

RESEARCH ALS TODAY

THE ALS ASSOCIATION | VOLUME 6 | SPRING 2010

INSIDE

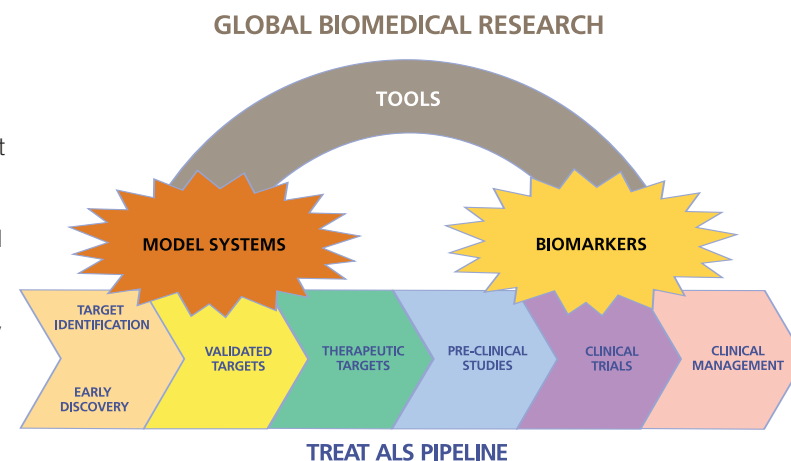
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TREAT ALS Research Program Pipeline to Success

The ALS Association's TREAT ALS (Translational Research Advancing Therapies for ALS) pipeline is a comprehensive and strategic research program ensuring that important laboratory findings receive the financial and scientific support to take discoveries from bench to bedside. The program supports early stage and translational research through a variety of funding approaches. Investigators submit proposals to The Association in response to a call for abstracts. The next call for proposals will be in July 2010, and investigators who would like to be added to the mailing list for program notifications should send an e-mail to researchgrants@alsa-national.org

Throughout the year, The Association identifies high priority areas together with a scientific advisory board, and investigators are solicited to undertake the research. An example of such an effort is the development of a rat model for ALS expressing mutant Cu/Zn Superoxide Dismutase 1 (SOD1). Many global consortia have been established to facilitate collaborative projects: a genetics consortium to identify new genes for familial ALS (this consortium facilitated the discovery of TARDBP and FUS/TLS); a genome-wide association consortium to identify genes linked to sporadic ALS; and a biomarker consortium for improved outcome measures in clinical trials.

More recently The Association has supported academic and biotech partnerships through providing milestone driven contracts to help move laboratory ideas into the clinic and provide funds for drug development. Two novel treatment approaches are now in clinical trials that have benefited from these programs: an antisense approach against mutant SOD1 and an approach to transplant neuralstem cells into the spinal cord of ALS patients to improve motor neuron survival. The TREAT ALS NEALS clinical trials network (described in this publication on page 4), is an important component of the pipeline to facilitate clinical trials for ALS.



Several ongoing pilot clinical studies are funded through TREAT ALS. The next call for proposals for pilot clinical studies will be issued in April 2011.

The Association supports clinician-scientists through a fellowship awarded in partnership with the American Academy of Neurology. Applications are due October 1, 2010. In addition, postdoctoral fellows are funded through The Milton Safenowitz Post-doctoral Fellowship Awards, and a call for proposals is issued annually at the time of the Society for Neuroscience meeting.

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International Symposium on ALS/MND

Orlando, Florida

December 11-13, 2010

Organizer: Motor Neuron Disease Association, United Kingdom

Host: The ALS Association

Abstract deadline May 3, 2010

Online submission

www.mndassociation.org



Technology Advances Significantly Impact Research Progress

This year proves to be an extremely promising year for ALS research and the advances in the field would not be possible without your contributions. Progress in ALS Research 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 Dr. Svendsen as this year's Sheila Essey recipient.



Lucie Bruijn, Ph.D.
Chief Scientist
The ALS Association

With the discovery of new genes, scientists are currently developing new model systems for ALS which will be invaluable to better understand the disease and for the development of new treatments. These discoveries have brought new scientists into ALS research. Furthermore, advances in technologies such as more rapid and cost effective gene sequencing and the generation of motor neurons and their surrounding cells from adult skin cells using induced pluripotent stem cell technology will accelerate the development of new in vitro model systems to understand the biology of the disease and for compound screening.

The TREAT ALS/NEALS clinical trials network, highlighted in this publication, has facilitated an increased number of clinical trials including two very novel approaches to treating ALS, a superoxide dismutase (SOD1) antisense approach that lowers the unwanted mutant protein in some familial forms of ALS and spinal cord stem cell transplants to test for safety of the procedure and ultimately to help protect surviving motor neurons.

We look forward to a productive year ahead and value all your contributions to forward discoveries in ALS and find meaningful treatments for ALS.

- *Lucie Bruijn*

The Power and Promise of Exome Sequencing

The last few years have seen amazing technological advances in genotyping and sequencing technology that have ushered in a new era of genomics. The first genome-wide association study of ALS was published in 2007 and was quickly followed by several similar studies. At its core level, a genome-wide association study compares the genome of a large number of patients diagnosed with sporadic ALS to the genome of neurologically normal individuals looking for a piece of DNA that is "associated" with disease. To date, there have been several promising "hits," and efforts are continuing to conclusively prove if these genomic regions are important in sporadic ALS.

The next stage in dissecting the genomics of ALS is to use exome sequencing to identify mutations underlying familial disease. This new technique allows us to rapidly sequence the 1% of the human genome that codes for proteins, which is where 85% of the mutations causing familial disease lie. These bits are called exons, hence the term "exome" sequencing. This approach has already been proven to work in other familial diseases. The other advantage of using exome sequencing is speed: we can now literally go from DNA to mutation in less than a month, as opposed to the years that a traditional linkage family study would take.

There are currently three major genes known to cause familial ALS, namely SOD1, TDP43 and FUS. Together, these account for about one third of familial cases, meaning that there are more ALS genes to be found. Exome sequencing makes this possible.

So what has happened to make exome sequencing a reality in 2010? The answer lies in the development of "next-generation sequencing." Each of our next-generation sequencing experiment generates 26 billion base pairs or bits of sequence data, truly mind-boggling numbers compared to the old Sanger sequencing method that analyzed a single 500 base pair fragment per day (if you were lucky!). To put this in perspective, our laboratory generates about 15 terabytes of data each month (1 terabyte = 1 trillion individual pieces of data), which is the equivalent of all of the books in the world's largest library,



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Exome Sequencing

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the Library of Congress. Sequencing of the first human genome was done using the old Sanger sequencing method in multiple laboratories around the world, cost \$2.7 billion and took 13 years to complete. Today, the commercial cost of sequencing a genome is ~\$5,000 and this price is dropping fast. The upshot of this ability to generate massive amount of sequence data is that we can reliably and rapidly detect all of the variants in the exome of an individual.

Of course, all new technologies have drawbacks and pitfalls, and exome sequencing is no exception. Substantial computing infrastructure and data handling expertise is required to analyze the massive amount of sequencing data generated in each experiment, and the cost of the hardware currently limits exome sequencing to well-resourced laboratories. However, even though the per-sample cost is relatively high for exome sequencing, only a small number of familial samples need to be sequenced to find the causative gene.

Identification of genes relevant to familial ALS will have a major impact, not just in medical terms, but will also allow for better understanding of the pathology underlying the disease. In our opinion, 2010 will be a landmark year in ALS research.

Dr. Clive Svendsen, Ph.D.



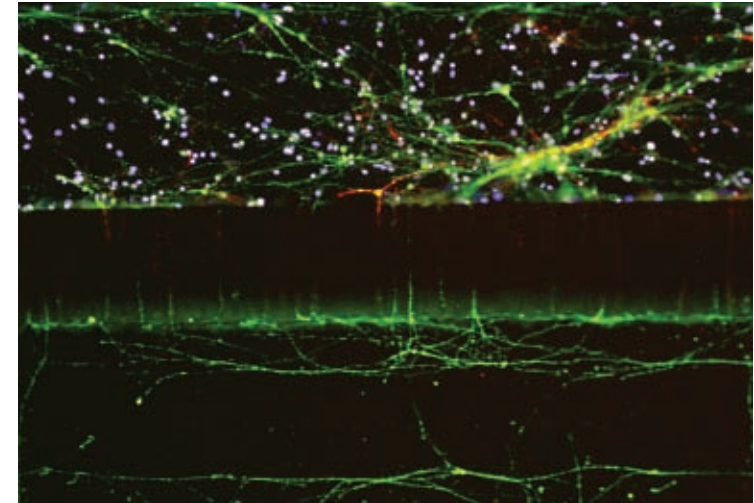
The ALS Association Presents the Sheila Essey Award for ALS Research to Clive Svendsen

The ALS Association joins the American Academy of Neurology in presenting the 2010 Sheila Essey Award for ALS Research to Dr. Clive Svendsen, a global leader for stem cell research. Dr. Svendsen has been instrumental in bringing stem cell approaches to the clinic.

Dr. Svendsen is currently the Director of the Cedars-Sinai Regenerative Medicine Institute in California. Initially focusing largely on Parkinson's disease, Dr. Svendsen received funding through The ALS Association to establish stem cell approaches for the treatment of ALS. Several of his published studies describe detailed and elegant work using modified neural stem cells to release powerful trophic factors such as glial-derived neurotrophic factor (GDNF) to surrounding motor neurons. These studies were performed in transgenic rats expressing mutant G93A Superoxide Dismutase 1 (SOD1), a rat model of ALS. These studies revealed that even though motor neurons releasing GDNF could survive and protect dying

motor neurons after transplantation, the rats did not show functional improvement.

Further studies from his group injecting GDNF releasing cells into the muscles rather than spinal cord did increase function in this ALS model system and highlighted the importance of maintaining appropriate connections at the neuromuscular junction. However, as the cause of sporadic ALS remains a mystery,



Motor neurons (SMI32, red) derived from patient-induced pluripotent stem cells put out axons (Tau, green) into chambers of a microfluidics device. —Photo courtesy of Clive Svendsen, Ph.D. and Jered McGivern, Ph.D.

either approach may have beneficial effects in the disease itself.

Dr. Svendsen has worked for many years in collaboration with Dr. Nicholas Boulis to help develop the appropriate surgical techniques in preparation for using these GDNF secreting cells in a clinical trial. These same surgical techniques are being used in the current Neuralstem trial. In addition, together with Derek Hei from the University of Wisconsin, his team has generated good manufacturing procedures (GMP) and a clinical grade bank of human cells producing GDNF for use in future clinical trials.

Dr. Svendsen and his group have also harnessed the induced pluripotent stem cell technology, using adult skin cells and reprogramming these cells to be able to generate a variety of neuronal cell types including

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TREAT ALS NEALS Clinical Trial Network

For the last 2 years, The ALS Association has funded the Translational Research Advancing Therapy for Lateral Sclerosis (TREAT ALS) Northeast ALS Clinical Trials Network

by Breen Power, Merit Cudkowicz, M.D., Alex Sherman, Jeremy Shefner, M.D., Ph.D.



Breen Power



Merit Cudkowicz, M.D.



Alex Sherman



Jeremy Shefner, M.D., Ph.D.

to develop the infrastructure necessary to rapidly complete clinical trials of new therapeutic agents, and to provide partial funding of individual trials. The Northeast ALS Clinical Trials Consortium (NEALS) is comprised of 92 clinical sites throughout the U.S. and Canada. Founded in 1996, NEALS has developed rigorous standards for clinical trial performance, standards for training and validation of individual sites, and much of the infrastructure to perform trials. The TREAT ALS NEALS Clinical Trials Network was established in 2007 to fulfill a number of specific goals.

First, the intent was to create a stable funding source to support and enhance a comprehensive clinical trials management system for the use by the ALS community in general, and for projects funded through The ALS Association's TREAT ALS initiative in particular. To this end, funding was granted to the two administrative centers of NEALS, Massachusetts General Hospital and SUNY Upstate Medical University. At the Massachusetts General Hospital in Boston, MA, project management and data management cores have been developed.

The TREAT ALS NEALS Network Platform, a sophisticated clinical trials Web-based system, was customized and redesigned

to accommodate the Network's goals. The platform helps to start new trials more quickly. An integrated project management system reduces much of the burden of running a clinical trial. This system makes tracking important trial documents easier. Another component of the system facilitates the collection and tracking of fluid and tissue samples collected as part of all trials. Additionally, an ALS biorepository is being developed that will aid in the search for biomarkers. This repository is intended to be a resource for the entire ALS community.

At Upstate Medical University in Syracuse, NY, funding allowed the establishment of a protocol to develop new outcome measures of use in ALS trials, to train NEALS sites to perform these measures, and to track reliability and training adequacy at all NEALS sites. During the last year 72 sites have been trained on outcomes measures including 21 new sites have received certification. Outcomes currently included in the training program are ALS Functional Rating Scale-Revised (ALSFRRS-R), vital capacity, quantitative strength measurement using Hand Held Dynamometry, and Motor Unit Number Estimation (MUNE). Clinical trial monitoring expertise was also developed so that trials performed by this network may be assured of excellent data quality.

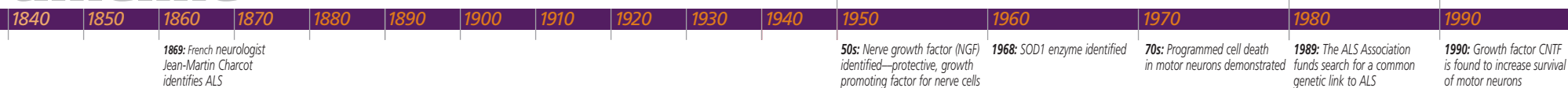
Additionally, TREAT ALS grant allowed for further training of new and existing investigators and clinical trials staff to

conduct high quality clinical studies. Beyond the training of high quality clinical sites, however, the ALS community requires more investigators trained and committed to the design and overall supervision of clinical trials. To fulfill this need, TREAT ALS funding helped in the design and presentation of a course specifically to train ALS investigators in the development and conduct of clinical trials. This course was first held in the spring of 2009, and several of the attendees are currently running trials through the TREAT ALS network. The grant also allowed to supply new sites with equipment needed to perform clinical investigation.

Finally, funding from the TREAT ALS NEALS Network has facilitated the conduct of a large number of new clinical trials, some of which have already yielded important results. Funding from the ALS Association, the NIH, and Health Canada allowed for the rapid design and implementation of a trial to test the efficacy of lithium carbonate in combination with Riluzole in people with ALS after the results of a small pilot trial in Italy suggested a dramatic benefit. Within a year of the original publication, patients have been enrolled in an innovative double-blind trial conducted at NEALS sites in the U.S. and Canada. The trial was terminated in October 2009 due to its achieving a faculty endpoint; while not the outcome of choice, the rapid design, implementation,

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timeline



TREAT ALS NEALS

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and enrollment of this trial was due in large part to the establishment of the TREAT ALS NEALS network, and the fact that a clear answer was reached so quickly allowed other new and promising treatments to be evaluated more rapidly.

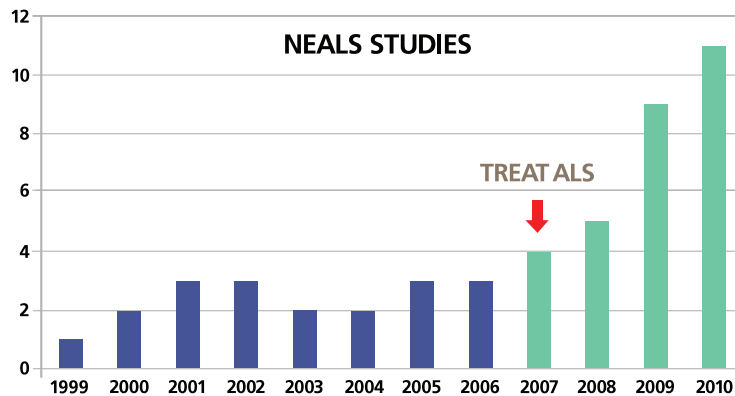
Currently, the TREAT ALS NEALS Network is actively involved in 12 trials that are either ongoing or in final planning stages. Among the most exciting is the first FDA-approved stem cell trial for ALS in the U.S.. This trial, supported by NeuralStem, is a Phase 1 study whose purpose is to determine the safety and tolerability of surgical implantation of embryonic stem cells within the spinal cord of ALS patients. This trial is being performed at Emory University in Atlanta under the supervision of Drs. Nick Boulis and Jonathan Glass, employing the NEALS TREAT ALS infrastructure.

Another trial that is evaluating a novel treatment is the trial of antisense oligonucleotides in SOD1 ALS patients. The study is supported by ISIS, The ALS Association,

and the Muscular Dystrophy Association. This trial is also a Phase 1 study, and is based on very exciting preclinical data showing that small molecules designed to interfere with the production of mutant SOD1 can in fact reduce SOD1 protein levels, and exert a positive effect on the SOD1 transgenic mouse. The human study is directed by Drs. Tim Miller of Washington University in Saint Louis and Merit Cudkowicz of MGH. The initial study will test the safety of a single infusion of antisense into the intrathecal space, with increasing doses planned as safety is shown. This trial also takes full advantage of the NEALS TREAT ALS clinical trials infrastructure.

The table shows the trials currently ongoing with help from the network. They include studies of biomarkers and nutrition as well as Phase 1-3 studies of experimental agents. The figure below also demonstrates the power of the NEALS/ALS Association collaboration; in the nearly 3 years since funding was arranged, the number of ongoing trials has almost tripled. We fervently hope that, in addition to facilitating more clinical trials being performed, we are coming closer to demonstrating a clear benefit in subjects that will translate into improved care for ALS patients.

Full study name	Principal Investigator	Type of Clinical Trial	Expected # of participants	# of Sites	Currently enrolling?
A Multicenter Study for the Validation of ALS Biomarkers	Merit Cudkowicz and Swati Aggarwal MGH	Observational	650	31	Yes
Clinical Trial of Ceftriaxone in Subjects with Amyotrophic Lateral Sclerosis (ALS)-Stage III	Merit Cudkowicz MGH	Interventional	600	58	Yes
The Pre-Familial Amyotrophic Lateral Sclerosis (Pre-fALS) Study	Michael Benetar Emory	Observational	30	1	Yes
Phase II/III Randomized, Placebo-Controlled Trial of Arimoclomol in SOD1 Positive Familial Amyotrophic Lateral Sclerosis	Michael Benetar Emory	Interventional	80	2	Yes
Validation of a New Device to Measure Neuromuscular Disease Progression	Patricia Andres MGH	Observational	70	4	Yes
Trial of High fat/High Calorie Diet versus Optimal Nutrition in Amyotrophic Lateral Sclerosis	Ann Marie Wills MGH	Interventional	60	6	Yes
Generation and Characterization of Cell Lines for Amyotrophic Lateral Sclerosis	Nick Maragakis and Jeffrey Rothstein JHU	Observational	25	1	Yes
An Open-Label, Safety and Tolerability, Study Evaluating KNS-760704 in Patients w/ Amyotrophic Lateral Sclerosis	Merit Cudkowicz	Interventional	Up to 94	19	No enrollment completed
A Phase 1, Double-Blind, Placebo-Controlled, Dose-Escalation Study of the Safety, Tolerability, and Pharmacokinetics of ISIS 333611 Administered Intrathecally to Patients with Familial Amyotrophic Lateral Sclerosis Due to superoxide Dismutase 1 Gene Mutations	Tim Miller Wash. U. and Merit Cudkowicz MGH	Interventional	32	6	Yes
A Phase II, Double-Blind, Randomized, Placebo-Controlled, Three-Way Crossover, Pharmacokinetic and Pharmacodynamic Study of CK-2017357 in Patients with Symptomatic Amyotrophic Lateral Sclerosis (ALS)	Jeremy Shefner SUNY Merit Cudkowicz MGH Nick Maragakis JHU Cytokinetics	Interventional	Up to 72	16	Currently recruiting
A Phase 1, Open-Label, First-in-Human, Feasibility and Safety Study of Human Spinal Cord Derived Neural Stem Cell Transplantation for the Treatment of Amyotrophic Lateral Sclerosis	NeuralStem	Interventional	Up to 18	1	Yes
Phase 2 Selection Trial of High Dose Creatine and Two Dosages of Tamoxifen in Amyotrophic Lateral Sclerosis (ALS)	Swati Aggarwal MGH	Interventional	60	6-8	Pending FDA review (anticipate July 2010 study start)



Please visit www.nealsconsortium.org for more information on NEALS and the TREAT ALS NEALS Clinical Trial Network.

Animal studies combining CNTF and BDNF demonstrate decreased motor neuron loss
GDNF rescues degenerating motor neurons during development in an in vitro experiment

timeline cont.

1991	1992	1993	1994	1995	1996	1997
Researchers link familial ALS to chromosome 21	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	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	

AAN Foundation—ALS Association Clinician-Scientist Development Three-Year Award

Co-sponsored by The ALS Association and American Academy of Neurology Foundation

Application Deadline October 1, 2010

The ALS Association and the American Academy of Neurology Foundation are pleased to announce a three-year Clinician-Scientist Development Award to support research into drug discovery and development of therapies that will effectively treat amyotrophic lateral sclerosis.

Developed as part of The ALS Association's research program TREAT ALS (Translational Research Advancing Therapy for ALS), the award aims to recognize the importance of good clinical research and encourage young investigators in clinical studies. The three-year award will consist of an annual salary of \$75,000 plus a \$5,000 institutional award. Only direct costs will be funded by this award.

All materials must be submitted online. Apply now at www.aan.com/view/CRTF.

TREAT Program

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The Association hosts several focused workshops and meetings throughout the year to initiate new collaborations and encourages participants from diverse fields to participate in discussions. The Association values its partnerships with The National Institute of Neurological Disorders and Stroke, Center for Disease Control, Department of Defense and numerous voluntary health organizations including The Robert Packard Center for ALS Research, The Therapy Alliance, Prize for Life, The ALS Society of Canada and The Motor Neuron Disease Association in the United Kingdom.

Sheila Essey Award

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motor neurons. Using this technology he is developing model systems for diseases such as Spinal Muscular Atrophy, Huntington's disease and ALS. "I'm very honored to have received this award and would like to dedicate it to my friend Jeff Kaufman who devoted his life to raising funds for ALS before finally falling to this horrific disease. We will use the award money to continue exploring novel stem cell and growth factor treatments," commented Dr. Svendsen.

In 1996 The ALS Association in partnership with the American Academy of Neurology inaugurated the Sheila Essey Award for ALS Research to acknowledge and honor an individual actively engaged in ALS research who is making significant contributions in research for the cause, treatment, prevention or cure for amyotrophic lateral sclerosis (ALS). The recipient receives a \$25,000 prize to be used specifically for continuing his/her ALS research. Funding of the award is made possible through The Essey Family Fund and The ALS Association. For a complete listing of previous recipients, go to: <http://www.alsa.org/research/essey.cfm?CFID=5728309&CFTOKEN=970e781654f3e198-AAFED8FF-188B-2E62-806B63164CEC1D9E>



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

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 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

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

The ALS Association/NINDS collaborative effort begins screening drugs

Department of Defense approves funding for ALS-specific research

*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*

timeline cont.

1998
RNAi discovered by Craig Mello and Andrew Fire

1999

2000

2001

2002

2003

Journal News

This issue highlights some of the recent publications with a focus on TDP43 model systems, biomarkers, a new gene that was identified this month linked to a single kindred and the results of the lithium clinical trial. If you would like certain news items featured, or have questions, please contact the research department:

researchgrants@alsa-national.org

TDP43 AND MODEL SYSTEMS

With the discovery of the mutations in the gene **TARDBP** on chromosome 1 linked to 4% of familial ALS several efforts are underway to develop new model systems to better understand the role of TDP43 in ALS and as a potential model for drug development. It remains unclear whether disease is linked to a loss or gain of function and whether mislocalization of the protein TDP43 from nucleus to cytoplasm and the formation of aggregates is the cause of toxicity and cell death. Many *in vitro* and *in vivo* experiments are addressing these questions. Dr. Baloh and his team at Washington University School of Medicine, St. Louis, developed a mouse model of TDP43 expressing the human mutation A315T under the control of the prion promoter. The mouse model is available at the Jackson Laboratories Repository, JAX stock number 010700.

<http://www.ncbi.nlm.nih.gov/pubmed/19833869>

Dr. Xia at Thomas Jefferson University, Philadelphia published this month the development of a rat model of TDP43. The team generated

a mini TDP gene from a BAC clone and expressed human wild type TDP43 or the human mutation M337V. Three founder mice overexpressing the mutation were generated, however, died at days 10, 13 and 18. Expression of wild type TDP43 did not result in a phenotype at 200 days. To generate viable lines the team used a tetracycline regulatory system. The rats generated show many of the features of ALS including cytoplasmic inclusions of TDP43.

<http://www.ncbi.nlm.nih.gov/pubmed/20361056>

Dr. Wu at Northwestern University School of Medicine, Chicago, published the development of a *Drosophila* model for TDP43 proteinopathy. The group overexpressed human wild type TDP43 in the eye which led to neurodegeneration. When expressed in motor neurons, TDP43 overexpression led to axonal swelling, reduction in axon branches and motor neuron loss. The investigators demonstrated that increasing levels of TDP43 resulted in cytoplasmic aggregates which led to cell death.

<http://www.ncbi.nlm.nih.gov/pubmed/20133767>

For a detailed review of the new genes FUS/TLS and TARDBP

<http://www.ncbi.nlm.nih.gov/pubmed/19303844>

For recent reviews of TDP43 in ALS and frontotemporal lobar degeneration

<http://www.ncbi.nlm.nih.gov/pubmed/20234357>

<http://www.ncbi.nlm.nih.gov/pubmed/20202122>

BIOMARKERS FOR ALS

Currently, the diagnosis of sporadic ALS is established by clinical measures as there are presently no molecular markers with proven reliability. Similarly, disease progression in both sporadic and familial

Continued on page 8

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 (Translational Research Advancing Therapies 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

First patients enrolled for antisense and stem cell trials in U.S.

timeline cont.

Study implicates smoking as likely risk factor in sporadic ALS

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

2004

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

2005

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

2006

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

2007

First genome screening data published based on NINDS ALS Repository

2008

Induced Pluripotent Stem Cell Technology opens up new avenues for ALS

2009

FDA approval of SOD1 antisense and stem cell trials in U.S.

2010

Journal News

Continued from page 7

ALS is assessed by clinical outcome measures such as the functional rating scales and tests of motor function. Although these measures have been standardized over the years, the identification of a molecular diagnostic, preferably in the blood, could facilitate the diagnosis and provide a more sensitive measure for disease progression. This marker would also be invaluable in assessing the effectiveness of a therapeutic intervention.

Levels of neurofilaments, abundant in the axons, are increased in the cerebrospinal fluid of ALS patients. To investigate whether levels are elevated in the blood of patients, Association-funded investigators Drs. Boylan, Borchelt and Shaw analyzed the levels of phosphorylated neurofilament H (pNF-H) in the blood of 20 ALS patients compared to 20 controls. In parallel, they characterized the levels of pNF-H in the mouse model expressing mutant SOD1 G93A. Elevated levels of pNF-H were detected in ALS patients and there was a trend towards increased severity of disease in patients with higher levels of pNF-H although the sample size is too small to confirm this and further studies are needed. In the mouse model, levels increased with disease progression whereas in patients with elevated levels, the levels of pNF-H remained fairly stable. Their data suggest that pNF-H could be a valuable biomarker for the disease and further studies are underway to validate this.

<http://www.ncbi.nlm.nih.gov/pubmed/19765193>

Several genome wide association studies (GWAS) have been performed to identify genetic variation involved in the susceptibility to ALS. Several genes have been published, not all validated in follow up studies. A larger study is underway as small sample sizes in the currently published studies as compared with other GWAS studies of complex traits may be the limitation. In a study published by association-funded Drs. Van den Berg and Ophoff, investigators describe the transcriptome of blood from 30 patients and 30 controls. Their findings were replicated in two additional sets of patients and controls. They showed dramatic changes between patients and controls and used weighted gene co-expression network analysis (WGCNA) to find disease-related networks and disease-related hub genes. The identification of molecular pathways associated with disease could provide useful biomarkers, improve our understanding of the disease process and lead to potential therapies. Identifying

possible networks in the blood overcomes the limitations of using human tissue at autopsy.

<http://www.ncbi.nlm.nih.gov/pubmed/19712483>

This month investigators led by Dr. Perrin published a transcriptome analysis of the brain, spinal cord, skeletal muscle, sciatic nerve, blood and adipose tissue of G93A SOD1 mice to identify relevant pathways. These studies identified a T cell co-stimulatory signature in spinal cord, skeletal muscle and peripheral nerves. They further showed that blocking the pathway with a monoclonal antibody to CD40L improved survival by 9 days if the animals were treated early, at 50 days, prior to overt symptoms. The monoclonal antibody did not show an effect in older animals at 80 days. Activation of this pathway was also seen in a subset of blood samples from ALS patients. The importance of this pathway in human disease and whether intervening with this pathway at time of disease onset in humans will impact survival is unclear. It will be of interest to determine whether this pathway is involved in other animal models of ALS as they emerge. The study used control mice but did not compare the transcriptome of transgenic mice expressing wild type SOD1.

<http://www.ncbi.nlm.nih.gov/pubmed/20348957>

NEW GENE LINKED TO FAMILIAL ALS

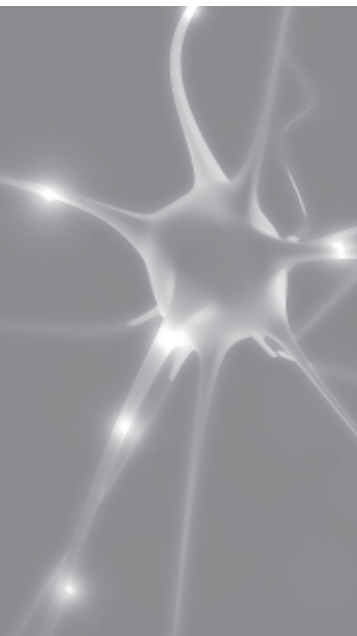
Dr. de Belleruche and colleagues published this month the discovery of a mutation in D-amino acid oxidase linked to a single ALS kindred. The mutation was not present in 1,002 unrelated individuals. The study was funded by The ALS Association and the Motor Neuron Disease Association of the United Kingdom. Although a rare mutation, understanding the role of this mutation in ALS may provide new clues for therapeutic intervention.

<http://www.ncbi.nlm.nih.gov/pubmed/20368421>

RESULTS OF A LITHIUM CLINICAL TRIAL

The ALS Association partnered with The National Institute of Neurological Disorders and Stroke and The ALS Society of Canada to fund a lithium clinical trial in response to a published study that showed promising results in ALS patients. The Northeast ALS and Canadian ALS consortia worked closely together to develop a novel trial design and rapidly enroll the patients. The double-blind placebo controlled trial with a time-to-event design enrolled 84 patients. The stopping boundary for futility was a p value of at least 0.68. There was no evidence that lithium in combination with riluzole slows progression of ALS more than riluzole alone.

<http://www.ncbi.nlm.nih.gov/pubmed/20363190>



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