Update on ALS and Related Neurodegenerative Disorders

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Disclosures (No conflicts for this talk)

FUNDING FOR THE SOME PROJECTS I’LL DISCUSS TODAY:

• NIH, ALSA, AND TARGET ALS

• Neuropathology Consults, LLC
  – For consult work I do for the Dept of Justice/HHS and for the Office of the Chief Medical Examiner of DC
Learning Objectives

At the end of this activity learners should be able to:

• Define the evidence that ALS and some FTLD diseases lie on a disease spectrum

• Describe the histopathological findings that define ALS and FTLD-MND

• Describe the genetic alterations found in familial and sporadic forms of ALS and FTLD-MND
TOPICS

• ALS REVIEW

• COLLABORATIVE SCIENCE TO STUDY PATHOGENESIS/PATHOPHYSIOLOGY OF ALS/FTLD

• BIOBANKING IN THE 21ST CENTURY AND ALS/FTLD BIOBANKING INITIATIVES
AMYOTROPHIC LATERAL SCLEROSIS FACTS

• ALS is a neurodegenerative disease causing progressive paralysis leading to death within 2-5 years in the majority of patients.
• ALS is highly variable in terms of early symptoms and patterns of progression.
• Most cases of ALS are sporadic with perhaps 20% familial.
• Only two FDA approved medications (Riluzole and Edavarone) exist which may provide a minimal therapeutic benefit of several months extended survival.
Other common names for this disease:

- Motor neuron disease (England and Australia)
- Charcot’s disease (French, 1869)
- Lou Gehrig’s disease (base ball player, Yankees)
THE MOTOR PATHWAY
Amyotrophic lateral sclerosis: a clinical review

**Motor features**

**Subtypes by regional onset**
- Classic ALS
- Bulbar ALS
- Spinal ALS

**Specific subtypes**
- Pseudobulbar palsy
- Progressive bulbar palsy
- Mill’s syndrome (hemiplegic)
- Respiratory ALS
- Axial ALS
- Flail arm syndrome
- Flail leg syndrome
- Pseudopolyneuritic ALS

**Subtypes by UMN vs LMN involvement**
- Primary lateral sclerosis (PLS)
- UMN predominant ALS
- ALS
- LMN predominant ALS
- Progressive muscular atrophy (PMA)

**UMN signs**
- Hyperreflexia
- Spasticity
- Slowing of movements

**LMN signs**
- Weakness
- Muscle atrophy
- Fasciculations

**Cognitive features**

**Behavioral variant (bvFTD)**

**Primary progressive aphasia (PPA)**

**Progressive nonfluent aphasia (naPPA)**

**Semantic dementia (svPPA)**

**Logopenic progressive aphasia (lvPPA)**
**Figure 4**  Muscle fiber type grouping in ALS. Skeletal muscle histochemically stained for ATPase activity (ATPase pH 9.4) shows groupings of type I (light fibers) and type II (dark fibers).

**Figure 5**  Target muscle fibers in ALS. Skeletal muscle histochemically stained for NADH shows central clearing of mitochondria conveying a 'shooting target' appearance.
ANGULATED, ATROPHIED ESTERASE POSITIVE MYOFIBERS
“LATERAL SCLEROSIS”
ALS PATIENT FROM TALS PM CORE

MOTOR CORTEX

CD68 positive microglia

SEN SORY CORTEX

GFAP positive astrocytes
TRANSACTIVE RESPONSE DNA-BINDING PROTEIN 43 (TDP43) AGGREGATES IN NEURONS AND GLIA
GENETICS OF ALS TIMELINE
A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD.


Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS.


<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein product</th>
<th>Protein function</th>
<th>Locus</th>
<th>Proportion of cases associated with gene*</th>
</tr>
</thead>
<tbody>
<tr>
<td>C9orf72</td>
<td>Chromosome 9 open reading frame 72</td>
<td>Nucleotide factor</td>
<td>9p21–22</td>
<td>Familial ALS 20–50% Sporadic ALS 10%</td>
</tr>
<tr>
<td>SOD1</td>
<td>Superoxide dismutase 1</td>
<td>Superoxide dismutase</td>
<td>21q22.1</td>
<td>Familial ALS 10–20% Sporadic ALS 2%</td>
</tr>
<tr>
<td>TARDBP</td>
<td>TDP43</td>
<td>RNA-binding protein</td>
<td>q36</td>
<td>Familial ALS 5% Sporadic ALS &lt;1%</td>
</tr>
<tr>
<td>FUS</td>
<td>Fused in sarcoma protein</td>
<td>RNA-binding protein</td>
<td>16p11.2</td>
<td>Familial ALS 5% Sporadic ALS &lt;1%</td>
</tr>
<tr>
<td>MET3</td>
<td>Matrin 3</td>
<td>RNA-binding protein</td>
<td>5q31.2</td>
<td>Familial ALS &lt;1% Sporadic ALS &lt;1%</td>
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<tr>
<td>HNRNPA1</td>
<td>Heterogeneous nuclear ribonucleoprotein A1</td>
<td>RNA-binding protein</td>
<td>12q13.1</td>
<td>Familial ALS &lt;1% Sporadic ALS &lt;1%</td>
</tr>
<tr>
<td>OPTN</td>
<td>Optineurin</td>
<td>Mediator of apoptosis, inflammation and vasoconstriction, cellular morphogenesis, membrane trafficking, vesicle trafficking, transcription activation</td>
<td>10p15–p14</td>
<td>Familial ALS 4% Sporadic ALS &lt;1%</td>
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<tr>
<td>UbQLN2</td>
<td>Ubiquilin 2</td>
<td>Ubiquitination and protein degradation</td>
<td>Xp11.23–Xp13.1</td>
<td>Familial ALS &lt;1% Sporadic ALS &lt;1%</td>
</tr>
<tr>
<td>SQSTM1</td>
<td>Sequestosome 1</td>
<td>Autophagosome cargo protein, targets proteins for autophagy</td>
<td>5q35.3</td>
<td>Familial ALS &lt;1% Sporadic ALS &lt;1%</td>
</tr>
<tr>
<td>TBK1</td>
<td>Serine/threonine-protein kinase TBK1</td>
<td>Phosphorylation of nuclear factor-xB, regulation of cell proliferation, apoptosis and glucose metabolism, promotion of autophagy via the ubiquitylation pathway</td>
<td>12q14.2</td>
<td>Familial ALS &lt;1% Sporadic ALS &lt;1%</td>
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<tr>
<td>VCP</td>
<td>Transitional endoplasmic reticulum ATPase</td>
<td>Ubiquitin segregase</td>
<td>9p13.3</td>
<td>Familial ALS 2% Sporadic ALS &lt;1%</td>
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<td>DCTN1</td>
<td>Dynactin subunit 1</td>
<td>Mediator of organelle transport, spindle formation and axonogenesis</td>
<td>2p13</td>
<td>Familial ALS 1% Sporadic ALS &lt;1%</td>
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<tr>
<td>ANG</td>
<td>Angiogenin</td>
<td>Ribonuclease</td>
<td>14q11</td>
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<td>PFN1</td>
<td>Profilin 1</td>
<td>Actin-binding protein</td>
<td>17p13.2</td>
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<tr>
<td>CHCHD10</td>
<td>Coiled-coil-helix-coiled-helix domain-containing protein 10</td>
<td>Maintenance of cristae morphology in mitochondria, oxidative phosphorylation</td>
<td>22q11.23</td>
<td>Familial ALS &lt;1% Sporadic ALS &lt;1%</td>
</tr>
<tr>
<td>TUBA4A</td>
<td>Tubulin a4A chain</td>
<td>Microtubule formation, maintenance of cytoskeleton and structure of cells</td>
<td>2q36.1</td>
<td>Familial ALS &lt;1% Sporadic ALS &lt;1%</td>
</tr>
</tbody>
</table>

ALS, amyotrophic lateral sclerosis; TDP43, TAR DNA-binding protein 43. *The proportion of ALS cases associated with each genetic mutation varies depending on the population studied.**

*Nature Reviews Neurology 17, 104–118 (2021)*
C9ORF72

- Reduced expression through impaired transcription and/or splicing
- Sequestration of RNA-binding proteins by repeat-expanded RNA
- Unconventional translation (RAN); peptide aggregation and toxicity
Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by a progressive loss of motor neurons, which leads to muscle weakness and eventual paralysis and respiratory failure. Mutations in the C9orf72 gene have been identified as the major cause of ALS, accounting for 40–50% of familial ALS cases and ~7% of sporadic cases. The mutations, which consist of hexanucleotide repeat expansions (GGGGCC) have also been linked to frontotemporal dementia (FTD).

The high prevalence of these mutations in ALS and FTD has led to the development of several mouse models, including several bacterial artificial chromosome (BAC) transgenic mice, harboring GGGGCC shown by Liu et al. could be reproduced in four different cohorts of FVB C9-500 BAC transgenic mice, including two new studies performed independently at the University of Bern and the University of Rochester Medical Center. In a previous report, Nguyen et al. had also shown that the phenotype of C9-500 mice including decreased survival, Dig1Gait abnormalities, open field abnormalities, motor neuron loss, RNA foci and RAN protein accumulation could be improved by targeting GA RAN proteins with a-GA1 antibody, which would further support that the FVB C9-500 phenotype is caused by RAN protein pathology and not a FVB-strain phenotype.

“Although occasional seizures occurred...
ALS AND FTLD AS A SPECTRUM OF DISEASES

Upper motor neuron signs
- Primitive reflexes
- Pseudobulbar affect
- Hyperreflexia
- Hypertonia
- Spasticity

Lower motor neuron signs
- Weakness
- Atrophy
- Fasciculations
- Hyporeflexia

ALS
- ALS-bi ALS-eci
- ALS-recl
- ALS-FTD

FTD-MND

FTD

Behavioural changes

Aphasia

BV-FTD

LV-PPA

NFV-PPA

SV-PPA
<table>
<thead>
<tr>
<th>Predominant pathology</th>
<th>Associated genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic ALS</td>
<td>TDP-43</td>
</tr>
<tr>
<td></td>
<td>ALS2, SETX, TARDBP, VAPB, CHMP2b, ANG, UBQLN2, OPTN, PPN1, TUBA4a, UNC13a, FIG4, ELP3, NEK1, C21orf2, SIGMAR1, DCTN1, MATR3, CHCHD10, VCP, hnRNPA1, hnRNPA2b1, NIPA1, SMN1, TBK1, ATXN2, MOBP, SARM1, UBQLN2, SQSTM1</td>
</tr>
<tr>
<td>Classic ALS</td>
<td>SOD1</td>
</tr>
<tr>
<td>Classic ALS</td>
<td>FUS</td>
</tr>
<tr>
<td>ALS with cognitive or</td>
<td>TDP-43</td>
</tr>
<tr>
<td>behavioural impairment</td>
<td>TARDBP, CHMP2b,</td>
</tr>
<tr>
<td>or comorbid FTD</td>
<td>TBK1, UBQLN2, SQSTM1, DCTN1, UNC13a</td>
</tr>
<tr>
<td>Classic ALS, ALS-FTD,</td>
<td>TDP-43, p62, dipeptide repeats, RNA foci</td>
</tr>
<tr>
<td>FTD</td>
<td></td>
</tr>
<tr>
<td>Multi-system</td>
<td>TDP-43</td>
</tr>
<tr>
<td>proteinopathy*</td>
<td>VCP, hnRNPA1, hnRNPA2b1, SQSTM1</td>
</tr>
<tr>
<td>Behavioural variant FTD</td>
<td>TDP-43</td>
</tr>
<tr>
<td></td>
<td>CHMP2, GRN</td>
</tr>
<tr>
<td>Behavioural variant FTD</td>
<td>FUS</td>
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<tr>
<td>Behavioural variant FTD</td>
<td>Tau</td>
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<td></td>
<td>MAPT</td>
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<tr>
<td>Semantic variant primary</td>
<td>TDP-43</td>
</tr>
<tr>
<td>progressive aphasia</td>
<td>GRN, C9orf72</td>
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<td>Semantic variant primary</td>
<td>Tau</td>
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<tr>
<td>progressive aphasia</td>
<td>MAPT</td>
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<tr>
<td>Logopenic and non-fluent</td>
<td>Tau</td>
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<tr>
<td>variant primary</td>
<td>MAPT</td>
</tr>
<tr>
<td>progressive aphasia</td>
<td></td>
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</tbody>
</table>

ALS = amyotrophic lateral sclerosis. FTD = frontotemporal dementia. *A familial disorder in which patients present with ALS, FTD, inclusion body myositis, Paget’s disease of the bone, or combinations thereof.

Table 3: The complex correlations between genes, pathology, and phenotypes
**WHY DO THIS PHENOTYPIC/GENOTYPIC CHARACTERIZATION?**

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Associated with long survival</th>
<th>Associated with short survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Flail arm variant; lower motor neuron-predominant disease; upper motor neuron-predominant disease; long time to diagnosis; young age at diagnosis</td>
<td>Bulbar-onset ALS; respiratory onset; executive dysfunction and comorbid FTD; poor nutritional status; neck flexor weakness; old age at diagnosis</td>
</tr>
<tr>
<td>Genetic factors</td>
<td>SOD1 mutations: Glu22Gly, Gly38Arg, Asp91Ala, Gly94Cys, and Ile114Thr; reduced EPHA4 expression</td>
<td>Ala5Val mutation in SOD1; repeat expansions in C9orf72 or ATXN2; mutations in FUS (also associated with early onset); homozygosity for the C allele of rs12608932 in UNC13α</td>
</tr>
<tr>
<td>Environmental and life style factors</td>
<td>None</td>
<td>Low socioeconomic status; smoking</td>
</tr>
<tr>
<td>Treatments</td>
<td>Riluzole treatment; non-invasive ventilation; enteral feeding; moderate exercise; multidisciplinary clinic care</td>
<td>Carbamazepine; minocycline; diaphragm pacing</td>
</tr>
</tbody>
</table>

ALS=amyotrophic lateral sclerosis. FTD=frontotemporal dementia.

*Table 2: Prognostic factors in amyotrophic lateral sclerosis*
Ideas about the Pathogenesis and Pathophysiology of ALS
Figure 12 Mitochondrial dysfunction in amyotrophic lateral sclerosis. The aggregation of mutant SOD1 causes a failure in energy production, a breakdown of the mitochondrial membrane potential, and a loss in Ca^{2+} buffering by mitochondria. The release of cytochrome c initiates apoptotic death in the affected neuron. ADP, adenosine diphosphate; ROS, reactive oxygen species.

Reproduced with permission from Ref. 20.
TNFα affects mitochondrial transport
hmSOD1 G93A transgenic rat
Howland, et al. PNAS 2002
Increased Microglia in Ventral Horn and White Matter Before and After Symptom Onset

Microglia (CD11b) in Spinal Cord

WT

Pre-Symptomatic

End-Stage

Graber et al. Journal of Neuroinflammation 2010, 7:8
TDP-43

- TDP-43 is a DNA/RNA binding protein with a number of different splice forms.

- It binds to a variety of RNA and DNA sequences, particularly to poly UG RNA sequences, as well as other proteins.

- It can shuttle back and forth from the cytoplasm. In FTD and ALS cases, affected neuron and glial cells show a variety of different TDP-43 forms that accumulate in inclusion bodies in the cytoplasm and/or nucleus with loss of normal diffuse nuclear distribution.
• Formation of intranuclear and cytoplasmic inclusions

• Hyperphosphorylation

• Cleavage generates C-terminal fragments of approximately 24–26 kDa

• Dramatic translocation from nucleus to cytoplasm
Diagram of Nanobody

a) Single domain nature
b) Small size
c) Increased hydrophilicity
d) High sequence stability
e) Extended CDR3 loop
f) Variable N terminal of CDR1

Potentially useful for diagnostics and Therapeutics
Cloning and nanobody production (collaboration with Sierks lab at ASU)

Isolation and characterization of antibody fragments selective for human FTD brain derived TDP-43 variants.
Venkataraman L, He P, Khan G, Harris BT, Sierks MR.

Novel atomic force microscopy based biopanning for isolation of morphology specific reagents against TDP-43 variants in amyotrophic lateral sclerosis.
Williams SM, Venkataraman L, Tian H, Khan G, Harris BT, Sierks MR.
New collaboration with NCI, NIH
Curt Harris, Chief Lab of Human Carcinogenesis and Casimir Turnquist, PhD
Investigating the role of p53 isoforms in brain aging, senescence, and neurodegeneration

Harris Lab, Georgetown University
Harris Lab, Laboratory of Human Carcinogenesis, NCI/NIH
What is senescence?

- Biological aging
- Gradual deterioration of functional characteristics
- Loss of a cell's power of division and growth (cellular senescence)
- Inevitable

- Can be also accelerated via: stress, disease, genetic mutations, chromosomal abnormality (Progeria, Down’s syndrome), UV radiation, DNA or cellular damage, etc.
- May be delayed – Drugs? Caloric restriction?
13 p53 isoforms

Amino acid number

(A) Schematic representation of p53 isoforms.

(B) Summary of p53 isoforms with highlighted amino acid numbers.

- p53α (p53)
- Δ40p53α
- Δ133p53α
- Δ160p53α
- p53β
- Δ40p53β
- Δ133p53β
- Δ160p53β
- p53γ
- Δ40p53γ
- Δ133p53γ
- Δ160p53γ


(p53Ψ) (PNAS 111: E3287, 2014)
Δ133p53 and p53β Regulate Cellular Senescence

- Δ133p53α
  - Downregulated at replicative senescence
  - Inhibits full-length p53
  - Degraded via selective autophagy

- p53β
  - Upregulated at replicative senescence
  - Cooperates with full-length p53
  - Regulated by alternative RNA splicing

Horikawa et al. Nat Commun 2014
Tang et al. Oncogene 2013
Marcel et al. Cell Death Differ 2014
Cellular Senescence of Astrocytes in Brain Tissues from Neurodegenerative Disease Patients

Expression of senescence-associated genes

Expression of Senescence-associated genes

Turnquist et al., CDD, 2016
p53β is Upregulated and Δ133p53 is Downregulated in Neurodegeneration and in Aged Astrocytes in vitro

**Human Brain Tissue**

<table>
<thead>
<tr>
<th>p53</th>
<th>ND</th>
<th>AD</th>
<th>ALS</th>
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<table>
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**Primary Human Astrocytes**

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<table>
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<table>
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</table>

*P < 0.05

Turnquist et al., *CDD*
Co-Culture of Human Astrocytes and Neurons

iPSC-derived neurons + Primary human astrocytes +p53β or +Δ133siRNA

24 hrs

Co-culture

- Quantification of neuronal apoptosis
- Neuronal survival

Astrocyte and Neuron co-culture

GFAP

NeuN

Merge

Scale bar
Increased Neuronal Death upon Co-culture with Δ133p53-knocked-down or p53β-overexpressing Astrocytes

Early-passage astrocytes (P5) + motor neurons

% Neuronal Apoptosis

Number of Neurons

DAPI    NeuN

+Cont    +Δ133si    +Δ133si

Neuron    Cleaved -caspase 3    Astrocyte    Merge

+p53β    +p53β

Number of Neurons

* P<0.05 ** P<0.01 *** P<0.001
Δ133p53 Overexpression Rescues Human Astrocyte SASP and Enhances Neurotrophic Factor Expression

* P<0.05  ** P<0.01  *** P<0.001
Model of p53 Isoform Regulation of Astrocyte-mediated Neuroprotection and Neurodegeneration
MY INSPIRATION TO BECOME A BRAIN BANKER...
YOUNG FRANKENSTEIN (1974)  
YES, IT’S ON NETFLIX
Twenty-first century brain banking. Processing brains for research: the Columbia University methods

Jean Paul G. Vonsattel · María Pilar del Amaya · Christian E. Keller
STORAGE OF TISSUES IN FIXATIVE AND BLOCKS
STORAGE OF TISSUES
FROZEN TISSUES AND MORE RECENTLY FFPE TISSUES

• Genomics
• Proteomics
• Transcriptomics
• Metabolomics
• Any "omics" you can think of
COMBINING OMICS WITH SPATIAL/HISTOPATHOLOGY:
Target ALS
Resources
- Biofluids, Tissues, Sequencing

Robert Bowser, PhD
Brent Harris, MD, PhD
Hemali Phatnani, PhD
Overall Goals

• Create Repositories of samples (longitudinal biofluids, post-mortem tissues) linked to sequencing information (WGS, RNA-seq), clinical information and at-home measures that capture the disease from diagnosis to end-stage.

• Includes ALS, healthy controls, and disease controls

• All coded samples, data and clinical information immediately available to the research community
Goal and Sites

• Collect, process, bank, analyze, and distribute postmortem CNS tissues and skeletal muscle from ALS and neurological disease-free controls

• Sites and PIs:
  • Barrow Neurological Institute – Robert Bowser, PhD
  • Columbia University – Neil Shneider, MD, PhD and Matt Harms, MD
  • UCSD – John Ravits, MD
  • Georgetown University – Brent Harris, MD, PhD
  • Washington University – Cindy Ly, MD, PhD and Timothy Miller, M.D., Ph.D.

Core co-Directors: Drs. Bowser and Harris
Core Neuropath Director: Dr. Harris
TALS PM CORE

Approximately 250 ALS Cases and 30 Control Cases

Now starting premortem longitudinal Biofluid collections to bank and match with clinical progression.
Genomics Data Overview
Postmortem Cortex Samples Identify Distinct Molecular Subtypes of ALS: Retrotransposon Activation, Oxidative Stress, and Activated Glia

Oliver H. Tam¹,⁹, Nikolay V. Rozhkov¹,⁹, Regina Shaw¹,⁹, Duyang Kim², Isabel Hubbard²,¹⁰, Samantha Fennessey², Nadia Propp², The NYGC ALS Consortium, Delphine Fagegaltier², Brent T. Harris³,⁴, Lyle W. Ostrow³,⁵, Hemali Phatnani²,³, John Ravits³,⁶, Josh Dubnau³,⁷,⁸, Molly Gale Hammell¹,³,¹¹,*
Summary

- ALS and FTLD sit on a spectrum of neurodegenerative diseases characterized by variable clinical, genetic, and cellular/molecular changes.
- Familial and sporadic forms exist and we can learn a lot from studying the genetic changes.
- Collaboration and biofluid/tissue banking are the only way we are going to make headway on this devastating group of diseases.
Special thank you to all the patients and families that volunteer for clinical trials and biobanking in order to help others with these devastating diseases.
ACKNOWLEDGEMENTS

LHC/NCI/NIH
Curt Harris
Izumi Horikawa
Casmir Turnquist
Jessica Beck
Kyra Ungerleider

NINDS/NIH
Eugene Major
Kenneth Fischbeck
Douglas Fields

Harris Lab/GBB
Galam Khan
Carolyn Ward
Andrew Wodrich
Karli Gilbert
Ashwini Gadalay

Target ALS Consortium
Bob Bowser
Manish Raisinghani
Hemali Phatnani

Sierks Lab/ASU
Michael Sierks
THANKS FOR YOUR ATTENTION!

QUESTIONS??
References


