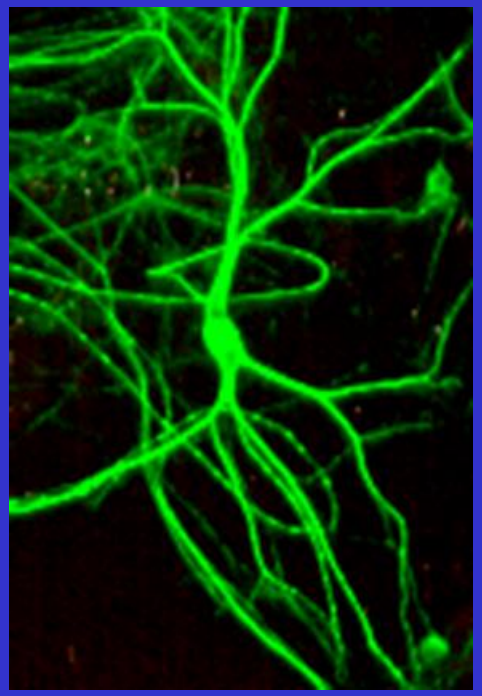
Research programs in light of ICE BUCKET CHALLENGE

ALS ASSOCIATION

TREAT ALS

Translational Research
Advancing Therapy for ALS



Presentation Overview

- The ALS Association Research Programs
- Opportunities and Challenges for Therapy Development in ALS

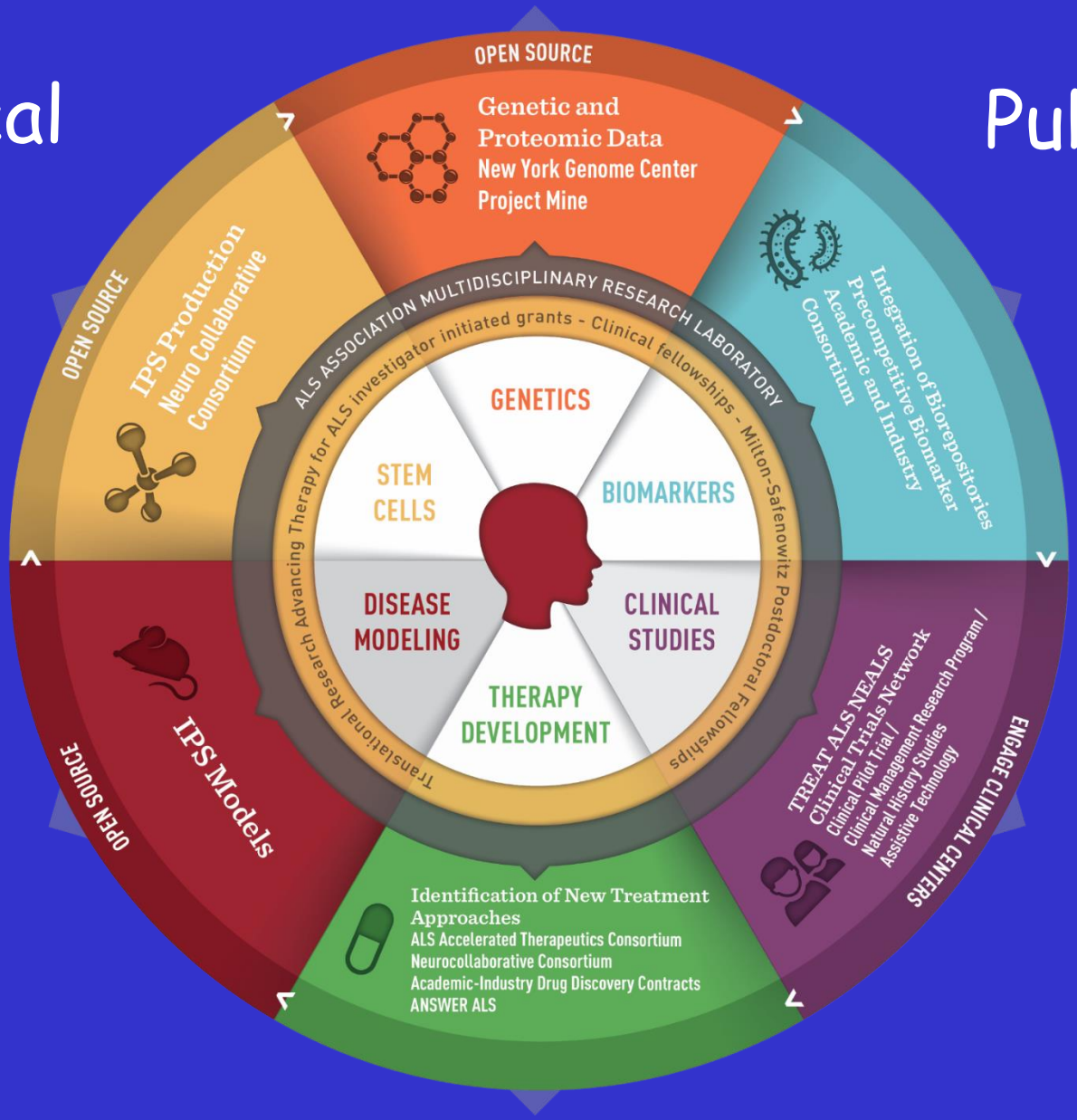
Research Program Strategies

- Establishment of a translational program TREAT ALS™
- Fund academic-industry partnerships
- Provide infra-structure for multi-center clinical trials
- Consortium initiatives and Global research

The ALS Association Research Institute

ALS Clinical Centers

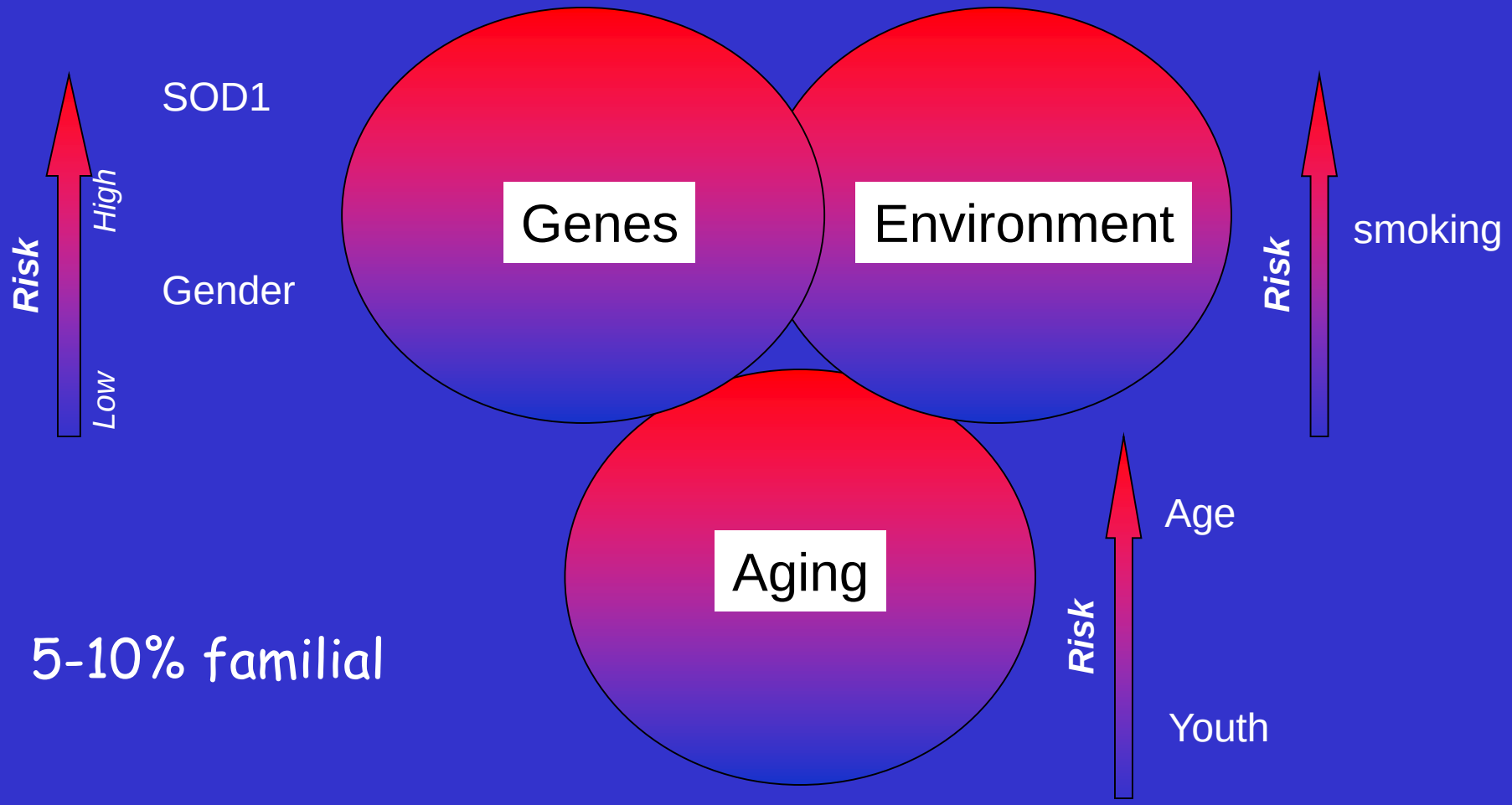
Public Policy



Key Focus Areas in ALS Research

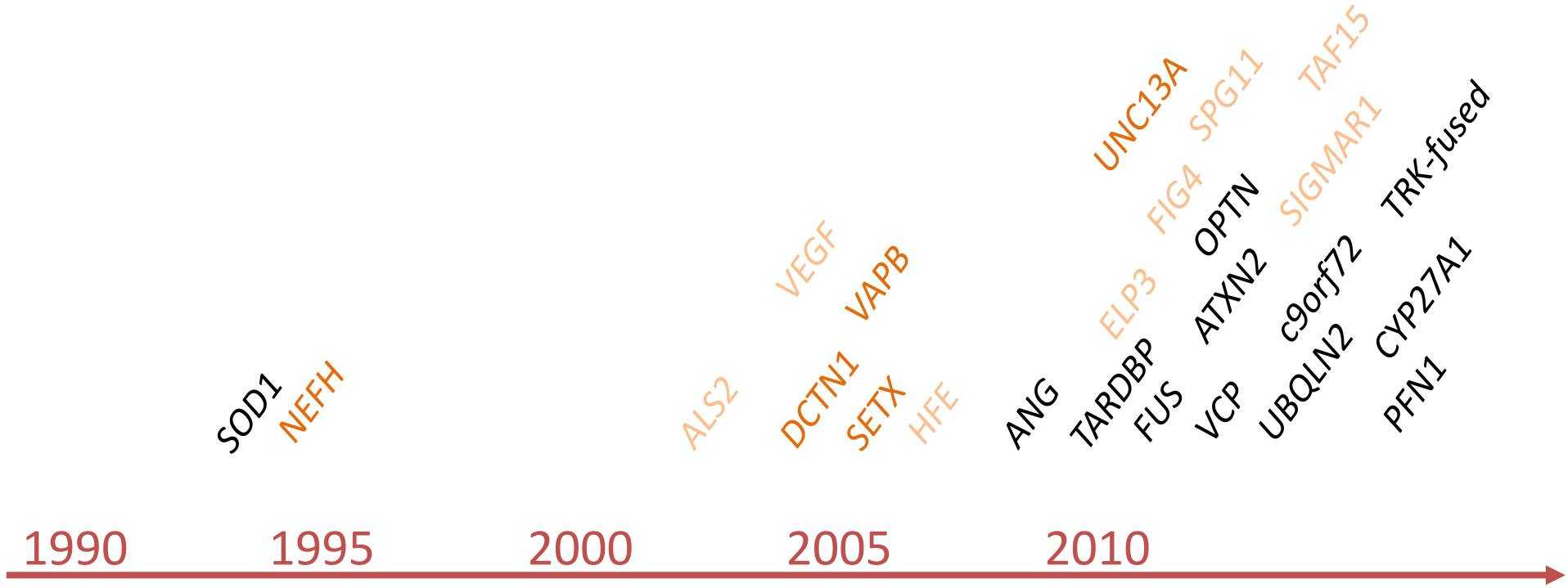
- Genetics
- Understanding Disease Mechanisms-disease modeling
- Therapeutic Development
- Stem Cells for therapy and drug discovery
- Clinical Studies-clinical trials and clinical management
- Biomarkers

Gene-Environment Interactions and Aging

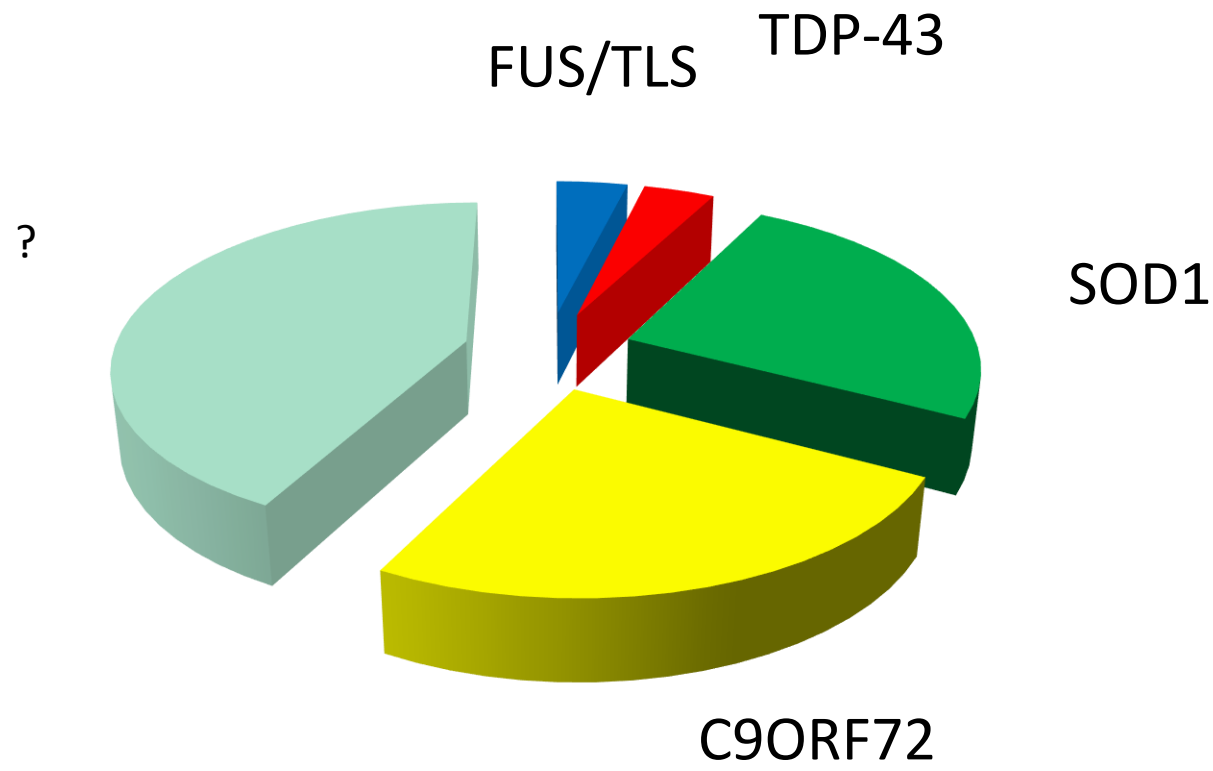


ALS genes timeline

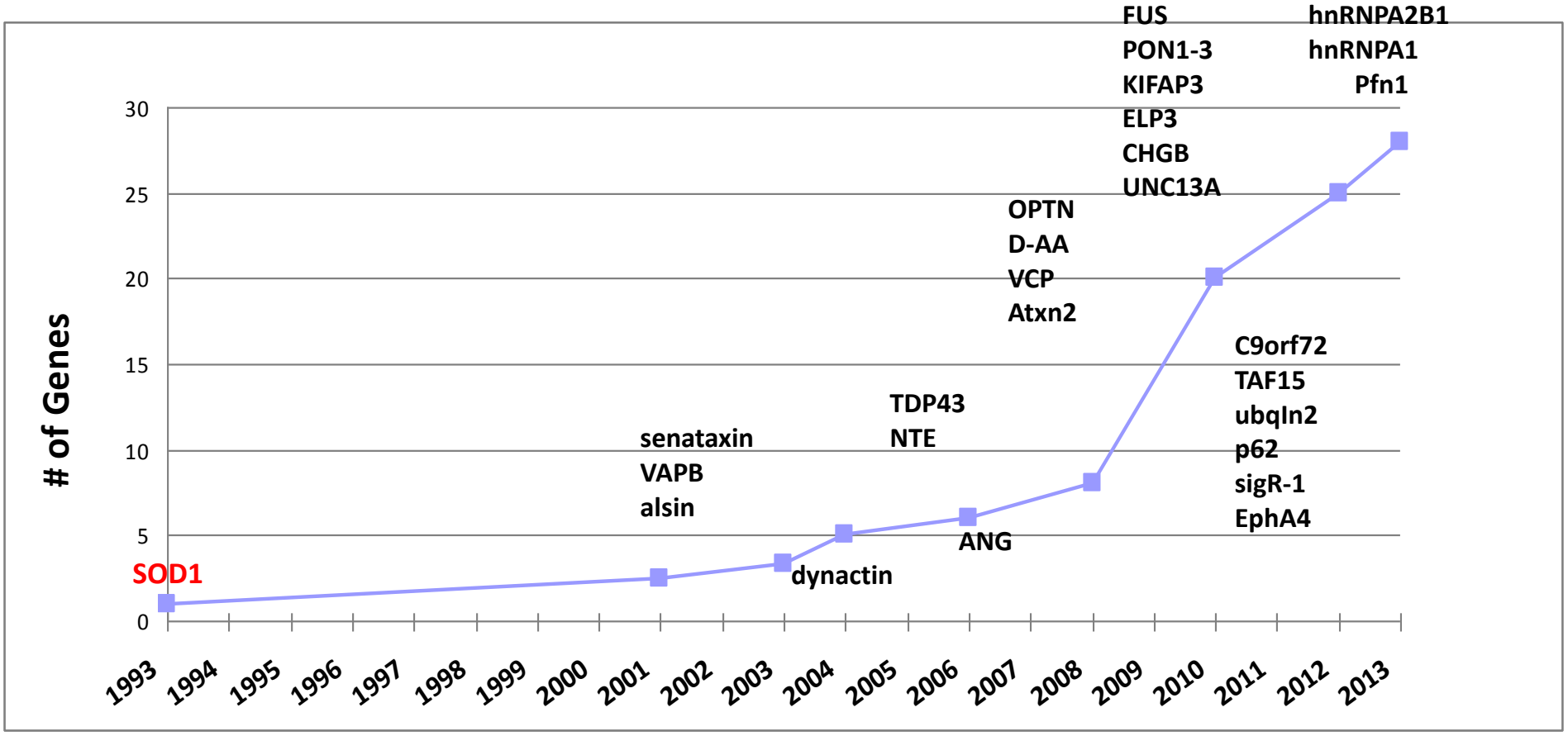
ALS genes timeline



Familial ALS



The rate of gene discovery in ALS is increasing:>25 ALS genes



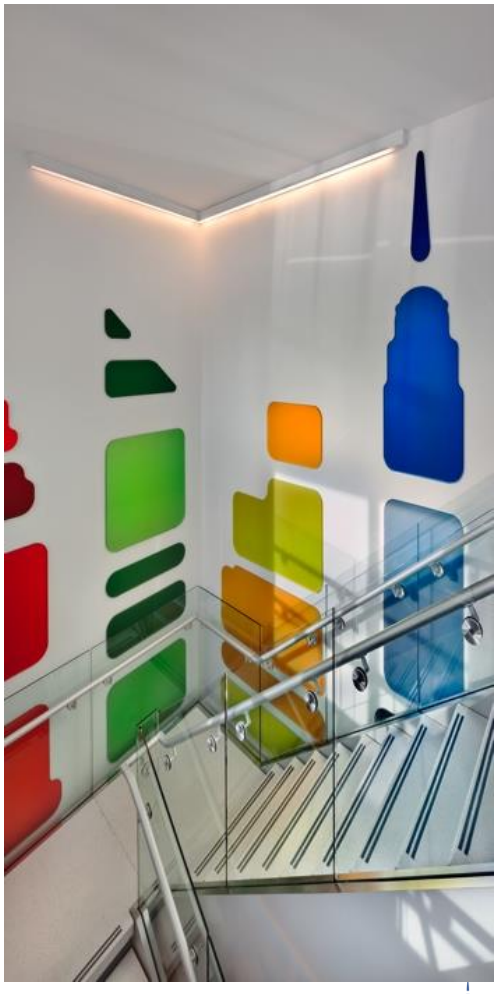
Each gene defines pathways and treatment targets.

First Four Initiatives

- New York Genome Center
- Project Mine
- Neurocollaborative
- ALS ACT (Accelerated Therapeutics)

NEW YORK GENOME CENTER & ALS RESEARCH

dedicated to applying genetics, genomics and bioinformatics to the study of neurodegenerative diseases, including ALS.



NEW YORK GENOME CENTER®

project MinE

Make it yours

accenture

Neurocollaborative

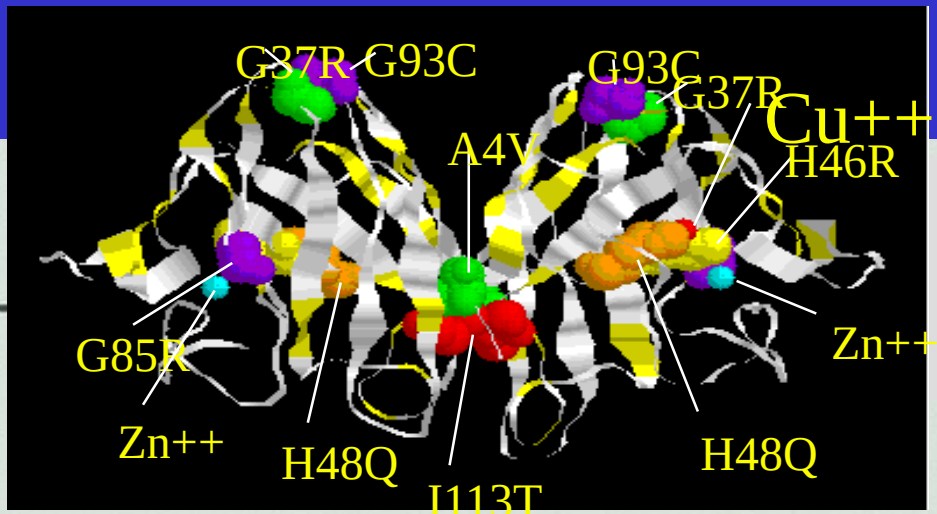
- Don Cleveland UCSD
- Steve Finkbeiner UCSF
- Clive Svendsen Cedar Sinai

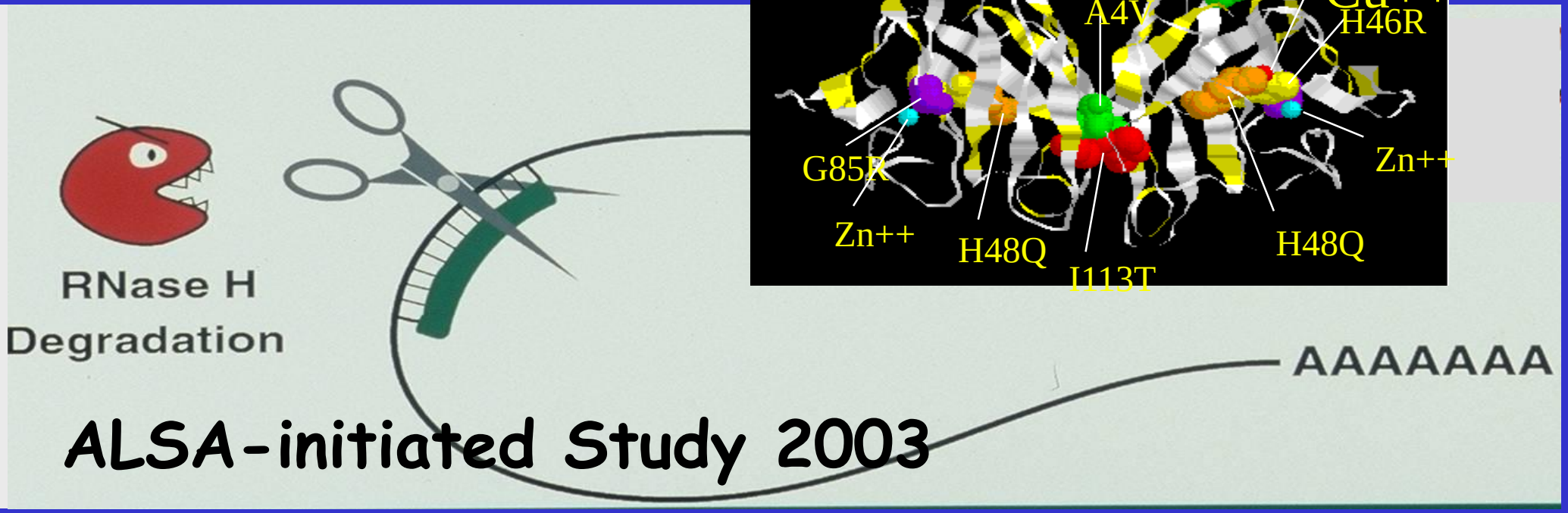
Innovative Approaches for Treatment and Drug Development

- Antisense Oligonucleotides
- Stem Cell Therapy
- Gene therapy
- Induced pluripotent stem cells for screening new compounds

Antisense Approach to Lower SOD1

Collaboration with ISIS



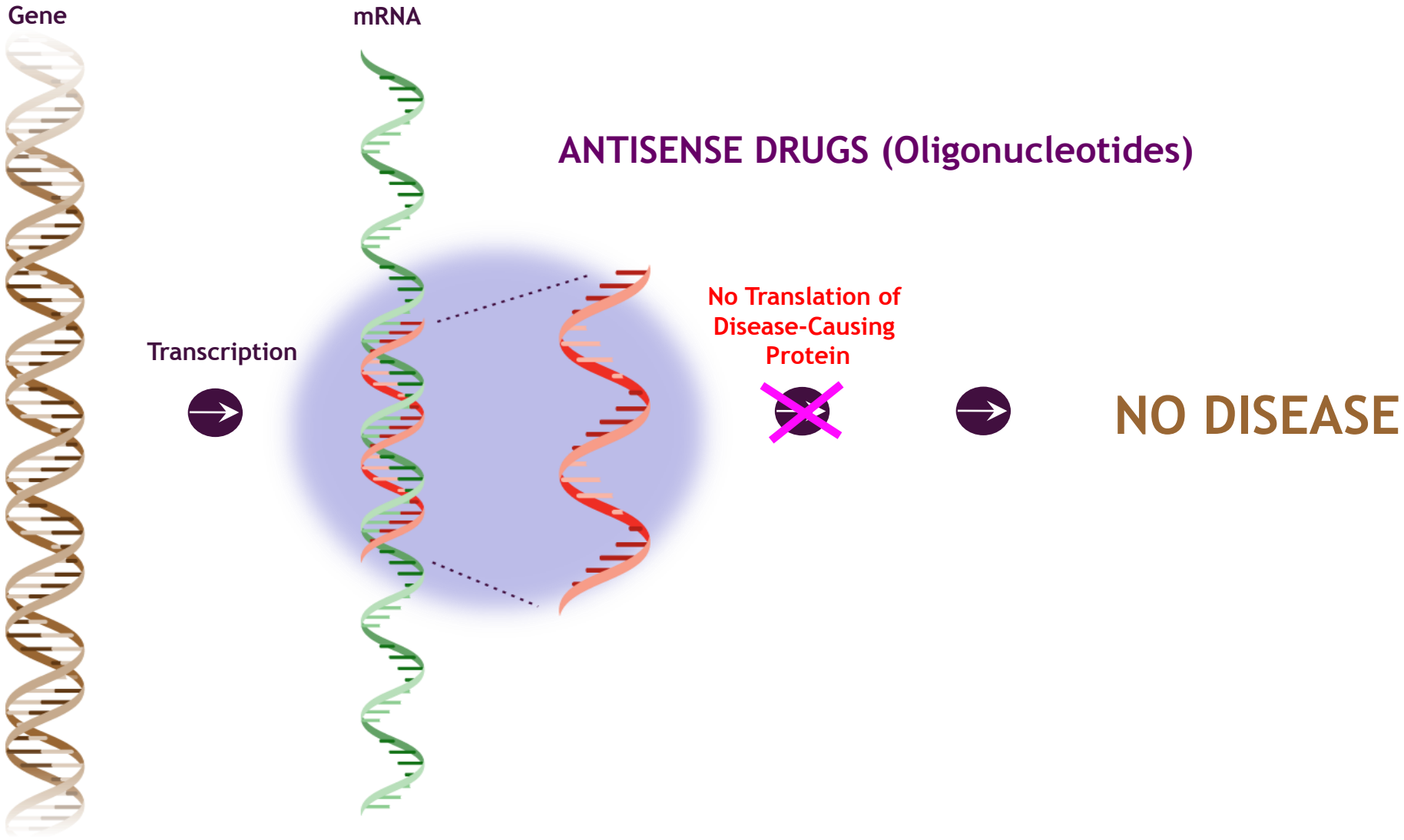


ALSA-initiated Study 2003

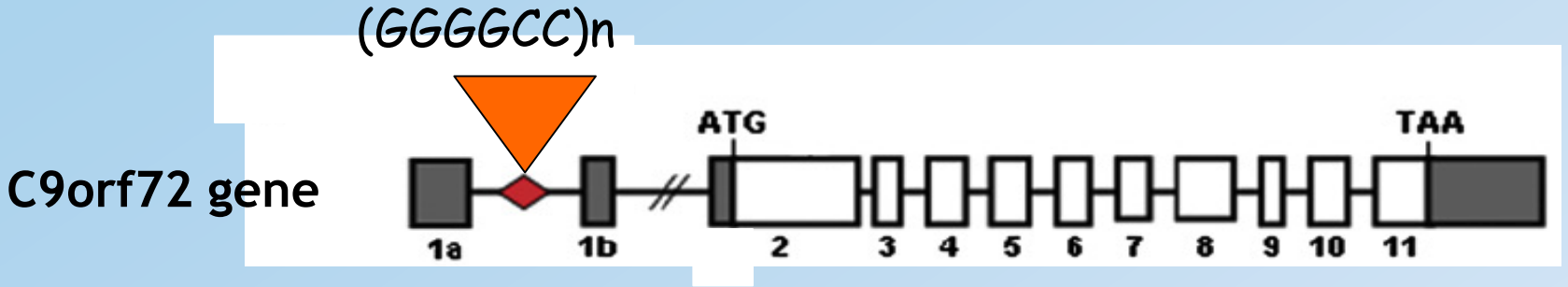
Endogenous RNase H mediated degradation of the mRNA in a DNA/RNA duplex

Cleveland, Miller, Smith

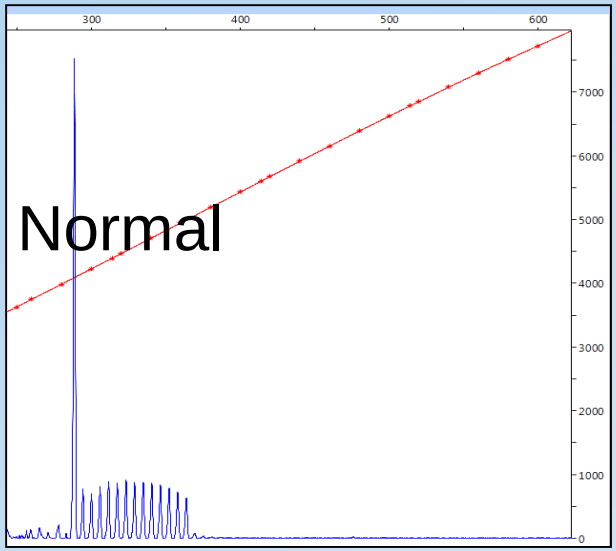
Antisense Drugs Target RNA, not Proteins



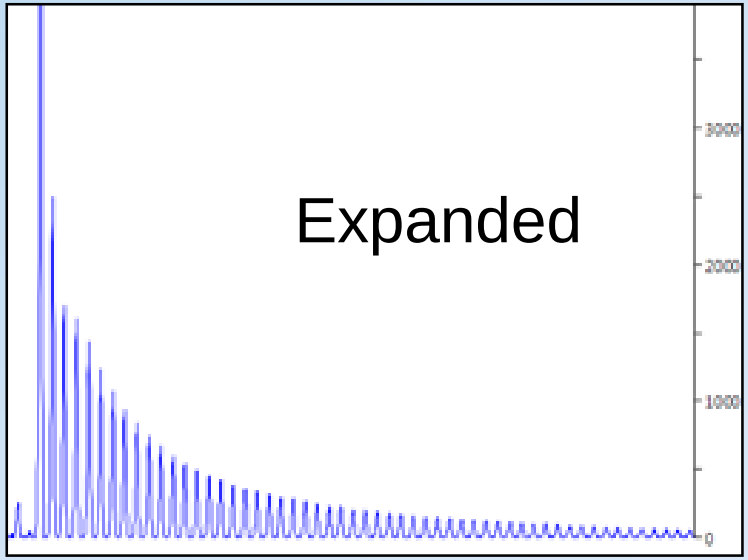
C9orf72 gene



Modified from DeJesus-Hernandez *Neuron (2011)*



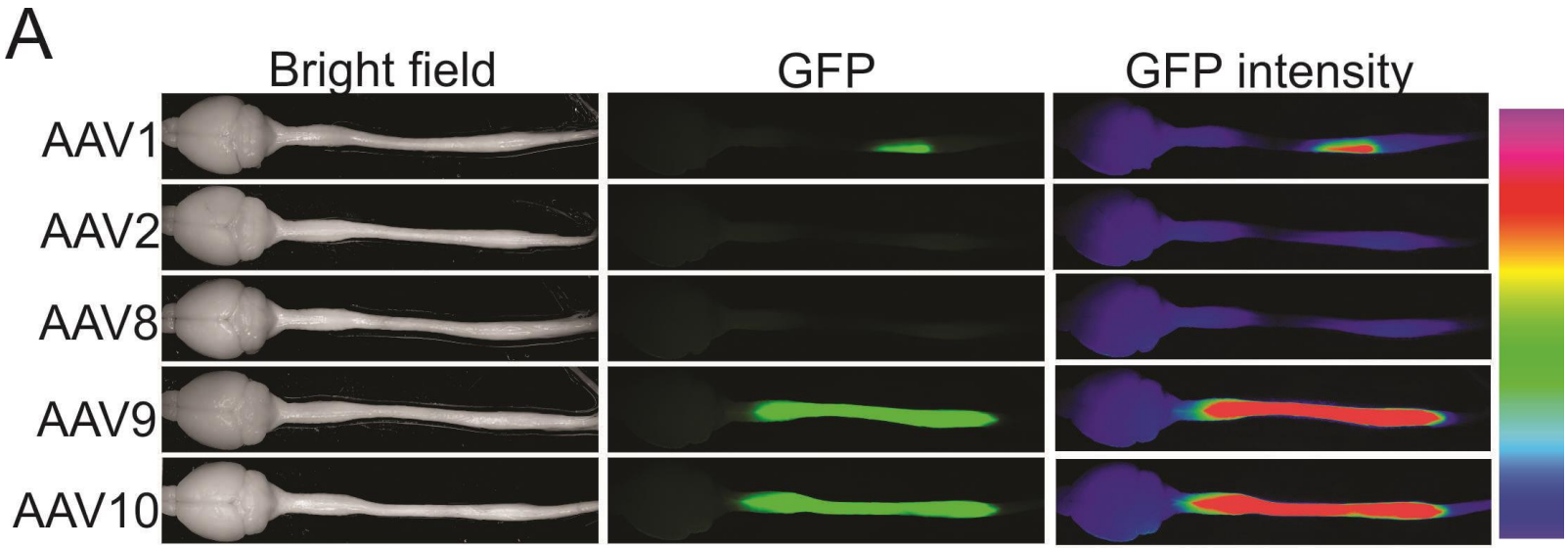
Repeat Primed PCR

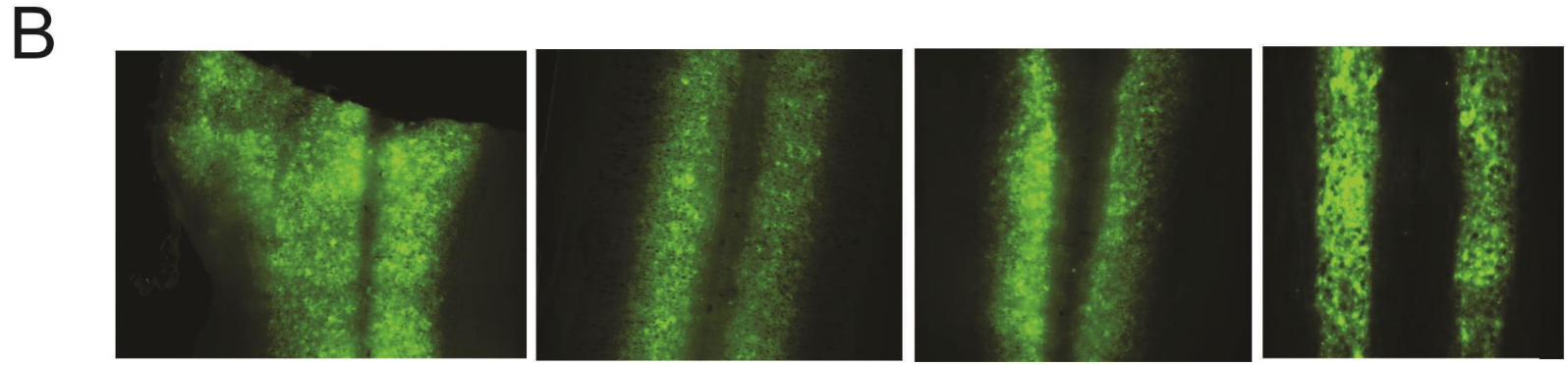


Southern:
Up to 1500 repeats

UC San Diego
SCHOOL OF MEDICINE

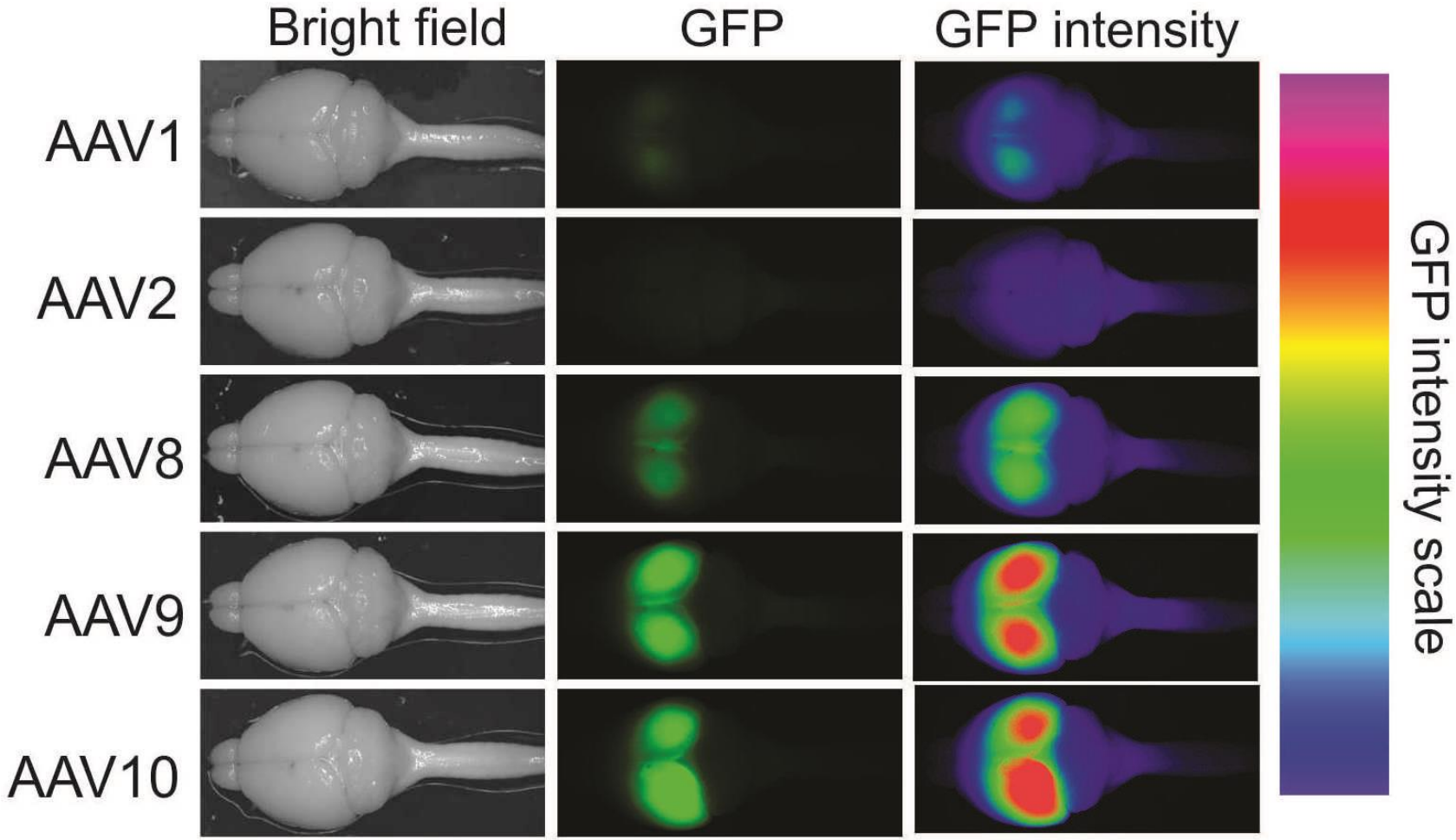
Intrathecal injection of AAV9 and AAVrh10 leads to transgene expression in the entire spinal cord and brainstem





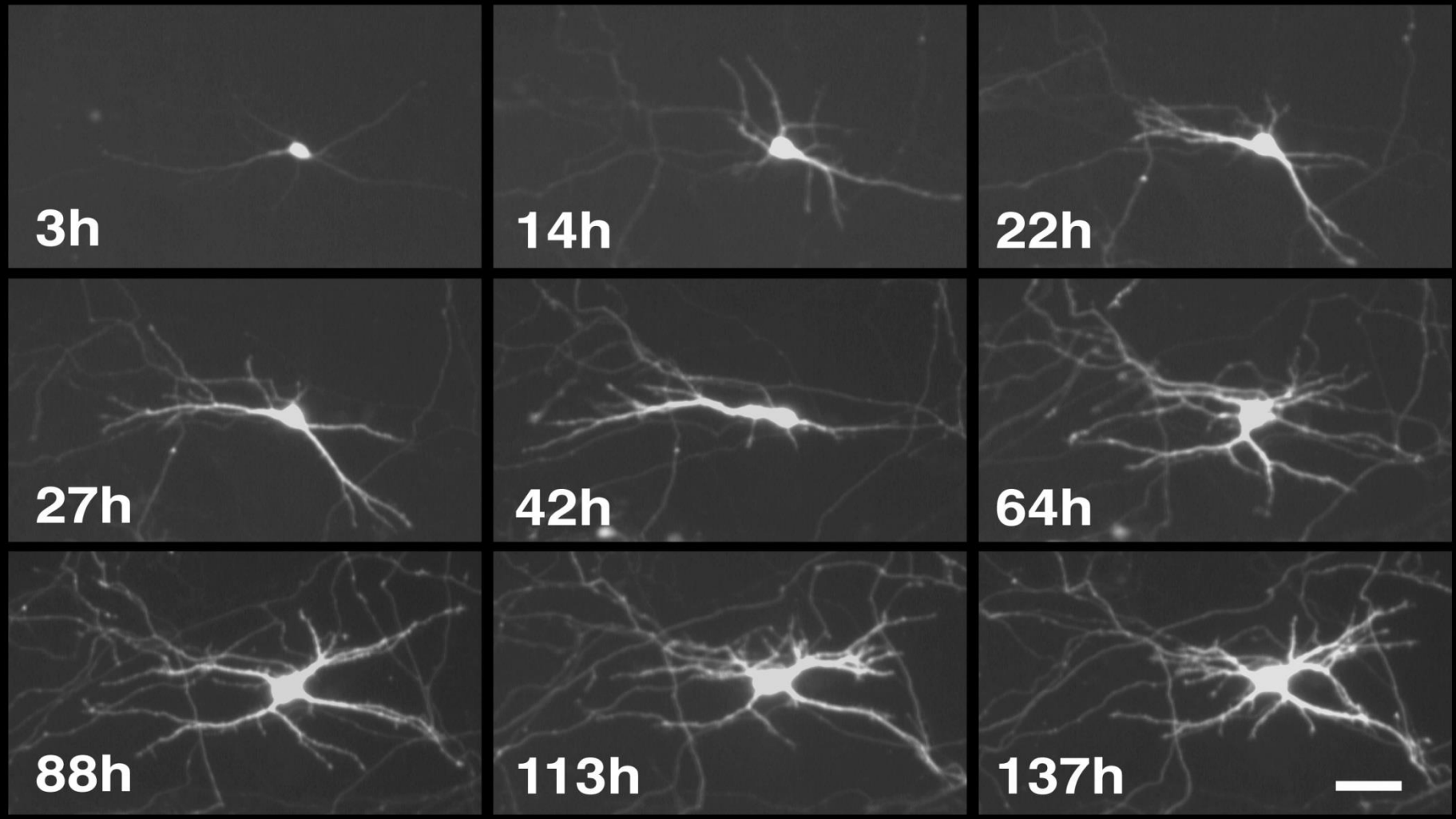
Zuoshang Xu

Intraventricular injection of AAV9 and AAVrh10 leads to widespread transduction in the forebrain including the motor cortex



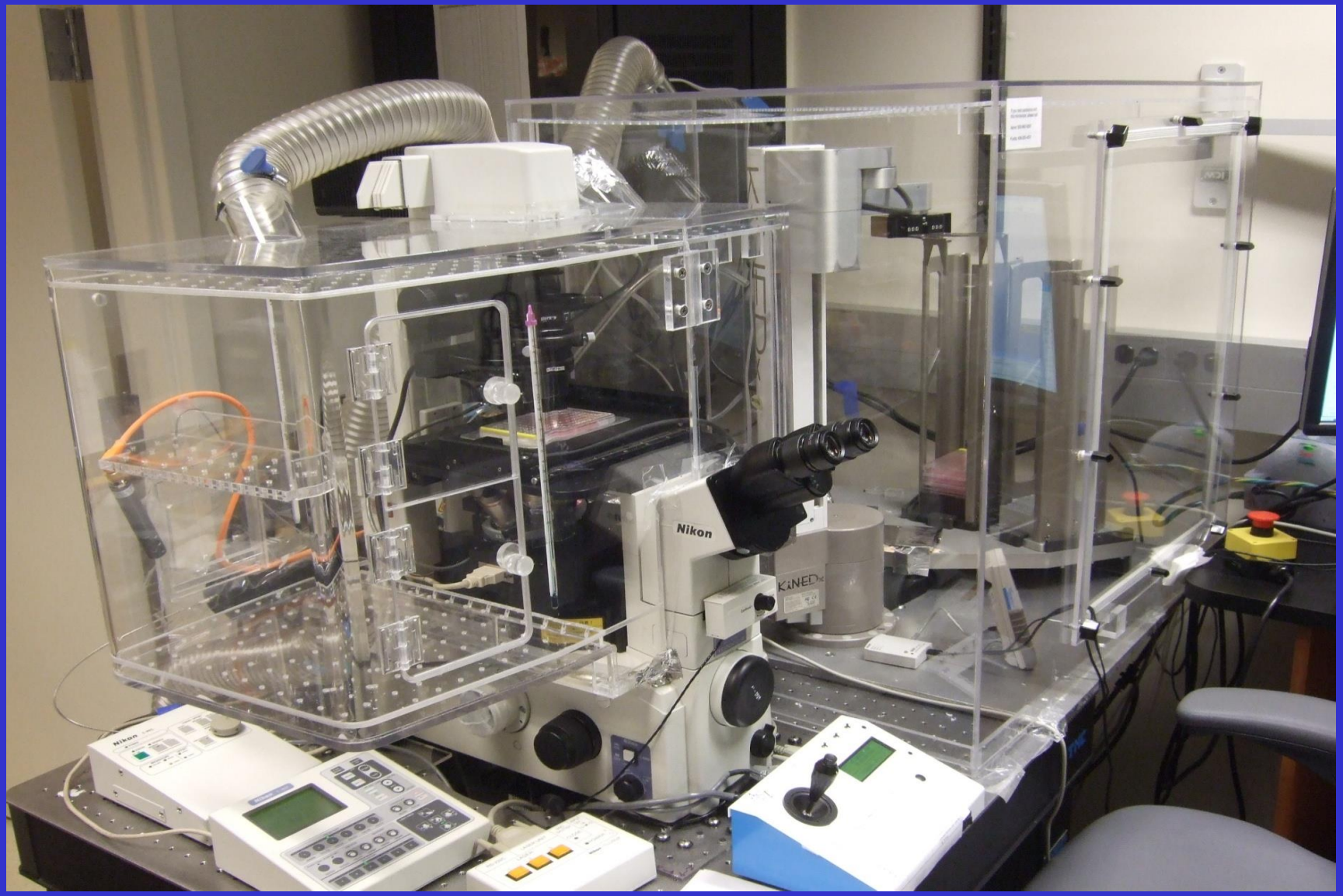
Zuoshang Xu

The System: Quantitative Automated Imaging Combined with Modified Survival Analysis



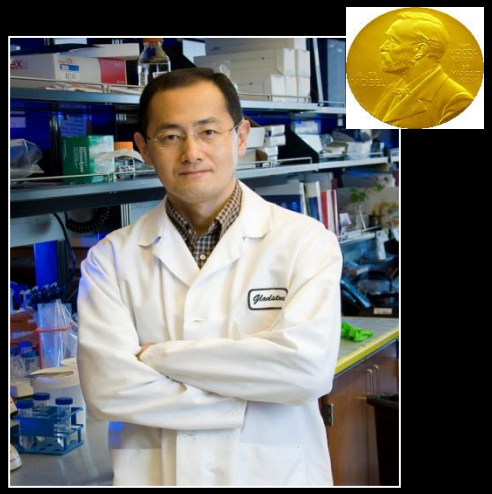
10^2-10^3 improved sensitivity Phenotypic screens Z' > 0.8

Automated Microscopy: A Powerful Tool for Unraveling Cause and Effect Relationships and Doing Clinical Trials in a Dish

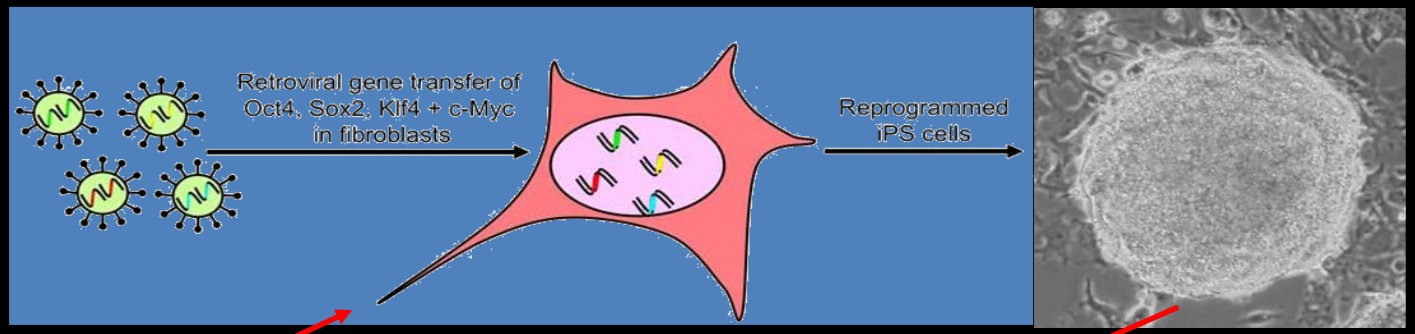


Steve Finkbeiner

Generation of Induced Pluripotent Stem (iPS) Cell Lines From Human Skin Cells

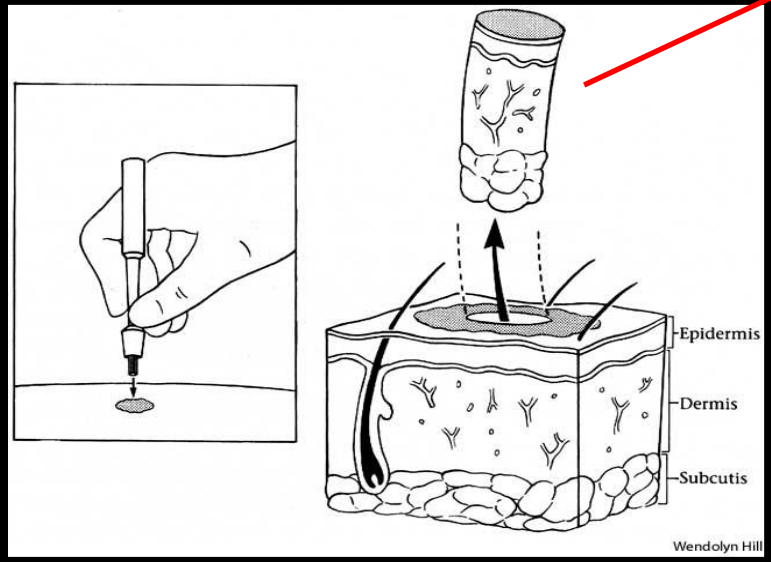


Dr. Shinya Yamanaka's Technology (2012 Nobel Prize)

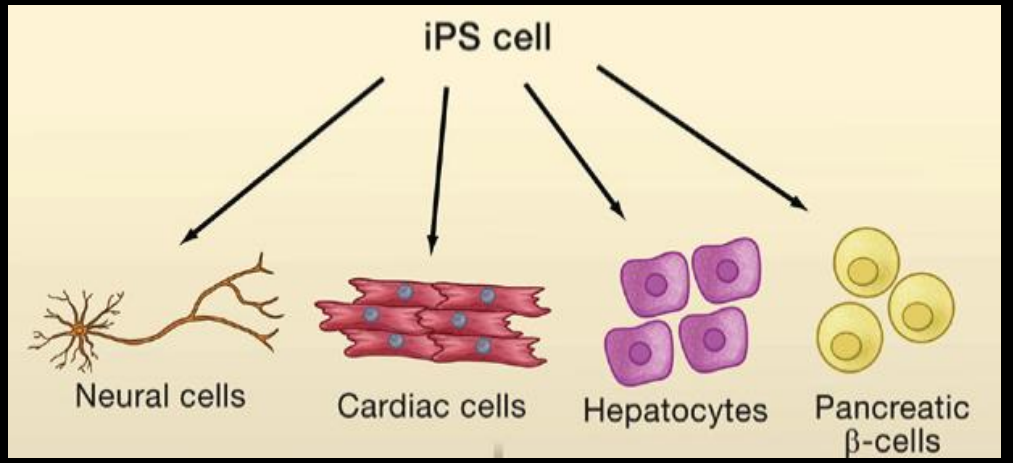


Skin Cells

Stem Cells

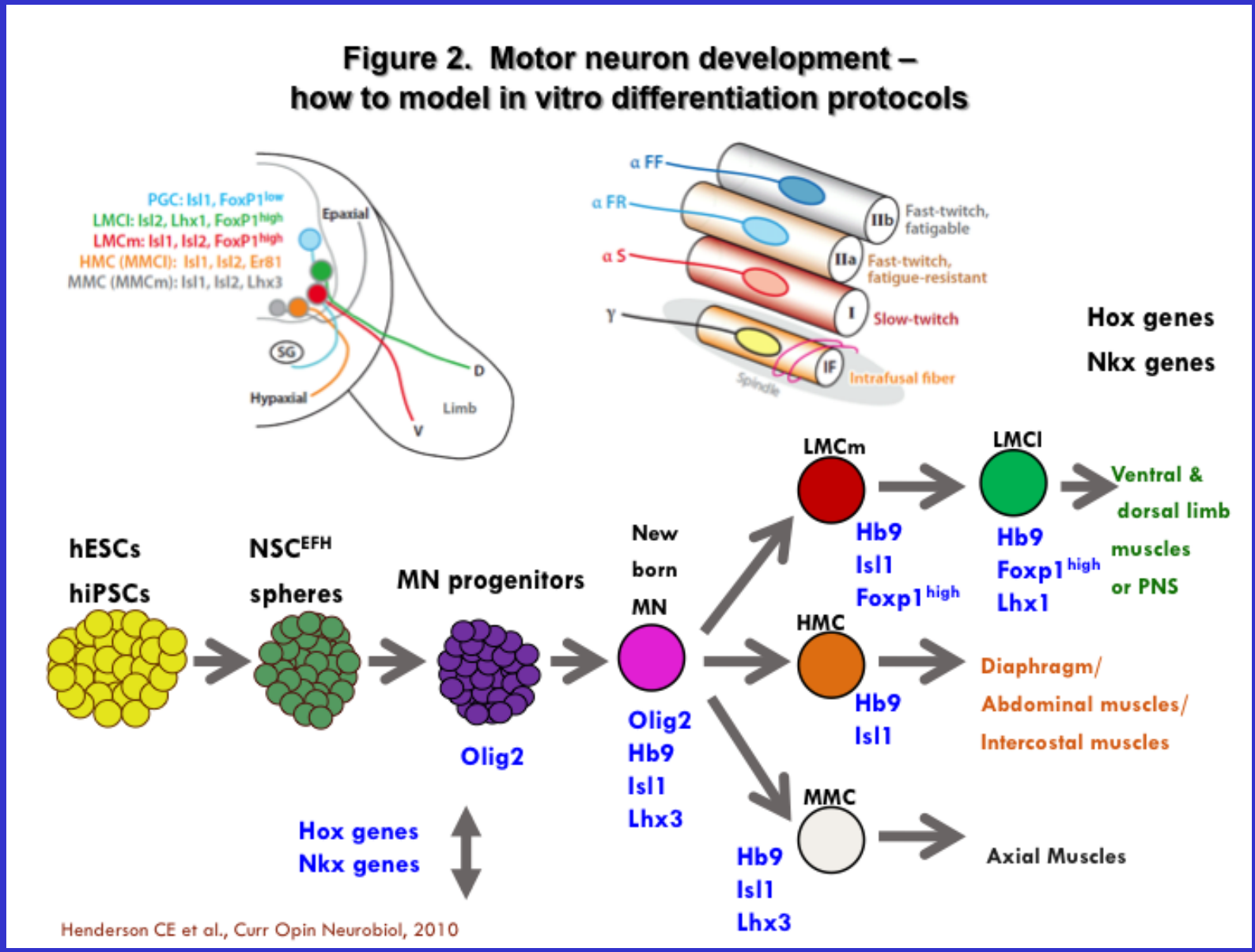


Human Skin Biopsy



Motor Neurons

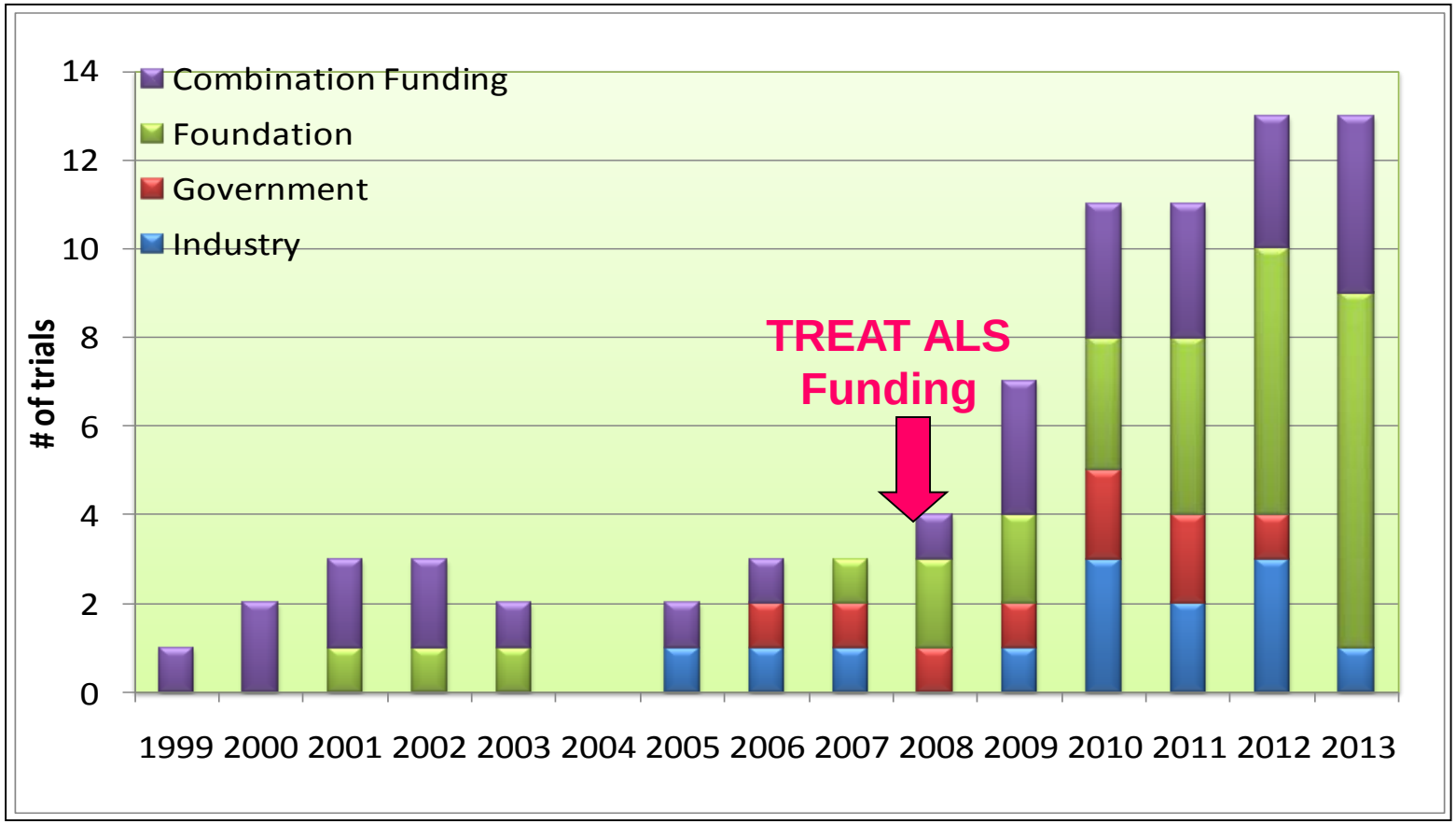
ALS Association/Cedar Sinai Stem Cell Core



ALS ACT (Accelerated Therapeutics)

- Partnership with MGH, General Electric and a Foundation
- Biomarker Development
- Therapeutic Development
- Neurobank-central to all four initiatives
- GUID
- Phase II A Pilot Studies
- Innovative call for novel ideas and biomarkers

TREAT ALS™NEALS Clinical Network leads to increased trials for ALS



NEALS

TREAT™ ALS/NEALS Clinical Network

(877) 458-0631
alstrials@partners.org

ALS ACT Clinical Pilot Studies RFA

- Released 22 October 2014
- Solicit letters of intent for phase II A clinical studies with a strong biomarker plan
- Proposals with additional funding partners will be favourably reviewed
- Open to academia and industry

Urgent Need for Biomarkers

- Improved Diagnosis
- Stratification in clinical trials
- Improved Clinical Trials-outcome measures;
- pharmocodynamic marker for target engagement

NEALS Biorepository

Request Sample Access: Tara Lincoln (tlincoln@partners.org)

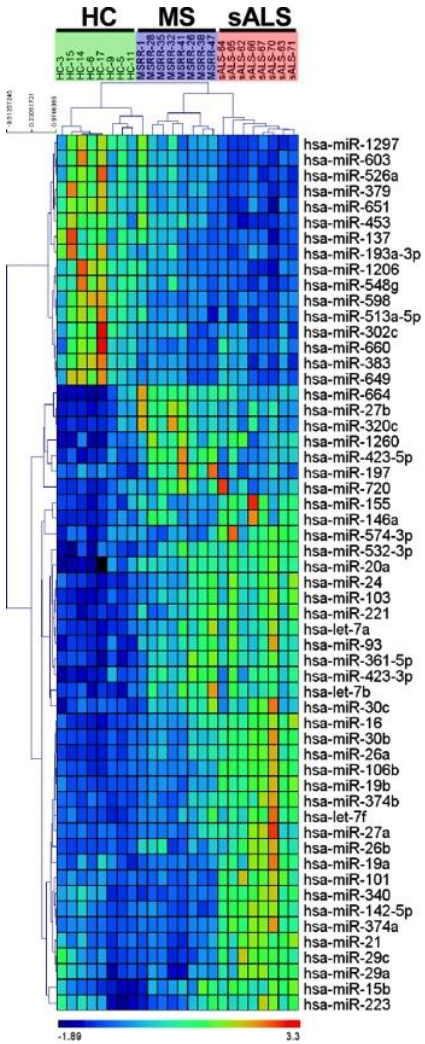
- Plasma, Serum, CSF, DNA
  - > 15,000 cryovials of plasma
  - ~ 1300 cryovials of serum
  - ~ 5000 cryovials of CSF
  - > 300 DNA samples

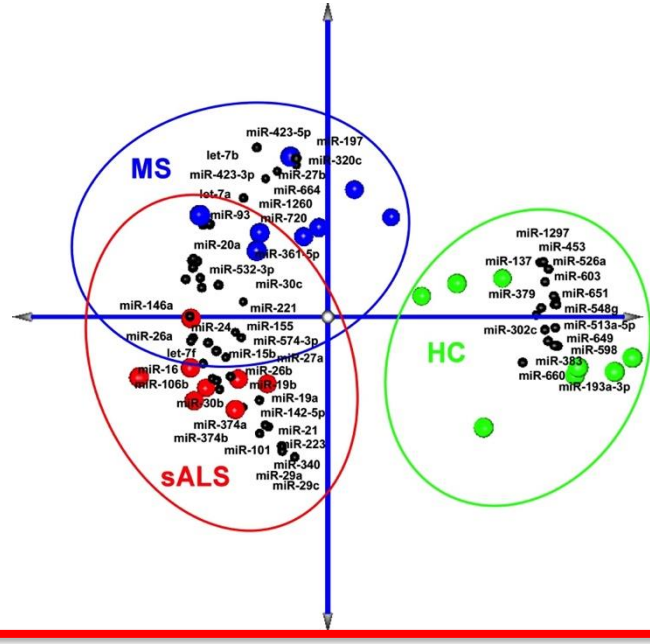
	Baseline Plasma	6mo Plasma	12mo Plasma	18mo Plasma	CSF	DNA
Early ALS	200	124	76	40	98	116
UMN/ LMN	49	28	12	9	24	39
Mimics	98	-	-	-	43	69
Healthy	102	-	-	-	52	52

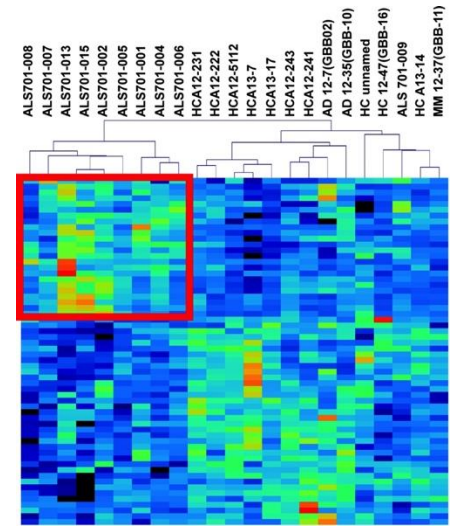
Identification of dysregulated microRNA signature in blood monocytes and spinal cord from ALS subjects

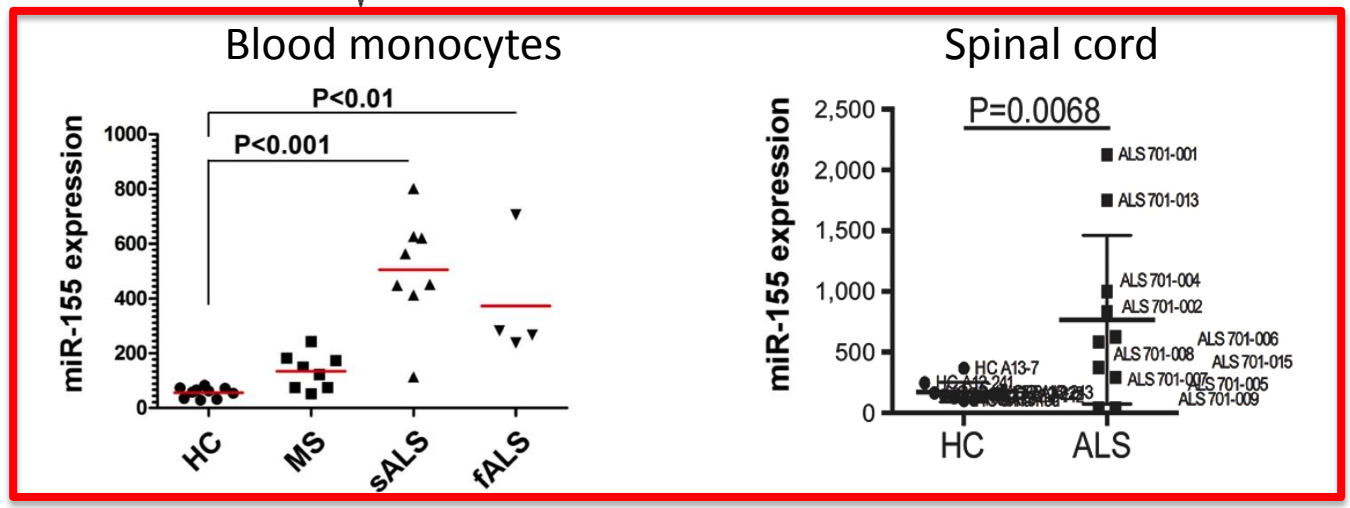
Blood monocytes

Spinal cord







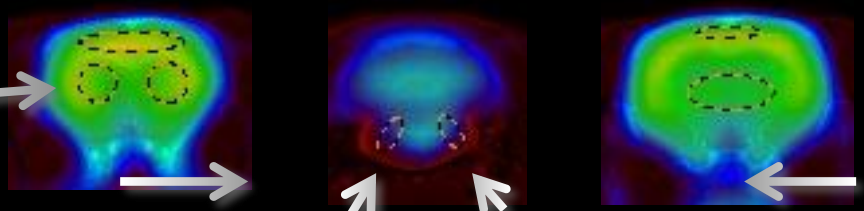


J Clin Invest. 2012

EAAT2 Rat PET Imaging: WT vs. ALS Model

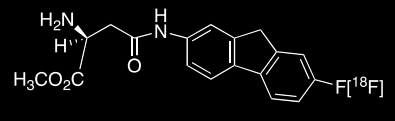
coronal

Frontal Cortex (FrCTx)
Caudate/Putamen (CP)



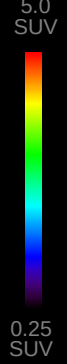
FrCTx
Thalamus (TH)

Motor nuclei (MNuc)



Prodrug tracer

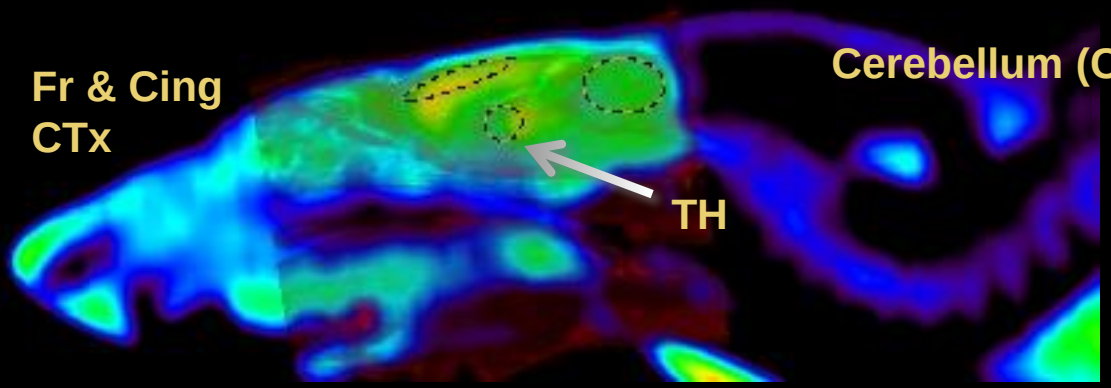
Sprague-Dawley rat
0.50 mCi of tracer
15 min post injection



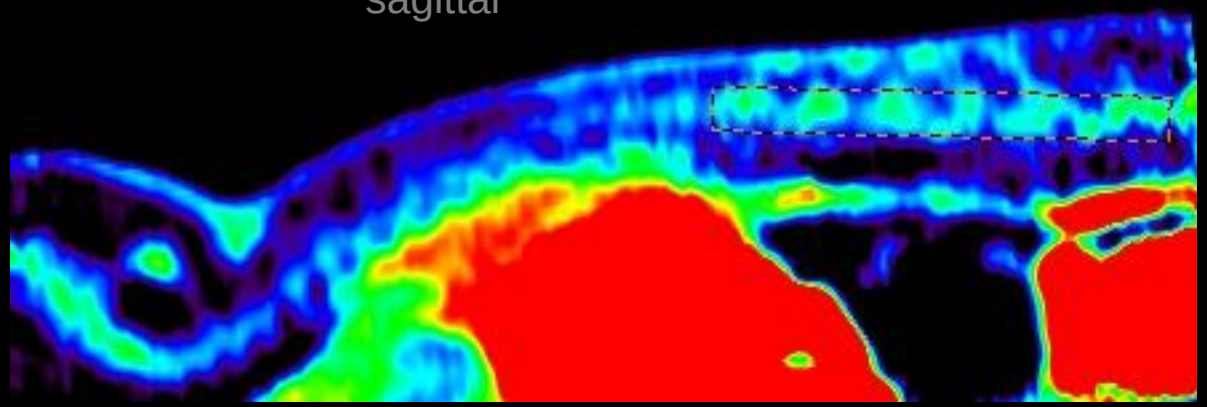
Fr & Cing CTx

Cerebellum (CE)

TH



sagittal



Lumbar spine

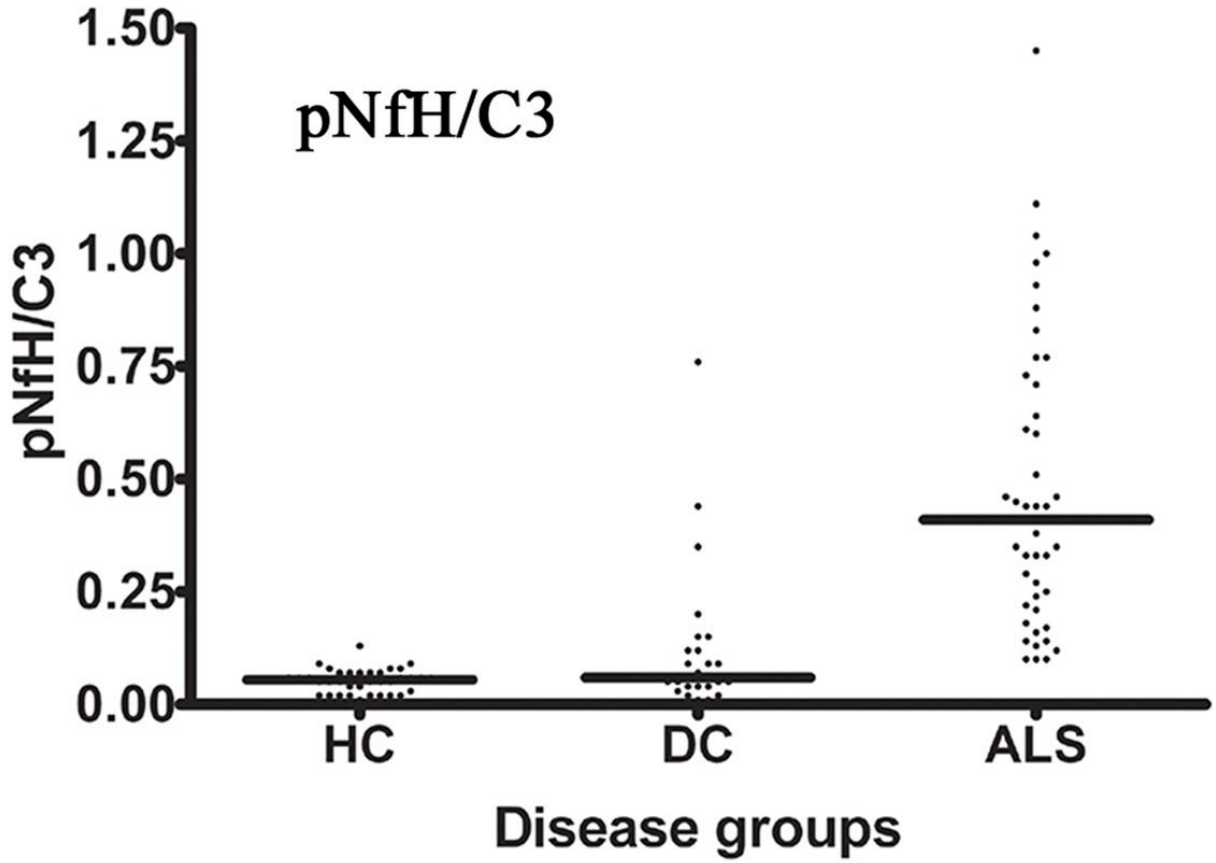
Decreasing spine signal In ALS rat model

JOHNS HOPKINS MEDICINE

UCSF University of California San Francisco advancing health worldwide

The University of Montana

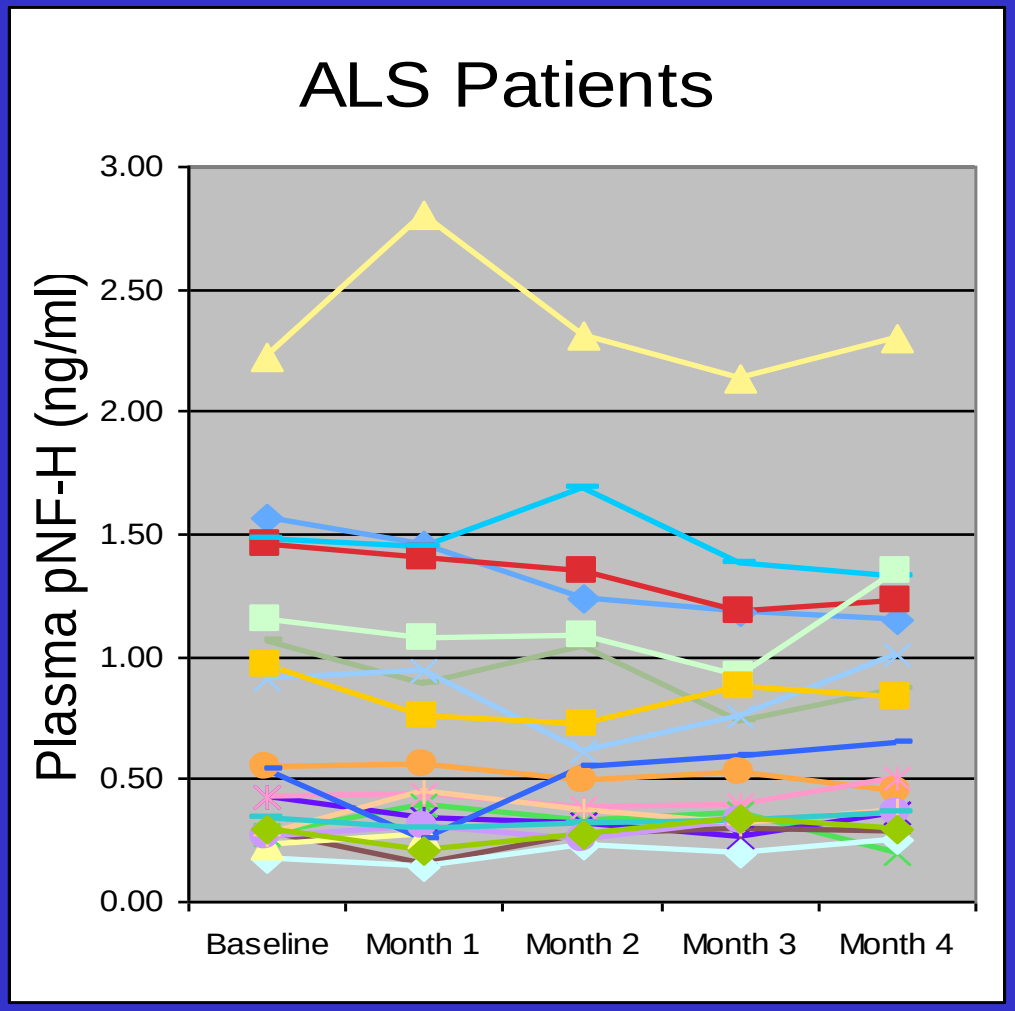
ALS diagnostic: Ratio of pNFH to complement C3 Levels

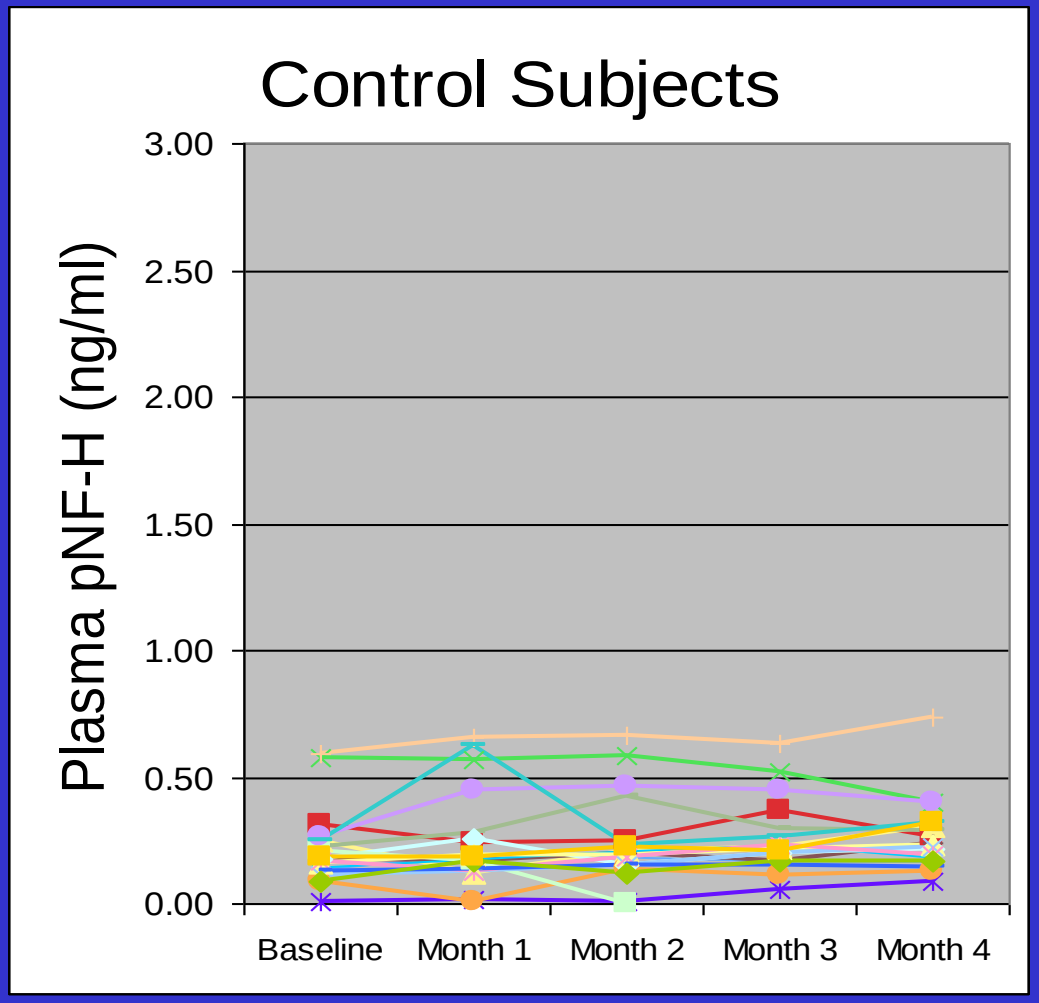


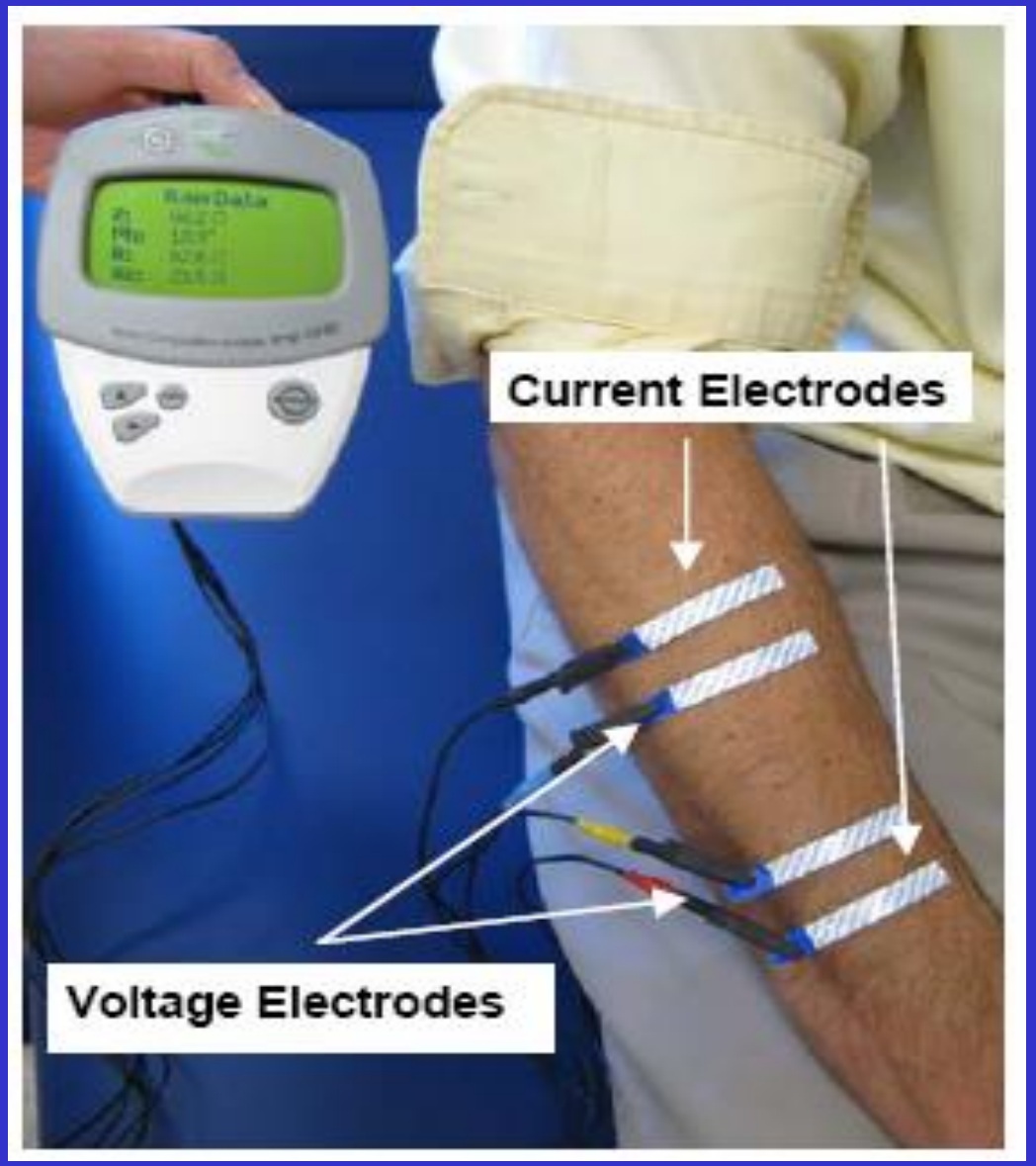
A cut-off value was obtained that was 90% accurate for ALS in 106 subjects in a retrospective study.

J Neurochem 117: 528-537 (2011)

Plasma pNF-H levels in 19 ALS and 19 Control patients over 4 months

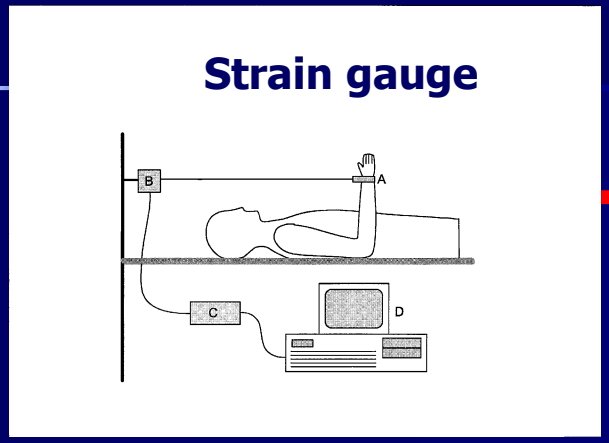






Seward Rutkove

Quantitative Isometric Strength Testing



ATLIS™
Accurate Test of Limb Isometric Strength

- Fixed, wireless load cell
- No position changes or stabilization required

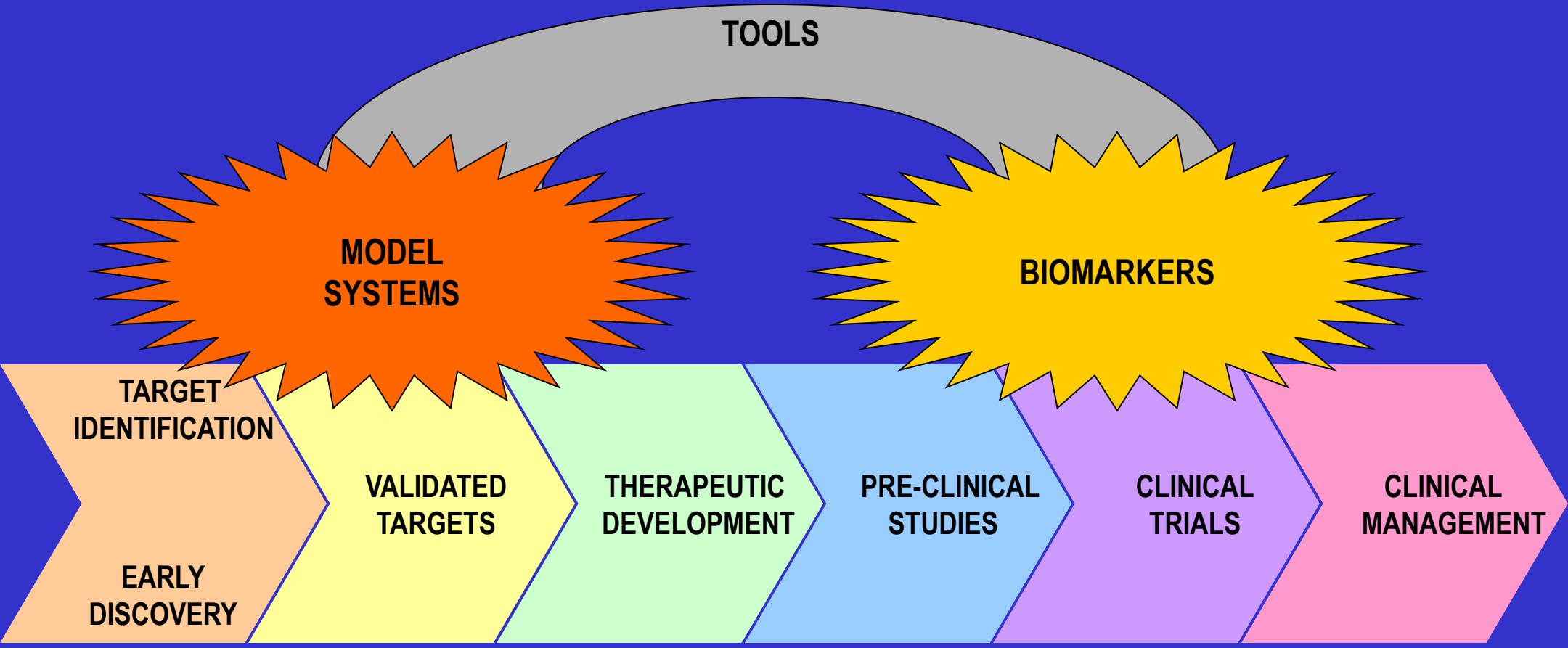
Disclosure: MGH holds a patent on this device. PL Andres is named inventor.

What Next ?

- Partnership with Jax Laboratories for mouse model development
- Drug Discovery Contracts
- Clinical Research Studies
- Continued support of investigator-initiated research and the Milton Safenowitz Fellowship Program
- Strategic Calls for proposals
- Focus on Biomarker Development and standardization

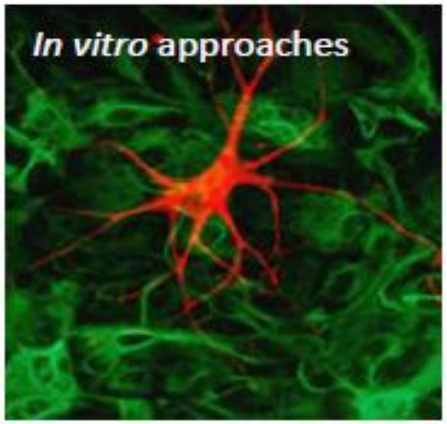
TREAT ALS PROGRAM

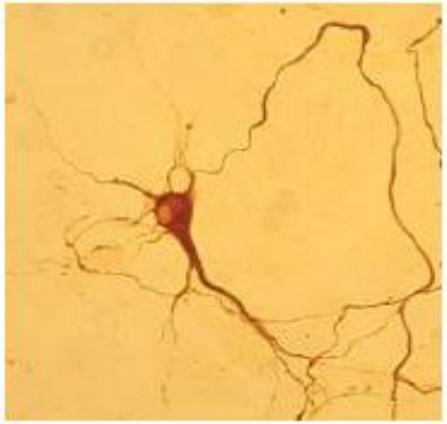
GLOBAL BIOMEDICAL RESEARCH

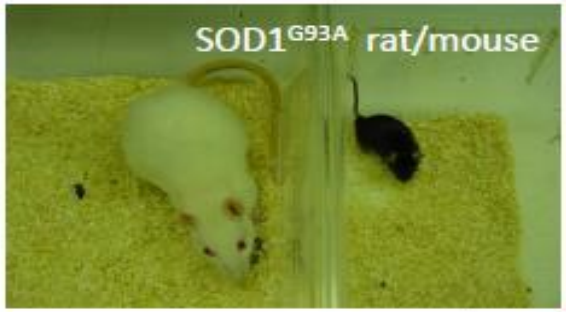


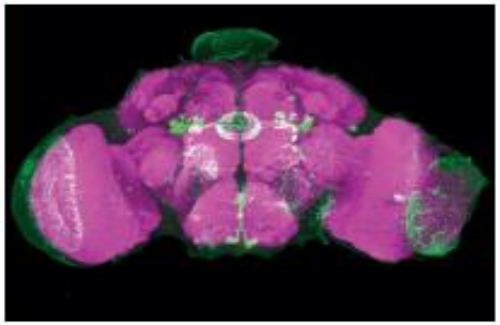
SOD1 antisense trial-UCSD/Isis Pharmaceuticals

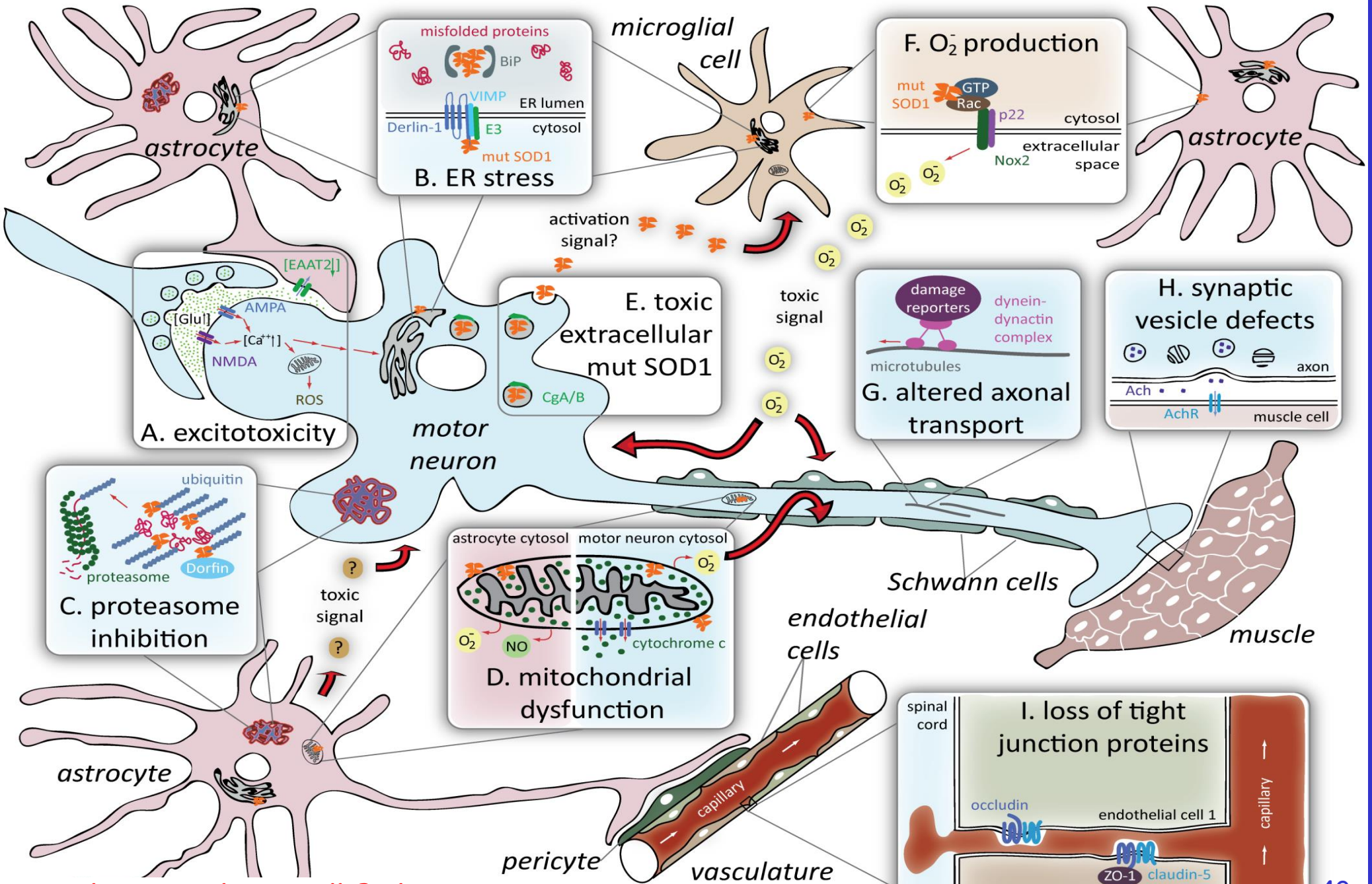
Model Systems to Understand Disease Mechanisms







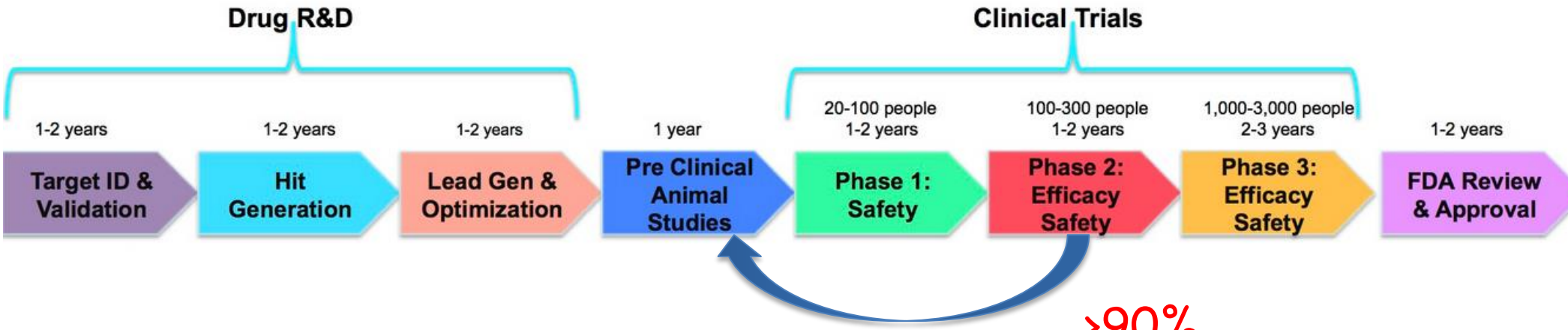




Ilieva et al, J. Cell Biol., 2009

Cat Lutz, Ph.D.
Director, Mouse Resources
Director, Rare and Orphan Disease
The Jackson Laboratory

Improving the Drug Discovery Pipeline



50% 10% 30% 30%

>90%
failure in phase IIB

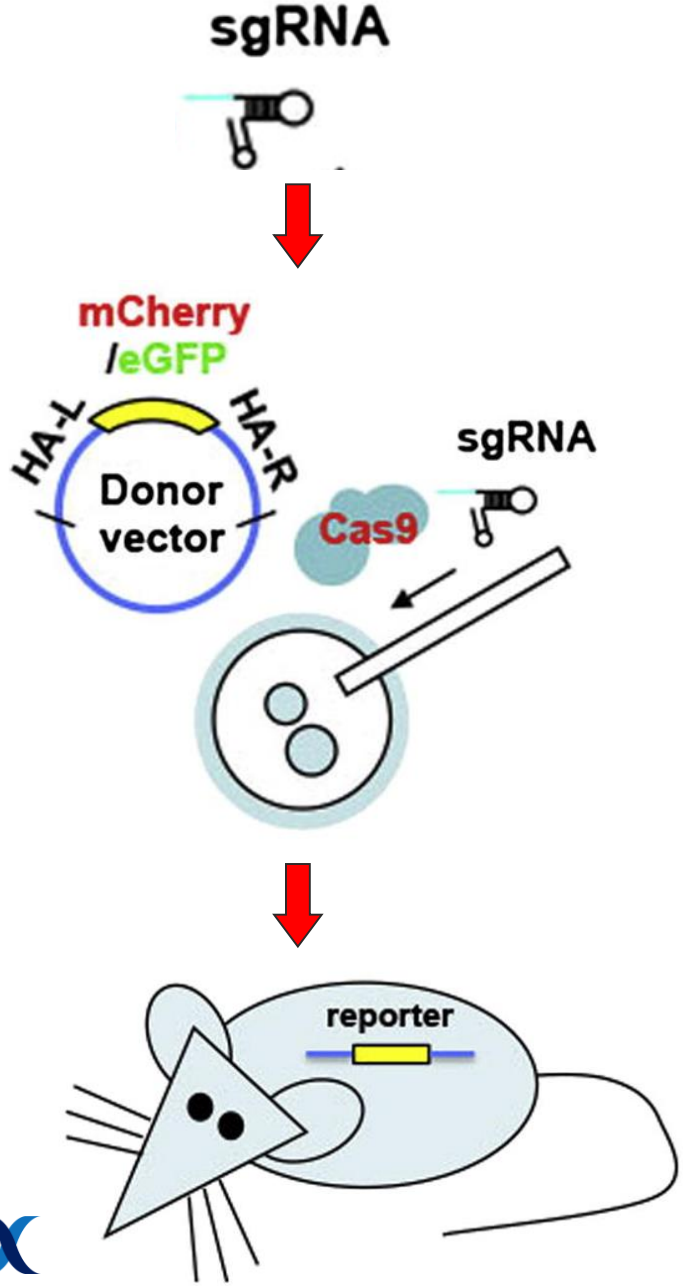
Better, Faster, Stronger

- Design
- Phenotypic validity
- Translational power
- Therapeutic platform

Challenge:

Can technological innovation lead us to process innovation?

Genetic Engineering Technologies at JAX



Milestone 1
Guide Design,
Synthesis & Testing

Milestone 2
Founder Generation

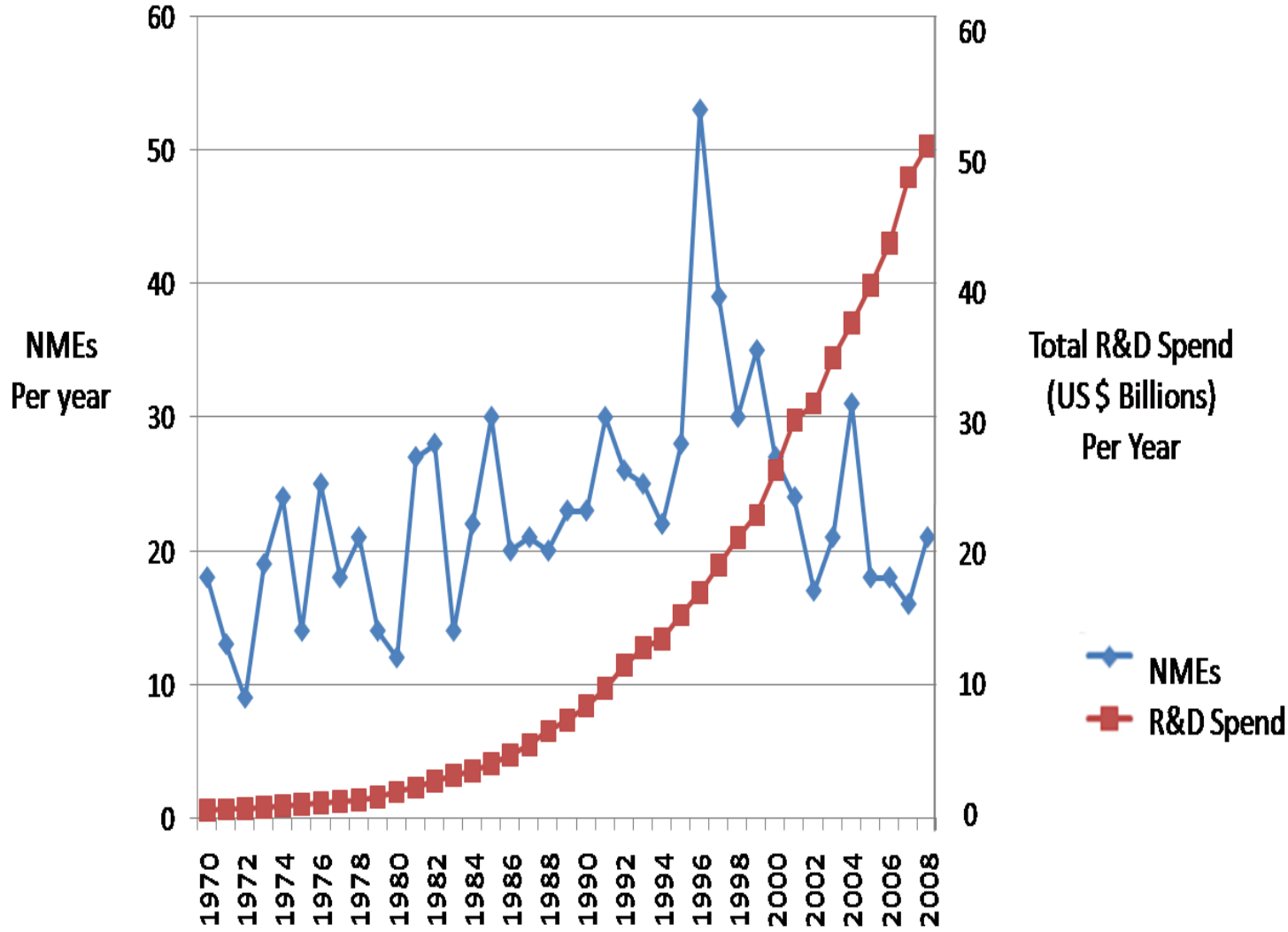
Milestone 3
Founder Identification

Timeline: 8 Weeks

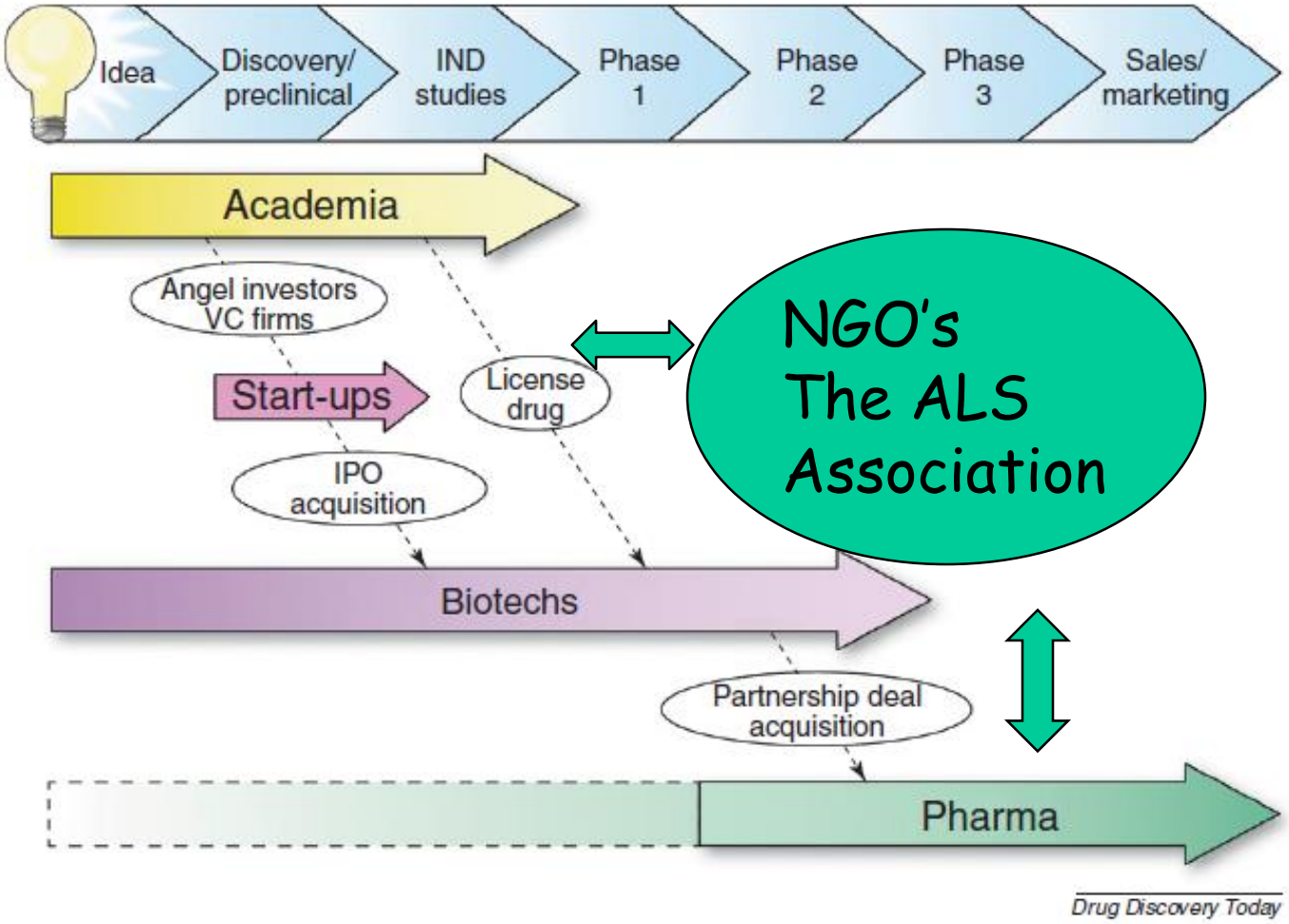
MOUSE MODEL RFA

- Request ideas for priority models to be developed
- Jax labs develops models
- The ALS Association owns models-no MTA blocking or delaying access to industry and other academic institutions
- Open Source availability of models for investigator community globally
- Two initial models already in planning to set up partnership

Challenges for Drug Discovery



Public-Private Partnerships



Fishburn 2012

Industry and Biotech focused on ALS

- Biogen Idec
- Bristol Myers Squibb
- Pfizer
- Genzyme/Sanofi Aventis
- Genentech/Roche
- Cytokinetics
- Neuraltus
- Neuralstem
- Synapse
- Avanir
- Amorfix
- ALS Biopharma
- Santhera
- UBC
- Biofocus
- Osainix

Milton-Safenowitz Post-Doctoral Fellowships