The Northeast ALS Consortium

ALS Clinical Trials: Pipeline Update Summer 2013

Merit Cudkowicz, MD, MSc
Massachusetts General Hospital, Boston MA
Co-Chair, Northeast ALS Consortium (NEALS)
ALS: Where we are now?

- Amazing new theories about disease mechanisms
- Substantial progress on therapeutics
  - Riluzole and Nuedexta; Multidisciplinary care
  - Pipeline of potential therapies is large and growing
  - >15 years experience in clinical trial design and conduct in ALS
- Therapy Development Challenges
  - Late diagnosis, heterogeneity, lack of biomarkers
  - Uncertainty of cause and targets
  - Decline in funding
The rate of gene discovery in ALS is increasing: >25 ALS genes

Each gene defines pathways and treatment targets.
• >60% of families known genetic mutations

• 7-10% “sporadic” ALS have C9orf72 mutations

Courtesy of Bryan Traynor, MD
Stem Cell Research: Understand ALS and discover treatments

- Disease Modeling (SALS)
- Insight to Disease Mechanisms
- High-throughput Drug Screening
- Cell Replacement Treatment

Eggn K et al. Science 2008
Kiskinis E et al. J Clin Inv 2010
Biomarkers are critical to speeding up finding treatments for ALS

A biomarker is a measure of a biological state or disease process

What could a biomarker be?

• **Imaging**: MRI, CT, PET (eg: changes on brain MRI as biomarkers of stroke)

• **Biofluid**: Genes and concentrations of certain chemicals in Blood or Spinal fluid (eg: Glucose level in blood is a biomarker of diabetes)

• **Tissue**: studying cells under the microscope (eg: biopsies can provide biomarkers for cancer)

• **Other**: Clinical testing, questionnaires, Breathing tests, Electrophysiology etc.
We should be collecting clinical and biological information from every person with ALS!

Critical to understanding disease heterogeneity, biology in people and accelerating therapy development.

Samples for biomarkers research must be specifically collected for that purpose and as dictated in the study consent form.

http://www.alsconsortium.org/search.php?v=a

To search for and learn more about enrolling biomarkers studies.
Goal: Create a large biorepository of high-quality samples linked to clinical information for biomarker research.

1) Reduce Pre-Analytical Sample Variation by Using Strict SOPs
2) Link Clinical Data
3) Identify and Validate Biomarkers
4) Share Samples (Blood, Skin, CSF, Clinical Info)

<table>
<thead>
<tr>
<th></th>
<th>Plasma</th>
<th>Serum</th>
<th>CSF</th>
<th>DNA/Whole Blood</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS</td>
<td>923</td>
<td>673</td>
<td>726</td>
<td>187</td>
<td>2509</td>
</tr>
<tr>
<td>Disease Control</td>
<td>196</td>
<td>127</td>
<td>212</td>
<td>14</td>
<td>549</td>
</tr>
<tr>
<td>Healthy Control</td>
<td>326</td>
<td>241</td>
<td>312</td>
<td>11</td>
<td>890</td>
</tr>
</tbody>
</table>

3948
ALSA TREAT ALS & NEALS – lower barriers to bring therapies to people

• 109 Centers, 400+ Members
• Clinical trials infrastructure for the use of the ALS community
• Clinical Research Learning Institute
  – Patient and Family Research Advocates
• Train new and existing investigators to conduct high quality clinical studies in ALS
• Assist with protocol development and project management to new investigators and industry
ALSA TREAT ALS & NEALS – lower barriers to bring therapies to people

• Shared Resources (data, samples)
• Prize4Life/NEALS ProACT Initiative
• New Initiatives to bring forward the best therapies efficiently
  – Call for Biomarker Driven Phase II Grants
  – Central IRB and Master Contracts for ALS Centers
    • Modeled after NeuroNEXT initiative for all neurological disorders (MGH Clinical Coordination Center)
Treatments
Multiple ALS therapies have been tested

One approved (riluzole) and seven with some positive Phase II human data*

### Anti-glutamate$^{1,2,3,4}$
- Riluzole
- Gabapentin
- Topiramate
- Dextro-methorphan
- ONO-2506
- Memantine
- *Talampanel*
- *Ceftriaxone*

### Growth factors$^1$
- BDNF-IT
- SC
- CNTF
- IGF-1
- Xaliproden

### Anti-inflammatory$^1$
- Celebrex
- Minocycline
- Nimesulide
- *NP001*

### Anti-oxidants/ bioenergetics$^{1,2,5}$
- Creatine (5 and 10 g)
- Vitamin E
- Acetylcysteine
- Coenzyme Q
- Olexosome
- *Dexpramipexole*
- *Tamoxifen*
- *MCI-186*

### Anti-apoptotic$^{1,6}$
- TCH346
- Pentoxyfilline

### Protein aggregation$^{2,3,7,8}$
- Arimoclomol
- *Lithium*

---

...the ALS pipeline has many treatments in development for ALS

• **Phase II**
  – Tirasemtiv (CK-2017357)
  – Immunosuppression (4)
  – Gilenya
  – Mexiletine
  – Nuedexta
  – Ursodiol
  – NurOwn™
  – Neuralstem
  – NP001
  – GSK1223249
  – High fat nutrition
  – Exercise
  – Tamoxifen/Creatine
  – Diaphragm pacing
  – GM604

• **FALS SOD1**
  – ISIS333611
  – Arimoclomol

• **FALS/SALS – C90rf72**

www.clinicaltrials.gov

www.alsconsortium.org
How Can I Find out More about Trials?

Browse Recruiting Trials

With help from the ALS Association, NEALS provides up-to-date information for finding both federally and privately funded clinical studies focusing on ALS and motor neuron diseases. You can locate both interventional trials, which examine if treatments are effective and safe under controlled environments, and observation trials, which examine people in more natural environments.

NEALS sources this database from public information posted on clinicaltrials.gov and other public websites. Therefore, not all trials included here are supported directly by the ALS Association and/or NEALS. Trials with a NEALS emblem are those in which NEALS has a supporting role. This feature is updated regularly, so please check back. If you need support please contact our ALS Trial Expert.

www.alsconsortium.org  1-877-458-0631  alstrials@partners.org
Phase 1 ISIS 333611-Single Dose, Dose Escalation Study in SOD1 fALS

• Single 11.5-hr intrathecal infusion
  – 4 sequential cohorts, doses of 0.15, 0.5, 1.5 and 3 mg
• 8 patients per cohort: 3 active:1 placebo
• Primary endpoints:
  – safety/tolerability and
  – pharmacokinetics (plasma and CSF drug levels)
• 4 sites in the US
• Subject participated in multiple dosage cohorts
Selection Trial of Tamoxifen and Creatine

- Safety: CRE 30g had more gastrointestinal AE’s
- Tolerability: CRE 30g had most drug discontinuations

### ALSFRS-R Change / mo
- CRE: -0.9
- T40: -1.0
- T80: -0.7

### FVC Change / mo
- CRE: -3.4
- T40: -2.9
- T80: -3.4

### HHD Change / mo (UE)
- CRE: -0.10
- T40: -0.09
- T80: -0.04 (p=0.002)

### HHD Change / mo (LE)
- CRE: -0.09
- T40: -0.07
- T80: -0.02 (p=0.002)
Two Regulatory Approved Phase I/II stem cells studies in ALS: Neuralstem and BrainStorm

• Neural stem cells engrafted into the spinal cord

• NurOwn™ Adult bone marrow-derived Mesenchymal Stromal Cells (MSCs)
Phase II Neuralstem

- Based on Phase I safety data, a Phase II dose-escalation and safety trial has begun enrolling by invitation in summer 2013 at at least two research sites:
  - Emory University
  - University of Michigan

- Primary objective: to determine the feasibility, safety, toxicity, and maximum tolerated (safe) dose of human spinal cord-derived neural stem cell transplantation for the treatment of ALS

- Estimated enrollment is 18 patients

- Inclusion criteria (additional criteria apply):
  - Laboratory-supported probable, probable or definite ALS
  - Symptom onset within 24 months of enrollment
  - 18 years or older
  - Geographic accessibility to study center
  - Vital capacity $\geq 60\%$ of predicted normal for age, height and gender measured in the seated position and $\geq 50\%$ in supine position 7 days prior to surgery
  - Ambulatory subjects with extremity weakness and/or spasticity due to ALS
  - Absence of any exclusion criteria
• Rationale for trial: to investigate the disease-modifying effect of the immunosuppression regimen used in the Neuralstem phase I trial

• Primary Objective: assess the clinical response rate of a novel immunosuppression regimen in a subset of ALS patients. Subjects will be randomly assigned to receive:
  • Basiliximab
  • Methylprednisolone/Prednisone
  • Tacrolimus
  • Mycophenolate mofetil

• Evaluate the effect of immunosuppression treatment in 30 people with ALS
Diaphragm Pacing Study

• Assess the ability of the NeuRx Diaphragm Pacing System (DPS) to improve respiratory function and quality of life in people with ALS

• Survival and shortness of breath will also be determined

• A group of people with ALS will receive the DPS and another group of people with ALS will receive the current standard treatment

• To enroll at approximately 20 NEALS sites in the US (anticipated to begin in late July 2013)
TDI-132/Gilenya

- ALS Therapy Development Institute (ALSTDI) was studying immune compounds in the ALS mouse and found interesting results with TDI 132 (Gilenya/fingolimod)
  - Decision made to move to humans
    - FDA-approved
    - Oral
    - In use for a neuroinflammatory CNS disease
- Primary Objective: determine the safety and tolerability of oral administration of 0.5 mg/day fingolimod vs. matched placebo
- Secondary Objective: quantify the effect of the treatment on circulating lymphocyte populations in patients with ALS
TDI-132/Gilenya Phase IIA Study Centers

University of California at Irvine
Dr. Namita Goyal
Georgia Health Sciences
Dr. Michael Rivner
Mass General Hospital
Dr. Nazem Atassi
Methodist
Dr. Erika Simpson

Site Contact Information

California
University of California, Irvine
Veronica Martin
vero@uci.edu
714-456-7760
Orange, California 92868
UNITED STATES

Georgia
Georgia Health Sciences University
Brandy Quares
bquares@georgiahealth.edu
706-721-2581
Augusta, Georgia 30912
UNITED STATES

Massachusetts
Massachusetts General Hospital
Owen O'Connor
ojoconnor@partners.org
617-726-5059
Boston, Massachusetts 02114
UNITED STATES

Texas
Methodist Neurological Institute
Sharon L Halton, LCSW, CCRC
shhalton@tmhs.org
713-441-3420
Houston, Texas 77030
UNITED STATES
TDI-132/Gilenya Phase IIa: Study Design

**Screening Period**
- 21 Days
- 10 Participants on Placebo
- 20 Participants on 0.5 mg fingolimod

**On Active Treatment**
- Procedures performed at Post-Dose Hour 1, 2, 3, 4, 5, 6, 7 & 8
- D1, Wk 1, Wk 2, Wk 3, Wk 4, Wk 8

**Washout Period**
- 20 Participants on 0.5 mg fingolimod
- Scrn Visit, Baseline Visit
GM604 Genervon: Multiple Target ALS Drug

• **ALS** is a complex interactive multiple targets multi-system neuro-degenerative disorder.

• Genervon has discovered GM604, a novel endogenous embryonic stage first-in-class regulator peptide drug of the human nervous system for ALS disease.

• GM604’s mechanisms of action against ALS involve 12 pathways and up to 22 biological processes. It modulates over 80 specific ALS related genes and proteins interactively, systemically and dynamically.

• In order to restore the normal function of the axonal transport and to delay ALS onset and death of neurons GM604 regulate 25 genes and proteins in this pathway alone, see the following mechanism of action diagram of Pathway #8.
GM604 Genervon: Multiple Target ALS Drug

Broadly inclusive ALS Phase 2 clinical trial of GM604

• Study Objectives are:
  – 1. To test the safety and tolerability of GM604 in a population of ALS patients.
  – 2. To test for changes in ALS biomarkers before and after treatment.
  – 3. To determine preliminary effects of injections of GM604 on measures of ALS disease biomarkers and clinical progression.

• 2 sites: Massachusetts General Hospital and Columbia Medical Center.
**Mexiletine Phase II (Dr. Weiss)**

**Purpose:** To determine whether mexiletine is safe and tolerable for patients with Sporadic Amyotrophic Lateral Sclerosis (SALS)

**Mexiletine**

- Sodium channel blocker that is FDA-approved for the treatment of cardiac arrhythmias
- Showed prolonged survival in animal models of ALS
- ~60 eligible Participants w/ ALS will be recruited at multiple US centers
  - 12 weeks: Mexiletine (300 mg/day or 900 mg/day) or placebo

**Research Sites**

**Currently Enrolling:**
- UCLA
- University of Iowa

**Not yet Enrolling:**
- University of Kansas
- Massachusetts General Hospital
- UMASS Worcester
- Washington University (St. Louis, MO)
- SUNY Upstate Medical Center
- Penn State Hershey
- University of Texas, Southwestern
- University of Washington
Nuedexta for bulbar symptoms

Currently enrolling at 6 sites:

- California Pacific Medical Center (San Francisco, CA)
- Hennepin County Medical Center (Minneapolis, MN)
- Neurology Associates (Lincoln, NE)
- Cleveland Clinic (Cleveland, OH)
- Providence ALS Center (Portland, OR)
- Georgetown University (Washington D.C.)

- **Purpose:** To determine whether Nuedexta® improves speech, swallowing, and saliva control in subjects with ALS. (Phase II)

- **60 participants**
  - 28 days (±3 days) with either Nuedexta® or placebo
  - Followed-by 10-15 day washout period will then occur
  - After the washout period, participants will be crossed-over to the other treatment arm for an additional 28 days (± 3 days) of treatment
  - A follow-up telephone call will occur approximately 28 days after completion of the study
Ozanezumab (GSK1223249) monoclonal antibody against Nogo-A

48-week, randomized, multi-center, double-blind, placebo-controlled, parallel group trial investigating efficacy and safety of IV GSK1223249 compared to placebo in participants with ALS

Eligible subjects will be randomized (1:1) to receive either IV placebo or IV ozanezumab every 2 weeks over 48 weeks

Primary objective: assess the effect of ozanezumab on the physical function and survival of ALS subjects over a treatment period of 48 weeks, measured by the ALSFRS-R.

Currently 26 international sites listed on clinicaltrials.gov / NEALS
Important Inclusion Criteria

1. Definite, possible, or probable ALS
2. A slow vital capacity of 60% or greater
3. Because we are interested in how *tirasemtiv* may change function in ALS, patients must have some functional abilities that are impaired but still sensitive to improvement
4. Since handgrip endurance is an important measure, patients must have good but not normal maximum handgrip strength

Where Are We Now?

1. 56 centers activated in North America, 19 centers activated internationally
2. Enrollment expected to be completed in Summer 2013
What was learned/gained from past human studies?

• Two therapies (riluzole and nuedexta) and multidisciplinary care

• Large experience in trials in ALS/Regulatory pathway

• Genetic studies define multiple critical pathways in ALS
  – New opportunities for the development of animal and cell-based models.

• Not one disease
  – Treatments -differentiated -- different cohorts
  – Treatments -target different pathways – cocktail
  – Timing of treatments may need to be tailored
What will help us learn more about ALS?

ALS Biomarkers are critically needed

- Early Diagnosis
- Understand the Disease
- Track Progression
- Identify Targets for Treatments
- Monitor Treatment
- Efficient Testing of Treatments
Thank you!

The Northeast ALS Consortium
www.alsconsortium.org

www.facebook.com/NortheastALSConsortium
@NEALSConsortium

Questions:
alstrialspartners.org
1-877-458-0631