

**NINDS Director's Report**  
**Advisory Committee to the Director**  
May 13, 2013

# Mission statements

- ❑ 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

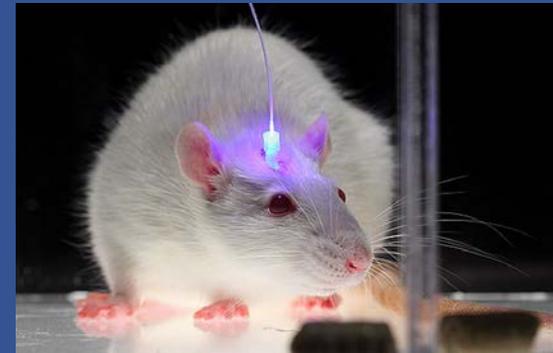
# Recent NINDS funded basic advances

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- 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

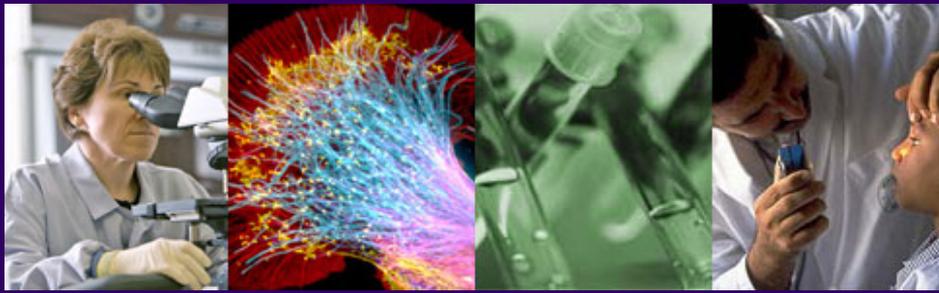


# NINDS is responsible for many diseases

- 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**

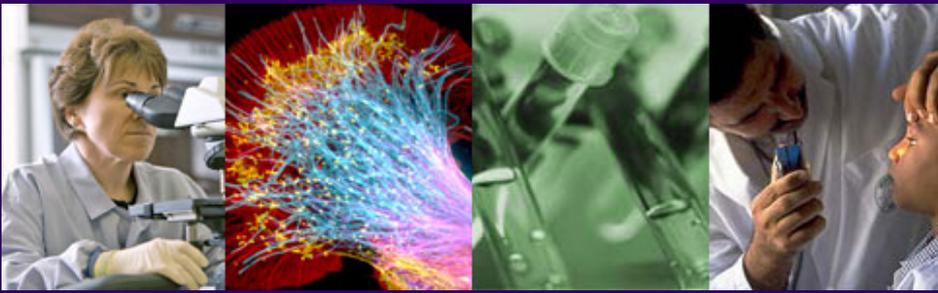
- Rapid advances in iPSC technology from 2006-2009
- Genes identified for neurodegenerative diseases
- NINDS repository to house and distribute cells

### **Consortium Concept**

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

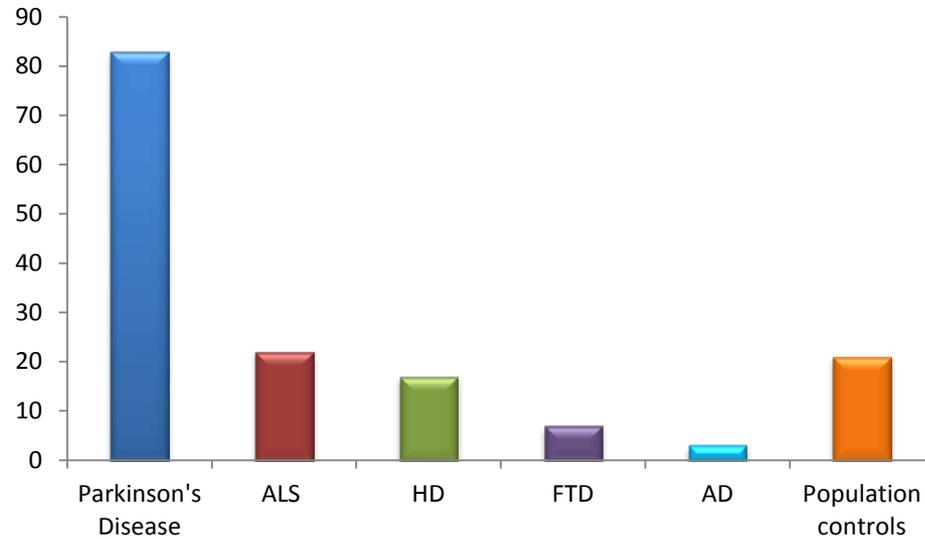
### **ARRA investment and renewed with public private partnerships**

- \$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

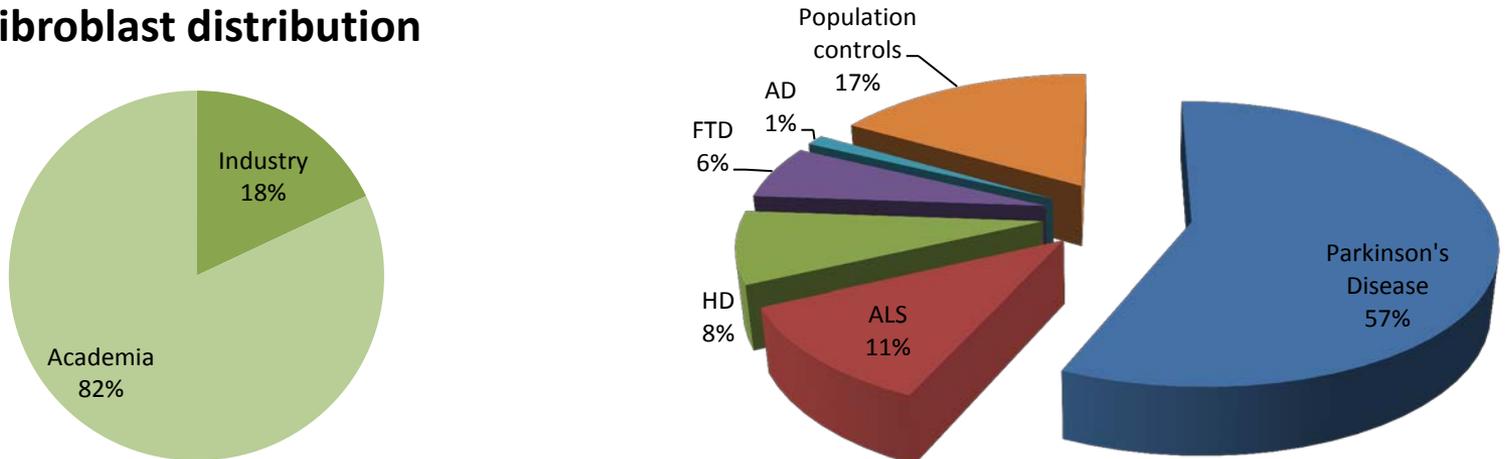


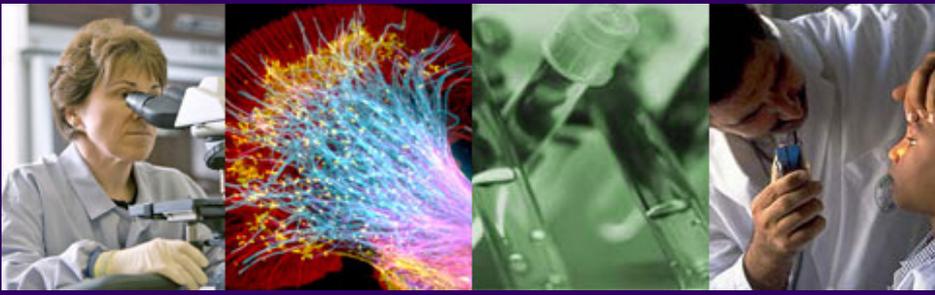
# Generating better models: Fibroblasts and iPSC

## Fibroblast lines in NINDS repository



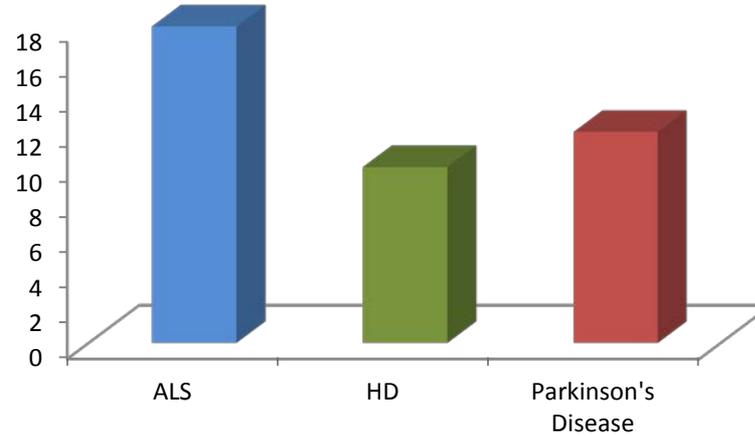
## Fibroblast distribution



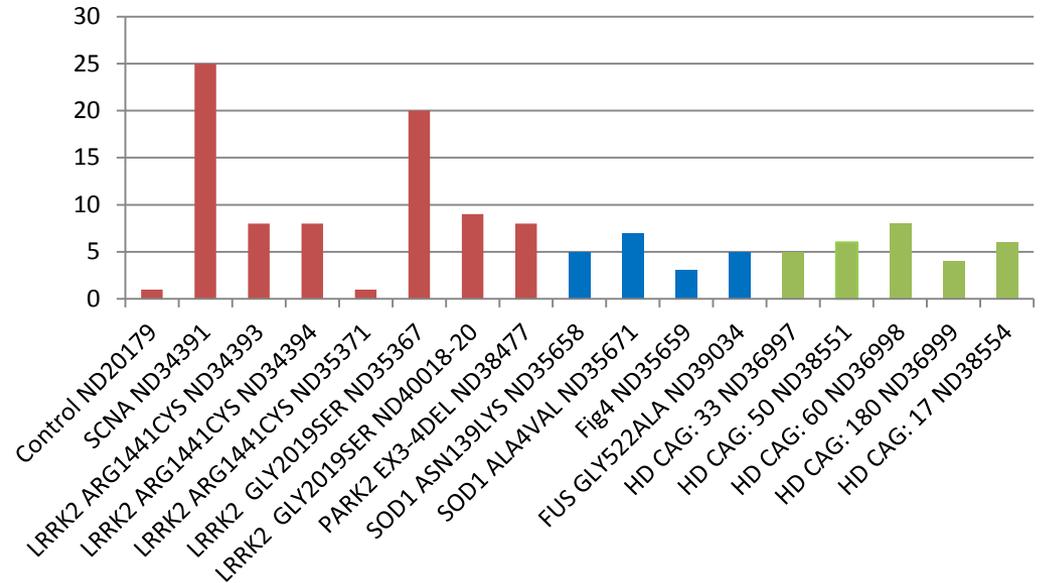
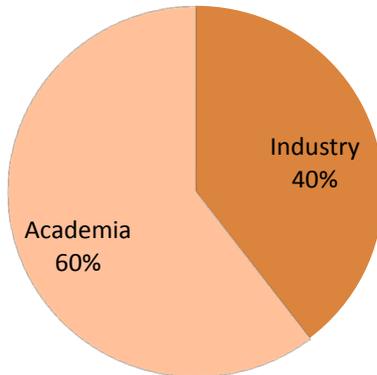


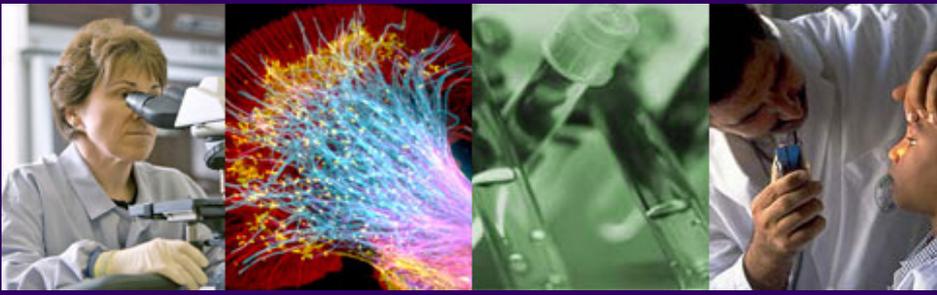
# Generating better models: Fibroblasts and iPSC

## iPSC lines in NINDS repository



## iPSC Distribution





# Generating better models: Fibroblasts and iPSC

## Primary Neuron Models of PD and HD

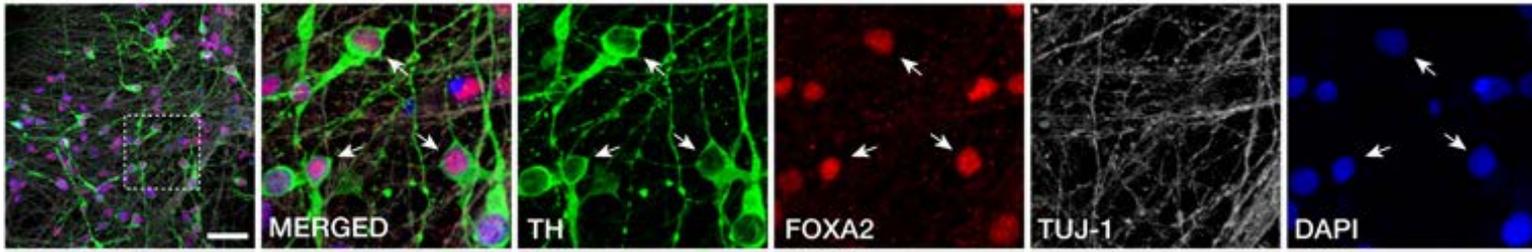
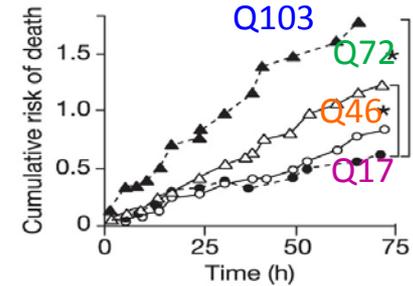
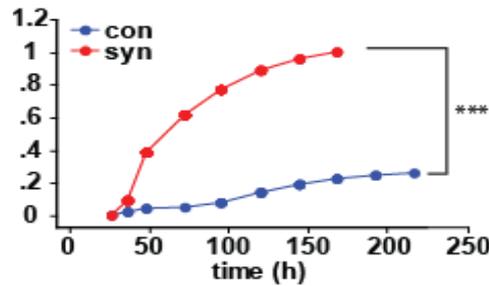
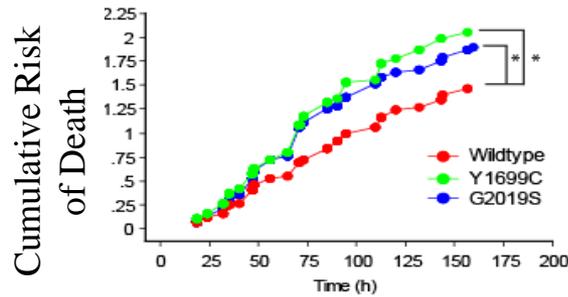
### Parkinson's Disease

### Huntington's Disease

#### LRRK2

#### Synuclein

#### Huntingtin

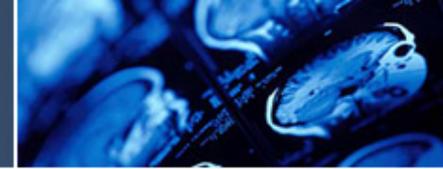


# The NINDS Cooperative Agreement Program for Translation

- 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

Principal Investigator	Institution	Disorder	Therapeutic Approach	Project End Date	Clinical Trial
Ralph Snodgrass	Vistagen Therapeutics, Inc.	Epilepsy / Neuropathic Pain	Drug	2008	Phase I
Howard Federoff	Georgetown University Medical Center	Parkinson's	Nucleic Acid Therapy	2009	Phase I
Xiao Xiao	University of North Carolina	Duchene Muscular Dystrophy	Nucleic Acid Therapy	2009	Phase I
Cesario Borlongan	University of South Florida	Stroke	Cell Therapy	2009	Phase II
Ronald Crystal	Weill Medical College – Cornell University	Batten Disease	Nucleic Acid Therapy	2010	Phase I/II
Guohua Xi	University of Michigan	Stroke	Drug	2012	Phase II



# 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

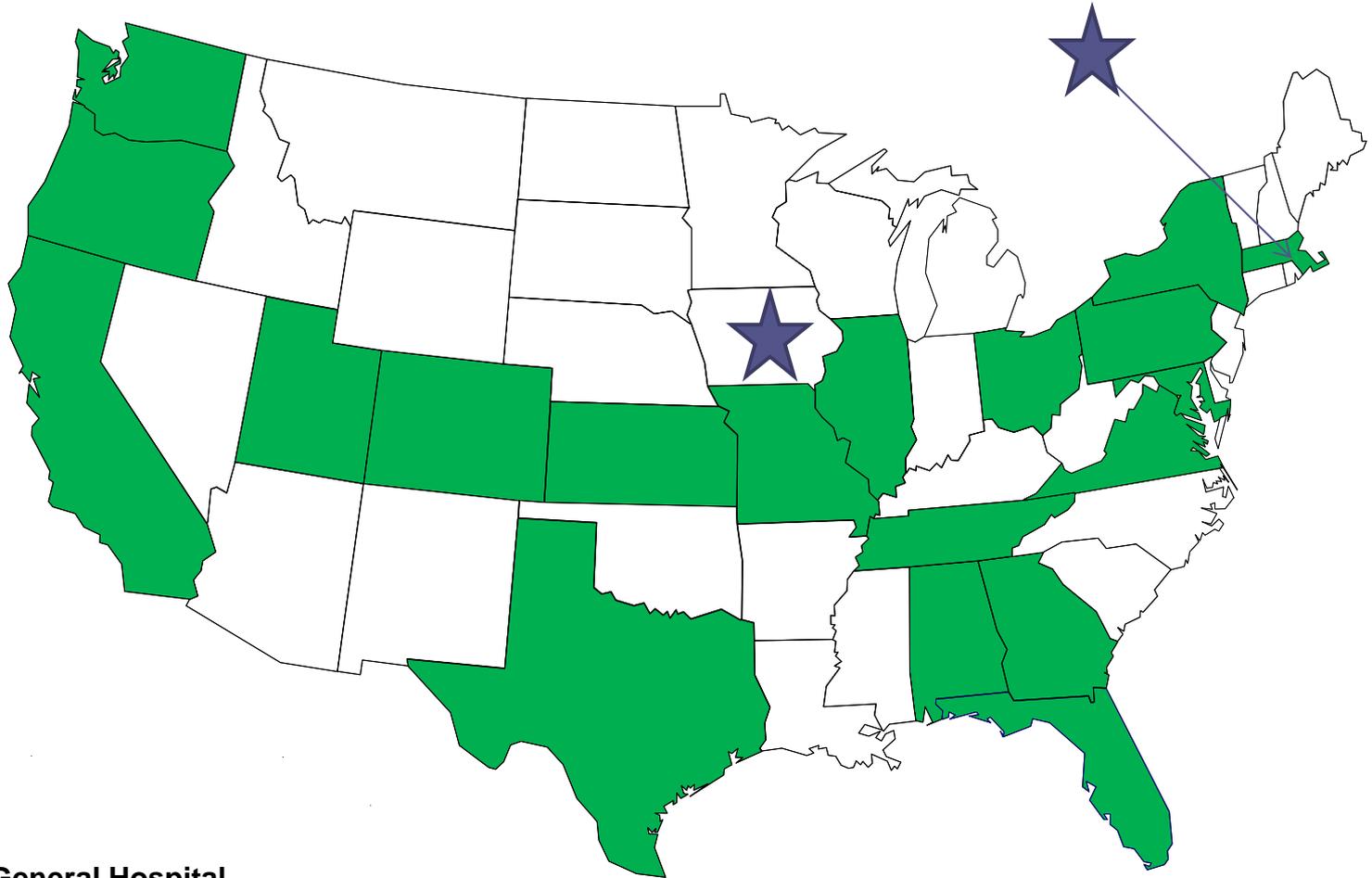
**NINDS  
Parkinson's  
Disease  
Biomarkers  
Program  
(PDBP)**



# 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 CTSA's (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

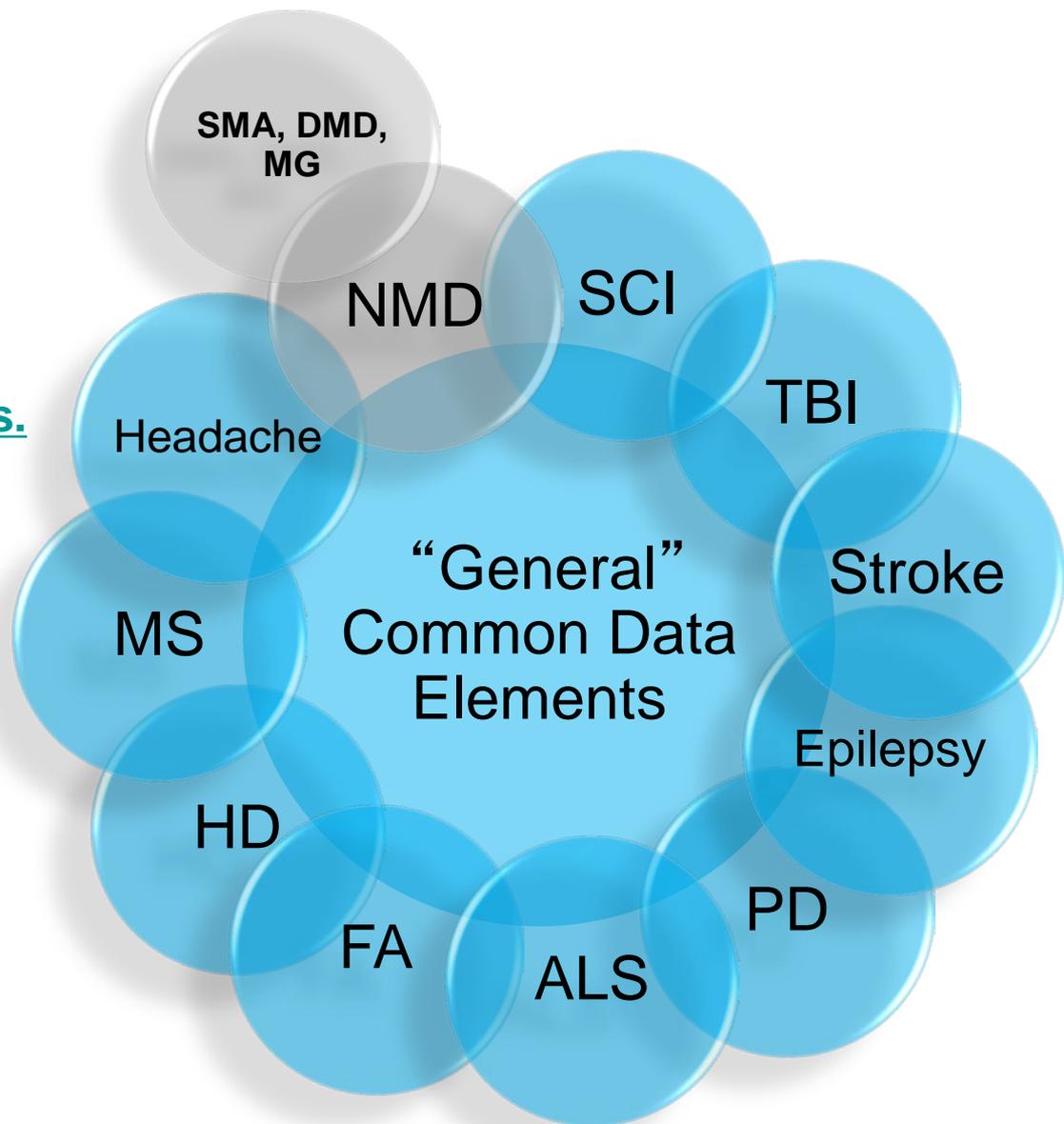


# Current Project Status

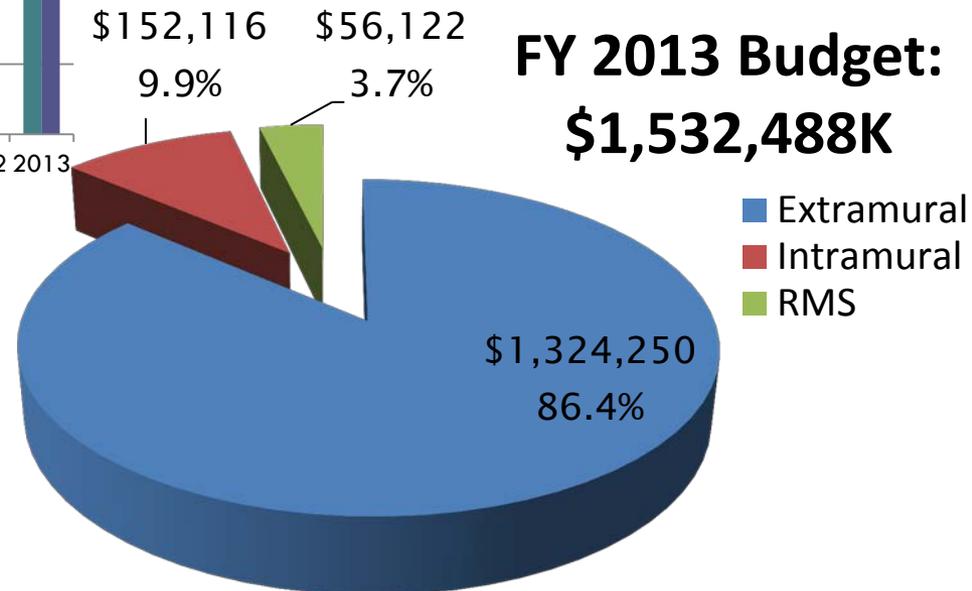
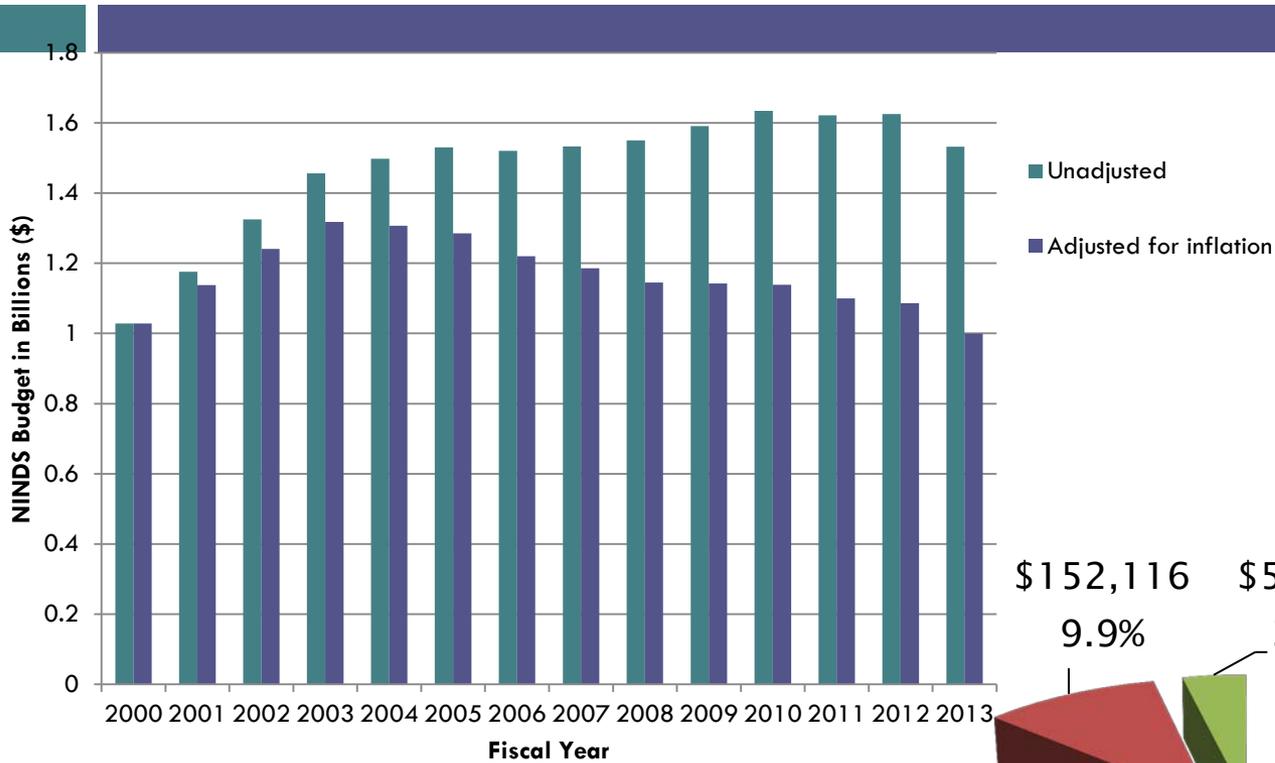
**CDEs available for use  
are found at:**

<http://www.commondataelements.ninds.nih.gov/>

-  **Available for use**
-  **In development**



# NINDS budget



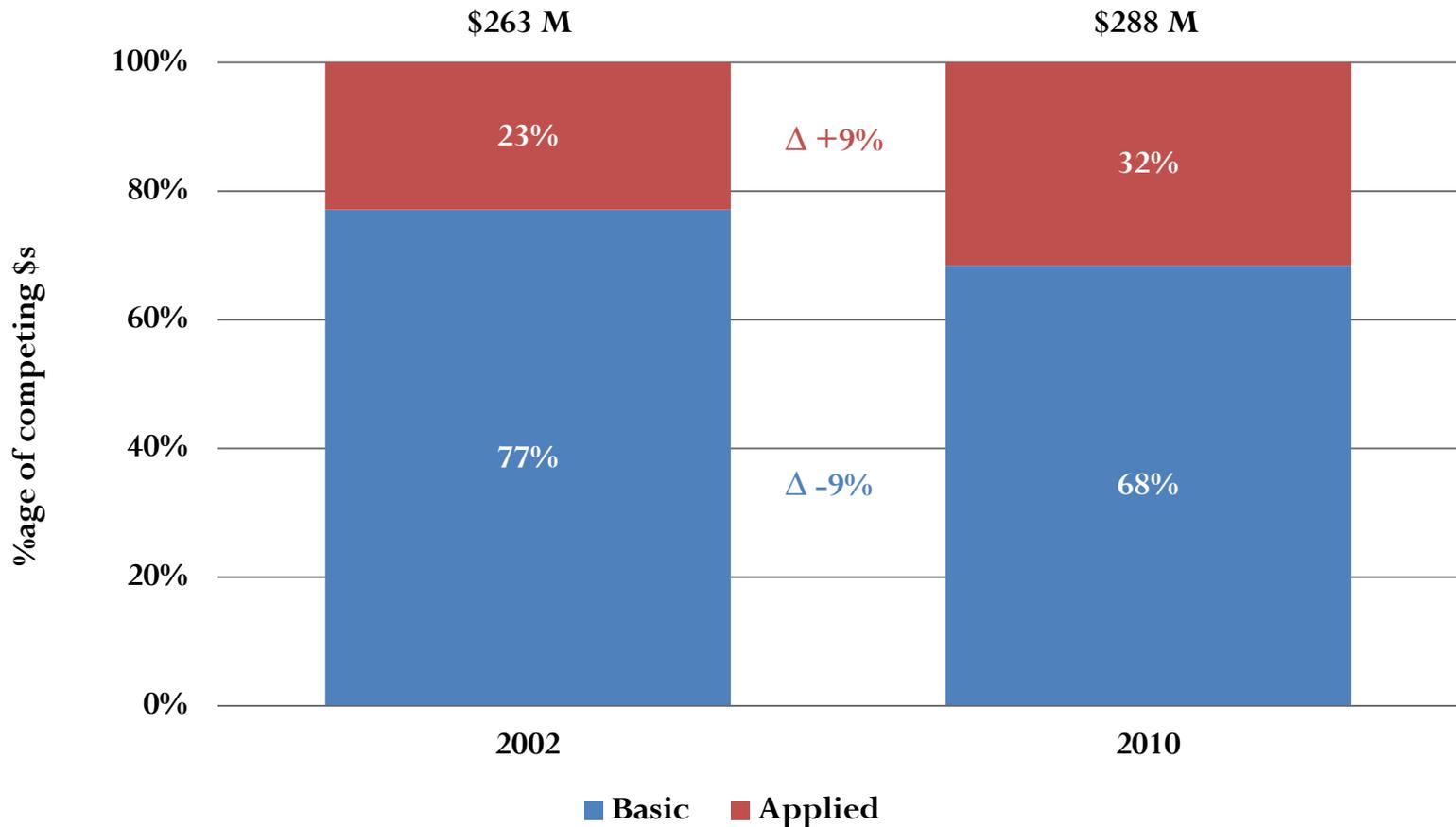
# Managing our budget

- In 2001, the midpoint of the doubling, our payline was the 26<sup>th</sup> 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 9<sup>th</sup> 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 14<sup>th</sup> percentile
- Need to find balance between basic, translational and clinical portfolios

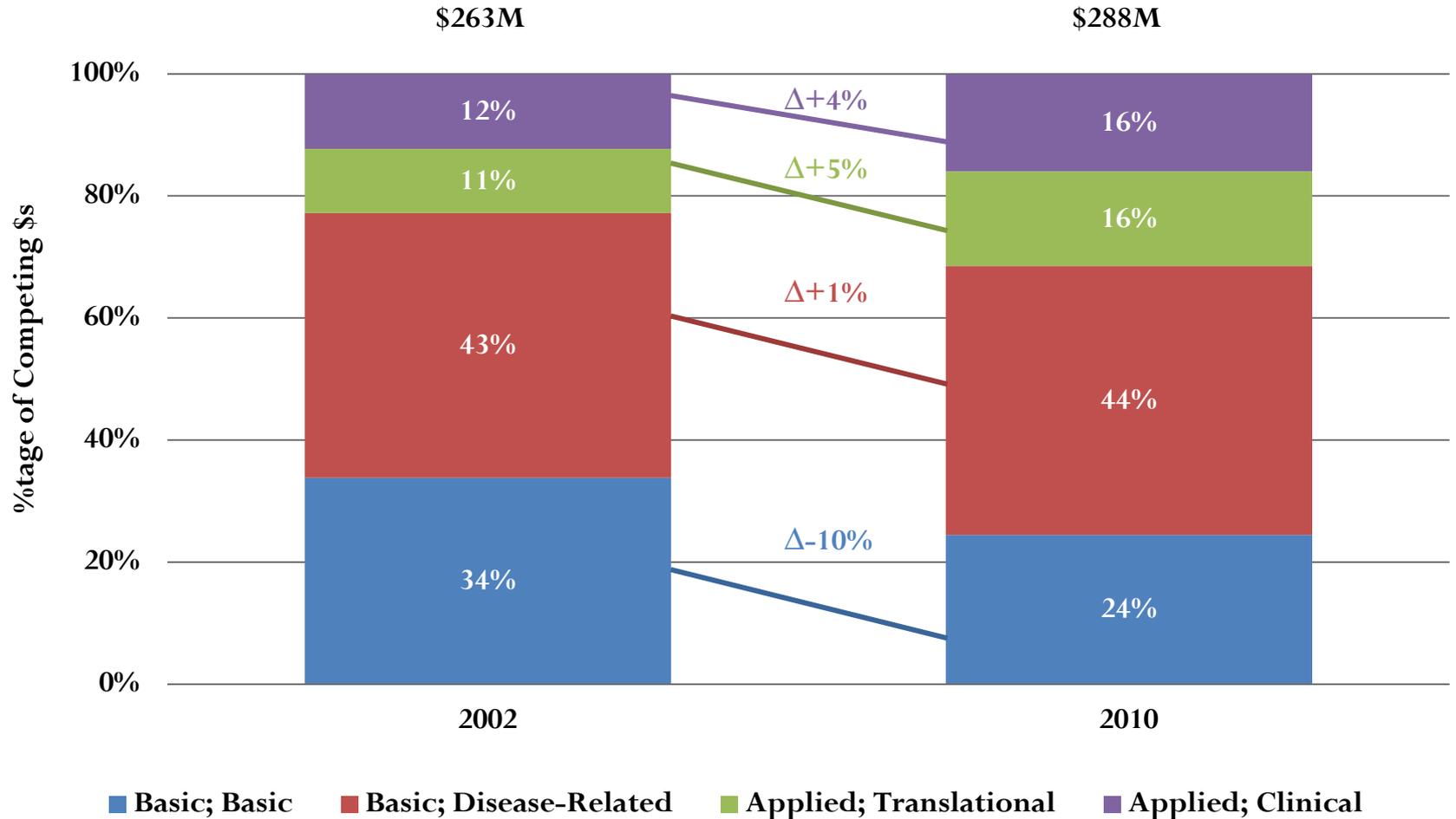
# Categories of Research

- **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.

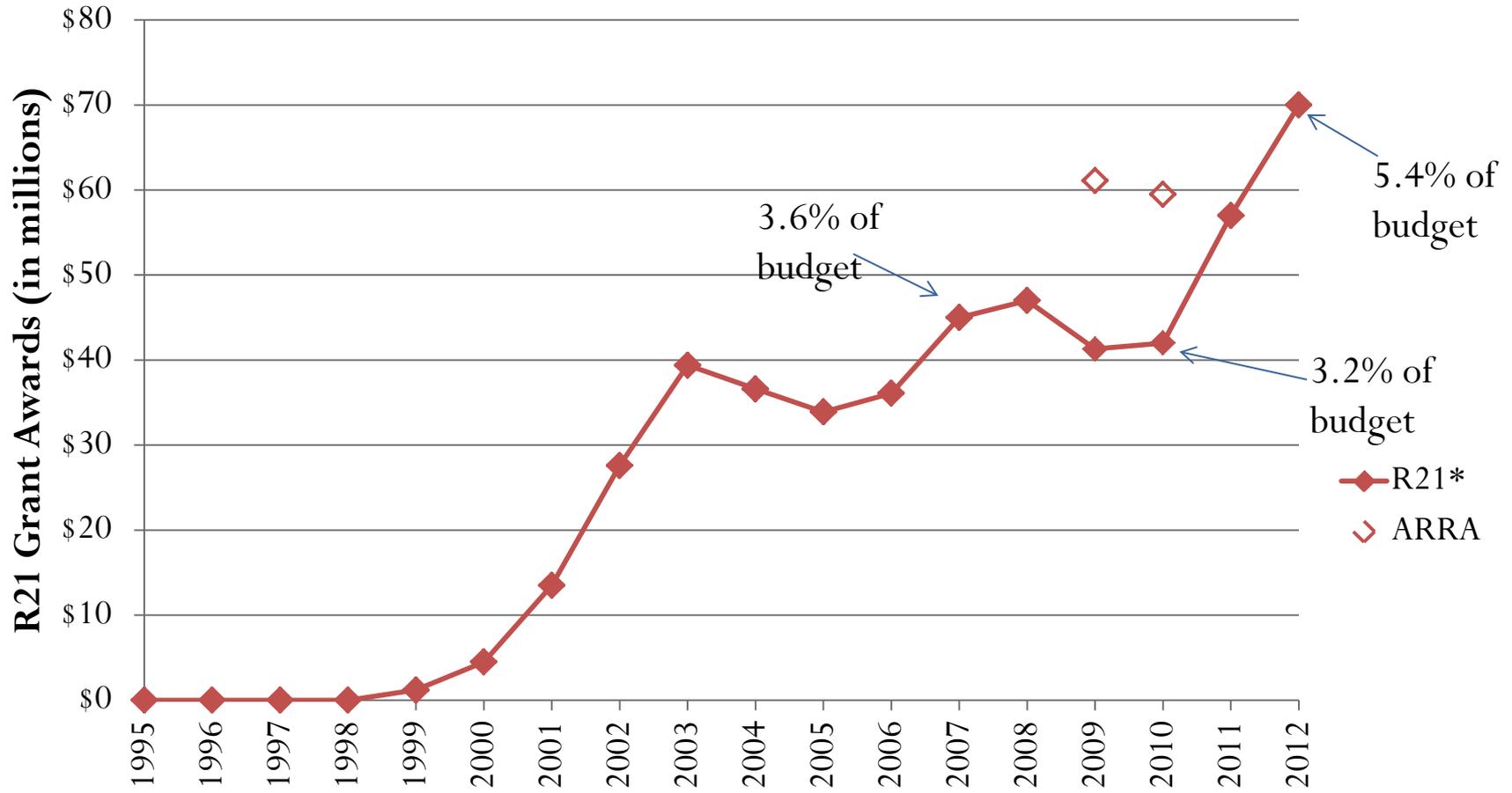
# Balance by competing dollars (basic vs applied)



# Balance by competing dollars (all categories)



# Total dollars spent on R21s has increased



\*Translational Program is not included

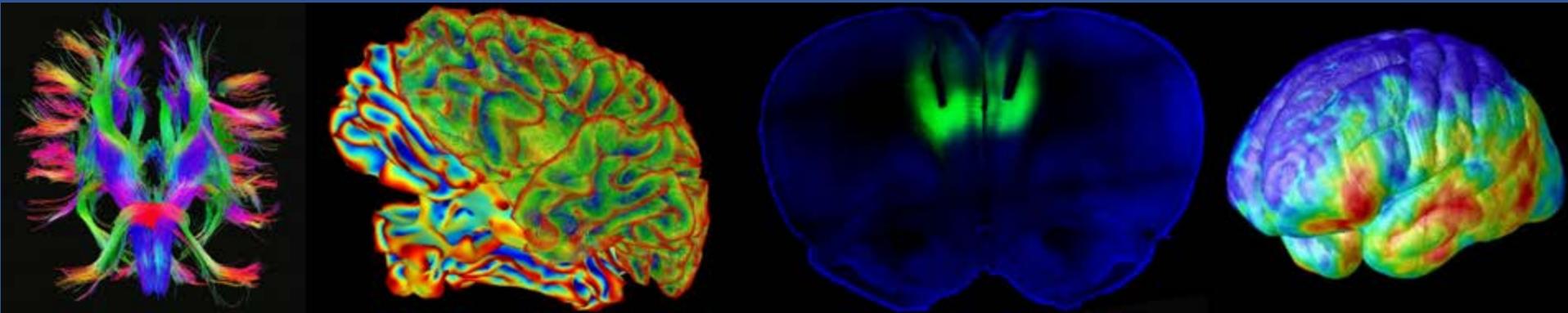
# The Porter Neuroscience Center

- 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***

The screenshot shows the NIF website interface. At the top, the NIF logo is displayed next to the text 'NEUROSCIENCE INFORMATION FRAMEWORK' and the 'incfnode' logo. Below the header is a search bar with the text 'Search for All Things Neuroscience'. The left sidebar contains a navigation menu with categories like 'ABOUT', 'NIF PRODUCTS', 'NIF DATA SHARING', 'NIF SYSTEM', 'SOCIAL MEDIA', 'NEUROLEX', and 'HELP'. The main content area features a map titled 'THE NIF RESOURCE LANDSCAPE' with a call to action 'GET ON THE MAP'. The right sidebar lists various data types and levels, including 'LITERATURE', 'DATA TYPE', and 'NERVOUS SYSTEM LEVELS'. The footer contains links for 'Community News & Events' and 'Twitter'.

*“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)

The image displays the Connectome Workbench interface, showing the process of overlaying myelin maps. The software is split into two windows: 'Connectome Workbench 1' and 'Connectome Workbench 2'.

**Connectome Workbench 1 (Left Panel):**

- Views: (1) CortexLeft, (2) CortexRight, (3) Surface Montage, (5) Whole Brain.
- Left Hemisphere: 249947.L.ve
- Right Hemisphere: 249947.R.ve
- Thickness: 20.0
- Yoking: Off

**Connectome Workbench 2 (Right Panel):**

- View: (4) Volume
- Volume: 249947.R.midthickness.164k\_fs\_LR.surf.gii
- Thickness: 20.0
- Yoking: Off

**Brain Visualizations:**

- Four brain surface renderings (top-left and bottom-left) showing myelin maps overlaid on a cortical surface. A color scale indicates myelin density, ranging from light (blue) to heavy (red/yellow).
- Four axial brain slices (top-right and bottom-right) showing the same myelin maps overlaid on a volume rendering. The slices are labeled with Y-coordinates: Y=0mm and Y=-92mm.

**Overlay ToolBox (Bottom Panels):**

The bottom panels show the 'Layers' and 'Connectivity' tabs of the 'Overlay ToolBox'.

On	Settings	Opacity	File	Map
<input type="checkbox"/>		1.0	LABEL Conte69.L.parcellations_VGD11b.164k_fs_LR	Composite Parcellation-lh (FRB08_OFPO3_retinotop)
<input type="checkbox"/>		1.0	LABEL Conte69.R.parcellations_VGD11b.164k_fs_LR	Composite Parcellation-rh (FRB08_OFPO3_retinotop)
<input checked="" type="checkbox"/>		1.0	METRIC 249947.L.SmoothedMyelinMap.164k_fs_LR	deformed_249947_L.Smoothed_Myelin_Map
<input checked="" type="checkbox"/>		1.0	METRIC 249947.R.SmoothedMyelinMap.164k_fs_LR	deformed_249947_R.Smoothed_Myelin_Map

The right 'Overlay ToolBox' shows a list of layers with checkboxes and opacity settings:

- Tab 3: 5.00 (249947.R.midthickness.164k\_fs\_LR.surf.gii)
- Lime: 0.50 (249947.L.white.164k\_fs\_LR.surf.gii)
- Lime: 0.50 (249947.R.white.164k\_fs\_LR.surf.gii)
- Blue: 0.50 (249947.L.pial.164k\_fs\_LR.surf.gii)

# Blueprint Neurotherapeutics Project: An experiment in combining strengths of NIH and industry

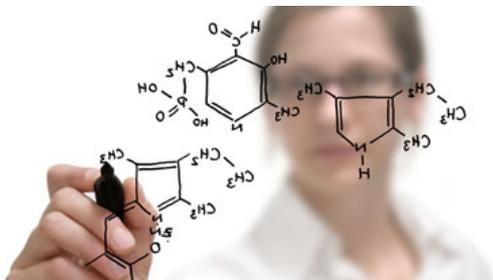
## NIH investigator-initiated ideas

- Novel drug targets
- Strong disease assays and models



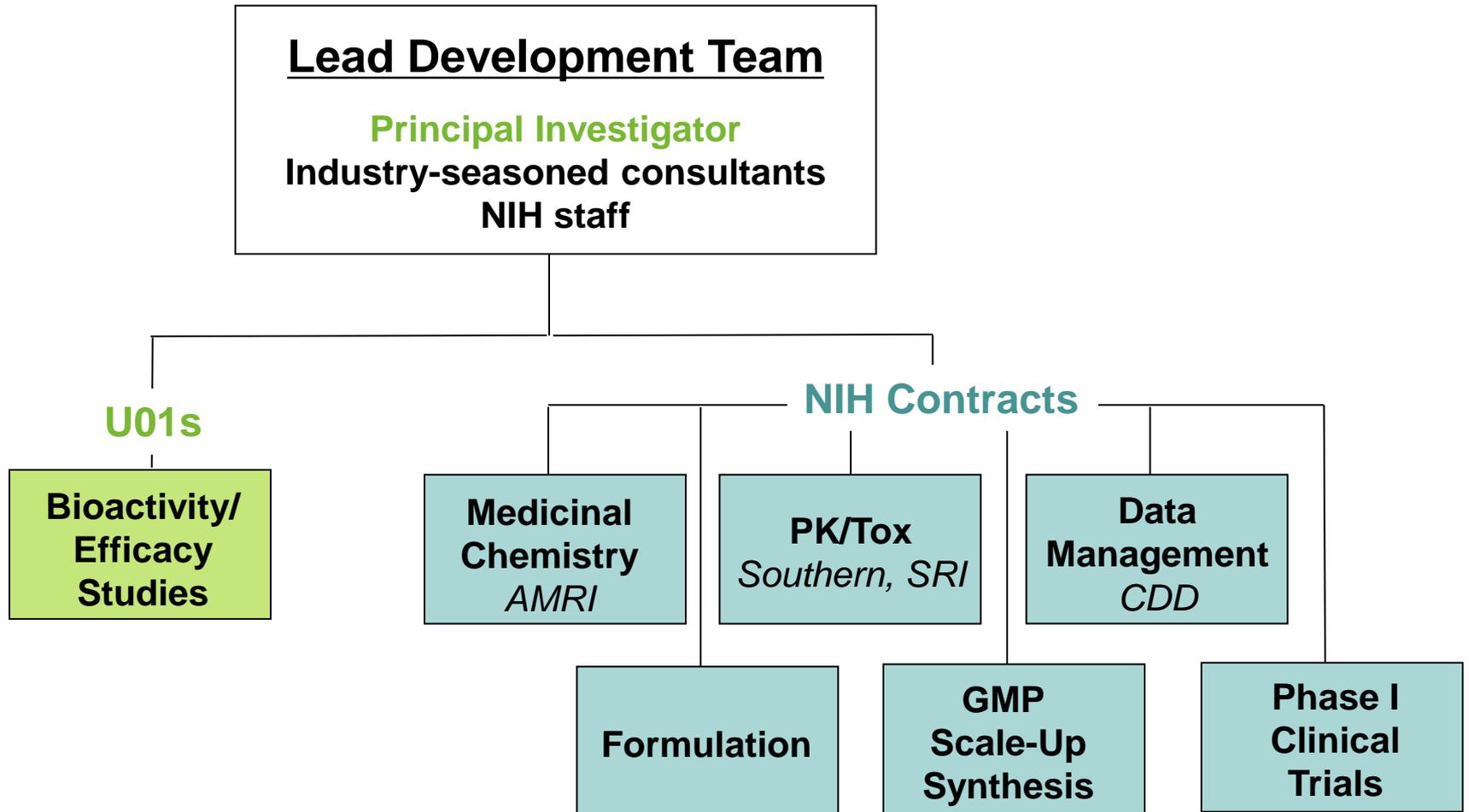
## Industry expertise

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



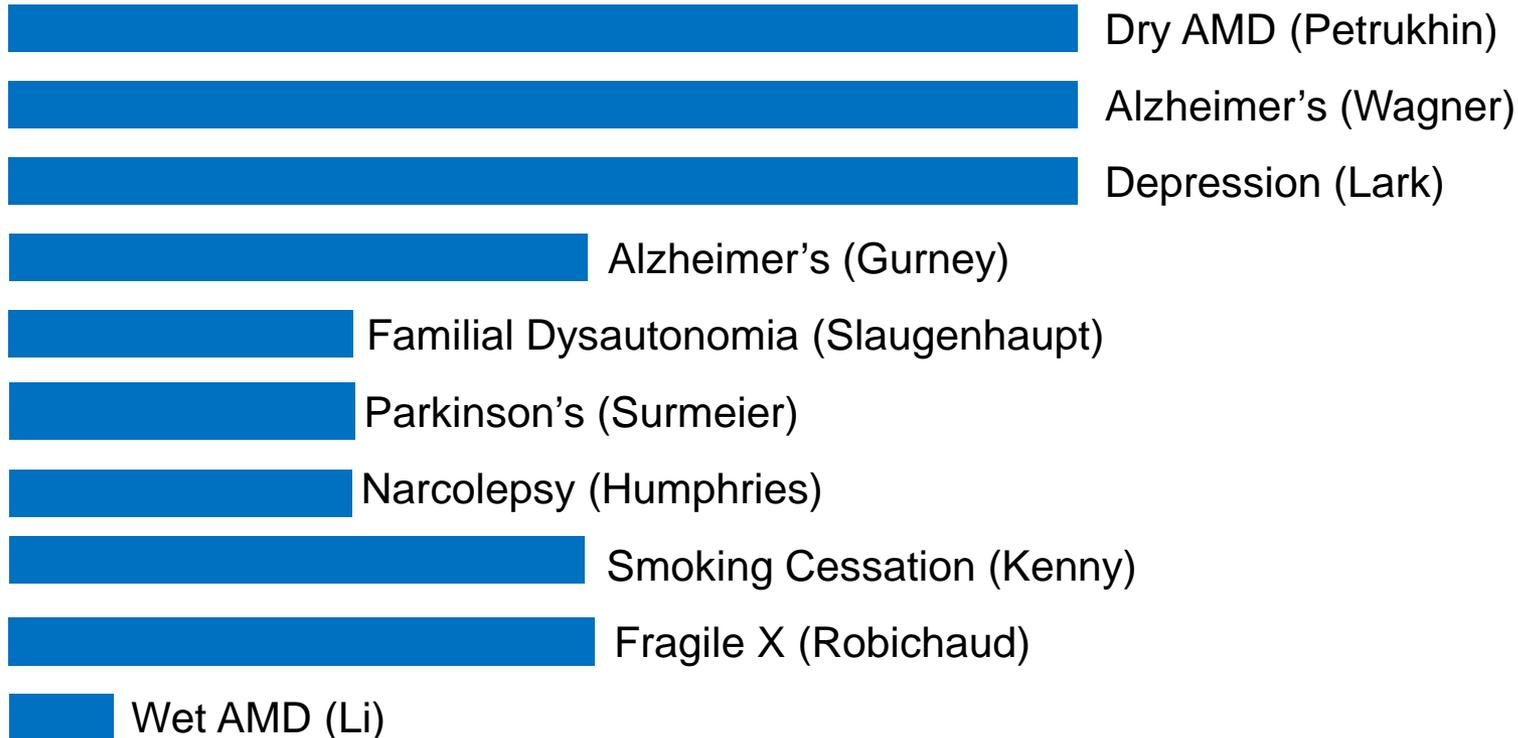
# “Virtual Pharma” Model

NIH Provides Drug Discovery Infrastructure, Expertise, and Funds



# Current BPN Portfolio

Assay Validation	Exploratory Chemistry	Hit-to-Lead Chemistry	Proof of Concept	Lead Optimization	Candidate Selection	Preclinical Safety	Phase I Trial
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*4 projects discontinued (not listed)*