



November 30, 2012

## **THE ALS ASSOCIATION ANNOUNCES RESEARCH AWARDS FOCUSING ON THERAPIES FOR LOU GEHRIG'S DISEASE**

The ALS Association's **Translational Research Advancing Therapies for ALS (TREAT ALS™)** program is funding ten new awards with a value of \$2.9 million focused on improved treatment for ALS. There is currently one FDA-approved drug for the treatment of Amyotrophic Lateral Sclerosis (ALS), riluzole (Rilutek™), improving survival by two to three months. There is an urgent need for improved therapies. With the recent progress in understanding ALS, the increased effort to develop tools to identify novel treatments for the disease and advances in technology, the opportunity to discover improved treatments for ALS could not be better. As part of TREAT ALS™, the Association is funding two clinical management grants. This program aims to improve care and living with ALS with a focus on clinical, psychological and/or social management of ALS. Three drug discovery contracts have been approved for funding. This milestone-driven program supports the pre-clinical assessment of therapeutics for ALS. The proposed studies are product-driven and focused on therapeutics. It is anticipated that these studies will lead to the advancement of new therapies for ALS. Two new clinical pilot studies will test novel treatment approaches in patients. These studies will utilize the TREAT ALS™ Northeast ALS (NEALS) Clinical Trials Network and funding is in partnership with the NEALS Consortium. In addition three biomarker studies have been selected for funding. Identifying appropriate biomarkers will significantly impact earlier diagnosis and speed up clinical trials.

### **Clinical Management**

**Researchers: Edward Kasarskis, M.D. and Richard Kryscio, Ph.D. University of Kentucky Research Foundation, Lexington, Kentucky**

**Topic:** Developing a virtual ALS center at a remote site incorporating regional resources and telemedicine links.

**Description:** ALS Care is best provided in a multidisciplinary clinic setting, attendance at which has been shown to extend survival. This is considered "standard of care" by the American Academy of Neurology (AAN) Practice Parameter. Nevertheless, this is difficult to achieve in reality if a patient lives at some distance from a major ALS center. Approaches have included travel by the ALS neurologist to a distant site for a clinic or interacting with a patient using telemedicine. A major limitation is the lack of a multidisciplinary team at the remote site with ALS expertise and knowledge of community resources. The

investigators propose to develop a local multidisciplinary team at a remote site and establish a consulting relationship by conducting "team check out" via a telemedicine link. This approach has a certain face validity inasmuch as it will develop local expertise in ALS. They propose to test the effectiveness of this approach by measuring adherence with the AAN Practice Parameter and developing metrics to ascertain the fiscal constraints and barriers to this approach. If successful and sustainable, it is anticipated that the "Virtual ALS Center" could become a clinical research venue for clinical drug trials in the future.

**Researchers: James Berry, M.D. and Merit Cudkowicz, M.D. Massachusetts General Hospital, Boston, Massachusetts**

Topic: Telehealth Program for the integrated care of patients with ALS (TelePALS)

Description: Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease causing progressive weakness and disability. Multidisciplinary ALS clinics, staffed by ALS physicians, nurses, and specialized physical, occupational, speech and respiratory therapists, improve quality of life and extend survival for people with ALS (PALS). Because ALS is uncommon, these clinics are regional, and PALS often travel great distances to attend, even as the disease impairs their mobility. Home care providers with no expertise in ALS often assume much of the care. The investigators propose an integrated Telehealth platform to expand patient access to multidisciplinary care and increase frequency of medical contact. Using a secure, medical-grade video conferencing environment, they will test methods for 1) conducting in-home follow-up visits with PALS, 2) holding case-conferences and educational seminars for home care providers for PALS, and 3) developing web-based educational materials about ALS for home care providers. The broad adoption of multidisciplinary ALS clinics has improved care for PALS who are able to attend. Investigators see the opportunity to use Telehealth to improve care and eradicate barriers to accessing care. They seek to determine if shifting their care delivery paradigm by extending multidisciplinary expertise to PALS in their homes can replicate and extend the in-person clinic experience.

### **Drug Discovery Contracts**

**Researcher: Oleg Butovsky, Ph.D., Brigham and Women's Hospital, Boston, Massachusetts**

Topic: Targeting miR-155 to treat ALS.

Description: Investigators believe the immune system plays an important role in ALS. Their hypothesis is that monocytes enter the spinal cord and damage motor neurons associated with paralysis in ALS. Monocytes are attracted to the spinal cord by cells in the nervous system called microglia. They have discovered factors in the monocytes and microglia that cause them to be inflammatory and cause damage in ALS. One of these factors is called miR-155 - a small genetic regulating factor. miR-155 is elevated in monocytes from the bloodstream of ALS patients. miR-155 is also elevated in monocytes of animals models of ALS and if suppressed there is a marked prolongation of life in the animals. The investigator's goal is to

suppress miR-155 in patients with ALS and prolong survival. Based on their animal experiments and studies on the monocytes from ALS patients, they believe all patients with ALS could potentially benefit from this treatment. They postulate that the treatment would be more effective earlier in the disease. The treatment would be given into the bloodstream or taken orally. These studies identify a new target to treat ALS and open up an important avenue focused on the immune system for the treatment of ALS. The investigators will partner with Santaris Pharma to develop this approach.

**Researcher: Steven Burden, Ph.D., Skirball Institute, New York University Medical School, New York**

Topic: Testing Musk Agonist Antibodies in ALS mice

Description: ALS is a devastating disease, progressing from detachment of motor nerve terminals to paralytic, lethal respiratory failure within five years of diagnosis. Most therapeutic approaches have been designed to inhibit motor neuron cell death, a late step in disease progression, by blocking cell-death pathways or providing broadly acting growth factors. These approaches have not only failed to provide substantial benefit to ALS mice, but even if successful such treatments are not readily transferable to a clinical setting. The investigators have taken a novel approach to ALS by targeting the signaling pathway that promotes attachment of nerve terminals to muscle. They reasoned that strengthening nerve-muscle attachment might delay denervation and improve motor function, improving the quality of life for patient and family. They have found that a modest increase in expression of MuSK, a receptor tyrosine kinase important for retrograde signaling (transporting signals from the muscle to the neuron), delays muscle denervation and improves motor function for over a month in ALS mice. They will carry out studies to determine whether agonist antibodies to MuSK likewise delay the onset and reduce the severity of denervation and neuromuscular dysfunction in ALS mice. If successful, this strategy, as well as other therapeutic approaches to enhance retrograde signaling, could be transferred to a clinical setting. The investigators will partner with Genentech to develop this therapeutic.

**Researchers: Rita Sattler, Ph.D. and Jeffrey Rothstein, M.D., Ph.D. Johns Hopkins University School of Medicine, Baltimore, Maryland**

Topic: Development of an antisense oligonucleotide therapeutic utilizing stem cell derived patient astrocytes and motor neurons to treat ALS caused by C9orf72 hexanucleotide expansion.

Description: The development of new therapeutics for amyotrophic lateral sclerosis (ALS) has been an enormous challenge. The ability to have human cells that represent the disease by carrying hereditary gene mutations will provide unprecedented tools. Investigators propose to study molecular events that may contribute to the disease of a newly discovered common gene mutation in ALS (C9orf72), which is found in inherited (familial) as well as the common sporadic forms of ALS. They will employ ALS patient-derived human fibroblasts and convert them into adult induced pluripotent stem (iPS) cells as well as differentiated central nervous system cell types such as astroglia and motor neurons. These human cells will

undergo a thorough analysis of their molecular genetic composition, which will then be compared to the genetic profile of cells obtained from healthy volunteers. Based on the differences, they will design and develop a molecular therapeutic agent targeted at the specific mutation responsible for the disease. They will further develop a biomarker, which will allow them to monitor the efficacy of these novel drugs when given to patients. The use of these human cells may allow them to efficiently and quickly develop a drug therapy for the C9orf72 form of ALS. The investigators will partner with Isis Pharmaceuticals to develop the therapeutic approach.

### **Clinical Pilot Studies**

**Researchers: Jonathan Glass, M.D.; Christina Fournier, M.D., Emory University, Atlanta, GA; Merit Cudkowicz, Maryland and James Berry M.D., MGH, Boston Massachusetts**

Topic: A novel immunosuppression intervention for the treatment of ALS

Description: Investigators are currently conducting a clinical trial to test the safety of stem cell injections into the spinal cord for patients with ALS. The patients in this trial get medications to suppress their immune system to try to prevent rejection of the stem cells, similar to patients that receive organ transplants. After receiving the immunosuppression medications and the stem cell surgery, one patient improved, and several patients seemed to have a slower than expected progression of their disease. The stem cells that were given to the patient that improved were only given in the lumbar spine region, making it less likely that the stem cell transplant caused the patient to have improvements in other regions, such as with his grip strength. These observations raise the possibility that some patients with ALS may respond to medications that suppress the immune system. Other studies of ALS have found supporting evidence for immune mechanisms playing a role in the ALS disease process. For this trial, investigators will determine whether they can identify a subset of patients with ALS that respond to immune suppressing medication.

**Researcher: Jeremy Shefner, M.D., Ph.D. SUNY Upstate Medical University, Syracuse, New York**

Topic: Cogane™ as a treatment for ALS

Description: Neuronal growth factors have been of therapeutic interest in ALS for more than 20 years, but delivery of neurotrophic factors has been challenging and inadequate delivery may be responsible for the lack of benefit in Phase III clinical studies. Cogane™ is a small, non-peptide agent, which can penetrate the brain and spinal cord and up-regulate production of neurotrophic factors thereby circumventing the technical problems associated with the delivery of neurotrophic factors. Cogane™ improves the survival of cultured spinal motor neurons and is efficacious in several preclinical models of ALS including the SOD1 G93A mouse model, the most commonly used preclinical model of ALS. In preclinical testing Cogane™ improved multiple end points including the number of functional motor units, behavior and the lifespan of ALS mice. Cogane™ has already been

approved for use in long-term clinical studies and therefore could rapidly be progressed in ALS. Currently, Cogane™ is being evaluated in a multi-dose, 28 week Phase II clinical study in Parkinson's disease with results expected in the first quarter of 2013.

### **Biomarker Studies**

**Researchers: Michael Benatar, M.D. and Joanne Wu, University of Miami Miller School of Medicine, Miami, Florida**

Topic: Natural history and biomarkers of presymptomatic ALS: Prelude to a prevention trial.

Description: Accumulating experience from a series of negative clinical trials is prompting a re-evaluation of how we approach therapeutic development for ALS. Increasingly, attention has focused on the idea that experimental therapeutics may be being used too late in the course of disease – only after irreversible neuronal loss has already occurred. This idea, coupled with the now well-established fact that the degenerative process in ALS begins before the appearance of typical clinical manifestations, is prompting a renaissance of the idea that earlier therapeutic intervention may be both feasible and more likely effective. In contemplating a preventive trial in people at genetic risk for ALS, however, investigators recognized that too little was known about the pre-symptomatic phase of ALS, including elements that would be critical to the design of a trial. To fill these knowledge gaps the investigator instituted *Pre-symptomatic Familial ALS (Pre-fALS)*, a longitudinal observational study of people at genetic risk for ALS. His team proposes to expand the *Pre-fALS* Cohort and to extend the duration of follow-up of those already enrolled, acquiring critical longitudinal biomarker data to characterize the pre-symptomatic stage of disease and to estimate the annual incidence rate with which pre-symptomatic subjects develop clinically manifest disease.

**Researcher: Patricia Andres, MGH, Boston Massachusetts**

Topic: Longitudinal Study Comparing the Responsiveness of Outcomes Measures in ALS Trials

*\*Supported by the EMD/ALS Biomarker Research Fund through the Keith Worthington Chapter of The ALS Association.*

Description: A clear unmet challenge in ALS clinical research is the ability to screen potential therapeutic agents quickly. Using more sensitive and accurate outcomes measures may improve clinical trial efficiency; requiring fewer subjects during a shorter time period. Quantitative strength measures accurately reflect disease progression in ALS. However, current methods are either very expensive and inconvenient or are unable to accurately measure strength throughout the entire strength range. Investigators developed a new device, Accurate Test of Isometric Strength (ATLIS) that is easy to use and accurately tests strength of strong and weak muscle groups with high reliability. The maximal force of 12 muscle groups in the arms and legs are tested using fixed, wireless load cells and a high-back, adjustable chair. Raw scores are converted to percent of predicted normal to

allow accurate comparisons between persons. Establishing a disease progression rate for each individual will allow investigators to detect small but clinically relevant therapeutic effects. This project will compare use of normalized ATLAS data with ALS-Functional Rating Scale-Revised and breathing capacity in a prospective, longitudinal study of 100 subjects tested bimonthly at four clinical sites. The study will determine the relative sensitivity of these 3 outcomes measures to define disease progression.

**Researchers: Lyle Ostrow, M.D., Ph.D.; Dean Wong, MD, Ph.D. and Jeffrey Rothstein, M.D., Ph.D. Johns Hopkins University, Baltimore, Maryland**

Topic: Metabotropic Glutamate Receptor 5 PET Imaging in ALS  
*\*Supported by the EMD/ALS Biomarker Research Fund through the Keith Worthington Chapter of The ALS Association*

Description: There is a great need in ALS research for biomarkers to aid in early and accurate diagnosis and for monitoring the response to treatments in clinical trials. This proposal describes a brain imaging technique called positron emission tomography (PET) enabling visualization of changes in the amount of a cell membrane protein called the metabotropic glutamate receptor type 5 (mGluR5). mGluR5 is increased in brain and spinal cord autopsy tissue from patients with ALS. Therefore, being able to quantify mGluR5 by PET imaging and detect changes in different brain regions may help diagnose ALS and follow disease progression. The purpose of this pilot study is to demonstrate whether mGluR5 PET imaging can distinguish between ALS patients and healthy controls. As a potential noninvasive biomarker, this imaging technique could be used to monitor the response to treatment in clinical trials designed to test future ALS therapies.