NINDS Office of Translational Research: New Programs to Support Therapy and Device Discovery and Development

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NINDS
rajesh.ranganathan@nih.gov

Number of companies investing in Neuroscience drug discovery

<table>
<thead>
<tr>
<th>2000</th>
<th>n=32</th>
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<tbody>
<tr>
<td>Abbott</td>
<td>JNJ</td>
</tr>
<tr>
<td>American Home Products/Wyeth</td>
<td>Lilly</td>
</tr>
<tr>
<td>Amgen</td>
<td>Lundbeck</td>
</tr>
<tr>
<td>Astellas</td>
<td>Merck</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>Novartis</td>
</tr>
<tr>
<td>Aventis</td>
<td>Otsuka</td>
</tr>
<tr>
<td>Bayer</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Biogen</td>
<td>Pharmacia</td>
</tr>
<tr>
<td>Boehringer Ingelheim</td>
<td>Rhone-Poulenc</td>
</tr>
<tr>
<td>Bristol Myers Squibb</td>
<td>Sanofi</td>
</tr>
<tr>
<td>Dainippon Sumitomo</td>
<td>Schering-Plough</td>
</tr>
<tr>
<td>Eisai</td>
<td>Serono</td>
</tr>
<tr>
<td>Elan</td>
<td>Solvay</td>
</tr>
<tr>
<td>Genentech</td>
<td>SmithKline Beecham</td>
</tr>
<tr>
<td>Glaxo</td>
<td>Takada</td>
</tr>
<tr>
<td>Janssen</td>
<td>UCB Pharma</td>
</tr>
</tbody>
</table>
**Number of companies investing in Neuroscience drug discovery**

- AbbVie
- Amgen
- Astellas
- AstraZeneca
- Biogen-Idec
- Boehringer Ingelheim
- Bristol Myers Squibb
- Daiichi Sankyo
- Eisai
- GlaxoSmithKline
- JNJ
- Lilly
- Lundbeck
- Merck
- Merck Serono
- Novartis
- Otsuka
- Pfizer
- Sanofi
- Takeda
- UCB Pharma

**CNS drug discovery portfolio**

![CNS Drug Discovery Portfolio Chart]

**BIG PHARMA AND CNS II**

- 2014: 129 programs
- 2009: 267 programs
Clinical Productivity: 2009-14

16 NCE approvals in CNS
Three represent a major advance in a treatment paradigm (RRMS): Gilenya, Tecfidera, Aubagio
One recent approval with yet-to-be-determined impact on the treatment paradigm for insomnia: Belsomra
No other significant treatment paradigm changes
Ecosystem is pursuing new models – eliminate silos

Pharma

Biotech

Academia

Project 1

Project 2

Project 3

What should NINDS’s role be in this changing climate?
### Appropriations (Dollars in Thousands)

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<thead>
<tr>
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<tbody>
<tr>
<td>NINDS</td>
<td>$1,622,003</td>
<td>$1,624,830</td>
<td>$1,533,795</td>
<td>$1,588,904</td>
<td>$1,604,607</td>
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<tr>
<td>NINDS % Change</td>
<td>Base</td>
<td>0.2%</td>
<td>-5.6%</td>
<td>3.6%</td>
<td>1.0%</td>
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<td>NIH</td>
<td>$30,687,290</td>
<td>$30,860,387</td>
<td>$29,151,462</td>
<td>$30,150,853</td>
<td>$30,311,349</td>
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<tr>
<td>NIH % Change</td>
<td>Base</td>
<td>0.6%</td>
<td>-5.5%</td>
<td>3.4%</td>
<td>0.5%</td>
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</tbody>
</table>

- Average IC increase was 0.31%
- NINDS and NIMH each received increase of $12.3 M for BRAIN Initiative
- Funding up to 14th percentile

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### Total NINDS Extramural Grants Budget

- NINDS Extramural
- adjusted to 1995 dollars
- with ARRA
- with ARRA--adjusted to 1995 dollars

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10/26/2015
FY 2013 Taxpayer Investment in Neuroscience Now Exceeds Cancer

Dollars in Billions (FY 2013)

- Cancer: 5.274
- Neurosciences: 5.34
- Infectious Diseases: 4.887

Research Category


NIH Neuroscience Research


Other Includes:
- FIC: 0.03%
- TYPE 1: 0.01%
- NLM: 0.02%
- NCMHD: 0.05%
- NCATS: 0.14%
- NHGRI: 0.26%
- NIDCR: 0.52%
- NIAID: 1.06%
- NIBIB: 1.22%
- NIEHS: 1.50%
- RMAP: 1.64%
- OD: 2.14%
The Problem

Unmet need in hundreds of neurological disorders

FY 2015 Appropriation Budget Distribution

FY 2015 Budget Authority: $1,604,607K

Dollars in Thousands

<table>
<thead>
<tr>
<th>Extramural</th>
<th>Intramural</th>
<th>RMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,385,870</td>
<td>159,498</td>
<td>59,239</td>
</tr>
<tr>
<td>86.4%</td>
<td>9.9%</td>
<td>3.7%</td>
</tr>
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</table>
**Mission:** To facilitate the preclinical discovery and development of new therapeutic interventions for neurological disorders

**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
NINDS uses a Variety of Translational Approaches

- **Discovery**
  - Anticonvulsant Screening Program (ASP) $3.5 M
  - Translational R21 (all modalities) / IGNITE $10 M
- **Preclinical Development**
  - CREATE Bio for Biotechnology Products and Biologics $19 M
  - CREATE Devices $2 M
- **Small Clinical Trials**
  - Small Business Program: SBIR & STTR $46 M
  - Blueprint Neurotherapeutics (BPN 2.0) for Small Molecules $14 M
  - Countermeasures Against Chemical Threats (CounterACT) $47 M

IGNITE: Innovation Grants to Nurture Initial Translational Efforts
CREATE: Cooperative Research to Enable and Advance Translational Enterprises

NINDS Anticonvulsant Screening Program (ASP)

**Approach:** Provide services and expertise to investigators developing anticonvulsants

- Established in 1975 (Dr. Steve White: PI, Univ. of Utah)
- Screening performed via a contract mechanism using a battery of seizure models
- NINDS staff report results to participants, advise on future development
- Supplier IP protected; confidentiality maintained
- Role in 10 marketed drugs since 1990
History of Antiepileptic Drugs (AEDs)

ASP Mission: To encourage and facilitate the discovery of new therapeutic agents for epilepsy

First generation

Second generation

Third generation

Start of ASP

Number of AEDs

Year of introduction

Adapted from Loscher & Schmidt, 2011, Epilepsia, 52:657
**NINDS uses a Variety of Translational Approaches**

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**IGNITE: Innovation Grants to Nurture Initial Translational Efforts**

**CREATE: Cooperative Research to Enable and Advance Translational Enterprises**

**Cooperative Program Purpose and Goals**

- Program launched in 2002 and includes drugs, biologics, and devices
- Purpose: To stimulate preclinical development of therapeutics in non-profit and small business sectors
- Features: Special review, milestone-based decisions
**Portfolio (n=80) by Indication (2002-2014)**

- **Other:**
  - Batten disease
  - Down Syndrome
  - Neurodegeneration
  - Neurofibroma
  - Insecticide poisoning
  - Peripheral nerve injury
  - Phenylketonuria
  - SMA
  - Spinal and Bulbar Muscular Atrophy

**Portfolio (n=80) by Interventional Modality (2002-2014)**

- **Other:**
  - Vaccine
  - Dog Center
  - Drug Discovery Center
Achievements of the Legacy Program

- At least 8 projects have graduated to clinical trials
  - 80+ projects actively managed in 10+ years
- Progressive strengthening of peer-review and milestone assessments
  - 15 discontinuations for not meeting milestones
- In 2014, at least 5 INDs were filed:
  - a small molecule in Alzheimer’s Disease;
  - a gene therapy in Glioblastoma;
  - gene therapy and antisense oligos in Muscular Dystrophy
**Case Study #1**

Mitochondrial inhibitor to treat acute spinal cord injury (SCI)

- Demonstrate recovery in a severe SCI model in either gender
- PK to determine treatment regimen
- Improve mitochondrial function in animals
- Demonstrate motor and sensory recovery
- Submit IND

<table>
<thead>
<tr>
<th>Year 01</th>
<th>Year 02</th>
<th>Year 03</th>
<th>Year 04</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>$ awarded</strong></td>
<td>6 month NCE to address differences in injury severity</td>
<td>And ultimately discontinued</td>
<td>Efficacy criteria not fully met in either gender</td>
</tr>
</tbody>
</table>

**Case Study #2**

Gene therapy to treat Batten Disease / late infantile neuronal ceroid lipofuscinoses (LINCL)

- Assess anti-vector immunity
- Demonstrate efficacy in LINCL KO mice
- Increase functional enzyme levels in NHP
- pre-IND meeting
- Manufacture vector
- biodistribution study and IND-enabling toxicity studies in rat and NHP
- IRB, RAC submissions
- Submit IND

<table>
<thead>
<tr>
<th>Year 01</th>
<th>Year 02</th>
<th>Year 03</th>
<th>Year 04</th>
<th>Year 05</th>
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</thead>
<tbody>
<tr>
<td><strong>$ awarded</strong></td>
<td><strong>$ awarded</strong></td>
<td>Modified milestones <strong>$ awarded</strong></td>
<td><strong>$ awarded</strong></td>
<td>Modified milestones Delayed funding until IND feedback. Reduced budget</td>
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<tr>
<td>Met criteria for enzyme expression</td>
<td>Met efficacy criteria in KO mice</td>
<td>Pre-IND meeting held Yr 2</td>
<td>Advance NHP milestone Yr 3</td>
<td>Passed vector lot release criteria</td>
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</table>
Translating a CSF delivered AAV9-SMN for treatment of Spinal Muscular Atrophy

Improving Single Injection CSF Delivery of AAV9-mediated Gene Therapy for SMA: A Dose–response Study in Mice and Nonhuman Primates


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 guidelines; increase progress review frequency
- Flexibility: Access to contracts and consultants; project entry at various points; supplements to address unanticipated needs
Cooperative Research to Enable and Advance Translational Enterprises (CREATE)

Funding to advance potential therapeutics (biologics or devices) into clinical development

CREATE Bio Program
Modality: Biologics/Biotechnology Products

Purpose
- Discovery: Optimization of therapeutic leads
- Development: IND-enabling studies/Early phase clinical trials

End Goals
- Discovery: Characterize and select a lead candidate
- Development: Submit an IND application

Animal POC
Leads Optimization
IND Enabling Studies
Small Clinical Trials
Clinical POC

Discovery Track
Candidate
Development Track
Preparatory UH2
IND Enabling UH3
Small Clinical Trials UH3 (optional)

Early Clinical Development Asset

<table>
<thead>
<tr>
<th>Discovery Track (U01)</th>
<th>Development Track (UH2/UH3)</th>
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</thead>
<tbody>
<tr>
<td>Budget per year</td>
<td>&lt; $0.5 M year</td>
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<tr>
<td>Duration</td>
<td>Up to 4 years</td>
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</table>

Next Application Date: August 11, 2015
Cooperative Research to Enable and Advance Translational Enterprises (CREATE)

Funding to advance potential therapeutics (biologics or devices) into clinical development

CREATE Devices Program
Modality: Therapeutic Devices

- Informing Device Design: Pre-clinical/clinical studies to inform final device design
- 510(k) Market Approval: Pre-clinical/clinical studies leading to a 510(k)/510(k) De Novo submission
- PMA or HDE*: Pre-clinical/early clinical studies leading to a full Feasibility Study/Pivotal Trial in support of a PMA/HDE

*Pre-Market Approval (PMA) or Humanitarian Device Exemption (HDE)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Pre-Clinical (UH2/U44-I)</th>
<th>Clinical Study (UH3/U44-II)</th>
<th>Pre-Clinical (UH3/U44-II)</th>
<th>Optional Clinical Study (UH3/U44-II)</th>
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<tbody>
<tr>
<td>Informing Device Design</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>510(k) Market Approval</td>
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<tr>
<td>PMA or HDE</td>
<td></td>
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- FDA Pre-Submission Guidance
- FDA Submission

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<thead>
<tr>
<th>Category</th>
<th>UH2/U44-I</th>
<th>UH3/U44-II</th>
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<tbody>
<tr>
<td>Budget per year</td>
<td>&lt;1 M</td>
<td>&lt;1.5 M</td>
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<tr>
<td>Duration</td>
<td>Up to 3 years</td>
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<tr>
<td>Budget total</td>
<td>&lt;3 M</td>
<td>&lt;6 M</td>
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Next Application Date: August 11, 2015
NINDS uses a Variety of Translational Approaches

<table>
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<tr>
<th>Phase</th>
<th>Program Description</th>
<th>Funding</th>
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<tr>
<td>Anticonvulsant Screening Program (ASP)</td>
<td>$3.5 M</td>
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<td>Countermeasures Against Chemical Threats (CounterACT)</td>
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IGNITE: Innovation Grants to Nurture Initial Translational Efforts
CREATE: Cooperative Research to Enable and Advance Translational Enterprises

Blueprint Neurotherapeutics Network (BPN)

Combining strengths of NIH and industry for small molecule therapeutics

**BPN Program**

**Modality: Small Molecule**
- Discovery: Hit-to-lead and lead optimization
- Development: Formulation, scale up and manufacture, IND-enabling studies, and first-in-man clinical trials

**End Goals**
- Discovery: Characterize and select a preclinical candidate
- Development: Complete IND-enabling studies, file an IND and complete first-in-man trial
- Advance projects for hand-off
**Blueprint Neurotherapeutics Network**
Offering Infrastructure, Expertise, and Funding

![Diagram of the Blueprint Neurotherapeutics Network](image)

**Lead Development Team**
Principal Investigator*
Industry-seasoned consultants
NIH staff

- Bioactivity/Efficacy Studies
- Medicinal Chemistry
- Data Management
- PK/Tox
- Formulation/Manufacturing
- Phase I Clinical Trials

*PI retains intellectual property

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**BPN Consultants**

- **Assay development, pharmacology**
  - Lisa Minor
  - Bill Martin
  - Jeff Conn

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

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

- **Toxicology**
  - Marc Bailie
  - Steve Duddy
  - Gary Wolfe

- **Development**
  - Peter Farina
  - Mike Detke
  - Cristina Csimma
  - Gian Luca Araldi
  - Jon P. Lawson
  - John M. "Jay" Sisco

- **Upcoming**
  - Regulatory affairs, Phase I Clinical Pharmacology, Medical Writing, & Business Development

See bios at http://neuroscienceblueprint.nih.gov/bpdrugs/bpn.htm
Projects are Milestone-Driven
External Review Committee Assesses Progress Biannually

- Projects Launched
- Exploratory Studies
- Optimization Chemistry
- Pre-clinical safety testing
- Human safety testing (Phase I)
- Validated Assays
- Emerging SAR
- Milestones

Projects are Milestone-Driven
External Review Committee Assesses Progress Biannually

- High attrition rate anticipated
- New drug candidates licensed

External Oversight Committee
Peter Farina, PhD (chair)
Jeffrey Conn, PhD
Michael J. Detke, MD, PhD
John McGall, PhD
Cristina Csimma, PhD

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

<table>
<thead>
<tr>
<th>Principal Investigator</th>
<th>Institution</th>
<th>Disorder</th>
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<tr>
<td>Mark Gurney</td>
<td>Tetra Discovery Partners</td>
<td>Alzheimer’s</td>
</tr>
<tr>
<td>Susan Slaugenhaupt</td>
<td>Mass. General Hospital</td>
<td>Familial Dysautonomia</td>
</tr>
<tr>
<td>Paul Kenny</td>
<td>Eolas Therapeutics</td>
<td>Smoking Cessation</td>
</tr>
<tr>
<td>Steven Wagner</td>
<td>UC San Diego</td>
<td>Alzheimer’s</td>
</tr>
<tr>
<td>Konstantin Petrukhin</td>
<td>Columbia University/Cura</td>
<td>Macular Degeneration</td>
</tr>
<tr>
<td>Kirill Ostanin</td>
<td>Navigen</td>
<td>Macular Degeneration</td>
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<tr>
<td>Paul Humphries</td>
<td>Reset Therapeutics</td>
<td>Narcolepsy</td>
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<td>George Maynard</td>
<td>Axerion</td>
<td>Alzheimer’s</td>
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<td>John Bixby</td>
<td>University of Miami</td>
<td>Optic Neuropathy</td>
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<tr>
<td>Raymond Dingledine</td>
<td>Emory University</td>
<td>Stroke</td>
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<td>Marcie Glicksman</td>
<td>Brigham and Women’s Hospital</td>
<td>ALS</td>
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<td>Michael Lark</td>
<td>Trevena</td>
<td>Depression</td>
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<tr>
<td>Al Robichaud</td>
<td>Sage Therapeutics</td>
<td>Fragile X</td>
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<td>Edwin Rubel</td>
<td>University of Washington</td>
<td>Hearing Loss</td>
</tr>
<tr>
<td>D. James Surmeier</td>
<td>Northwestern University</td>
<td>Parkinson’s</td>
</tr>
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See abstracts at http://neuroscienceblueprint.nih.gov/bpdrugs/bpn.htm

Advance Projects for Hand-Off

Entry:
• Strong science
• BPN mission

Exit:
• External funding/partnership
• Other grants
• Attrition

Decreases risk as projects successfully advance development stages
BPN Recent Successes

Facilitated licensing of drug candidates:

- Macular degeneration drug candidate licensed to iCura
- New drug for mild cognitive impairment led to investment by Johnson & Johnson to project’s industry partner, Tetra Discovery Partners
- Orexin-1 receptor antagonist as a tobacco addiction treatment licensed to Eolas, who just signed an agreement with Astra Zeneca

What’s New in BPN 2016-2020

- 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

Preparatory Phase

<table>
<thead>
<tr>
<th>Discovery</th>
<th>Development</th>
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<tbody>
<tr>
<td>Hit to Lead</td>
<td>Lead Optimization</td>
</tr>
<tr>
<td></td>
<td>IND Enabling</td>
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</tbody>
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General (UH2/UH3)
- UH2: Up to $300K direct costs x 1 year
- UH3: Up to $1.5M/year direct costs x 4 years

SBIR (U44-I/II)
- Phase I: Up to $400K total costs x 1 year
- Phase II: Up to $4M total across 3 years

Next Application Date: August 11, 2015

Now Accepting New Applications

- PAR-14-293 for all applicants
- PAR-14-292 for small businesses (SBIR)
- Next applications due Aug. 11, 2015
- Peer review in Dec. 2015 (special review panel)
- For the following indications
  - Psychiatric disorders
  - Neurological disorders
  - Degenerative dementias of aging
  - Developmental disorders
  - Chronic pain conditions
  - Alcohol dependence
  - Drug addiction
NINDS uses a Variety of Translational Approaches

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IGNITE: Innovation Grants to Nurture Initial Translational Efforts
CREATE: Cooperative Research to Enable and Advance Translational Enterprises

Small Business Program Overview

- Congressionally mandated set-aside programs
- R&D with potential for commercialization
- ~$46M in FY2015 (3.3% of the extramural budget)
- Broad scope
  - Neurotherapeutics, diagnostics, and tools for neuroscience research
  - Bench research, translational research, and early stage clinical trials
Three Phase Program

- **Phase I**
  - Feasibility Study
  - $225K for up to 2 years
  - ($700K if a waiver topic)
- **Phase II**
  - Full Research/R&D
  - $1.5M for up to 3 years
  - ($3M if a waiver topic)
- **Phase IIIB**
  - Full Research/R&D
  - $1M/yr for up to 3 years
- **Phase III**
  - Commercialization Stage
  - Use of non-SBIR/STTR funds

Applicants should propose a budget that is reasonable and appropriate for completion of the research project.

Please contact us for guidance.

Small Businesses by Modality

- 2014:
  - Diagnostic: 19%
  - Biologic: 19%
  - Small molecule: 18%
  - Tool: 20%
  - Therapeutic device: 21%
  - Other: 3%
SBIR Recent Success

Lift Labs funded by SBIR to develop a spoon or fork attachment that cancels out hand tremor. Company acquired by Google in 2014.

http://www.google.com/liftware/

Additional Pipeline Needs to be Addressed

- Basic science
- In Vitro Assays
- Animal models
- Tools
- Bioactive Compounds
- Technology
- PD Markers
- Rigorous POC
- CREATE/BPN 2.0
Innovation Grants to Nurture Initial Translational Efforts (IGNITE)

1. Establish essential assays (in vitro and in vivo) to identify and optimize bioactive leads(s)
2. Characterize bioactive lead(s)
3. Deliver in vivo efficacy data using clinically relevant outcome measures and/or in vivo target engagement

Proposed Feeder Programs for Translational Pipeline

- **IGNITE (Animal Model Dev.)**: Launch late 2015
- **CREATE Devices**
- **CREATE Bio for Biotechnology Products and Biologics**
- **Blueprint Neurotherapeutics (BPN 2.0) for Small Molecules**
- **IGNITE (Platform Technology)**: Launch 2016
IGNITE

Planning/Development Phase
PAR-15-070: Assay Development and Validation
PAR-15-071: Further compound characterization including pharmacokinetic studies and planning for in vivo and pharmacodynamic studies

☑ Meet Milestones

Execution Phase
PAR-15-071: Pharmacodynamic, in vivo characterization of compound(s)

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<th>R21</th>
<th>R33</th>
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<tbody>
<tr>
<td>Budget per year</td>
<td>&lt; $0.25M</td>
</tr>
<tr>
<td>Duration</td>
<td>No more than 2 years</td>
</tr>
<tr>
<td>Budget total (R21/R33)</td>
<td></td>
</tr>
</tbody>
</table>

IGNITE Key Advantages

- Provides funding to seamlessly advance projects from the early discovery stage into late-stage translational funding programs
- Encourages investigators to clearly focus on stage-specific drug discovery goals and allows the time to do so
- Encourages:
  1. Characterization of therapeutic agents
  2. Planning, set up, and validation of testing paradigms and models
  3. Employment of RIGOR guidance
  4. Partnerships between academics and industry
NINDS uses a Variety of Translational Approaches

- Anticonvulsant Screening Program (ASP) $3.5 M
- Translational R21 (all modalities) / IGNITE $10 M
- CREATE Bio for Biotechnology Products and Biologics $19 M
- CREATE Devices $2 M
- Small Business Program: SBIR & STTR $45 M
- Blueprint Neurotherapeutics (BPN 2.0) for Small Molecules $14 M
- Countermeasures Against Chemical Threats (CounterACT) $47 M

Mission:
To develop FDA-approved therapeutics and diagnostic technologies that will reduce mortality and morbidity during and after chemical emergency events.
NIH Biodefense Program

NIAID Oversight

<table>
<thead>
<tr>
<th>Biological (~$1.7B)</th>
<th>Radiation/Nuclear (~$46M)</th>
<th>Chemical (~$47M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category A, B, C</td>
<td>Bomb detonation</td>
<td>Neurological, e.g., WMDs, sarin, pesticides</td>
</tr>
<tr>
<td>Bacterial, e.g., anthrax</td>
<td>Radiation Dispersal Device</td>
<td>Pulmonary, e.g., chlorine, phosgene</td>
</tr>
<tr>
<td>Viral, e.g., small pox</td>
<td>Attack on n. reactor or on spent fuels</td>
<td>Metabolic, e.g., cyanide, H₂S</td>
</tr>
<tr>
<td>Toxins, e.g., botulinum</td>
<td></td>
<td>Vesicants, e.g., arsenicals</td>
</tr>
</tbody>
</table>

Chemical Warfare
- World War I and II: thousands of fatalities
- Iran-Iraq War (1980-88): thousands of fatalities
- Current conflicts in the Middle East: thousands of fatalities

Terrorism/Non-military malicious use
- Jonestown mass suicide (1978): 900 dead
- Tylenol and Excedrin poisonings (1980’s): few fatalities

Industrial Accidents
- Occur Daily; thousands of injuries and fatalities annually
  - Dupont Corp. (WV – 2010): 3 Phosgene releases in 1 week
  - Bhopal Union Carbide disaster (1984): 5,000 fatalities from Methyl Isocyanate

General Poisonings
- 2.2 million calls to Poison Control Centers in 2012 alone
  - Brodifacoum, Pesticides

Burden of Illness

National Institutes of Health
Turning Discovery Into Health
Mission

The mission of the NIH CounterACT Program is to understand fundamental mechanisms of toxicity caused by chemical threat agents and the application of this knowledge to develop promising therapeutics for reducing mortality and morbidity caused by these agents.
**Products in the Pipeline**

<table>
<thead>
<tr>
<th>Basic</th>
<th>Translational</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target ID</td>
<td>Assay Development</td>
<td>Screening</td>
</tr>
<tr>
<td>NIH</td>
<td>BARDA</td>
<td></td>
</tr>
</tbody>
</table>

- Over 30+ “hits” and/or targets identified
- Neuregulin
- Brovana*
- Cobinamide (M)
- Midazolam*
- Rolipram
- Sulfanegen
- Galantamine*
- LY293558
- AEOL 10150 (M)
- Doxycycline*
- *BARDA: Biomedical Advanced Research & Development Authority

* Denotes FDA-approved compound for another indication

**Drug indication:**
- Black = Vesicants
- Red = Nerve Agents
- Blue = Pulmonary Agents
- Green = Cyanide
- (M) = multiple indications

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**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 FOAs (these are not typical NIH application)**
- **Show the data for assay validation, target validation, etc.**

[Review FAQs at program websites]
Prepare a robustness data package

Have multidisciplinary team to formulate the plans

Propose rigorous experiments with clear milestones for success and go/no-go

Talk to NINDS Program Staff

Check out FAQs, examples, and resources in the NINDS program website

Address IP Strategy

Plan ahead

Know the review environment - NINDS review

Rigorous Study Design and Reporting

Initial plans for clinical POC trial

Target Product Profile (TPP)

Talk to NINDS Program Staff
Questions?

rajesh.ranganathan@nih.gov

http://www.ninds.nih.gov/otr