



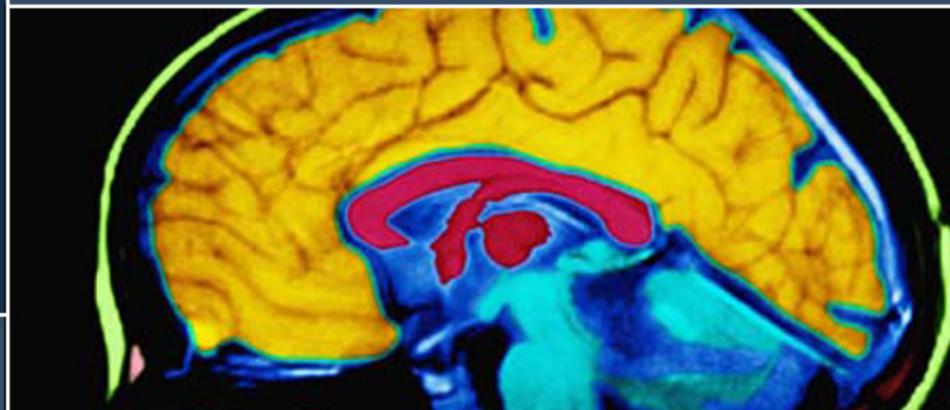
National Institute of
Neurological Disorders
and Stroke

Translational Programs Proposed Redesign

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NINDS Translational Guiding Principles

- Need to get therapeutics to humans (not bench to bookshelf)
 - Develop translatable measures of PK/PD and target engagement
 - Integrate clinical perspective
- Establish fail-early, fail-fast approach to portfolio management
 - Milestone assessment critical to project progression
 - Embrace early termination as success and learning opportunity
- Can't do it alone – need partnerships and handoffs
 - De-risk projects for downstream funding
 - Actively facilitate partnership discussions

TRANSLATION BEGINS AND ENDS WITH THE PATIENT



OTR Programs to Support Translation

Basic Research/
Assay
Development

Hit to Lead/Proof of
Principle

Proof of Principle/
Lead Optimization

IND Enabling
Tox; Clinical
Readiness

Small Clinical
Trials

Anti-Convulsant Screening Program (contract)

Exploratory/Developmental Projects in Translational Research
(tR21)

Cooperative Program in
Translational Research
(U01)

Blueprint Neurotherapeutics (BPN)

R01s for assays
and probe

Small Business Program: SBIR & STTR

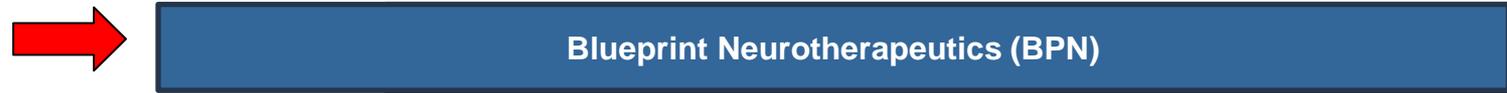
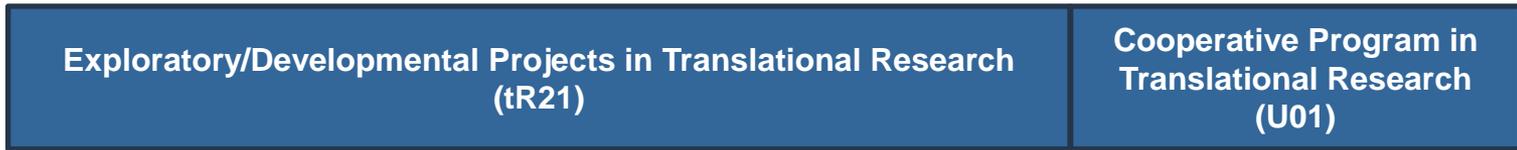
Countermeasures Against Chemical Threats (CounterACT)



OTR Programs to Support Translation



Anti-Convulsant Screening Program (contract)



R01s for assays and probe

Small Business Program: SBIR & STTR

Countermeasures Against Chemical Threats (CounterACT)

Current Translational Programs at a Glance

Current tR21

Current U01

BPN 1.0

End goal
other than
Pre-U01

Hit to Lead/Proof
of Principle

Proof of
Principle/Lead
Optimization

IND Enabling
Tox; Clinical
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Small Clinical
Trials

Translational R21

U01

- Small molecules, proteins/peptides, oligos, gene/cell therapy, devices
- 53 active projects
- 80% end-goal other than therapy development

- Small molecules, proteins/peptides, oligos, gene/cell therapy, devices
- 34 active projects
- Milestone-driven

Blueprint Neurotherapeutics (BPN)

- Small molecules only
- 2 active NINDS projects out of 5 initiated
- Contracts and consultants integral to “virtual pharma” structure
- Milestone-driven

Achievements To Date

- At least 8 U01s have graduated to clinical trials
 - > 70 U01s actively managed in 10+ years
- First cohort of BPN small molecule projects advancing into development
 - 15 BPN small molecule projects (5 NINDS) initiated in 2.5 years
- Progressive strengthening of peer-review and milestone assessments
- Recent interest from potential partners in BPN and SBIR projects

Redesign Team

OTR

- Hao Wang
- Linda McGavern
- Christina Vert
- Rebecca Farkas
- Amir Tamiz
- Chuck Cywin
- Stephanie Fertig
- Pat Walicke
- John Kehne
- David Jett

OSPP

- Bob Zalutsky

OCR

- Elizabeth McNeil
- Wendy Galpern

Review

- Bill Benzing
- Ernie Lyons
- Birgit Neuhuber
- Natalia Strunnikova

DER

- Francesca Bosetti
- Jane Fountain
- Amelie Gubitz
- Jim Koenig
- Kip Ludwig
- Laura Mamounas
- Jill Morris
- David Owens
- John Porter
- Ursula Utz
- Vicky Whittemore

Opportunities for Further Enhancement

- Tailored approach: Cater to the various modalities
- Transitions: Reduce delay between funding mechanisms
- Risk management: More points for attrition
- Due Diligence:
 - Implement RIGOR
 - Increase progress review frequency
- Flexibility:
 - Access to contracts and consultants
 - Project entry at various points
 - Supplements to address unanticipated needs

Features of the UH2/UH3 grant mechanism

- New mechanism at NIH since 2008
- ~100 grants across 12 ICs (None at NINDS)
- 5 years combined; flexible budgets
- Allows for attrition between stages
- Allows for intermediate milestones

New Program Design at a Glance

Current tR21

Current U01

Blueprint 1.0

End goal
other than
Pre-U01

Hit to Lead/Proof
of Principle

Proof of
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IND Enabling
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Integrated Vision: a core set of FOAs tailored for each treatment modality

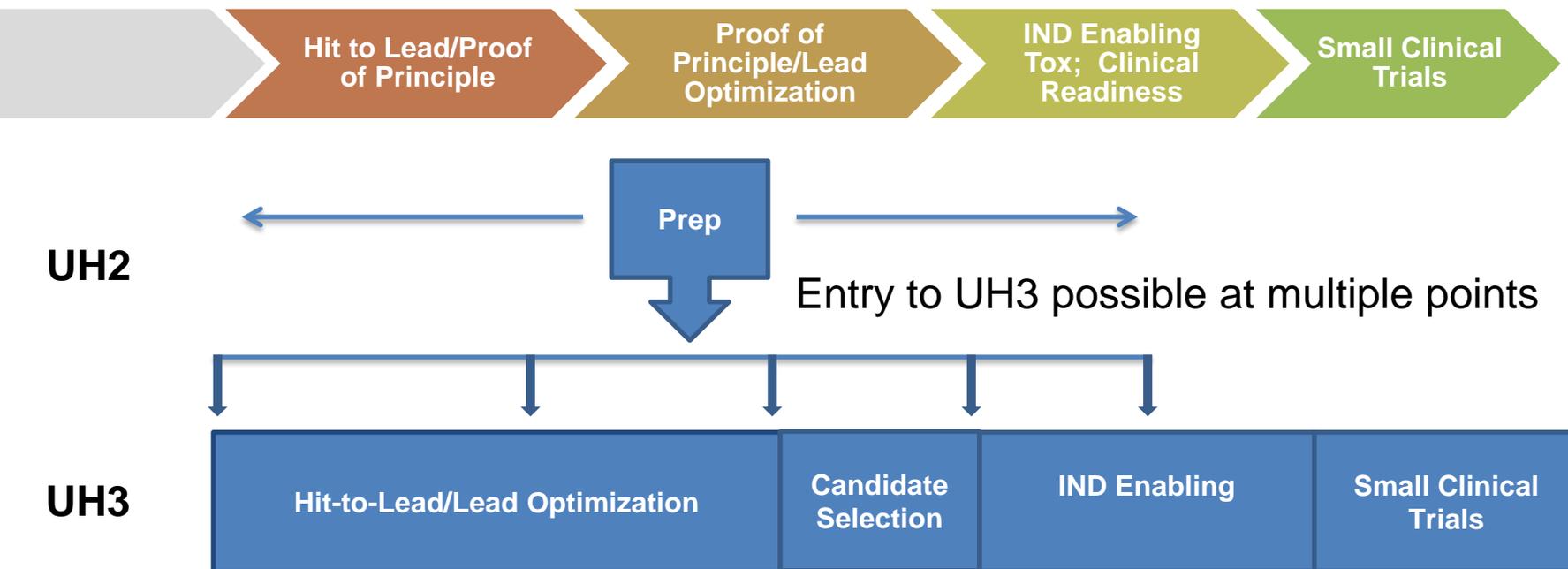
Blueprint 2.0 for small molecules

CREATE for biologics and biotech products

CREATE for devices

CREATE: Cooperative Research to Enable and Advance Translational Enterprises

BPN 2.0 for Small Molecules: A Closer Look

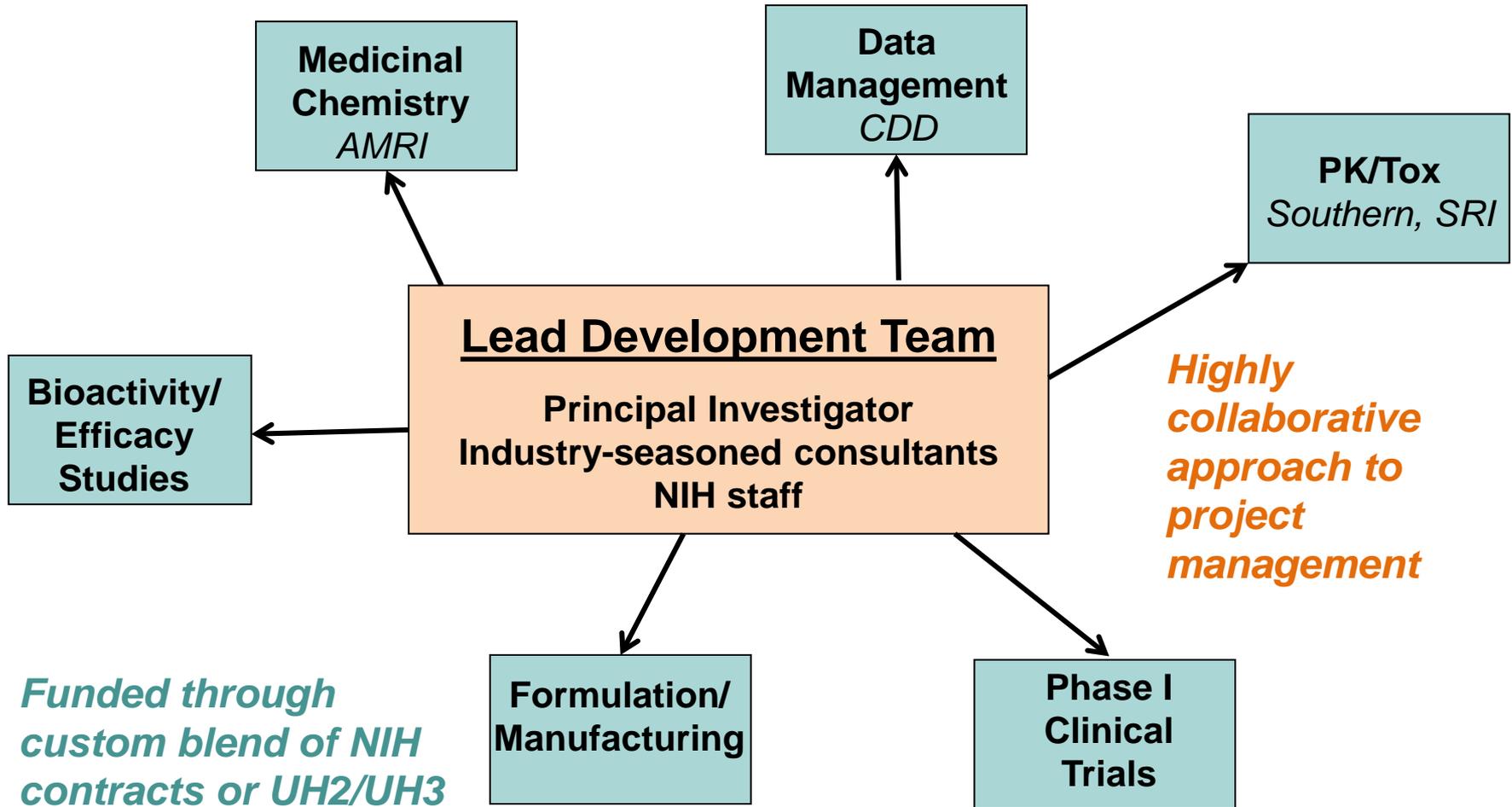


	UH2	UH3
Budget per year	< \$0.3 M	< \$1-1.5 M
Duration	Up to 1 year	Up to 5 years
Budget total	< \$0.3 M	< \$5-8 M

Prep = confirmatory studies, due diligence, strengthen package

Blueprint Neurotherapeutics Network 2.0

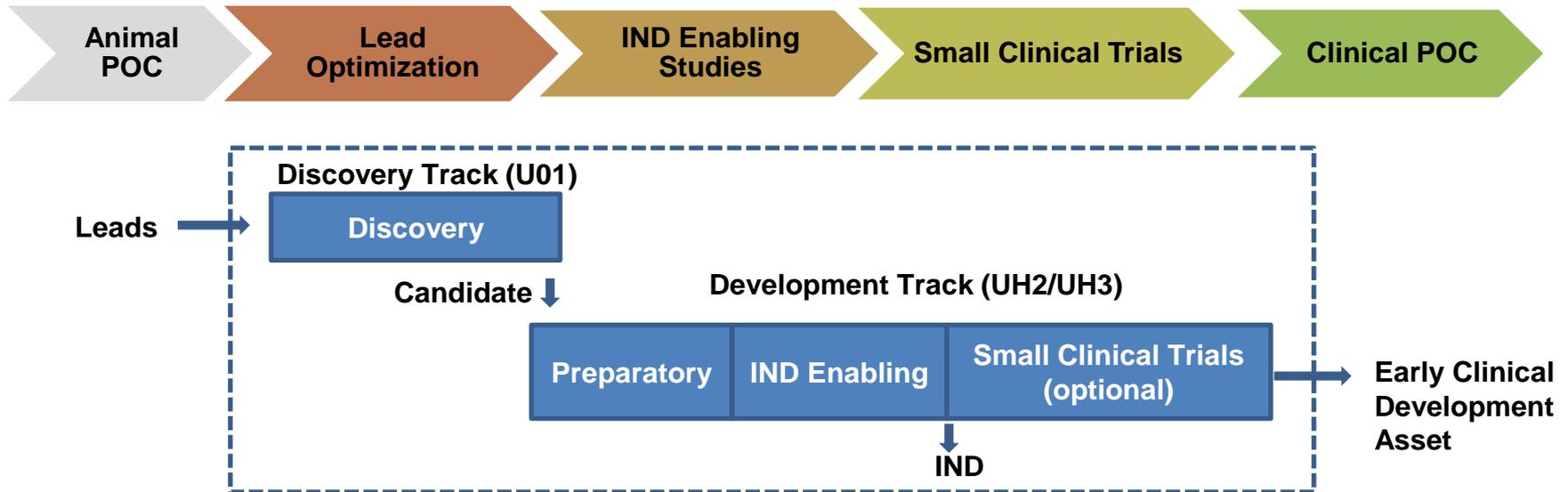
Combining Infrastructure, Expertise, and Funds



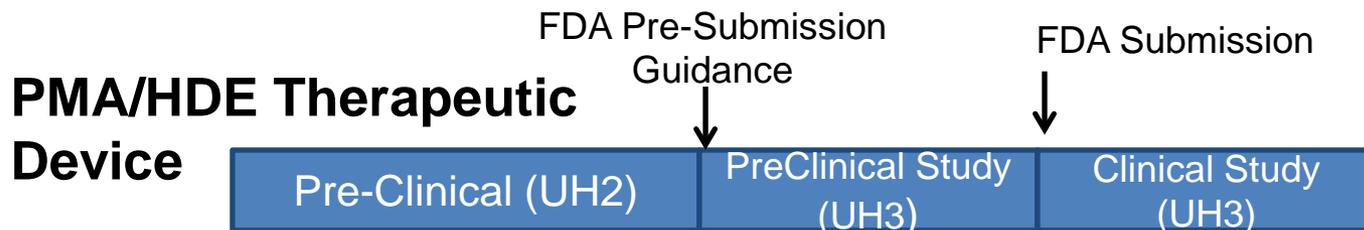
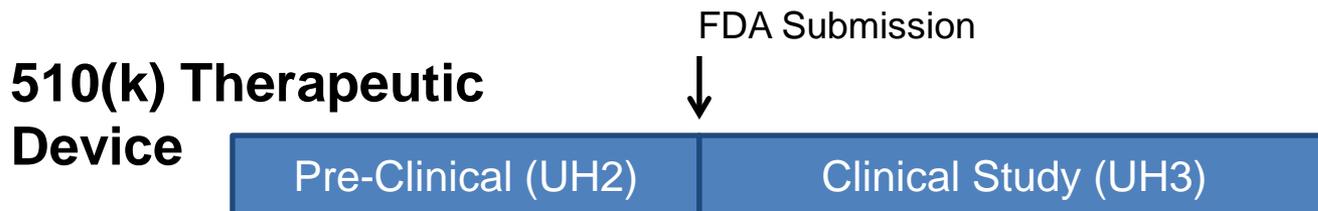
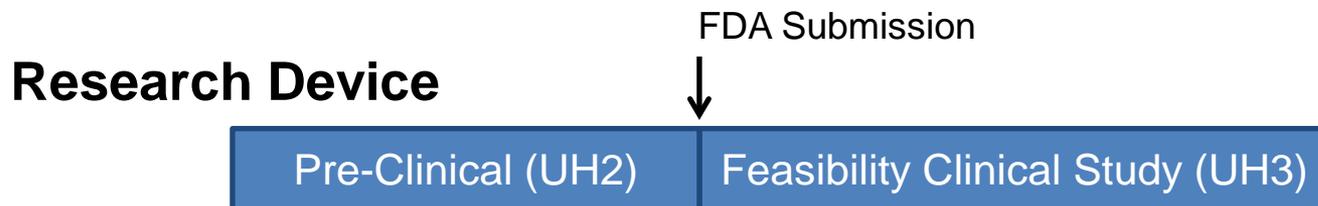
Highly collaborative approach to project management

Funded through custom blend of NIH contracts or UH2/UH3 awards to PI

CREATE Bio Program



CREATE Devices: A Closer Look



	UH2	UH3
Budget per year	\$1 M	\$1.5 M
Duration	Up to 3 years	Up to 4 years
Budget total	\$3 M	\$6 M

BPN 2.0/CREATE Prepare and Conduct Clinical Trials

- Clinical trials must be planned and completed within 2 years max and cost \leq \$3 M (4 years and \leq \$3 M for devices)
- Small clinical trial = First Human Study
 - Phase 1 Single Ascending Dose/Multiple Ascending Dose, small open label or controlled study
 - <80 healthy volunteers or patients (<10 for some devices)
 - Outcomes: safety, PK, PD. *Not efficacy studies (except some devices).*
- OCR safety review and SRB protocol review inform release of clinical funds

Proposed Timeline for BPN 2.0/CREATE FOAs

- Concept approval – January 2014
- Publish FOAs – June 2014
- First receipt date – August 2014
- New grants to council – January 2015

In parallel:

Begin redesign to cover scope of the remaining 80% of tR21s

- Concept approval – September 2014 (tentative)
- First receipt date – February 2015 (tentative)
- New grants to council – September 2015 (tentative)

Discussion

Rigor, Reproducibility, and Robustness

- Thus far
 - Landis et. al. (2012) highlighted the issues
 - NINDS FOAs now incorporate guidance
 - Journals (Nature, Science) have adopted guidance
 - NIH-wide adoption of recommendations (Collins and Tabak, Nat. 2014)
 - Science Exchange initiative launched
- Looking ahead
 - What else should NINDS do to implement these guidelines?

Proposal: The NINDS Rigor, Reproducibility, and Robustness (R3) Program

Primary Short-Term Objective:

To allow NINDS to generate the critical experimental data to increase the likelihood of success of therapy development and clinical trials

Team: John Kehne, Pat Walicke, Shai Silberberg, Kirk Davis, Jason Williams with input from most DER PDs

Features of the R3 Program

- Uses contract mechanism
- Support decisions in newly proposed translational programs
- Testing key preclinical findings for NINDS clinical networks,
such as NeuroNext
- Not always a strict “replication”

Proposed 5 Year Pilot Phase

- Project Selection Criteria:
 - Nominated by NINDS Program staff, post-review
 - Recommended in consultation with *ad hoc* external experts
 - Approved by Extramural Science Committee
 - Tied to existing or to-be-awarded grant
- Timing:
 - Prior to the commencement of grant funding OR
 - Prior to release of funds at predefined stages (e.g., transition from UH2 to UH3) OR
 - In parallel to funding translational or clinical work

Contract Structure

- Suite of 3-5 contracts with access to:
 - *In vitro* and *in vivo* models covering key NINDS disorders
 - Transgenic and interventional disease models
 - Specialized academic or private laboratories via subcontracting
 - Large animal models
- Allows NINDS to compete studies between contractors and select best bid

Ongoing Market Research

Identified 29 US/international preclinical CROs

- Operating principles consistent with RIGOR recommendations
- Independently reproducing or extending previously published results
- CRO business models include in-house and/or outsourcing

Portfolio and Budget Estimates

- Proposed number years: 5
- Total cost: \$3M/yr with options to increase funding
- 4-6 concurrent studies (average cost \approx \$500 – 750K)
- Interim evaluation proposed after 3 years or when 20 studies are completed

Anticipated Outcomes of R3

- Short term
 - Provide NINDS leadership with confidence to invest in translational or clinical studies
- Long term
 - Dissemination of concepts throughout the research community
 - Support for better validated translational and clinical grants
 - More effective use of the NINDS extramural budget
 - Serves NINDS mission: greater success for patients in need

Questions?

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Backup slides

17+ BPN Consultants

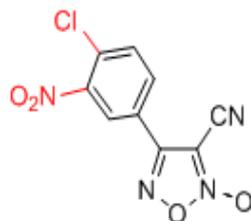
- **Assay development, pharmacology**

- Lisa Minor
- Bill Martin
- Vince Groppi
- Jeff Conn*
- Bryan Roth*



- **Medicinal chemistry**

- Graham Johnson
- Donna Romero
- Neil Moss
- Paul C. Anderson
- Steve Young
- John McCall*



- **DMPK**

- Paul Pearson
- Jiunn Lin
- Ron White

- **Toxicology**

- Marc Bailie
- TBD

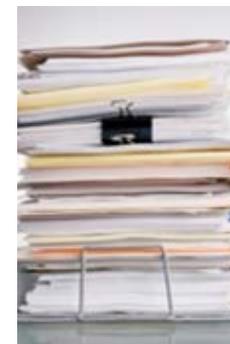


- **Development**

- Peter Farina*
- Mike Detke*
- CMC consultant TBD
- Process chemist TBD

- **Regulatory affairs**

- TBD



* Steering Committee member