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

February 2014

Rajesh Ranganathan, PhD
Director, Office of Translational Research
NINDS
rajesh.ranganathan@nih.gov
## Appropriations (Dollars in Thousands)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NINDS</strong></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>
</tr>
<tr>
<td><strong>NINDS % Change</strong></td>
<td>Base</td>
<td>0.2%</td>
<td>-5.6%</td>
<td>3.6%</td>
<td>1.0%</td>
</tr>
<tr>
<td><strong>NIH</strong></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>
</tr>
<tr>
<td><strong>NIH % Change</strong></td>
<td>Base</td>
<td>0.6%</td>
<td>-5.5%</td>
<td>3.4%</td>
<td>0.5%</td>
</tr>
</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
Total NINDS Extramural Grants Budget

NINDS Extramural Grant Dollars (in Billions)

- NINDS Extramural
- adjusted to 1995 dollars
- with ARRA
- with ARRA--adjusted to 1995 dollars
FY 2013 Taxpayer Investment in Neuroscience Now Exceeds Cancer

Dollars in Billions (FY 2013)

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

The Problem

Unmet need in hundreds of neurological disorders
FY 2015 Appropriation Budget Distribution

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

- Extramural: 1,385,870 (86.4%)
- Intramural: 159,498 (9.9%)
- RMS: 59,239 (3.7%)

Dollars in Thousands
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)
  o Develop translatable measures of PK/PD and target engagement
  o Integrate clinical perspective

• Establish fail-early, fail-fast approach to portfolio management
  o Milestone assessment critical to project progression
  o Embrace early termination as success and learning opportunity

• Can’t do it alone – need partnerships and handoffs
  o De-risk projects for downstream funding
  o Actively facilitate partnership discussions
NINDS uses a Variety of Translational Approaches

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
- Second track added in 2007 for chemical nerve agent countermeasures
- 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

Adapted from Loscher & Schmidt, 2011, Epilepsia, 52:657
History of Antiepileptic Drugs (AEDs)

Adapted from Loscher & Schmidt, 2011, Epilepsia, 52:657
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
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
Cooperative Agreement Projects active in 2014 (n=18)

*Other: One project to make DBS compatible with MRI
Portfolio (n=80) by Interventional Modality (2002-2014)

- Small Molecule: 36.4%
- Nucleic Acid: 27.3%
- Device: 13%
- Protein: 9%
- Cell Therapy: 6.5%
- Peptide: 3.9%
- Other: 3.9%

Other: Vaccine, Dog Center, Drug Discovery Center
Translational R21 by Indication 2014 (n=54)

Other: Arteriovenous Malformation, CIDP, Guillain-Barre Syndrome, HIV, Huntington's, Neonatal Encephalopathy, Nerve Injury, Neurodegenerative Diseases, Neurofibromatosis, Neuropathy, Parkinson's, PSP, Rett's Syndrome, Spinocerebellar Ataxia, TBI
Translational R21 by Approach 2014 (n=54)
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
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

Kathrin Meyer¹, Laura Ferraiuolo¹, Leah Schmelzer¹, Lyndsey Braun¹, Vicki McGovern², Shibi Likhite¹,³, Olivia Michels¹, Alessandra Govoni¹, Julie Fitzgerald⁵, Pablo Morales⁴, Kevin D Foust⁵, Jerry R Mendell¹,³,⁵, Arthur HM Burghes² and Brian K Kaspar¹,³,⁵
Cooperative Research to Enable and Advance Translational Enterprises (CREATE)

- **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

- **Modalities: Biologics and Devices**

Funding to optimize therapeutic biologic leads or devices and to advance these potential therapeutics into clinical development.
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
CREATE Bio Program

Animal POC ➔ Lead Optimization ➔ IND Enabling Studies ➔ Small Clinical Trials ➔ Clinical POC

Discovery Track
- U01
- Preparatory (UH2)
- Development (UH2/UH3)
- IND
- Early Clinical Development Asset

Development Track
- IND Enabling (UH3)
- Small Clinical Trials (UH3, optional)

Candidate

<table>
<thead>
<tr>
<th></th>
<th>Discovery Track (U01)</th>
<th>Development Track (UH2/UH3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budget per year</td>
<td>&lt;$0.5 M year</td>
<td>&lt; $1 - 1.5 M</td>
</tr>
<tr>
<td>Duration</td>
<td>Up to 4 years</td>
<td>Up to 5 years</td>
</tr>
</tbody>
</table>
CREATE Devices

Research Device

Pre-Clinical (UH2)  Feasibility Clinical Study (UH3)

510(k) Therapeutic Device

Pre-Clinical (UH2)  Clinical Study (UH3)

PMA/HDE Therapeutic Device

Pre-Clinical (UH2)  PreClinical Study (UH3)  Clinical Study (UH3)

<table>
<thead>
<tr>
<th></th>
<th>UH2</th>
<th>UH3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budget per year</td>
<td>&lt;$1 M</td>
<td>&lt;$1.5 M</td>
</tr>
<tr>
<td>Duration</td>
<td>Up to 3 years</td>
<td>Up to 4 years</td>
</tr>
<tr>
<td>Budget total</td>
<td>&lt;$3 M</td>
<td>&lt;$6 M</td>
</tr>
</tbody>
</table>

Pre-Market Approval (PMA) or Humanitarian Device Exemption (HDE)
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
BPN: Combining 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

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

*PI retains intellectual property

Medicinal Chemistry
Data Management
PK/Tox
Formulation/Manufacturing
Phase I Clinical Trials

Bioactivity/Efficacy Studies

*PI retains intellectual property

AMRI
CDD
Southern Research Institute
NIH
BPN
MRI Global
SRI International

NIH
National Institute of Neurological Disorders and Stroke
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://neuroscienceblueprint.nih.gov/bpdrugs/bpn.htm
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)
- New drug candidates licensed

Milestones
Validated Assays
Emerging SAR

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

<table>
<thead>
<tr>
<th>Principal Investigator</th>
<th>Institution</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<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>Kirill Ostanin</td>
<td>Navigen</td>
<td>Macular Degeneration</td>
</tr>
<tr>
<td>Konstantin Petrukhin</td>
<td>Columbia University/iCura</td>
<td>Macular Degeneration</td>
</tr>
<tr>
<td>Paul Humphries</td>
<td>Reset Therapeutics</td>
<td>Narcolepsy</td>
</tr>
<tr>
<td>George Maynard</td>
<td>Axerion</td>
<td>Alzheimer’s</td>
</tr>
<tr>
<td>John Bixby</td>
<td>University of Miami</td>
<td>Optic Neuropathy</td>
</tr>
<tr>
<td>Raymond Dingledine</td>
<td>Emory University</td>
<td>Stroke</td>
</tr>
<tr>
<td>Marcie Glicksman</td>
<td>Brigham and Women’s Hospital</td>
<td>ALS</td>
</tr>
<tr>
<td>Michael Lark</td>
<td>Trevena</td>
<td>Depression</td>
</tr>
<tr>
<td>Al Robichaud</td>
<td>Sage Therapeutics</td>
<td>Fragile X</td>
</tr>
<tr>
<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>
</tbody>
</table>

See abstracts at [http://neuroscienceblueprint.nih.gov/bpdrugs/bpn.htm](http://neuroscienceblueprint.nih.gov/bpdrugs/bpn.htm)
Phosphodiesterase 4D (PDE4D) Allosteric Modulators for Treating Cognitive Impairment in Mild to Moderate AD
Mark Gurney, PhD, Tetra Discovery Partners

CENTRAL HYPOTHESIS
Allosteric modulators that do not fully inhibit PDE4D will improve cognition without the emetic side effects of active-site inhibitors
Goal: Advance Projects for Hand-Off

- Strong biological validation
- Compounds amenable to med. chem.
- Robust assays for optimization

Milestone driven, expert review, industry validation, cost sharing…

Risk decreases as projects successfully advance
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 Feasibility

Hit-to-Lead/Lead Optimization (SAR)  IND-Enabling  Phase I Trials

Discovery  Development

UH3 U44-II  UH2 U44-I  General SBIR
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
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
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
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
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
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
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 - $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

NIH National Institute of Neurological Disorders and Stroke
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 IIB**
  - 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: 21%
- Small molecule: 18%
- Tool: 19%
- Therapeutic device: 3%
- Other: 20%

NIH National Institute of Neurological Disorders and Stroke
The goal of this Fast Track application is to move stromab further towards human trials by following FDA guidance to: 1) determine the optimal formulation and therapeutic time window for treatment, 2) produce and purify stromab under GLP conditions, 3) investigate the safety, pharmacokinetics and pharmacodynamics of stromab and, 4) submit an IND to the FDA.

Feb 3 2015
StromAb, First-In-Class Antibody Dissolves Thrombus In ACUTE Stroke & Cardiovascular Disease, In Production Phase I Clinical Trials

Translational Sciences Inc. announces that StromAb is in production on Phase I Clinical Trials.

http://www.prweb.com/releases/2013/11/prweb11351177.htm
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
Innovation Grants: Preparation for Advanced Discovery and Early Development

1. Characterize bioactive lead(s)

2. Establish essential assays (in vitro and in vivo) to identify and optimize bioactive leads(s)

   Deliver in vivo efficacy data using clinically relevant outcome measures and/or in vivo target engagement
Proposed Feeder Programs for Translational Pipeline

- **IGNITE (Assay Development)**: Launch Dec. 2014; First receipt date Feb. 2015
- **IGNITE (PD & Efficacy)**: Launch Dec. 2014; First receipt date Feb. 2015
- **IGNITE (Animal Model Dev.)**: Launch mid 2015
- **CREATE Devices**: Launch mid 2015
- **CREATE Bio for Biotechnology Products and Biologics**: Launch mid 2015
- **Blueprint Neurotherapeutics (BPN 2.0) for Small Molecules**: Launch mid 2015

IGNITE: Innovation Grants to Nurture Initial Translational Efforts

IGNITE: Innovation Grants to Nurture Initial Translational Efforts
### 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)

<table>
<thead>
<tr>
<th></th>
<th>R21</th>
<th>R33</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Budget per year</strong></td>
<td>&lt; $0.25M</td>
<td>&lt; $0.5M</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>No more than 2 years</td>
<td>No more than 2 years</td>
</tr>
<tr>
<td><strong>Budget total (R21/R33)</strong></td>
<td>&lt;0.75M for Entire 3 Year Period</td>
<td>&lt;0.75M for Entire 3 Year Period</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

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 $45 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
NIH CounterACT
Countermeasures Against Chemical Threats

Mission:
To develop FDA-approved therapeutics and diagnostic technologies that will reduce mortality and morbidity during and after chemical emergency events.
Burden of Illness

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
- Tokyo Subway Attacks (1995): *thousands affected; 12 dead*
- 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
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.
NIH Biodefense Program

NIAID Oversight

### NIAID Management

**Biological (~$1.7B)**
- Category A, B, C
- Bacterial, e.g., anthrax
- Viral, e.g., small pox
- Toxins, e.g., botulinum

**Radiation/Nuclear (~$46M)**
- Bomb detonation
- Radiation Dispersal Device
- Attack on n. reactor or on spent fuels

### NINDS Management

**Chemical (~$47M)**
- Neurological, e.g., WMDs, sarin, pesticides
- Pulmonary, e.g., chlorine, phosgene
- Metabolic, e.g., cyanide, H₂S
- Vesicants, e.g., arsenicals
Products in the Pipeline

**Basic**
- Target ID
- Assay Development
- Screening

**Translational**
- Proof of Principle
- Optimization/Preclinical Efficacy
- Pre-IND/IDE Studies

**Clinical**
- Clinical Trials

NIH   |   BARDA

Over 30+ “hits” and/or targets identified

Neuregulin
Brovana*
Rolipram
Sulfanegen
Galantamine*
LY293558
AEOL 10150 (M)
Doxycycline*

Cobinamide (M)
Midazolam*

*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
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
Planning Essentials

- Keep the end in mind ...
  Target Product Profile (TPP)
  Initial plans for clinical POC trial

- Have multidisciplinary team to formulate the plans

- Prepare a robustness data package
  Propose rigorous experiments with clear milestones for success and go/no-go

- Know the review environment - NINDS review

- Rigorous Study Design and Reporting

- Talk to NINDS Program Staff

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

- Address IP Strategy

- Plan ahead
Planning Essentials

Talk to NINDS Program Staff
Questions?

rajesh.ranganathan@nih.gov

http://www.ninds.nih.gov/funding/areas/translational_research/index.htm