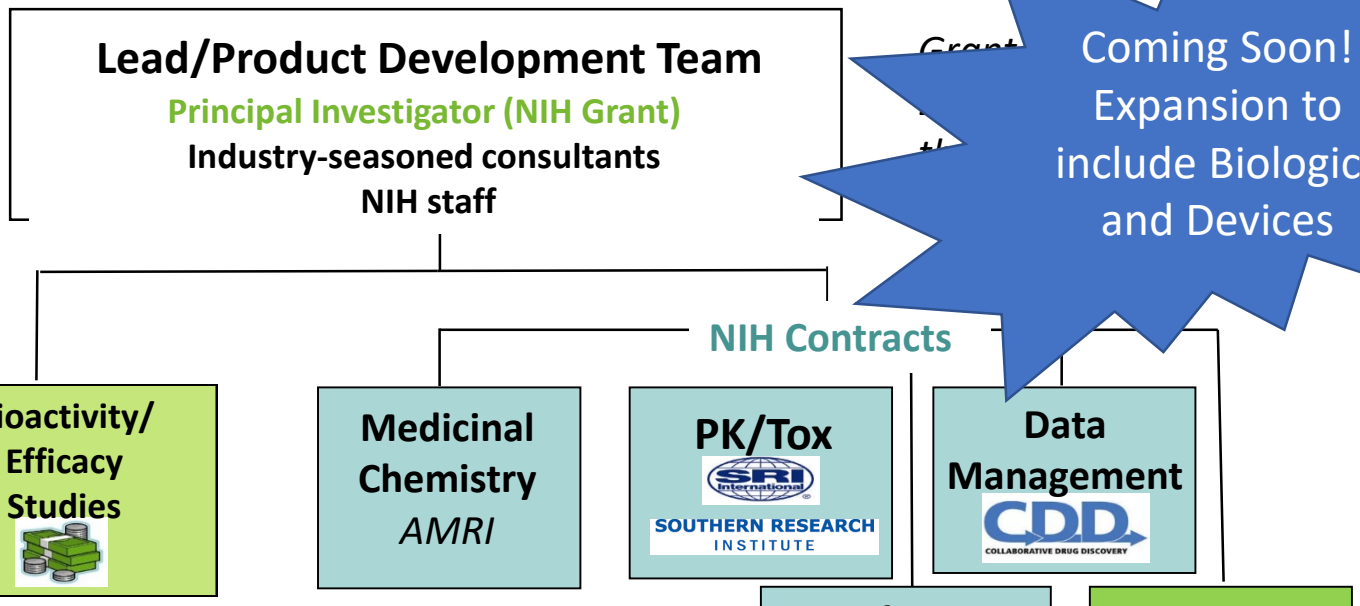


- Contract resources are tailor-made to support project
- Program progression is milestone driven
- **PI team's Intellectual Property Retained by PI's Institution**

Contact: Chuck Cywin, PhD (Charles.cywin@nih.gov)

Therapeutic Development: NIH Blueprint Neurotherapeutics Network for Small Molecules

NIH Blueprint Neurotherapeutics Network



- Contract resources are tailor-made to support project
- Program progression is milestone driven
- **PI team's Intellectual Property Retained by PI's Institution**

Contact: Chuck Cywin, PhD (Charles.cywin@nih.gov)

NINDS Therapeutic Development: CREATE Bio for Biologics

Modalities: Peptides, Proteins, Oligonucleotides, Gene and Cell Therapies

Purpose

- Optimization (U01 PAR-17-456/U44 PAR-17-457)
  Optimization of therapeutic agents
- Development (U01 PAR-18-542/U44 PAR-18-543)
  IND-enabling studies/Early phase clinical trials

End Goals

- Optimization: Characterize and select a lead candidate
- Development: Submit an IND application and/or conduct Phase I Trials

Contact: Chris Boshoff, PhD chris.boshoff@.nih.gov

NINDS Therapeutic Development: Device Program

Concept Generation → Device Development → Device Optimization → Pre-IDE Studies → First in Human / EFS → Clinical Trials

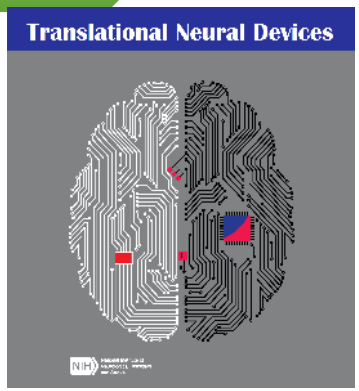
NINDS Exploratory Research
(R21) (PA-18-358)

NSF-NIH Smart and Connected Health
(NSF-18-541)

Bioengineering Research Grants
(R01) (PAR-18-206)

Bioengineering Research Partnerships
(U01) (PAR-18-208)

Translational Neural Devices
(UG3 / UH3 / U44) (RFA-NS-18-011 / RFA-NS-18-012)



Exploratory CTs
(U01 / R42 / R44)
(PAR-18-420 / PAR-15-277 / PAR-15-278)

Clinical Trial Networks:

NeuroNext (R01/U01)
(PAR-18-528 / PAR-18-268)

StrokeNET (R01/U01)
(PAR-18-561 / PAR-18-563)

Program Goal:
Support development, optimization, and translational activities and small clinical studies involving therapeutic and diagnostic devices for disorders that affect the nervous or neuromuscular systems

Contact: Nick Langhals, PhD (nick.langhals@nih.gov)

NINDS Small Business Program

- Congressionally mandated set-aside (3.65%)
- For R&D with potential for commercialization
- Broad scope:
  - Therapeutics, diagnostics, tools for research
  - Bench research, translational research, early stage clinical trials
- Multiple Funding Opportunities:
  - A majority of our applications are investigator-initiated and come in through the omnibus solicitations
  - Specific funding opportunities for late-stage translational projects and clinical trials
- Larger budgets for some topics (e.g. animal and clinical studies)

Contact: Emily Caporello, PhD (emily.caporello@nih.gov)

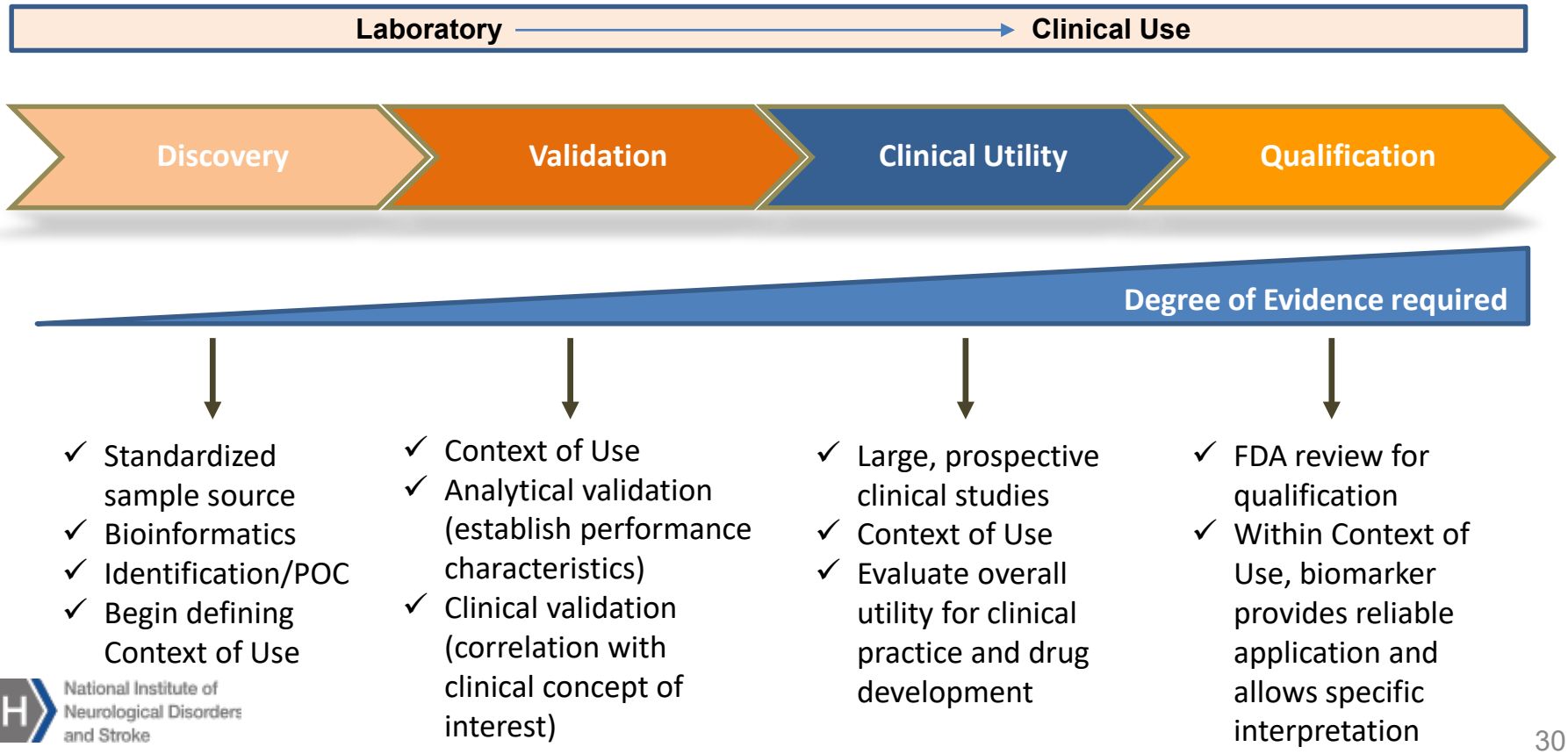
Advancing a Biomarker Candidate from Discovery Through Qualification

FDA-NIH Definitions

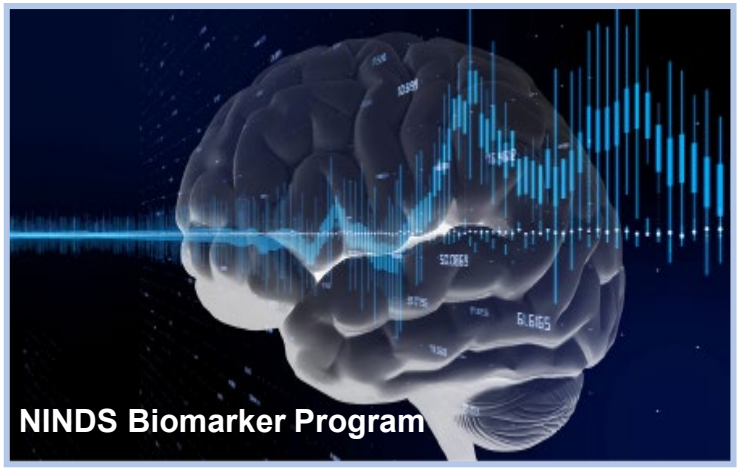
Biomarker: Indicator of a normal or pathological process or of a response to a therapeutic

Context of Use: Manner and purpose of use of a biomarker

Fit for Purpose: Refers to degree of validation (dependent upon intended use of biomarker)



Translational Drug Development Tools: NINDS Biomarker Program



Identification, Develop Detection Method
Obtain Pilot Proof of Concept

Discovery of Biomarkers and Biomarker Signatures for Neurological and Neuromuscular Disorders
PAR-19-315

Determine Precision, Sensitivity, Stability of Detection Method in Real World Setting

Analytical Validation of a Candidate Biomarker for Neurological Disease
PAR-21-056, PAR-21-057

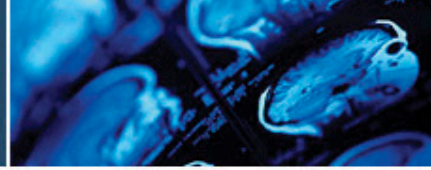
Determine Sensitivity, Specificity, Positive Predictive Value, etc of Biomarker in Real World Setting

Clinical Validation of a Candidate Biomarker for Neurological Disease
PAR-21-058, PAR-21-059

Contact: Mary Ann Pelleymounter, PhD (mary.pelleymounter@nih.gov)

Research Supplements to Promote Diversity (PA-18-906): Feeder Program and Bridge to Transition

- Administrative supplements to existing NIH research grants (R,P,U, etc.) - high school to faculty level
- Supplements provide salary and fringe benefits; funds for supplies and travel
- Sets up mentoring relationships with individual development plans
- Typically 2-3 years of funding to provide "bridge funds" while the supplementee gains the research experience, preliminary data, and other requirements to develop an application for more traditional NIH funding.
- Feeder program for our Diversity F31s and K01s
- Specific funds for grants funded by BRAIN Initiative, ADRD and SBIR/STTR FOAs



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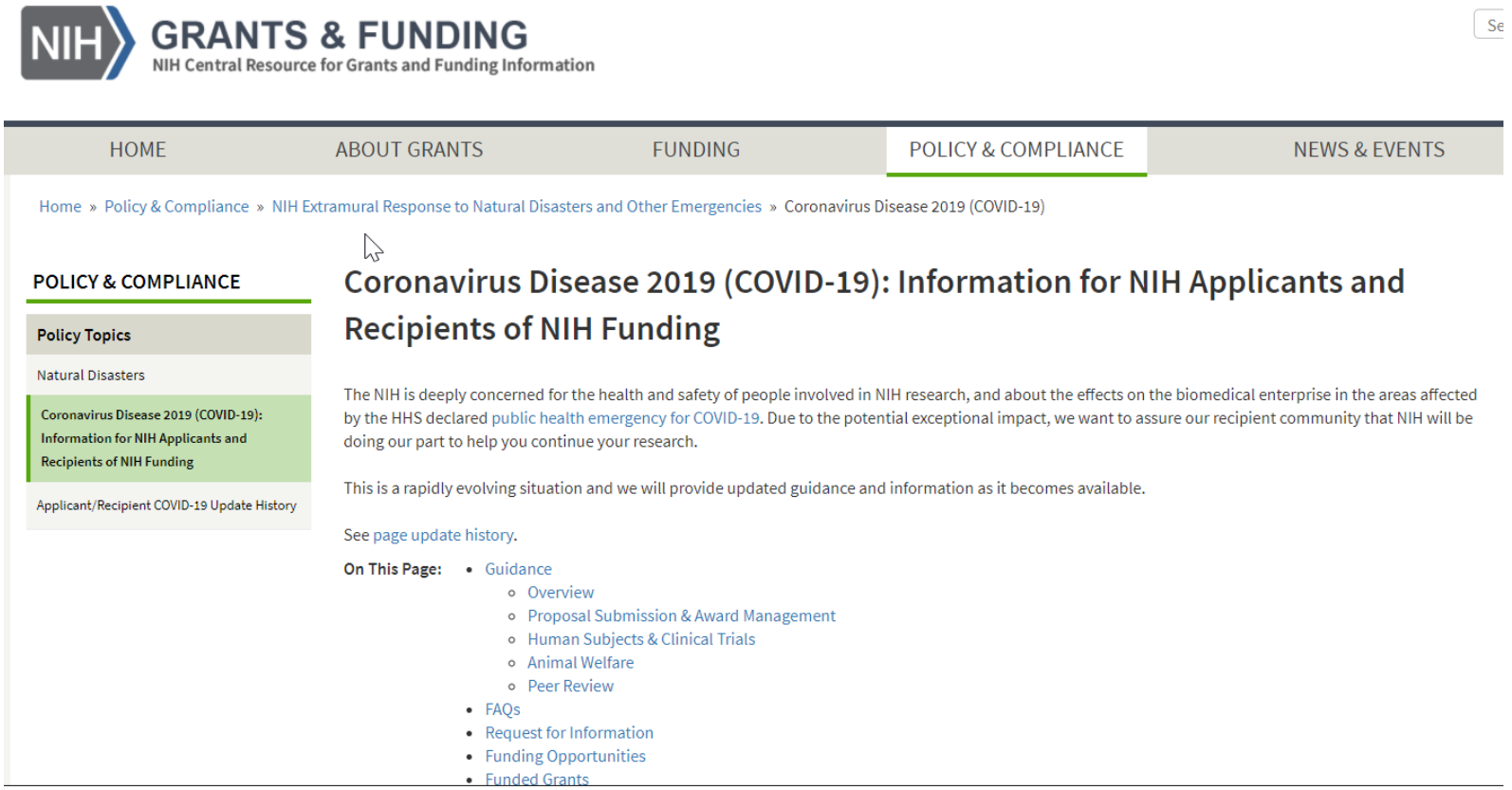
National Institute of Neurological Disorders and Stroke

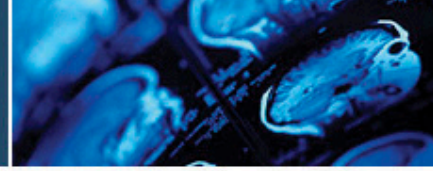
COVID-19 Guidance

- NIH Guidance to NIH Applicants and Recipients of NIH Funding regarding COVID-19: https://grants.nih.gov/policy/natural-disasters/corona-virus.htm



National Institute of Neurological Disorders and Stroke

RIGOR and REPRODUCIBILITY



https://www.nih.gov/research-training/rigor-reproducibility/updated-application-instructions-enhance-rigor-reproducibility

National Institutes of Health
Turning Discovery Into Health

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COVID-19 is an emerging, rapidly evolving situation.

- Get the latest public health information from CDC »
- Get the latest research information from NIH »
- NIH staff guidance on coronavirus (NIH Only) »

Home » Research & Training » Rigor and Reproducibility

RIGOR AND REPRODUCIBILITY

Rigor and Reproducibility

Reporting Guidelines

Application Instructions

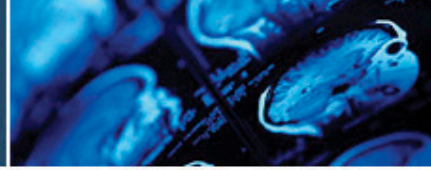
Updated Application Instructions to Enhance Rigor and Reproducibility

Related Links

NIH Grants & Funding Rigor and Reproducibility Webpage

Rigor and Reproducibility FAQs

RIGOR and REPRODUCIBILITY



NIH ENHANCING REPRODUCIBILITY GUIDELINES

what you need to know

WHAT ARE THE FOUR ELEMENTS OF RIGOR?

1. RIGOR OF THE PRIOR RESEARCH
2. RIGOR OF THE PROPOSED RESEARCH
3. BIOLOGICAL VARIABLES
4. AUTHENTICATION

Send inquiries to reproducibility@nih.gov

See also NIH Notice NOT-OD-18-228

https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-228.html

WHERE IN THE APPLICATION?

1 RESEARCH STRATEGY

The research strategy is where you discuss the significance, innovation, and approach of your research plan. Let's look at an R01, for example:

The research strategy guidelines require that you:

- Describe the strengths and weaknesses in the rigor of the prior research that serves as key support.
- Describe plans to address weaknesses in the rigor of the prior research.
- Describe how your experimental design and methods will achieve robust and unbiased results.
- Explain how relevant biological variables, such as sex, are factored into research designs and analyses.

2 ATTACHMENT FOR AUTHENTICATION OF KEY BIOLOGICAL AND/OR CHEMICAL RESOURCES

You must briefly describe methods to ensure the identity and validity of key biological and/or chemical resources used in the proposed studies.

These include, but are not limited to:

CELL LINES ↔ SPECIALTY CHEMICALS

ANTIBODIES ↔ OTHER BIOLOGICS

Standard laboratory reagents that are not expected to vary do not need to be included in the plan. Examples are buffers and other common biologicals or chemicals.

- **DO NOT** put experimental methods or preliminary data in this section
- **DO** focus on authentication and validation of key resources

3 REVIEW GUIDELINES

Here are the additional criteria the reviewers will be asked to use:

- Is the prior research that serves as the key support for the proposed project rigorous?
- Have the investigators included plans to address weaknesses in the rigor of prior research that serves as the key support for the proposed project?
- Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed?
- Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects?

Reviewers will also be asked to comment on that new attachment (see Update 2)!

Writing your grant application

Some do’s, don’ts, and pointers

What are some Do's?

- Do start early
- Do enlist collaborators, if appropriate
- Do make sure you understand the funding mechanism
- Do submit when the application will be the most competitive
- Do show feasibility (for new PIs preliminary data is not required but…)
- Do provide a timeline and realistic budget for the work proposed; Be sure to justify
- Do pay attention to other scorable items (e.g., Vertebrate Animals) and non-scorable items

Some more Do's

- Do focus on Impact
- Do provide a strong premise/rigor of prior research
- Do show evidence of Rigor and Reproducibility
- Do provide alternative possibilities and technical limitations
- Do take the reviewers by the hand and lead them to where you would like them to go
  - Reviewers don't think about your research 24/7
  - Make it reviewer friendly (helpful figures)

What are some 'Don'ts?

- Don't let the reviewers characterize your application as either 'descriptive' or one that makes 'incremental' advances
  - Emphasize the big picture of your studies in terms of impact and innovation
- Don't write a diffuse, unfocused proposal
- Don't propose an overly ambitious application
- Don't propose aims that are dependent on each other
- Don't write with the assumption everyone knows as much about the subject as you do

Some more 'Don'ts

- Don't assume your hypothesis is correct and all experiments will work perfectly
  - Include a section, e.g., 'potential problems and alternative explanations'
- Don't be unaware of changes to NIH applications
  - e.g., premise, rigor and reproducibility
- Don't show evidence of poor 'grantmanship'
  - Small figures, no 'white spaces' in application
- Don't repeat same mistakes as you did in earlier applications

Summary Statement

PROGRAM CONTACT: Stuart Moss
(301) 435-6979 mossstua@mail.nih.gov

SUMMARY STATEMENT (Privileged Communication)
Release Date: **03/27/2016**

Application Number: **1 R21 HDXXXXX-01**
Principal Investigator **CURIE, MARIE, PHD**
***Applicant Organization*:** **University of Paris**
Review Group: **CMIR** ***Meeting Date:*** **03/23/2016**
RFA/PA: **PA11-261**
Council: **MAY 2014** PCC: **RS -SM**
***Requested Start*:** **07/01/2016**
***Project Title*:** **The Effect of Radium on the Testis**

* ***SRG Action:*** **Impact/Priority Score: 30 Percentile: 22 #**
***Human Subjects*:** **10-No human subjects involved**
***Animal Subjects*:** **30-Vertebrate animals involved –no SRG concerns noted**

Priority/Impact Score and Percentile

- Applications in the bottom half of pre-discussion average scores are not discussed: ND (++)
  - ND – fall into bottom 50% based on preliminary scores
- All discussed applications receive a priority/impact score (PS)
  - PS = the average of all final scores, multiplied by 10
- Most priority/impact scores are ranked by converting them to a percentile
  - ICs fund to a certain percentile based upon their budgets (and 'other' factors)

What is the **OVERALL IMPACT** of an application?

- Two questions drive reviewer determination about the likelihood that the proposed studies will have a strong and sustained impact on the scientific field
  - ***Should they do it?***
  - ***Can they do it?***
- The overall impact is NOT mathematically related to individual criteria scores.

Should they do it?

- Are the specific goals of the application based on a well-reasoned premise so an important and significant advancement to the field is likely?
  - Significance and innovation
  - Is the premise strong?
  - Not an incremental advance in the field

Can they do it?

- Considering the approach, the investigators and the environment, are the goals of the proposal likely to be met?
  - Is the experimental strategy sound and rigorous?
  - Is there confidence that the research will be reproducible?
  - Have potential confounding variables been considered?

Scoring

Overall Impact:
The likelihood that a project will have a sustained and powerful influence on science (and/or clinical practice and/or technological developments?)

Overall Impact	High	Medium	Low
Score	1 2 3	4 5 6	7 8 9

Evaluating Overall Impact:
Consider the 5 criteria: significance, investigator, innovation, approach, environment (weighted based on reviewer's judgment)

e.g. Applications are addressing a problem of high importance in the field. May have some or no technical weaknesses.

e.g. Applications may be addressing a problem of high importance in the field, but weaknesses in the criteria bring down the overall impact to medium.

e.g. Applications may be addressing a problem of moderate importance in the field, with some or no technical weaknesses

e.g. Applications may be addressing a problem of moderate/high importance in the field, but weaknesses in the criteria bring down the overall impact to low.

e.g. Applications may be addressing a problem of low or no importance in the field, with some or no technical weaknesses.

5 is a good medium-impact application, and the entire scale (1-9) should always be considered.

Summary Statement

RESUME AND SUMMARY OF DISCUSSION:

Written by the SRO based on the final outcome of the discussion, summarizes strengths & weaknesses mentioned by all reviewers, highlights areas of concurrence & disagreement between reviewers.

CRITIQUE 1

Significance: 3

Investigator: 1

Innovation: 1

Approach: 4

Environment: 1

These scores are indices only. They have no mathematical relationship to the priority score.

Overall Impact:

Written by the individual reviewer to summarize their opinion on the overall strengths and weaknesses of the application.

Consider the criteria scores carefully

- The written comments and summary of discussion will tell a more complete story
- *However*, pay special attention to Significance and Approach
  - Low significance, no matter what the other scores are, might be hard to fix
  - High significance but weak approach may be fixable

Other Considerations

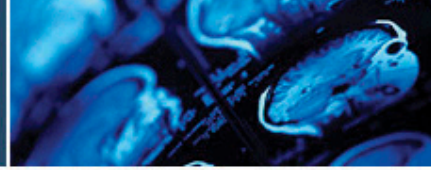
- Scoreable items
  - Vertebrate Animals
    - Address four points
  - Human Subjects
    - Inclusion/exclusion criteria
    - Women/children/minority
    - Power analysis
  - Biohazards
- Non-scorable items
  - Budget, time, resource/data sharing
  - Authentication of Key Biological Resources

Are you a new investigator (NI), an early stage investigator (ESI)?

- Pertains to R01 applications
- NI - never has been awarded a R01
- ESI – never been awarded a R01 and is within 10 years of terminal degree
- Does it make a difference?
  - In a study section, NI and ESI R01 applications are clustered and reviewed together
  - At the institute level, ESI and sometimes NI applications have a preferential ‘payline’

Are you a new investigator (NI), an early stage investigator (ESI)?

- Preliminary data not required for New PI/ESI, but…
- Published and/or preliminary data is required to support your scientific premise
- Feasibility is required for the experimental design
  - Published and/or preliminary data
  - Expertise and publications of a collaborator
    - Include biosketch and letter of support



Thank you!

- Questions?