Neuroscience at NIH

- 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.
- NIH invests 5.5B in neuroscience
- Eight institutes are major funders but all fund some
  - NINDS, NIMH, NIDA, NIA, NICHD, NEI, NIDCD, NIAAA
  - Each has its own disease mission
  - All fund basic science
The “undoubling” of the NINDS extramural grants budget

- Total NINDS Extramural Grant Funds
- Total NINDS Extramural Grant Funds--adjusted to 1995 dollars
NINDS funding plan for FY13

- Sequester: NINDS budget is 5.7% less than FY12
- Each IC has developed a plan that balances cuts across extramural, intramural and RMS
- NINDS will cut 3.5% from R and P non-competing grants, intramural and extramural
- Our payline is set at the 14th percentile and we will continue our commitments to training and career awards
- Able to maintain payline because of grant turnover, program closure and efficiencies in clinical trial efforts
Mutant SOD1 mice and rats accurately recapitulate clinical, pathological and pharmacological profiles of sporadic ALS.
Enhanced survival of SOD1 transgenic mice with minocycline led to a Phase III clinical trial for ALS patients

412 patients treated for 9 months
Randomized placebo controlled
Patients treated with minocycline failed more rapidly than those on placebo

Did the animal study not translate to patients because the animal model is bad or because the preclinical study was not rigorous?

The study had 10 animals per group, it was not blinded and the animals were not randomized.

- SOD1$^{G93A}$ transgenic mice
- Treatment started at 5 weeks of age
- i.p. 10mg/kg/day
- Nature 2002
The fewer methodological parameters are reported, the greater the apparent efficacy!

Effect size for studies of **FK506** (Tacrolimus) in experimental stroke.

Improving the Quality of NINDS-Supported Preclinical and Clinical Research through Rigorous Study Design and Transparent Reporting

Notice Number: NOT-NS-11-023
Release Date: August 10, 2011
Issued by: National Institute of Neurological Disorders and Stroke (NINDS)

Purpose:

…..NINDS believes that applications that propose preclinical research, or that are based on previous preclinical data, will be greatly strengthened if the design, execution, and interpretation of the proposed studies and supporting data are adequately described. NINDS encourages investigators, whenever possible, to address these elements directly in their applications.
Actions taken by NINDS:
Workshop
“Optimizing the Predictive Value of Preclinical Research”

- Guidance crafters
- Journal editors
- Reviewers
- End users

A call for transparent reporting to optimize the predictive value of preclinical research


Nature 2012; 490: 187-191
Workshop Recommendations

- All relevant stakeholders share the responsibility of bringing about meaningful improvement in the quality of reporting.

- Grant applications and scientific publications which include *in vivo* animal experiments should, at a minimum, report on:
  - Randomization
  - Blinding
  - Sample size estimation
  - Handling of all data

- Clear guidance (e.g. checklist) to submitters and reviewers

- Education and training
White House “Grand Challenge”

“the next great American project”
“As humans, we can identify galaxies light years away, we can study particles smaller than an atom. But we still haven’t unlocked the mystery of the three pounds of matter that sits between our ears. But today, scientists possess the capability to study individual neurons and figure out the main functions of certain areas of the brain... So there is this enormous mystery waiting to be unlocked, and the BRAIN Initiative will change that by giving scientists the tools they need to get a dynamic picture of the brain in action and better understand how we think and how we learn and how we remember. And that knowledge could be -- will be -- transformative.”

-- Remarks by the President on the BRAIN Initiative and American Innovation, April 2, 2013
Advances in Understanding Brain Structure

Brainbow (Livet et al., 2007)

CLARITY (Chung et al., 2013)

Human Connectome (Wedeen et al., 2012)
Advances in Understanding Brain Function

Zebra fish larvae (Ahrens et al., 2013)

1202 hipp neurons (Schnitzer laboratory)

21 transient co-activation networks (U-Minn/Was U)
Goals of NIH BRAIN

• Accelerate the development and application of innovative new technologies to construct a dynamic picture of brain function that integrates neuronal and circuit activity over time and space.

• Build on the growing scientific foundation of neuroscience, genetics, physics, engineering, informatics, nanoscience, chemistry, mathematics and other advances to catalyze an interdisciplinary effort of unprecedented scope.

• Disease agnostic and will provide investigators with tools to advance their own research goals.
How will NIH BRAIN work?

• Plan to be developed by ACD BRAIN working group
  – Selected for visionary leadership and expertise, including
    • Experimental neuroscience
    • Technology development
    • Computation and theory
    • Human neuroscience
  – Charged with articulating the scientific goals and developing a multi-year plan, including timetables, milestones, and costs

• Informed by experts across sectors and disciplines

• Recommendations will be Implemented by the Blueprint for Neuroscience Research via RFAs
NIH Neuroscience Planning Team

Cornelia Bargmann, PhD *(co-chair)*
The Rockefeller University

Bill Newsome, PhD *(co-chair)*
Stanford University

David Anderson, PhD
California Institute of Technology

Emery Brown, MD, PhD
Massachusetts Institute of Technology

Karl Deisseroth, MD, PhD
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Mark Schnitzer, PhD
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Terry Sejnowski, PhD
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David Tank, PhD
Princeton University

Roger Tsien, PhD
University of California, San Diego

Kamil Ugurbil, PhD
University of Minnesota

**EX OFFICIO MEMBERS**

Kathy Hudson, PhD
National Institutes of Health

Geoffrey Ling, MD, PhD
Defense Advanced Research Projects Agency

John Wingfield, PhD
National Science Foundation
Moving Forward

• The Working Group will
  – Seek input broadly from the scientific community, patient advocates, and the general public;
  – Hold open meetings and workshops on specific topics
  – Deliver an interim report with initial list of high-priority areas for FY14 funding in summer, 2013; final report in June, 2014

• The public will be able to receive updates and contribute to the discussion at http://www.nih.gov/science/brain/
<table>
<thead>
<tr>
<th>Government Agencies</th>
<th>FY14 Investment</th>
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<tr>
<td>NIH (National Institutes of Health)</td>
<td>$40 million</td>
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<tr>
<td>DARPA (Defense Advanced Research Projects Agency)</td>
<td>$50 million</td>
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<tr>
<td>NSF (National Science Foundation)</td>
<td>$20 million</td>
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BRAIN Initiative Partners
Private Organizations

- Allen Institute for Brain Science
- HHMI: Howard Hughes Medical Institute
- Salk Institute for Biological Studies
- The Kavli Foundation
Increased R21 funding

- In 2010 NINDS spent $42M on R21s (3.2% of the extramural budget)
- In 2012 NINDS spent $70M (4.2% of the extramural budget)
- Applications increased from 850 in 2010 to 1160 in 2012.
- Success rates remained constant

WHY?