NINDS Director’s Report
Advisory Committee to the Director
May 13, 2013
The mission of **NINDS** is to reduce the burden of neurological disease…. To support this mission, NINDS conducts, fosters, coordinates, and guides research on the causes, prevention, diagnosis, and treatment of neurological disorders and stroke, and supports basic research in related scientific areas.

**NIH’s** mission is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce the burdens of illness and disability.
Funding of basic neuroscience is shared

- Early predoctoral training is jointly supported
  - T32 program initiated by Zach Hall
  - 182 slots from 8 IC
  - NINDS provides about 50%
- Seven plus Institutes fund basic neuroscience
  - NEI, NIDCD, NIDA, NIAAA, NICHD, NIA, NIMH
- Proportion and emphasis varies with IC mission
- NIH Blueprint for Neuroscience serves to coordinate efforts and to support some projects
Recent NINDS funded basic advances

- Identification of itch specific primary sensory neurons through their expression of a specific G-protein coupled receptor
- Recently born neurons in the hippocampus are essential for memory retrieval
- Expanded hexanucleotide repeat in C9ORF72 causes FTD and ALS
- $\alpha$ synuclein fibrils injected into mouse striatum leads to cell-cell transmission and dopamine cell death
Disseminating optogenetics tools

- In 2006 Karl Deisseroth developed a research tool to turn the activity of specific subsets of brain cells on and off with pulses of light
- NINDS ARRA funding adapted technology to non-genetic animal models
- NINDS grant supplements to allow technology adoption
- Hundreds of investigators now use to dissect neural circuits
- Defining how deep brain stimulation and the direct and indirect pathways affect basal ganglia in Parkinson’s
- Identification of a neural circuit for fear memory
NINDS is responsible for many diseases

- Common diseases: stroke, epilepsy, Parkinson’s and multiple sclerosis
- Rare disorders: ALS, spinal muscular atrophy, muscular dystrophies, lysosomal storage disorders
- Treatments for some
  - tPA for stroke
  - New antiepileptics
  - DBS for Parkinson’s
  - Copaxone, B-interferon, immunomodulators etc for MS
- Little or no pharma interest
Recent Phase 3 clinical trial results

- Coenzyme Q10 is safe but not beneficial for Parkinson’s Disease patients
- Aggressive medical treatment alone is better for intracranial stenosis than treatment plus stenting
- Clot retrieval devices failed to improve stroke related disability
- Medical management is superior to intervention for patients with unruptured brain arteriovenous malformations
- Intramuscular midazolam is the optimal prehospital treatment for status epilepticus
Generating better models: Fibroblasts and iPSC

Opportunity
• Rapid advances in iPSC technology from 2006-2009
• Genes identified for neurodegenerative diseases
• NINDS repository to house and distribute cells

Consortium Concept
• Identify leaders in stem cells and neurodegenerative diseases
  Create teams work effectively in a competitive space
• Engage industry

ARRA investment and renewed with public private partnerships
• $11 M for 3 consortia addressing Huntington’s Disease,
  Parkinson’s Disease and amyotrophic lateral sclerosis
• $6M for extension – 4.5M NINDS 1.5 CIRM and NGOs
• In-kind industry contributions
Fibroblast lines in NINDS repository

Fibroblast distribution

Generating better models: Fibroblasts and iPSC
Generating better models: Fibroblasts and iPSC

iPSC lines in NINDS repository

iPSC Distribution

Industry 40%

Academia 60%

ALS
HD
Parkinson's Disease

iPSC Distribution

Control ND20179
SCNA ND32391
LRRK2 ARG1441CRY ND34392
LRRK2 ARG1441CRY ND34393
LRRK2 ARG1441CRY ND35371
LRRK2 GLV2015SER ND35367
LRRK2 GLV2015SER ND38477
PARK2 EX3 4DEL ND38477
PARK2 EX3 4DEL ND38477
PARK2 EX3 4DEL ND38477
PARK2 EX3 4DEL ND38477
FUS GLV22ALA ND39034
HD CAG: 33 ND35698
HD CAG: 50 ND38551
HD CAG: 60 ND38554
HD CAG: 17 ND38554
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Generating better models: Fibroblasts and iPSC

Primary Neuron Models of PD and HD

Parkinson’s Disease

- LRRK2
- Synuclein

Huntington’s Disease

- Huntingtin

Cumulative Risk of Death over Time (h)

- Q103
- Q72
- Q46
- Q17

Microscopy images:
- MERGED
- TH
- FOXA2
- TUJ-1
- DAPI
The NINDS Cooperative Agreement Program for Translation

• Provide support to investigators to obtain IND or IDE
• Projects must have a therapeutic lead with *in vivo* proof-of-concept efficacy data
• OR *in vivo* models that include a pharmacodynamic biomarker for the intended therapeutic using clinical route of administration
• Device projects must have a clinically meaningful outcome based on clinician and patient input
• Milestone driven
• Activities include:
  • Preclinical efficacy testing
  • Predictive ADME (*absorption, distribution, metabolism, and excretion*)
  • Toxicology testing
  • IND/IDE submission
  • Phase 0 clinical trials
# Translational Projects Reaching IND and Beyond

<table>
<thead>
<tr>
<th>Principal Investigator</th>
<th>Institution</th>
<th>Disorder</th>
<th>Therapeutic Approach</th>
<th>Project End Date</th>
<th>Clinical Trial</th>
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<tbody>
<tr>
<td>Ralph Snodgrass</td>
<td>Vistagen Therapeutics, Inc.</td>
<td>Epilepsy / Neuropathic Pain</td>
<td>Drug</td>
<td>2008</td>
<td>Phase I</td>
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<td>Howard Federoff</td>
<td>Georgetown University Medical Center</td>
<td>Parkinson’s</td>
<td>Nucleic Acid Therapy</td>
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<td>Xiao Xiao</td>
<td>University of North Carolina</td>
<td>Duchene Muscular Dystrophy</td>
<td>Nucleic Acid Therapy</td>
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<td>Cesario Borlongan</td>
<td>University of South Florida</td>
<td>Stroke</td>
<td>Cell Therapy</td>
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<td>Phase II</td>
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<td>Ronald Crystal</td>
<td>Weill Medical College – Cornell University</td>
<td>Batten Disease</td>
<td>Nucleic Acid Therapy</td>
<td>2010</td>
<td>Phase I/II</td>
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<td>Guohua Xi</td>
<td>University of Michigan</td>
<td>Stroke</td>
<td>Drug</td>
<td>2012</td>
<td>Phase II</td>
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</table>
Translational Research: PD Biomarkers Programs

Trials to develop neuroprotective therapies require 5-7 years and 1000’s of patients.

Need to have biological markers of efficacy that will provide answers in 2-3 years

PDBP Goal: to rapidly identify and develop biomarkers to improve the efficacy and outcome of clinical trials, and to advance therapeutic discovery for PD

- Studies in Parkinson’s Disease Biomarkers Discovery (U18)
- Exploratory Laboratory and Analysis Projects in Parkinson’s Disease Biomarkers (U01)

BioFIND: new NINDS and MJFF collaboration for biomarkers discovery
A filter for Phase 3 trials: NeuroNEXT

- Test promising therapeutics in Phase 2 trials
  - Using biomarkers when available
  - Providing results for Go/No go decisions
- Accelerate drug development through an established clinical trials infrastructure
  - Build on strengths of the NCATS CTSAs (21 of 25 sites)
  - Sharing expertise between disease areas
- Decrease the time/cost between trial design and completion
  - Using a central IRB and standing master trial agreements
- Coordinate public private sector efforts
  - Testing the best therapeutics whether from academic or industry
  - Leveraging NINDS relationships with academic investigators and patient groups
NeuroNEXT: Sites

CCC-Mass General Hospital
DCC-University of Iowa
NeuroNEXT: Is it working?

- All NeuroNEXT sites executed a reliance agreement with the central IRB (CIRB) with an average of 25 days.
- All NeuroNEXT sites executed their master clinical trial agreements with an average time of 50 days.
- Spinal Muscular Atrophy (SMA) Biomarkers in the Immediate Postnatal Period PI: Kolb at OSU
  - 15 sites; 54 subjects
  - Central IRB approval of parent protocol in 55 days.
- Phase II Clinical Trial of Ibudilast in Progressive MS: Fox at Cleveland Clinic
  - Evaluate activity and safety of ibudilast, a PDE inhibitor with anti-inflammatory properties that suppresses glial activation.
  - Use imaging markers of tissue integrity.
  - IRB submission of protocol March, first patient in Oct.
- Have already made changes to streamline processes.
Common Data Elements (CDE) Project

• There are no widely used data standards in NINDS funded clinical research

• Identify common data elements (CDEs) used in clinical research and develop definitions

• Standardize case report forms and provide standard format so that clinical data are systematically collected across research community

• Facilitate data sharing and meta-analyses
Current Project Status

CDEs available for use are found at: http://www.commondataelements.ninds.nih.gov/
NINDS budget

FY 2013 Budget: $1,532,488K

- Extramural: $1,324,250 (86.4%)
- Intramural: $152,116 (9.9%)
- RMS: $56,122 (3.7%)
Managing our budget

- In 2001, the midpoint of the doubling, our payline was the 26th percentile.
- Grants/initiatives expanded during the doubling.
- As budget flattened the NINDS payline dropped 3 or 4 percentile points each year and by FY07 it was the 9th percentile.
- Guided by recommendations from an extensive planning process, we closed programs, changed strategies and improved management of our clinical and translational programs.
- Our FY13 payline is 14th percentile.
- Need to find balance between basic, translational and clinical portfolios.
Categories of Research

• **Basic:**
  - **Basic/Basic:** Research to understand the normal functions of the nervous system, whether in vitro, in animals, or in humans (e.g. ion channel structure; cognitive neuro)
  - **Basic/Disease-Related:** Research on disease mechanisms, and research that derives its primary rationale from diseases whether in vitro, in animals, or in humans (e.g. research on disease gene identification; normal functions of disease-causing genes)

• **Applied:** Research to develop or test diagnostics, therapeutics, or preventive interventions, whether in animals, humans, or in vitro. Includes all stages of development from proof of concept in disease models to human clinical trials.
  - **Applied - Translational:** Translational should include all studies up to (but not including) first in human studies
  - **Applied - Clinical:** Clinical should include first in human studies through phase III trials. Category will essentially include all applied research in humans.
Balance by competing dollars (basic vs applied)

<table>
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<tr>
<th>Year</th>
<th>Basic</th>
<th>Applied</th>
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<tbody>
<tr>
<td>2002</td>
<td>77%</td>
<td>23%</td>
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<tr>
<td>2010</td>
<td>68%</td>
<td>32%</td>
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</tbody>
</table>

Δ +9%  
Δ -9%
Balance by competing dollars (all categories)

- **2002**: $263M
  - Basic; Basic: 34%
  - Basic; Disease-Related: 11%
  - Applied; Translational: 43%
  - Applied; Clinical: 12%

- **2010**: $288M
  - Basic; Basic: 24%
  - Basic; Disease-Related: 16%
  - Applied; Translational: 44%
  - Applied; Clinical: 24%

Changes:
- Basic; Basic: ∆+4%
- Basic; Disease-Related: ∆+5%
- Applied; Translational: ∆+1%
- Applied; Clinical: ∆-10%
Total dollars spent on R21s has increased

- 3.6% of budget for 2012
- 3.2% of budget before 2012
- 5.4% of budget

*Translational Program is not included*
The Porter Neuroscience Center

- A research building devoted to brain sciences
- Phase 1 completed 2003
- Phase 2 scheduled for fall 2013
- ARRA funded
- 600,000 sq ft
- 85 investigators
- 10 Institutes
NIH Blueprint for Neuroscience Research

- Sixteen Institutes, Centers and Offices
- Participating ICs contribute 0.6% of their neuroscience budget to a common fund
- Annual budget of 36M is < 1% of NIH investment in neuroscience research
- Funds allow exploration of new strategies to accelerate progress in the neurosciences
NIF: Neuroinformatics Framework

- The largest searchable collation of neuroscience data on the web
- The largest catalog of biomedical resources (data, tools, materials, services) available
- The largest ontology for neuroscience
- NIF search portal: simultaneous search over data, NIF catalog and biomedical literature
- Neurolex Wiki: a community wiki serving neuroscience concepts
- A reservoir of cross-disciplinary biomedical data expertise

“This unique data depository serves as a model for other Web sites to provide research data. “ - Choice Reviews Online
Human Connectome Project
09/15/2010 – 08/31/2015 (approx $40M Blueprint)

Two Research Teams: MGH – UCLA & Washington U-U Minnesota
Both are advancing technology for brain imaging and mapping neural circuits

**MGH - UCLA**
- Optimize *Connectom* for the collection of *in vivo* structural connectivity data from healthy adult humans.
- Disseminate new acquisition for tractography and connectomics

**Wash U – U Minn**
- Study twins and their non-twin siblings in a cohort size of 1,200 subjects (~300 families).
- Characterize adult human brain circuitry, including its variability and its relation to behavior and genetics.
- Freely available data; user-friendly informatics platform and workbench
- Resource for discovery science and baseline for brain disorders
- First 68 connectomes available
Connectome Workbench:
Overlay myelin maps (Glasser & Van Essen, 2011)
Blueprint Neurotherapeutics Project:
An experiment in 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
“Virtual Pharma” Model
NIH Provides Drug Discovery Infrastructure, Expertise, and Funds

Lead Development Team
Principal Investigator
Industry-seasoned consultants
NIH staff

- U01s
  - Bioactivity/Efficacy Studies

NIH Contracts
- Medicinal Chemistry
  - AMRI
- PK/Tox
  - Southern, SRI
- Data Management
  - CDD
- Formulation
- GMP Scale-Up Synthesis
- Phase I Clinical Trials
# Current BPN Portfolio

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<thead>
<tr>
<th>Assay Validation</th>
<th>Exploratory Chemistry</th>
<th>Hit-to-Lead Chemistry</th>
<th>Proof of Concept</th>
<th>Lead Optimization</th>
<th>Candidate Selection</th>
<th>Preclinical Safety</th>
<th>Phase I Trial</th>
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4 projects discontinued (not listed)