RESEARCH ALS TODAY

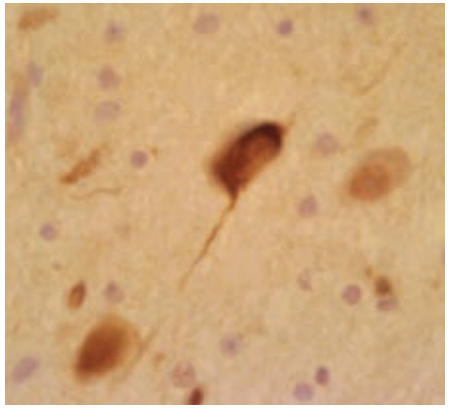
THE ALS ASSOCIATION | VOLUME 5 | SPRING 2009

New Gene Mutations Linked to ALS

The Potential Role of Alterations in RNA Processing in Familial and Sporadic ALS.

Lucie Bruijn, Ph.D.

Studies to find new genes linked to amyotrophic lateral sclerosis are a high priority for The Association's research portfolio. With the identification of new genes, we begin to understand how each of these



A large inclusion is detected by anit-FUS antibodies within the cytoplasm of an anterior horn motor neuron in a patient who carried the R521H FUS mutation. The adjacent motor neurons reveal normal nuclear staining and no inclusion. Immunopositive neuronal processes are also noted.

Source:
Dr. Tibor Hortobágyi,
Senior Lecturer and
Consultant Neuropathologist,
MRC Centre for Neurodegeneration Research,
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King's College London

gene mutations may contribute to a common mechanism in both familial and sporadic ALS. The Association's research team has played an integral role by establishing a consortium of international scientists and geneticists to work together on this effort.

The first discovery implicating alterations in RNA processing came with the identification of the 43 kD TAR DNA-binding protein (TDP-43) as a major component of ubiquitinated accumulations in sporadic and familial cases of ALS and ALS associated with frontotemporal dementia. Although compelling, it remained unclear whether the pathology described was a direct cause of ALS.

The identification of mutations in TARDBP on chromosome 1, the gene encoding TDP-43, confirmed that this protein is indeed directly involved in the disease process. To date, 20 different mutations have been identified in 13 unrelated families and 14 sporadic cases. TDP-43 is normally widely expressed with a predominantly nuclear localization. ALS patients carrying TDP-43 mutations display a typical ALS phenotype with some variability in site and age of onset within families.

Mutations in the protein lead to mislocalization and accumulation in the cytoplasm of glial cells (support cells for the motor neurons) and motor neurons. Although the mutations are inherited in an autosomal dominant fashion (a single copy of the gene is sufficient to cause ALS) it is currently unclear whether the alterations in the protein lead to the gain of one or more toxic properties or the loss of the proteins normal function.

The development of animal models is underway to address these questions. All but one of the mutations are located in the C-terminal region of the protein, the region believed to be involved in interaction with other proteins. Current studies focus on identifying these interacting proteins.

Based on the identification of mutations in the first DNA/RNA binding protein linked to ALS and through the continued efforts of the international consortium of investigators King's College, United Kingdom), mutations in a gene on chromosome 16 encoding a DNA/RNA binding protein, fused in sarcoma

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ALS Association
TREAT ALS
Translational Research Advancing Therapy for ALS

Third International Research Workshop on Frontotemporal Dementia in ALS

June 21-25, 2009
London Ontario, Canada

Hosted by The ALS Association, The ALS Society of Canada, Windsor-Essex County ALS Society, and The University of Western Ontario, Canada, London Health Sciences Center.

The international workshop provides a forum for Amyotrophic Lateral Sclerosis and frontotemporal dementia investigators to explore common areas. The invited speakers are leading researchers who will cover topics including clinical aspects of the two disorders, pathology, genetics and biology including a focused day on animal models of TDP-43.

For registration and program details please refer to http://www.ftdalsconference.ca/

New Avenues of Research Opened!

This edition marks another milestone for ALS research. The announcement in February that mutations in FUS/TLS are linked to familial ALS, together with a growing body of evidence for the potential role of altered RNA processing in ALS and other neurodegenerative disorders, has opened up new avenues of research. How the cell translates DNA messages to RNA from the nucleus to the cytoplasm to correctly assemble proteins is a complex multi-step process (known as RNA processing) crucial to the health of the cell. Experts in this field are now turning their attention to ALS. The focus is on developing new model systems, understanding which genes interact with these binding proteins and the downstream consequences of these changes.

Lucie Bruijn, Ph.D.
Senior Vice President, Research and Development
The ALS Association

Progress in ALS and the potential of finding new therapies for ALS relies on a vibrant, talented research pool of biomedical researchers and clinicians. In this edition we are pleased to recognize the talents of established clinician scientists as well as the newer fellows committing their energy and expertise to ALS research. Clinician scientists have the unique opportunity to bring research knowledge directly to patients through a focus on clinical trials, biomarker studies and epidemiology.

Participation from those living with ALS is crucial to these studies in order to make progress in developing treatments. I hope this edition inspires scientists and/or clinicians entering the field, people suffering with this devastating disease and established researchers to collaborate together as this is indeed an extremely promising time for ALS research with the potential to develop meaningful treatments.

- Lucie Bruijn, Ph.D.

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Cudkowicz and Hardiman Receive Essey Award

The ALS Association joins the American Academy of Neurology in presenting The 2009 Sheila Essey Award for ALS Research to two clinician scientists who have significantly impacted clinical trials, epidemiology and genetics in ALS.

Dr. Merit Cudkowicz

Dr. Merit Cudkowicz, Associate Professor of Neurology at Massachusetts General Hospital, Boston, Mass., is an international leader of clinical therapeutics in ALS. She is co-founder and co-director of the Northeast ALS Consortium (NEALS) a clinical trials network of 76 clinical sites throughout the U.S. and Canada dedicated to performing academic led clinical trials. The trials network has completed six trials: three phase III efficacy studies (topiramate, creatine and celecoxib) and three phase II studies (coenzyme Q10, sodium phenylbutyrate, arimoclomol).

Dr. Cudkowicz is currently playing a leadership role in three clinical trials through this network: ceftriaxone, lithium and arimoclomol in patients with SOD1 mutations. (The latter two trials are featured in this edition on page 6.)

In 2007 through The Association's **T**ranslational **Re**search **A**dvancing **T**herapies of **ALS** (TREAT ALS) program, The Association partnered with NEALS to establish the TREAT ALS/ NEALS clinical network facilitating broader participation in ALS clinical trials. In addition, Dr. Cudkowicz has been advisor to The Association's pilot clinical trial program, which is currently funded by The Association for the SOD1 antisense trial in familial ALS and has established a repository for patient samples. (See page 4 and 5.)

Ongoing studies in her group, facilitated by this resource, attempt to find biomarkers or signatures for the disease to allow for earlier diagnosis and improved clinical trials. Furthermore, Dr. Cudkowicz recognizes the importance of encouraging young clinician scientists in ALS and has mentored, among others, Dr. Aggarawal, recipient of this year's AAN/ALS Association Clinician Scientist Development Award. Her group has focused on adaptive clinical trial design to identify promising treatments for ALS more rapidly.

"It is an honor to receive this award for my research team at the Massachusetts General Hospital Neurology Clinical Trial Unit and our collaborators in the Northeast ALS consortium. The Sheila Essey

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Essey Award cont.

Continued from Page 2

award will be used to support a novel approach to more quickly develop treatments for people with ALS. The award will help continue our mission to find new treatments for people with ALS," commented Dr. Cudkowicz.

Dr. Orla Hardiman, Professor of Neurology, Trinity College Institute of Neuroscience, Dublin, Ireland, developed the longest running population based register of ALS in the world. The register is now part of the European ALS group, founded by Dr. Hardiman.

Many of her studies in clinical trials, outcome measures and patient care have led to important changes in how people with ALS are cared for. Her group undertook a systematic review of the impact of ethnicity on ALS epidemiology and demonstrated that the frequency of ALS is not uniform across the world. In addition, capitalizing on the relative homogeneity of the Irish population, her group identified a series of novel mutations in angiogenin (involved in formation of blood vessels and also thought to play a role in the protection of motor neurons) linked to some cases of ALS.

Dr. Orla Hardiman

Dr. Hardiman is currently part of an international consortium using genome wide technology to identify potential genes linked to sporadic cases of ALS. Dr. Hardiman, funded by The ALS Association, is undertaking a detailed population-based longitudinal survey of cognition in ALS. Her group's data suggest that cognitive impairment in ALS occurs in about 40% of patients and occurs early in the disease. This work has generated an important resource of DNA from patients followed longitudinally with detailed neuropsychological profiling. "This is a great honor for my research team, our Irish and international collaborators and the Irish ALS community. Finding the causative genes in small homogeneous populations and looking for protective genes in ethnically mixed populations can help to identify new pathways that lead to neurodegeneration. This award will be used to help to develop our research ideas, with the overall aim of finding pathways in ALS that can be harnessed to develop new treatments," said Dr. Hardiman. "We are grateful to The ALS Association for their continued support of our work."

The $25,000 prize honors the memory of Sheila Essey and was made possible through the generosity of the Essey Family Fund. Past recipients have often used the funds to support research of promising young scientists on their teams.

Clinician Scientist Receives Award

The AAN/TREAT ALS Clinician Scientist Development Award is funded through The Neil Bourman, M.D. ALS Research Fund.

The ALS Association and the American Academy of Neurology (AAN) are pleased to announce that **Swati Aggarwal, M.D.** from Massachusetts General Hospital, Massachusetts, is this year's recipient for the 2009 AAN/ALS Association Clinician Scientist Development Award as part of TREAT ALS (**T**ranslational **Re**search **A**dvancing **T**herapies for **ALS**). The purpose of the award is to recruit talented and promising young clinicians to the ALS research field, and to foster their development to make significant contributions to ALS clinical research. Dr. Aggarwal's study will focus on selection trial design for promising therapeutics in ALS.

The process of developing new drugs for ALS is particularly challenging. The trials are generally very long and the number of patients that need to be recruited for the trials is large due to the lack of good biomarkers for the disease. This puts a demand on trials to enroll sufficient patients for the now growing number of trials in a disorder which is relatively rare. At least 32 compounds have been tested in safety and efficacy trials (phase II and phase III) over the past 15 years. Currently seven therapy trials are underway, at least four additional trials in planning, and many more drugs in early discovery stages. The focus of the study in Dr. Aggarwal's three year award will be to use a selection trial design to more rapidly identify the best therapies to test.

Dr. Swati Aggarwal, M.D.

"I am honored to receive this award. I am very thankful to Dr. Cudkowicz, The ALS Association and my colleagues at the Neurology Clinical Trials Unit at Massachusetts General Hospital for their guidance and ongoing support," commented Dr. Aggarwal.

New Gene Mutations

Continued from Page 1

(FUS) or translocation in liposarcoma (TLS) was identified. The protein is structurally and functionally similar to TDP-43 with a normal localization predominantly in the nucleus, and when mutated, forms abnormal accumulations in the cytoplasm of motor neurons. It has not yet been reported whether these accumulations are also present in glial cells. Interestingly, as with TDP-43, the mutations reported so far are localized to the c-terminal fragment of the protein, a region also implicated in interacting with other proteins.

The exact roles of TDP-43 and FUS/TLS are not fully determined; however, both are multifunctional proteins that have been associated with several steps of gene expression, regulation including transcription, RNA splicing, RNA transport and translation. Abnormalities in many of these processes have been implicated in other motor neuron diseases such as spinal muscular atrophy, a childhood motor neuron disease. These exciting findings open up a whole new avenue of research with efforts underway to develop new model systems and to determine both the normal and altered functions of these proteins. These new opportunities will ultimately provide us with important clues to develop meaningful therapies for ALS.

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Biomarkers in ALS Clinical Trials

Seward Rutkove, M.D.
Beth Israel Deconess Medical Center
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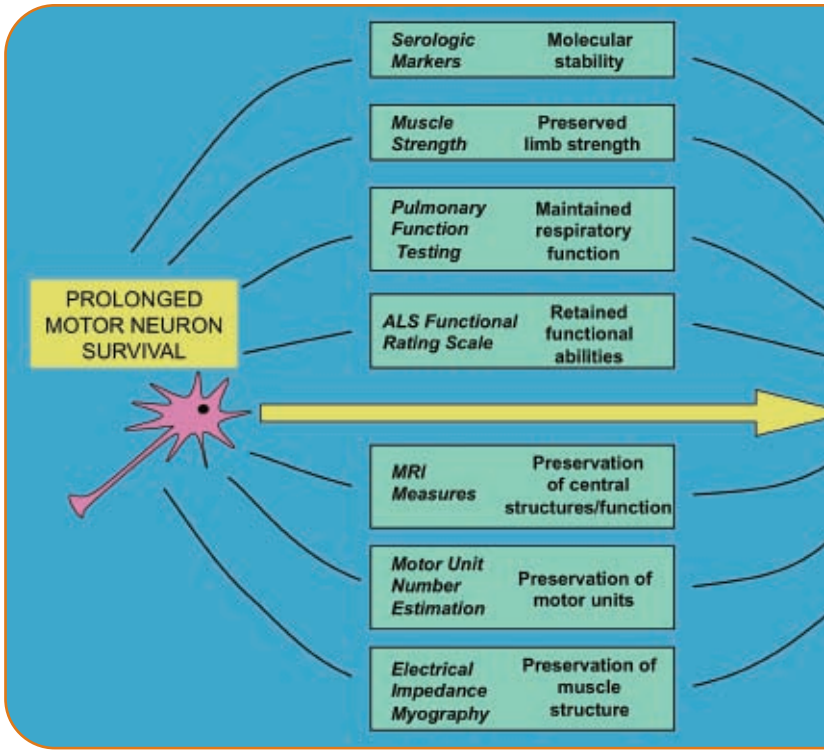
A biomarker provides a measure of the essential nature and behavior of a disease and can serve two distinct purposes. First, it can help with early disease diagnosis or even serve as a screening tool for the disease.

When an effective therapy is identified someday for ALS, early diagnosis will be of paramount importance since patients could be treated quickly in the hope of preserving function and extending life for as long as possible. Second, and perhaps of more immediate relevance, a biomarker can also provide a means of assessing efficacy of a potential therapy.

Traditionally, the term biomarker, as applied to ALS, has referred to an actual molecule in the blood or cerebrospinal fluid. A recent article by Matthew Turner and colleagues in Lancet Neurology reviewed research into more than a dozen such factors, including amino acid profiles, insulin-like growth factor, interleukins, and a glycoprotein called fibronectin. An ongoing effort between The ALS Association and the Northeast ALS Trials Consortium is also aimed at characterizing other such molecular markers.

However, a biomarker can also refer to any kind of measure—not just a molecule—that can inform us about the inherent nature of the disease process. In fact, these markers can be used to measure a central characteristic of ALS that is unique to each patient: the actual rate of motor neuron loss. To some extent, by accurately gauging this one parameter, we may most effectively follow the disease's biology and the effect of potential therapy. Stated another way, if an individual's rate of motor neuron loss can be slowed, that person will likely survive longer. A variety of such non-molecular "surrogate markers" have surfaced. These are summarized in Figure 1 and include:

1. Strength measurements. Measuring strength in a disease that produces global weakness makes intuitive sense. Indeed, strength measurements have long been one of the ways of monitoring disease progression. Measuring strength accurately, however, is not a trivial matter, and a variety of approaches has materialized, from simple subjective strength assessments to advanced isometric systems. Currently, dynamometry using a hand-held strength gauge is gaining favor. One of the major limitations of any form of strength testing is that by the time a muscle becomes clinically weak, it has already lost many functioning motor neurons. In addition, the measurements tend to be variable, and data from multiple muscles needs to be averaged to make it reliable.



Summary of potential ALS biomarkers.

2. Pulmonary function testing and the forced vital capacity (FVC). Measuring pulmonary function in a disease that produces respiratory muscle weakness is also logically appealing. Indeed, the FVC, of all parameters, is most closely aligned with respiratory function and the ability to live independently. However, respiratory measures only take into account a very small group of muscles. Especially early in the disease, the FVC may remain stable while substantial weakness develops in the limbs. Thus, using this one biomarker as a measure of disease progression in all patients has important limitations.

EIM performed on the wrist extensors. The outer electrodes apply the current and the inner measure the resulting voltage across the muscles. The device shown here is a commercial product that is FDA-approved for standard bioelectrical impedance testing.

timeline

1840 1850 1860 1870 1880 1890 1900 1910 1920 1930 1940 1950 1960 1970 1980 1990

1869: French neurologist Jean-Martin Charcot identifies ALS

50s: DNA structure solved

50s: Nerve growth factor (NGF) identified—protective, growth promoting factor for nerve cells

1968: SOD1 enzyme identified

70s: Programmed cell death in motor neurons demonstrated

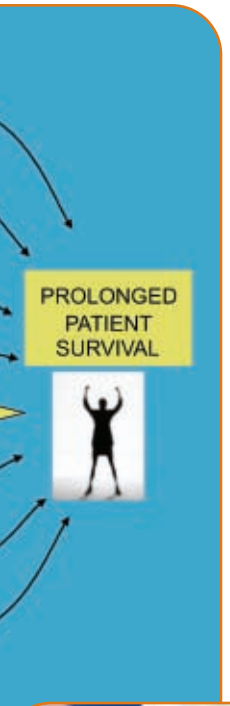
1985: The ALS Association funds study of inherited motor neuron disease

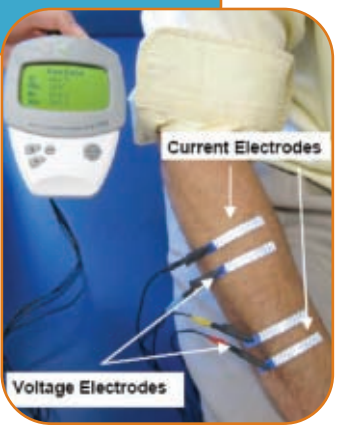
1986: Genes for muscular dystrophy identified

1989: The ALS Association funds search for a common genetic link to ALS

1990: Congress declares the 1990s the "Decade of the Brain"

1990: Growth factor CNTF is found to increase survival of motor neurons





3. ALS Functional Rating Scale. This simple measure offers a validated questionnaire that can quantify functional loss over time. One major advantage over other approaches is that it can be performed by caregivers at home or by researchers over the telephone or internet. Its greatest limitations are that it is relatively insensitive to minor changes and can be substantially impacted by non-ALS related medical conditions.

4. Magnetic Resonance Imaging (MRI). Measurement of certain structures in the brain that undergo degeneration in ALS may also provide a useful means of following ALS progression. However, the sensitivity and specificity of these markers is still under investigation and obviously very dependent on the extent that the disease is affecting the brain itself in a given person. Performing other MRI-based techniques, including magnetic resonance spectroscopy and diffusion tensor imaging, also may hold promise.

5. Motor unit number estimation (MUNE). This electrophysiological technique is especially alluring since it offers the possibility of virtually counting the number of functioning motor neurons controlling a specific muscle. A variety of technical approaches for performing MUNE have been described, each with its unique pros and cons. Unfortunately, for a variety of technical reasons, MUNE remains challenging to employ and like many other measurement approaches, may be ineffective at identifying early, subtle motor neuron loss. Moreover, it is limited to studying a relatively small number of distal arm and leg muscles and requires substantial training to perform well.

6. Electrical Impedance Myography (EIM). The "newest kid on the block" among ALS biomarkers, EIM utilizes an imperceptible electrical current that is passed through a small region of muscle tissue using surface electrodes (see Figure 2). It provides a quantitative assessment of muscle fiber atrophy and other ALS-associated structural changes. It also holds the promise of being able to detect declines in muscle health prior to the onset of clinical weakness. Unlike other techniques, it can also flexibly focus on specific regions of the body, including the bulbar and thoracic regions. This can be of particular importance since ALS, especially in its early stages, often involves one region of the body (e.g., one arm or leg) to a much greater extent than any other. EIM application could thus be tailored to each patient individually to match that one region of the nervous system most rapidly undergoing motor neuron loss during the time of the clinical trial. Doing so could substantially strengthen our ability to effectively measure a potential therapy's efficacy. EIM's major limitation is its sensitivity to electrode placement and limb position. EIM is currently being evaluated in a multi-center study supported by The Association's TREAT ALS funding initiative in which it is being compared to some of the other biomarkers described above, including MUNE, the ALS Functional Rating Scale and strength measurements. Regardless of the outcome, this study will hopefully provide new insights into the value of all of these biomarkers in assessing disease progression.

The potential value of these biomarkers is greatest in clinical trials in which a relatively quick "read out" regarding potential efficacy is required—so called, Phase II trials. By using a biomarker that is extremely sensitive to motor neuron loss, the length, complexity and cost of such trials can be dramatically reduced. Promising therapies can then be streamlined into large clinical trials—Phase III trials—where additional standard criteria, including survival, can be assessed. With this approach, each of these biomarkers, alone or in combination, is likely to play an increasingly important role in ALS clinical trials research in the coming years.

Sample Repository Available to ALS Researchers

The North East ALS Consortium (NEALS) and the Massachusetts General Hospital Neurology Trials Unit (NCTU) have a repository of serum, plasma and cerebrospinal fluid (CSF), and urine samples from NEALS and NCTU research studies of amyotrophic lateral sclerosis (ALS). The repository is partially funded by The ALS Association and samples from this repository are available to researchers for the purpose of furthering the understanding of ALS or developing disease biomarkers.

For details on how to get access to samples
http://www.nealsconsortium.org/news.html

For people with ALS who would like to contribute to the repository please contact: Daniel Grasso, B.A., Project Manager, Massachusetts General Hospital, (617) 726-0842

RESOURCES

Visit **www.alsa.org** and click on the blue research tab for these resources:

- SOD1 mutations database
  www.alsod.iop.kcl.ac.uk/als
- Coriell NINDS DNA repository
  http://ccr.coriell.org/ninds/
- ALS Epidemiology
  http://aces.stanford.edu/ForRes.html
- SOD1 mutant rats, Taconic,
  http://www.taconic.com/wmspage.cfm?parm1=258
- SOD1 mutant mice, The Jackson Laboratory
  http://jaxmice.jax.org/models/als.html

1991	1992	1993	1994	1995	1996	1997
Researchers link familial ALS to chromosome 21	*The ALS Association begins workshops* *Glutamate transporter shown to be defective in ALS* *Growth factor BDNF found to increase survival of motor neurons*	*SOD1 gene mutation (chromosome 21) discovered in familial ALS* *Trials using glutamate blocker riluzole begin*	*Animal studies combining CNTF and BDNF demonstrate decreased motor neuron loss* *GDNF rescues degenerating motor neurons during development in an in vitro experiment* *Transgenic animals carrying mutated human SOD1 gene exhibit ALS-like symptoms and pathology*	*FDA approves riluzole*	*Toxic properties of the SOD1 enzyme discovered and linked to familial ALS*	

Trial of Arimoclomol in SOD1-Positive Familial ALS Opens for Enrollment

Michael Benatar, M.D.
Emory University
Atlanta, GA

A clinical trial of arimoclomol in patients with rapidly progressive forms of familial ALS caused by mutations in the superoxide dismutase (SOD1) gene has begun enrollment at Emory University in Atlanta, GA. This trial has been supported by The ALS Association as part of the **T**ranslational **Re**search **A**dvancing **T**herapies for **ALS** (TREAT ALS).

Arimoclomol acts by upregulating heat shock proteins. It is effective in the Superoxide Dismutates 1 (SOD 1) mutant mouse model of ALS even when initiated after the onset of symptoms and was found to be safe and well tolerated in a previous phase II clinical trial that included patients with sporadic ALS.

Previously, medications that have been found to be effective in the mouse model of ALS have not shown benefit when brought to human clinical trials. Investigators at Emory University and Massachusetts General Hospital (MGH) in Boston, led by Drs. Michael Benatar and Merit Cudkowicz, believe that the SOD1 mouse model of ALS most closely resembles SOD1-positive familial ALS in humans, and hence, this is the population most likely to benefit from arimoclomol.

The target population for this double-blind, placebo-controlled, seamless adaptive design phase II/III clinical trial is patients with rapidly progressive ALS due to select mutations in the SOD1 gene. The trial aims initially to recruit 30 ALS patients in order to evaluate drug safety and tolerability. Thereafter, approximately 50 more patients will be recruited. All study participants will be treated for a total of 12 months. Study visits will occur monthly for the first six months and every other month thereafter. Participants in the trial will travel (at the study's expense) either to Emory or MGH for the initial and month-two study visits. All other study visits will take place in individual patients' homes, to alleviate their burden of travel especially as the disease progresses.

For additional information on the trials visit:
http://www.alsa.org/patient/drug.cfm and
http://clinicaltrials.gov/ct2/show/NCT00706147?term=Benatar&rank=1

Enrollment Opens for a Double-blind, Randomized, Placebo Controlled Trial of Lithium Carbonate in ALS

Jeremy M. Shefner, M.D., Ph.D., SUNY Upstate Medical University
Merit Cudkowicz, M.D., Massachusetts General Hospital

Enrollment has begun for a trial of lithium carbonate in combination with riluzole for patients with ALS. This trial is jointly sponsored by The ALS Association, ALS Society of Canada, and National Institute of Neurological Disorders and Stroke.

The impetus for this trial was the intriguing clinical data presented by Fornai et al., 2008 (1), who studied 16 subjects taking low doses of lithium carbonate and compared them to 28 subjects taking only riluzole, at the standard dose of 100 mg daily. Subjects taking lithium were maintained at blood levels of between 0.4 mEq/L and 0.8 mEq/L, significantly lower than the levels used when lithium is given to patients with psychiatric illness.

A dramatic difference was noted between lithium treated and non-treated patients in long term survival as well as functional measures. While the data presented by Fornai et al were potentially very exciting, the small sample size, lack of complete blinding, and the apparently slow progression of subjects in this pilot trial made it essential to conduct a well designed, pivotal trial.

The objectives of the current trial are to determine as rapidly as possible whether lithium in combination with riluzole has a robust and beneficial effect. This study has started less than one year after the initial report by Fornai was published. Designing a study, obtaining funding, and working through the logistics of a multinational project all within one year was a heroic achievement made possible by the collaboration of multiple funding agencies and the Northeast ALS Clinical Trials Consortium (NEALS), whose clinical trial infrastructure is supported by The ALS Association's TREAT ALS initiative. The trial intends to enroll 250 subjects with ALS, all of whom are taking riluzole, with subjects equally divided

CONTACT *For Clinical Management Research Grant Program (only), contact Sharon Matland, vice president, Patient Services at (818) 587-2217. For all other grant information or to be added to our mailing list, please contact researchgrants@alsa-national.org.*

timeline cont.

1998
- *RNAi discovered by Craig Mello and Andrew Fire*

1999

2000
- *The ALS Association co-sponsors workshop on high-throughput drug screening with NINDS*
- *NINDS issues first ever RFA (request for applications) specifically for ALS research*

2001
- *A transgenic rat is designed; efforts start on fly model*
- *Attention turns to support cells of nerve tissue to find role in ALS*
- *Inflammation and programmed cell death gather research interest*
- *ALS2 gene (alsin protein) linked to juvenile ALS*
- *The ALS Association/NINDS collaborative effort begins screening drugs*

2002
- *The ALS Association holds scientific workshop on "Environmental Factors and Genetic Susceptibility"*
- *Aggressive search for new ALS genes funded by The ALS Association*
- *Scientists complete map of mouse genome*
- *Agency of Toxic Substances and Disease Registries awards 5 grants focused on ALS*
- *Department of Defense approves funding for ALS-specific research*

2003
- *Study shows surrounding support cells play key role in ALS*
- *Study shows that human embryonic stem cells can be stimulated to produce motor neurons*
- *Gulf War study shows that vets deployed to Persian Gulf in 1991 developed ALS at twice the rate of those not deployed there*
- *IGF-1 gene therapy study proves beneficial in mice with ALS*
- *VEGF gene abnormalities shown to be potential factor in ALS*
- *The ALS Association collaborates with U.S. Department of Veterans Affairs to enroll all vets with ALS in registry*
- *Early tests of ceftriaxone appear to increase survival in mice with ALS*
- *Combination of creatine and minocycline prove more effective together in mouse model than either drug alone*

between superimposed lithium and placebo treatment. Lithium blood levels will be monitored to match those achieved in the earlier pilot trial. A frequently utilized and well validated outcome measure, the ALS Functional Rating Scale (ALSFRS), is being employed as the primary outcome measure. However, in order to enhance subject enrollment and to achieve a result as rapidly as possible, the ALSFRS is being used in a novel way. Subjects will be followed until their ALSFRS score has dropped by a predetermined amount; the rate of change of ALSFRS from study onset until this "time to failure" will be compared for lithium and placebo groups.

It is hoped that using the ALSFRS in this new way will provide a clear result in about half the time of a more traditional trial. In addition, this should serve as a recruiting tool, as subjects on placebo will be switched to lithium treatment as soon as their ALSFRS score has dropped by the preset amount. Subjects will be followed for a maximum of 1 year.

Another U.S. trial has recently completed enrollment of 100 subjects into an open label trial of lithium in ALS. While we hope that important results are generated, we worry that the lack of placebo group will seriously impair the interpretation of results. Although the ALSFRS scale is quite robust and rate of decline has not changed systematically over the years, there is great variability in the rate of decline from trial to trial. For example, in the recently reported trials of TCH, minocycline, and IGF-1 in ALS, subjects in the placebo group declined by 0.78, 1.07, and 2.2 points per month, respectively (2-4). Thus, without a concurrent placebo group, a vast range disease progression rates may be difficult to determine as being normal or a positive effect of treatment. For this reason, we expect that the placebo controlled trial now enrolling will provide critical additional information.

For enrollment details please go to The ALS Association website **http://www.alsa.org/patient/drug.cfm?**

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active *Research Projects cont.*

Continued from Back Cover

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Raoul, Ph.D., Cedric / *INMED, FRANCE*
Sanelli, Ph.D., Teresa / *University of Toronto, Toronto, CANADA*
Seburn, Ph.D., Kevin / *The Jackson Laboratory, Bar Harbor, ME*
Tsuda, Ph.D. / *Baylor College of Medicine, Houston, TX*
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MITOCHONDRIA

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SOD1 (COPPER ZINC OXIDE DISMUTASE 1)

Beckman, Ph.D., Joseph / *Oregon State University, Corvallis, OR*
Bosco, Ph.D., Daryl / *Massachusetts General Hospital, MA*
Hayward, M.D., Ph.D., Lawrence / *University of Massachusetts, Worcester, MA*
Julien, Ph.D., Jean-Pierre / *Laval University, Quebec, CANADA*
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STEM CELLS

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Svendsen, Ph.D., Clive / *University of Wisconsin, Madison, WI*
Strittmatter, M.D., Stephen / *Yale University, New Haven, CT*
Zhang, MD, Ph.D., Su-Chun / *University of Wisconsin, Madison, WI*

ALS research knowledge platform: Brown, K. / Innolyst, Inc. CA

grants

Study implicates smoking as likely risk factor in sporadic ALS

Study releases evidence that mitochondrial malfunction may play an important role in ALS

Ceftriaxone increases levels of the glutamate transporter GLT1 in a mouse model of ALS

RNAi treatment to silence the mutant SOD1 gene yields increased survival in mice

First international workshop on frontotemporal dementia discusses link to ALS

Stem cells engineered to make GDNF survive when transplanted into rats modeling ALS

Publication identifies potential biomarkers for ALS

Early data suggests that mutant SOD1 may be secreted by and may activate microglia

*Launch of TREAT ALS initiative (**T**ranslational **Re**search **A**dvancing **T**herapies for ALS) to accelerate clinical trials in ALS*

ALS patient samples collected to NINDS ALS Repository

Repository samples allow genome analysis for sporadic ALS

First TREAT ALS clinical trials funded

First TREAT ALS clinical trials begun

Stem cell study shows SOD1 mutant support cells can kill any motor neuron

ALS U.S. registry efforts gaining ground in Congress

Fish model of ALS: Progress reported

SOD1 in altered form common to both sporadic and inherited ALS

Engineered stem cells making GDNF help motor neurons survive in SOD1 mutant rats

Stem cells generated from ALS patients

Discovery of DPP6 in two genome-wide association studies in ALS

Mutations in TDP-43 linked to familial and sporadic ALS

Identification of new gene linked to familial ALS, Fused in Sarcoma (FUS) on chromosome 16

2004 | **2005** | **2006** | **2007** | **2008** | **2009**

Study funded by The ALS Association to find biomarkers in cerebrospinal fluid and blood

VEGF increases survival in a rat model of ALS while improving motor performance

TDP-43 discovered as a common link in FTD, ALS
Chromosome 9 region intense focus for FTD, ALS

First genome screening data published based on NINDS ALS Repository

Induced Pluripotent Stem Cell Technology opens up new avenues for ALS

active

Research Projects of The ALS Association Spring 2009

ALS Association

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AXON DYNAMICS

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BIOMARKERS

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Weiner, M.D., Michael / *San Francisco VA Medical Center, CA*
Wiedau-Pazos, M.D., Martina / *University of California, Los Angeles, CA*

CELL DEATH AND APOPTOSIS

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Trotti, Ph.D., Davide / *Farber Institute for Neurosciences, Philadelphia, PA*

CELL TARGETS

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CLINICAL TRIALS

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COGNITIVE CHANGE WITH ALS (FRONTOTEMPORAL DEMENTIA)

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DRUG DISCOVERY AND DEVELOPMENT

Jansen, Ph.D., Richard / *BioFocus DPI, a Galapagos company, Leiden, NETHERLANDS*
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Rubin, Ph.D., Lee / *Harvard University, Cambridge MA*
Yang, Ph.D., Miranda / *Harvard University, Cambridge MA*

ENVIRONMENTAL FACTORS

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GENE THERAPY

Bartus, Ph.D., Raymond / *Ceregene Inc., San Diego, CA*
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GENETICS OF ALS

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Traynor, M.D., Bryan / *National Institute on Aging, Baltimore, MD*
Russ, Ph.D., Carsten / *Broad Institute, Cambridge, MA*

GLUTAMATE

Methner, M.D., Axel / *University Hospital, Dusseldorf, GERMANY*
Schubert, Ph.D., Dave / *Salk Institute, La Jolla, CA*

INFLAMMATION

Carroll, Ph.D., Michael / *The CBR Institute for Biomedical Research, Inc., Boston, MA*
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Heiman-Patterson, M.D., Terry / *Drexel University, Philadelphia, PA*
Moeller, Ph.D., Thomas / *University of Washington, Seattle, WA*
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LABORATORY MODELS OF ALS

Barrett, Ph.D., Ellen / *University of Miami, FL*
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