Research programs in light of ICE BUCKET CHALLENGE
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
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

5-10% familial

High
Low

Risk

Gender
SOD1

Risk

smoking

Age
Youth
ALS genes timeline


SOD1
Familial ALS

- SOD1
- C9ORF72
- FUS/TLS
- TDP-43
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.
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
Endogenous RNase H mediated degradation of the mRNA in a DNA/RNA duplex

Cleveland, Miller, Smith
Antisense Drugs Target RNA, not Proteins

Gene → mRNA → ANTISENSE DRUGS (Oligonucleotides) → No Translation of Disease-Causing Protein → NO DISEASE
C9orf72 gene

Modified from DeJesus-Hernandez *Neuron* (2011)

Repeat Primed PCR

Normal

Expanded

Southern:
Up to 1500 repeats
Intrathecal injection of AAV9 and AAVrh10 leads to transgene expression in the entire spinal cord and brainstem.

A

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<th>GFP intensity</th>
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B

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

Human Skin Biopsy

Motor Neurons

Skin Cells

Stem Cells

Human Skin Biopsy

Motor Neurons
Figure 2. Motor neuron development – how to model in vitro differentiation protocols

hESCs $\rightarrow$ NSC$^{EFH}$ spheres $\rightarrow$ MN progenitors $\rightarrow$ Olig2 $\rightarrow$ New born MN

Hox genes
Nkx genes

Hb9
Is1
Lhx3

Diaphragm/
Abdominal muscles/
Intercostal muscles

Aventral &
dorsal limb
muscles
or PNS

Axial Muscles

Henderson CE et al., Curr Opin Neurobiol, 2010
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

![Graph showing increased trials for ALS](chart.png)

- Combination Funding
- Foundation
- Government
- Industry

TREAT ALS Funding
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;
- pharmacodynamic marker for target engagement
• Plasma, Serum, CSF, DNA
  – > 15,000 cryovials of plasma
  – ~ 1300 cryovials of serum
  – ~ 5000 cryovials of CSF
  – > 300 DNA samples

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

Blood monocytes

Spinal cord

EAAT2 Rat PET Imaging: WT vs. ALS Model

Frontal Cortex (FrCTx) Caudate/Putamen (CP)

Cerebellum (CE)

Motor nuclei (MNuc)

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

Decreasing spine signal In ALS rat model

Lumbar spine
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.
Quantitative Isometric Strength Testing

ATLIS™
Accurate Test of Limb Isometric Strength

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

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

TARGET IDENTIFICATION
EARLY DISCOVERY
VALIDATED TARGETS
THERAPEUTIC DEVELOPMENT
PRE-CLINICAL STUDIES
CLINICAL TRIALS
CLINICAL MANAGEMENT
MODEL SYSTEMS
BIOMARKERS

Laboratory  bedsid
SOD1 antisense trial-UCSD/Isis Pharmaceuticals
Model Systems to Understand Disease Mechanisms
Cat Lutz, Ph.D.
Director, Mouse Resources
Director, Rare and Orphan Disease Center
The Jackson Laboratory
Improving the Drug Discovery Pipeline

Drug R&D
- Target ID & Validation: 1-2 years
- Hit Generation: 1-2 years
- Lead Gen & Optimization: 1-2 years
- Pre Clinical Animal Studies: 1 year

Clinical Trials
- Phase 1: Safety: 20-100 people, 1-2 years
- Phase 2: Efficacy Safety: 100-300 people, 1-2 years
- Phase 3: Efficacy Safety: 1,000-3,000 people, 2-3 years
- FDA Review & Approval: 1-2 years

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
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

![Graph showing NMEs and Total R&D Spend](chart.png)

- NMEs Per year
- Total R&D Spend (US $ Billions) Per Year

Legend:
- NMEs
- R&D Spend

Public-Private Partnerships

NGO's
The ALS Association

Drug Discovery Today
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