National Institute of Neurological Disorders and Stroke

NIH Blueprint for Neurotherapeutics: A novel approach to early stage drug discovery research funding

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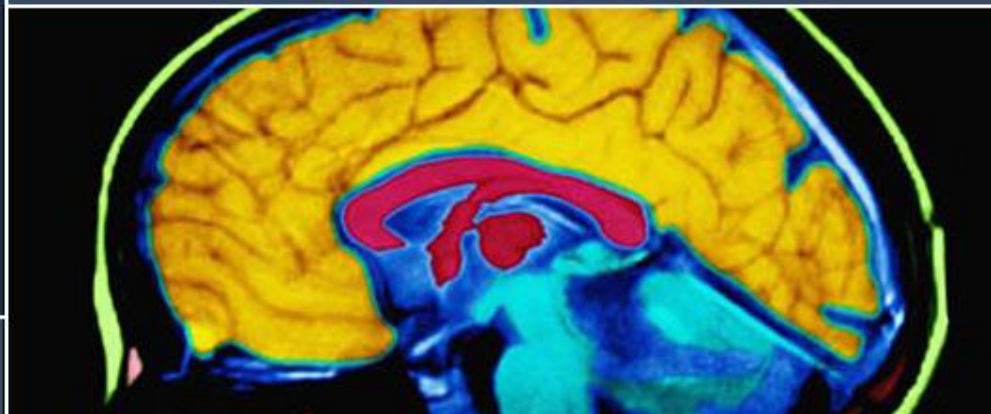


Program Vision

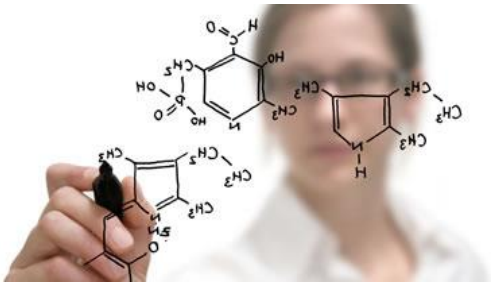
Combine Strengths of NIH and Industry

NIH investigator-initiated ideas

- Novel drug targets
- Strong disease assays and models

Industry expertise

- Advisors with extensive pharma experience
- Industry-standard contract services



Blueprint Neurotherapeutics Network

Offering Infrastructure, Expertise, and Funding

AMRI

Medicinal Chemistry

CDD COLLABORATIVE DRUG DISCOVERY

Data Management

SOUTHERN RESEARCH INSTITUTE

PK/Tox

SRI International

PI

Bioactivity/ Efficacy Studies

Lead Development Team

Principal Investigator*
Industry-seasoned consultants
NIH staff

PI retains intellectual property

Formulation/ Manufacturing

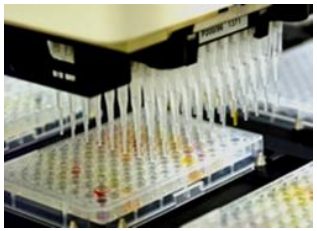
TBD Jan. 2015

TBD 2016

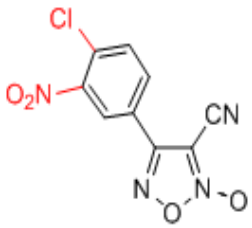
Phase I Clinical Trials

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



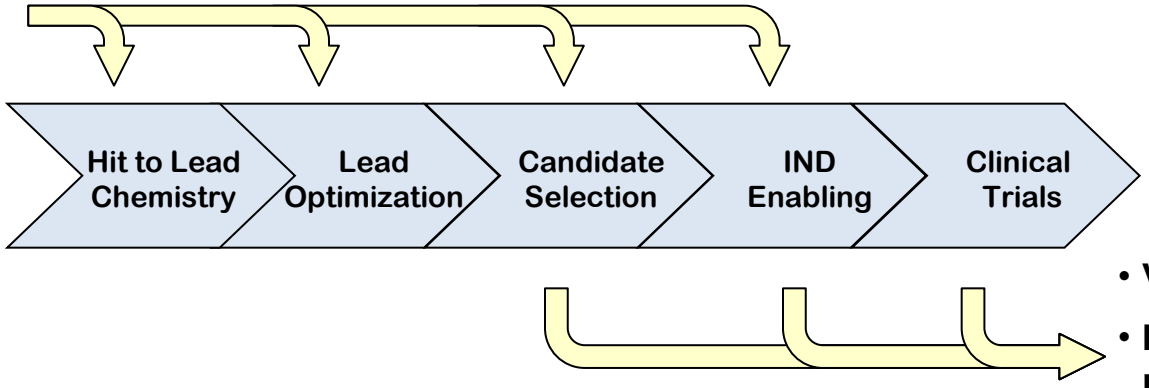
- **DMPK**
  - Paul Pearson
  - Jiunn Lin
  - Ron White

- **Toxicology**
  - Marc Bailie
  - TBD
- **Development**
  - Peter Farina
  - Mike Detke
  - Gian Luca Araldi
  - Jon P. Lawson
  - John M. “Jay” Sisco
- **Regulatory affairs**
  - TBD

See bios at http://neurosciencebluprint.nih.gov/bpdrugs/bpn.htm

Goal: Advance Projects for Hand-Off

- Strong biological validation
- Stage-appropriate compounds
- No IP constraints



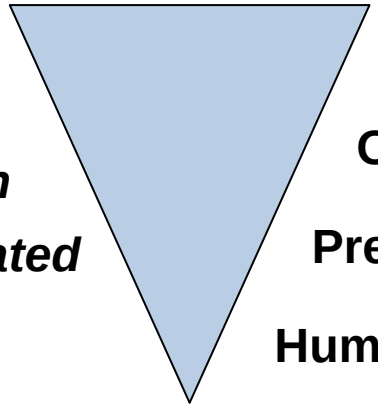
- Venture funding
- Industry partnership
- Other grants
- Project conclusion

Risk decreases as projects successfully advance

Projects are Milestone-Driven

External Review Committee Assesses Progress Biannually

Projects Launched



High attrition rate anticipated

Exploratory Studies

Optimization Chemistry

Pre-clinical safety testing

Human safety testing (Phase I)

Milestones
Validated Assays
Emerging SAR

New drug candidates licensed

External Review Committee

Peter Farina, PhD (chair)
Jeffrey Conn, PhD
Michael J. Detke, MD, PhD
John McCall, PhD
Bryan Roth, MD, PhD

Confidentiality and IP Protection

Confidentiality

- Applications reviewed in closed (non-public) meetings
- Reviewers are under strict confidentiality agreements
- Only funded abstracts are made public
- NIH contracts with consultants, research service providers, and steering committee members include confidentiality requirements
- NIH employees are required to protect confidentiality by law

Intellectual Property

- Goal: Unencumbered IP, controlled by PI's institution
- Consultants and chemistry contractor assign IP rights up front to the PI's institution
- NIH has no stake in the IP

Who Applies for BPN?

- Researchers who are new to drug discovery
- Researchers who are experienced in drug discovery but lack necessary research facilities
- Academic labs and small businesses

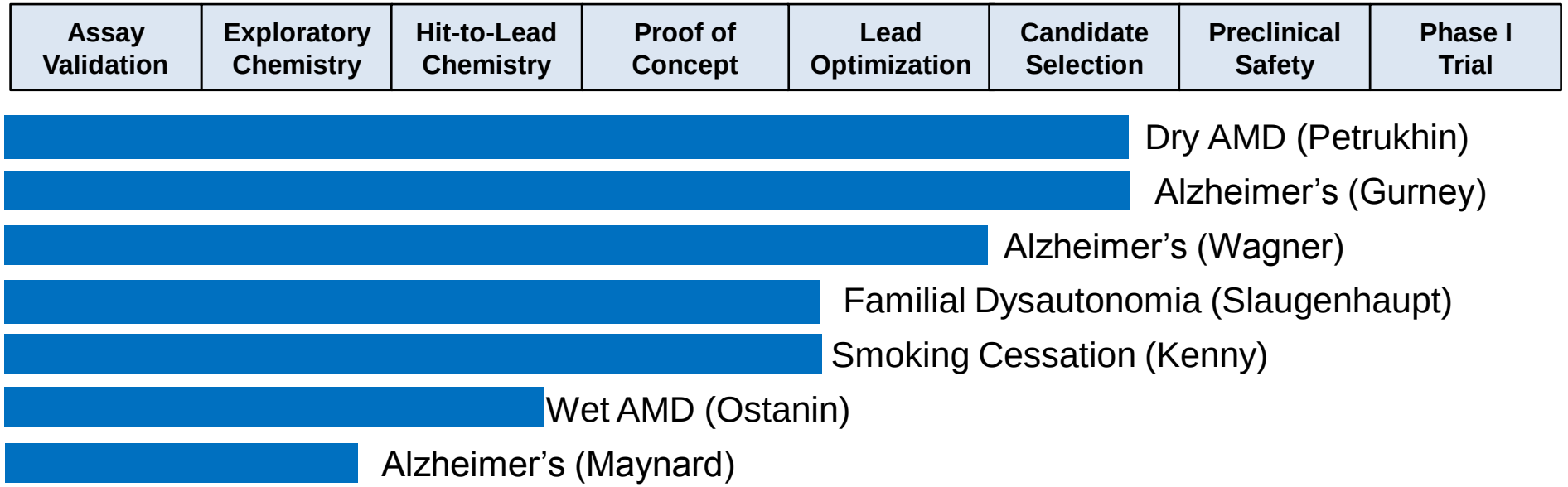
15 Projects Initiated 2011- 2013

Principal Investigator	Institution	Disorder
Mark Gurney	Tetra Discovery Partners	Alzheimer's
Paul Humphries	Reset Therapeutics	Narcolepsy
Paul Kenny	Eolas Therapeutics	Smoking Cessation
George Maynard	Axerion	Alzheimer's
Kirill Ostanin	Navigen	Macular Degeneration
Konstantin Petrukhin	Columbia University	Macular Degeneration
Susan Slaugenhaupt	Mass. General Hospital	Familial Dysautonomia
Steven Wagner	UC San Diego	Alzheimer's
John Bixby	University of Miami	Optic Neuropathy
Raymond Dingledine	Emory University	Stroke
Marcie Glicksman	Brigham and Women's Hospital	ALS
Michael Lark	Trevena	Depression
Al Robichaud	Sage Therapeutics	Fragile X
Edwin Rubel	University of Washington	Hearing Loss
D. James Surmeier	Northwestern University	Parkinson's

Discontinued

See abstracts at http://neuroscienceblueprint.nih.gov/bpdrugs/bpn.htm

Current BPN Portfolio



Interested in licensing opportunities?

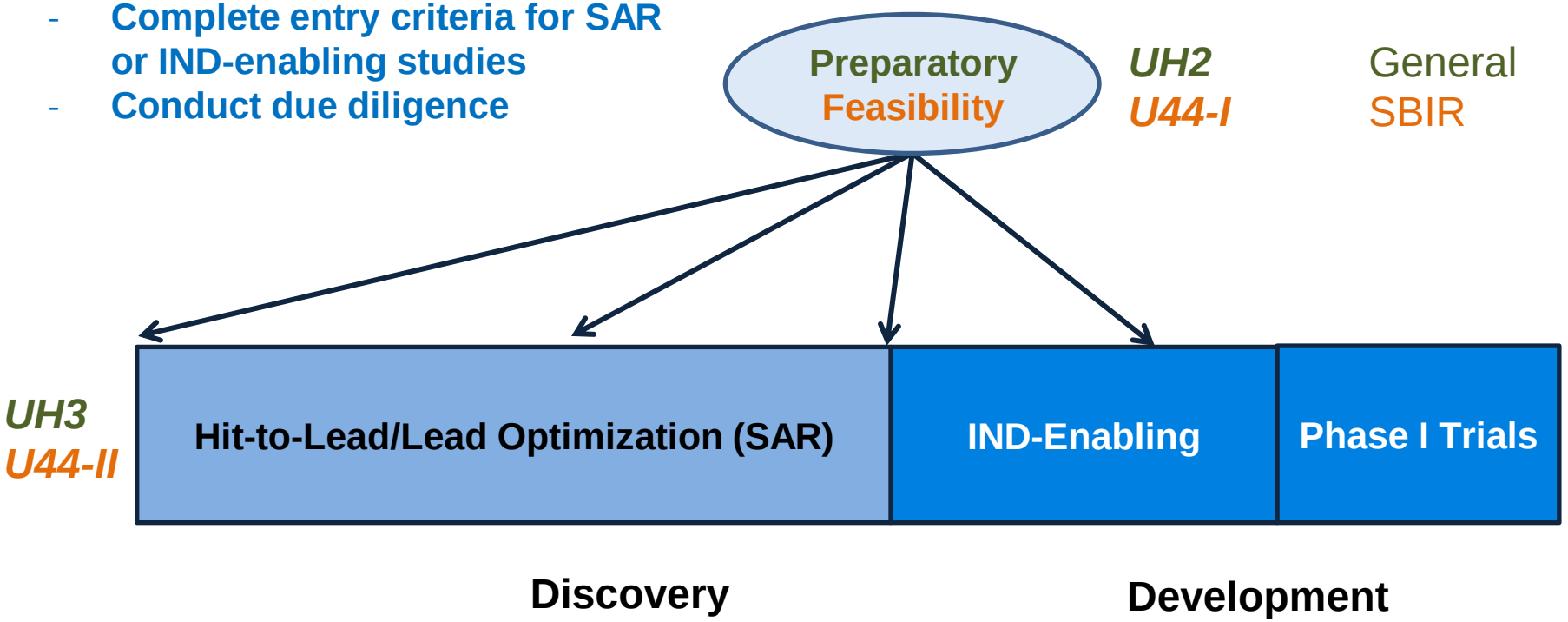
http://neuroscienceblueprint.nih.gov/bpdrugs/NIH-BPN_project_business_contacts.pdf

What's New in BPN

- Flexibility in mix of contract access and grant support
  - Investigators choose what combination best fits their needs
  - Offers option for grant-only support
- Flexibility in entry point
  - Projects can enter during Discovery or Development
- Phased funding allows for due diligence, filling in data gaps
- SBIR track available

Projects Can Enter at Any Preclinical Stage
All Projects Begin with Preparatory Phase

- **Complete entry criteria for SAR or IND-enabling studies**
- **Conduct due diligence**



Examples of Preparatory Activities

Discovery Phase: Get Ready for Med Chem

- Form Lead Development Team
  - Define milestones, goals for optimization
  - Establish compound testing funnel
- Optimize, validate assays to drive SAR
- Assay correlation studies to define advancement criteria
- ADMET profiling to identify compound liabilities
- Studies to address questions on proof-of-concept

Examples of Preparatory Activities

Development Phase: Get Ready for IND-Enabling Studies

- Establishment of a preclinical development plan
- Design and planning for the first-in-human clinical trial
- Replication/confirmation of key in vivo pharmacology data
- Scale-up synthesis
- Salt and polymorph screening
- Compound stability studies
- Pre-formulation studies
- Multiple-dose rodent PK testing, with PD correlations if applicable
- Dose-range finding toxicology
- Metabolite identification

Now Accepting New Applications

- **PAR-14-293** for all applicants
- **PAR-14-292** for small businesses (SBIR)
- First applications due Oct 21, 2014
- First peer review in February 2015 (special review panel)
- First grants awarded July 2015
- For the following indications
  - Psychiatric disorders
  - Neurological disorders
  - Degenerative dementias of aging
  - Developmental disorders
  - Chronic pain conditions
  - Alcohol dependence
  - Drug addiction

Network Entry Criteria

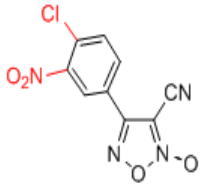
Discovery Stage

Disease biology

- **Novel target for the disease**
- **Strong biological validation**
  - *in vivo* PD read-out desirable
  - *in vivo* efficacy not absolutely required
- **Feasible path to the clinic**

Assays

- **Robust in vitro assay for optimization**
- **Strong confirmatory assays**

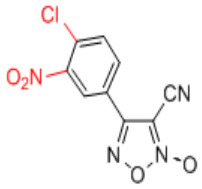


Compounds

- **Project must require medicinal chemistry**
- **Amenable to chemistry**
- **IP free of obvious roadblocks**

Network Entry Criteria

Development Stage



Fully Optimized Compound

- **Strong data linking target to disease**
- **Biological & ADMET activity appropriate for intended clinical use***
  - Efficacy/PD when delivered by clinically intended route
  - Fully profiled, defensible ADMET results†
- **Feasible path to the clinic**
- **IP free of obvious roadblocks**

*** Must be consistent with Target Product Profile**
† Must have fully completed Compound Profile Table

Budget Guidance

Grant pays for PI-led work only

- NIH pays BPN contractors directly
- PI may select own contractors and include in grant budget

If no BPN contracts are used,* PI may request:

- General
  - UH2: Up to $300K direct costs x 1 year
  - UH3: Up to $1.5M/year direct costs x 4 years
- SBIR
  - Phase I: Up to $400K total costs x 1 year
  - Phase II: Up to $4M total across 3 years

*** If work will be conducted by BPN contractors, the grant budget should be offset accordingly**

Applications $500K+ (direct) must be pre-approved by NIH staff for submission

Advice for Preparing an Application

- **Contact NIH staff**
  - Confirm which entry stage is best fit
  - Discuss activities for Preparatory Phase
  - Applications $500K+ must be preapproved to submit
- **Read the FOA (this isn't a typical NIH application)**
- **Show the data for assay validation, target validation, etc.**

See FAQs at
http://neuroscienceblueprint.nih.gov/bpdrugs

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