

Research Along the FTLD-ALS Spectrum Virginia M.Y. Lee, Ph.D. and Karen Kreeger



Virginia M.Y. Lee, Ph.D.

In late 2006, the husband-and-wife team of Virginia M.Y. Lee, Ph.D., and John Q. Trojanowski, M.D., Ph.D., at the University of Pennsylvania's Center for Neurodegenerative Disease Research and Institute on Aging, found that abnormal TDP-43 proteins accumulated in post-mortem brain tissue from individuals diagnosed with certain types of frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS), or Lou Gehrig's Disease. The misfolded disease protein was recovered only from affected central nervous system regions, including the hippocampus, neocortex, and spinal cord of patients with FTLD or ALS but not from control subjects.

The approach that led to this finding was a study of proteins that behaved abnormally, initially only in FTLD cases. Unexpectedly, they also found a form of abnormal TDP-43 in almost all of the ALS cases they subsequently studied. Although there were suspicions for many years that FTLD and ALS may co-occur and share similar mechanisms of disease onset and progression, the 2006 study by the Lee-Trojanowski team provided the first solid molecular evidence to support this concept.

"Since many cases of ALS and FTLD were studied, the data became very compelling,"

recalled Dr. Lee. Still, skepticism about TDP-43 being to blame for the pathology of ALS was part of the scientific discussion at the time of this 2006 report in the journal *Science*.

Two years later, further proof that TDP-43 is the misfolded disease protein in ALS and FTLD patients emerged through findings that TDP-43 mutations track with disease. Many reports, including one from Penn, showed that DNA isolated from brain tissue of ALS and FTLD patients harbored mutations in the gene that encodes TDP-43.

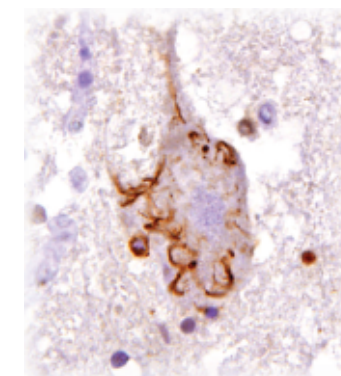
"When all the mutations began to appear in 2008, investigators who expressed some doubts about our finding were won over," said Dr. Trojanowski.

Since then it has become apparent that the TDP-43-related proteinopathies—diseases linked to misfolding and aggregation of TDP-43—are truly many diseases along a spectrum of disorders all linked to TDP-43 pathology. They span from those that manifest with cognitive impairments like FTLD to those that manifest with motor weakness like ALS, as well as those in which patients show both motor and cognitive deficits. Dr. Lee recently shared her story of discovery with The ALS Association.

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Clinical and Pathological Relationships Between ALS and FTLD-U (FTLD-TDP)

MND



ALS spinal cord motor neuron containing TDP-43 skein-like pathology. TDP-43 pathology is found in selectively vulnerable neuronal populations in ALS, including upper and lower motor neurons and neurons outside of the motor system.

Request for Proposals
Clinical Research Pilot Study

Deadline: May 28, 2011



Exciting New Clinical Trials Begin Enrolling Patients

Research continues to focus on understanding the disease process in ALS. Virginia Lee, Ph.D., describes the complexity of the disease and the emerging understanding of the protein changes associated with the various forms of ALS and frontotemporal lobar dementia. In the meantime, efforts continue to bring important laboratory findings into clinical testing with the hope of developing new treatments for the disease. Clinicians emphasize the importance of participation in clinical trials and describe a few of the current trials that are enrolling patients. Understanding the complexity of the disease will also impact clinical trial design as it is very possible that treatments effective in some forms of ALS may not be effective for all patients.



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

The ALS Association is proud to honor two awardees, Dr. Leonard van den Berg, the Sheila Essey Award recipient, and Dr. Steve Han, TREAT ALS/AAN Clinician Scientist Fellow. With the growing understanding of the complexity of ALS and the need to more directly relate findings in animal models to humans with the disease, there is an increasing collaboration between clinicians and scientists in the field. Dr. van den Berg has made significant contributions in identifying new genes linked to the disease, as well as improving trial design and patient care. Dr. Han will combine his clinical expertise with laboratory skills and develop induced pluripotent stem cells from ALS patients to better understand the disease and develop therapies.

Progress in ALS and the potential of finding new therapies for ALS relies on a vibrant, talented research pool of biomedical researchers and clinicians. Participation from those living with ALS is crucial to these studies and necessary to make progress in developing treatments. I hope this edition inspires scientists and clinicians entering the field, people suffering with this devastating disease, and established researchers, as this is indeed an extremely promising time for ALS research with the potential to develop effective treatments.

- Lucie Bruijn, Ph.D.

Sheila Essey Award 2011

The ALS Association joins the American Academy of Neurology in presenting The 2011 Sheila Essey Award for ALS Research to Leonard van den Berg, M.D., Ph.D.



Dr. Leonard van den Berg

Leonard van den Berg, Professor of Neurology, University Medical Center, Utrecht, founded the first integrated Netherlands ALS Center. He has initiated a nationwide population-based study aiming at complete ascertainment of incident ALS patients (Prospective ALS study in the Netherlands, PAN). He has established a detailed database and biobank of more than 3,000 individuals. It has generated a combination of large-scale genetic as well as environmental datasets. To better differentiate motor neuron variants and treatable mimics from ALS he has performed prospective natural history studies of patients suffering from pure lower or upper motor neuron syndromes. In addition to his clinical expertise in ALS, Dr. van den Berg leads a competitive and productive ALS genomics team. His laboratory was amongst the first to use the technology of genome-wide association studies (GWAS) in ALS.

To translate new discoveries in ALS research into treatment for patients effectively, Dr. van den Berg has set up an infrastructure to perform web-based, investigator-initiated placebo-controlled trials. He has introduced the futility, sequential trial designs for ALS as an alternative to

“It is a great honor to receive this internationally recognized and prestigious award. Receiving this award is recognition for the hard and excellent work of the researchers in my group. This award will encourage us to reach our obligation to find a cure for our patients suffering from ALS and related diseases.”

–Dr. Leonard van den Berg

Essey Award

Continued from page 2

a classic trial design, in which sample size is fixed. This trial design allows trial cessation as soon as a treatment effect can be significantly demonstrated or denied. Trials on creatine and valproate have been completed and a third trial is currently underway using lithium. Capitalizing on his experience in the Netherlands, Dr. van den Berg is leading a European Consortium (European Network for the Cure of ALS or ENCALS) to develop a Clinical Trials and Research Network modeled on the successful initiative of the North Eastern ALS Consortium (NEALS).

His untiring commitment to ALS has produced an international center of clinical excellence in Holland. Dr. van den Berg has integrated his research program into the day-to-day management of people with ALS. He has made important observations about risk factors for ALS including smoking, and has shown that moderate alcohol consumption might be protective. His group has designed and organized a series of clinical trials of drugs that might be beneficial, and his research into trial design has been exciting and innovative. His group has been amongst one of the first to identify new genes for ALS using modern technology, and his observations have been important in improving our understanding of the complexity of ALS.

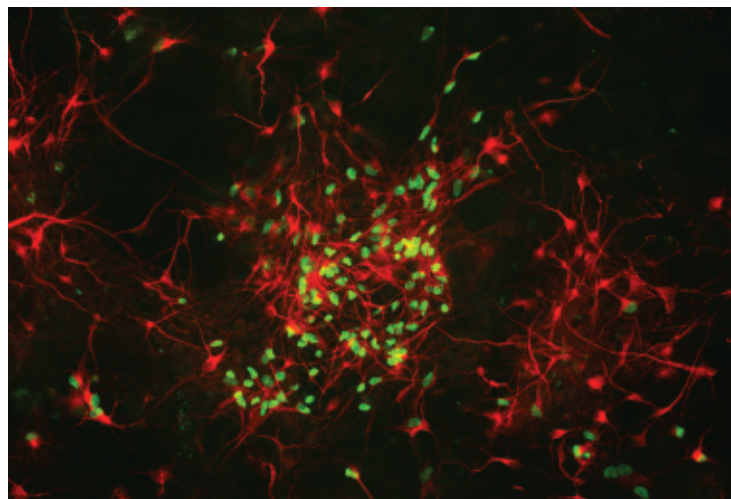
The \$25,000 prize honors the memory of Sheila Essey and was made possible through the generosity of the Essey Family Fund. Past recipients have often used the funds to support research of promising young scientists on their teams.



Dr. Steve Han

“...I am delighted to be a recipient of this prestigious award, which will enable me to achieve my career goals.”

—Dr. Steve Han



Clinician Scientist Award

The ALS Association and the American Academy of Neurology (AAN) are pleased to announce that Steve Han, M.D., Ph.D., from the Department of Neurology, Massachusetts General Hospital, Boston, Mass., is this year's recipient for the AAN/ALS Association Clinician Scientist Development Award as part of The Association's research program TREAT ALS (**T**ranslational **R**esearch **A**dvancing **T**herapy for ALS). The purpose of the award is to recruit talented and promising young clinicians who propose innovative clinical research and to foster their development to make significant contributions to ALS clinical research. Dr. Han has joined Dr. Kevin Eggan's laboratory at Harvard University, where he will develop the expertise to undertake the proposed study.

The objectives of the study is to test the overall hypothesis that markers of the ALS pathology can be recapitulated in motor neurons generated from patient-specific induced pluripotent stem cells. Having a robust source of patient-specific motor neurons in culture may be useful for the development of “humanized” in vitro disease models and therapeutic drug

screens for ALS. The aims of the proposal are to establish four cell lines for each of the different groups of individuals: sporadic ALS patients, familial patients with FUS or TDP-43 mutations and control subjects. Once established, assays will be developed for characteristic markers of disease. These include cell survival, morphological abnormalities, mislocalization of TDP-43 and FUS, ubiquitinated inclusions, and mitochondrial abnormalities.

The proposed experiments will help validate a novel human stem cell-based model of ALS. Once validated they will be adapted for large-scale small-molecule screening to identify potential treatments for ALS.

The project combines expertise from the Eggan laboratory at Harvard University in stem cell reprogramming technology and ALS disease modeling with the clinical expertise and resources of the MGH ALS clinical directed by Merit Cudkowicz, M.D. for ALS scientific and clinical collaboration.

“In the process of planning and coordinating these and subsequent experiments in conjunction with my strong educational plan, I hope to develop the necessary skills and expertise to successfully transition to an independent clinical scientist in the field of ALS.

I am delighted to be a recipient of this prestigious award, which will enable me to achieve my career goals,” commented Dr. Han.

Directed spinal motor neuron differentiation of iPS cells derived from skin fibroblasts of a 43-year-old man with ALS linked to a mutation in TARDBP. MAP2 (red) and Islet 1/2 (green) double-labeled cells identify motor neurons. 20x magnification.

An Overview of Clinical Trials in ALS

by Breen Power, Richard Bedlack, M.D., Ph.D., and Merit Cudkowicz, M.D., MSc



Breen Power



Richard Bedlack, M.D., Ph.D.



Merit Cudkowicz, M.D., MSc

Clinical trials are the most effective and efficient approach to develop new treatments for people with amyotrophic lateral sclerosis (ALS). Many important properties of new treatments are determined from clinical trials, including whether the treatment is effective and safe as well as the optimal dosage and delivery method. With every clinical study, we learn more about ALS and how to develop new promising treatments. There are currently many exciting clinical studies for people with ALS.



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: Nerve growth factor (NGF) identified—protective, growth promoting factor for nerve cells	1968: SOD1 enzyme identified	70s: Programmed cell death in motor neurons demonstrated	1989: The ALS Association funds search for a common genetic link to ALS	1990: Growth factor CNTF is found to increase survival of motor neurons

Interesting Phase II Trials

There are typically three phases to drug development. In Phase I studies, the safety and drug distribution of single and multiple doses are determined. In Phase II studies, many important questions are addressed, including safety over a longer period of time, determination of whether the treatment has the desired biological effect, and whether there is evidence of preliminary efficacy. Most Phase II trials test a drug against a placebo (a pill without active drug). Current Phase II studies in ALS include:

A Study of NP001 in Subjects with Amyotrophic Lateral Sclerosis

Neuraltus Pharmaceutical has developed a compound, NP001, which is designed to transform select immune cells (macrophages) from a neurotoxic state to a neuroprotective state, normalizing the cellular environment of critical nerve cells. A Phase I clinical trial of NP001 showed a dose-dependent, statistically significant improvement in blood levels of a biomarker thought to be involved in ALS disease progression.

Neuraltus Pharmaceutical is now conducting a Phase II randomized, double-blind, placebo-controlled study of its drug NP001 in ALS. People will receive either a placebo or one of two dosages of NP001. Study medication will be given intravenously. Approximately 105 people will be enrolled in this study. Recruitment is expected to begin in the first half 2011.

Reference: www.neuraltus.com; www.clinicaltrials.gov / ClinicalTrials.gov identifier: NCT01281631

A Study of a High Fat Diet in ALS

It is hypothesized that high fat may be beneficial to people with ALS. This study is a Phase II double-blind, placebo-controlled clinical trial designed to study the safety, tolerability, and feasibility of a high-fat/high-calorie diet versus both a high-calorie diet and a normal diet. In this study, energy needs for each subject will be calculated based on measured energy expenditure using indirect calorimetry and basal metabolic rate (BMR). The control diet will be treated with optimal calorie replacement while both intervention arms will be provided a high-calorie diet 1.25 times their calculated energy needs.

This study is currently recruiting 60 volunteers who are already receiving percutaneous nutrition. Volunteers will be randomly placed into each treatment arm and followed for five months. Volunteers will remain in the study four weeks after the end of the dietary intervention, allowing time for further observation. Reference: www.alsconsortium.org; www.clinicaltrials.gov / ClinicalTrials.gov identifier: NCT00983983

Creatine and Tamoxifen Selection Design Study

In this double-blind, randomized, selection design trial, researchers will evaluate the safety and effectiveness of creatine and tamoxifen in volunteers with ALS. The current research strategy to find an effective treatment for ALS is to test one drug at a time against a placebo. "Selection Design" is a different type of study design. A Selection Design study uses multiple drugs to screen against each other and picks the winner to take to a larger study. This design can speed the search for effective drugs to treat ALS. In this Selection Design study, each volunteer will take one active study drug—creatine 30mg, tamoxifen 40mg, or tamoxifen 80mg—and one placebo.

Approximately 60 eligible volunteers with ALS will be recruited from 10 sites in the United States. Volunteers will be randomly assigned equally to the three treatment arms: creatine 30mg/day, tamoxifen 40mg/day and tamoxifen 80mg/day. Recruitment is expected to begin in the first half of 2011. Reference: www.clinicaltrials.gov / ClinicalTrials.gov identifier: NCT01257581b

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

1986: Genes for muscular dystrophy identified

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

Promising Phase III Trials

A Phase III trial is considered the definitive test of whether a drug is effective. A Phase III trial in ALS enrolls many more participants than a Phase II trial. It is usually conducted by multiple researchers at multiple different sites around the country or even around the world. A treatment that succeeds in a Phase III trial is considered to be truly effective. Once a successful trial is completed a sponsor can apply to the United States Food and Drug Administration (FDA) for permission to market the drug for treatment of ALS. Currently there are three active Phase III trials in ALS.

A Safety Extension Study of TRO19622 in ALS

Trophos, a clinical pharmaceutical company, is conducting a European Phase II/III trial of its drug TRO19622, a mitochondrial pore modulator compound. Preclinical studies demonstrated that these types of compounds promote the function and survival of neurons and other cell types under ALS-relevant stress conditions. Enrollment is complete and participants are being actively followed. Reference: www.trophos.com; www.clinicaltrials.gov / ClinicalTrials.gov identifier: NCT01285583

A Phase III Study of Ceftriaxone in ALS

It is known that nerve cells called motor neurons die in the brains and spinal cords of people with ALS. However, the cause of this cell death is unknown. Researchers think that increased levels of a chemical called “glutamate” may be related to the cell death. For this reason researchers want to study drugs that decrease glutamate levels near nerves. Ceftriaxone—a semi-synthetic, third generation cephalosporin antibiotic—may increase the level of a protein that decreases glutamate levels near nerves. Studies of ceftriaxone in the laboratory suggest that it may protect motor neurons from injury.

Ceftriaxone is approved by the U.S. Food and Drug Administration (FDA) for treating bacterial infections but not for treating ALS. Also, ceftriaxone has not been given to people over a long period of time, such as months or years. The goals of this study are to evaluate the safety and effectiveness of ceftriaxone as a treatment for ALS, and to determine the safety and effectiveness of long-term use of the drug in people with ALS. This study is currently enrolling patients. A total of 600 eligible people with ALS will be enrolled in this multi-center research study. Participants are randomly assigned to receive treatment with ceftriaxone (2/3 of participants) or a placebo (1/3 of participants) for at least 12 months. Reference: www.alsoconsortium.org; www.clinicaltrials.gov / ClinicalTrials.gov identifier: NCT00349622

A Phase III Study of Dexamipexole in ALS

Biogen Idec and Knopp Neurosciences have entered into an exclusive, worldwide license agreement under which Biogen Idec will develop and commercialize dexamipexole for the treatment of ALS and potentially for other indications. Results of the Phase II study were presented in Berlin at the International Motor Neuron Disease meeting. Recruitment for the Phase III international trial is planned for the first half of 2011.

Reference: www.alsoconsortium.org; www.clinicaltrials.gov / ClinicalTrials.gov identifier: NCT01281189

Trials in Familial ALS

The majority of people with ALS have no family history of ALS. However, for a small minority of people (10%) there exists a family history of ALS (fALS). Recent advances in gene therapy have provided new potential targets for intervention in people with fALS, especially those cases with a superoxide dismutase 1 (SOD1) gene mutation. Currently there are a few and potential therapies for fALS cases.

The ISIS SOD1Rx Study

ISIS Pharmaceuticals, in collaborating with the Northeast ALS Consortium, the ALS Association, and the Muscular Dystrophy Association, is performing a Phase I study of its new investigational drug, antisense oligonucleotide ISIS 333611. Expression of mutant SOD1 in mice and rats causes death of motor neurons and an ALS-like phenotype. ISIS 333611 decreases levels of mutant SOD1 in rodents and may be therapeutic in people with SOD1-positive fALS.

The drug is administered intrathecally (using an external pump and a temporary catheter to deliver drug into the spinal fluid) during a single, 12-hour infusion. Four dosage cohorts will each include eight participants. The study is currently recruiting volunteers nationally at six sites.

Reference: www.alsoconsortium.org; www.clinicaltrials.gov / ClinicalTrials.gov identifier: NCT01041222

The Trial of Arimoclochol in SOD1 Positive fALS

The purpose of this Phase II/III study is to demonstrate the safety, tolerability, and efficacy of arimoclochol in subjects with SOD1 positive familial ALS. Researchers hypothesize that the drug Arimoclochol, taken in a dose of 200mg three times daily, will reduce disease progression in people with SOD1 fALS. Three sites in the United States are currently recruiting volunteers. Reference: www.alsoconsortium.org; www.clinicaltrials.gov / ClinicalTrials.gov identifier: NCT00706147

Biomarkers

Researchers are looking for new biological markers of ALS to help diagnosis ALS, monitor disease progression, and help shorten the length of clinical trials. There are a few different ways to determine a biological marker of a disease. One common method is studying the components of human tissue and fluid.

Validation of Biomarkers in ALS

The purpose of this study is to collect 650 blood and 300 cerebrospinal fluid (CSF) samples from people with ALS, pure lower or upper motor neuron diseases, and other neurodegenerative diseases as well as people with no neurological disorder. Through comparison of these samples, the researchers hope to learn more about the underlying cause of ALS, as well as find unique biological markers, which could be used to diagnose ALS and monitor disease progression.

Additionally, up to 600 blood samples will be collected for a sub-study for DNA analysis. Studying components of the blood, such as DNA, may help us understand what happens when genes function abnormally and how it might be related to disease. Reference: www.alsoconsortium.org; www.clinicaltrials.gov / ClinicalTrials.gov identifier: NCT00677768

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timeline cont.

1991

Researchers link familial ALS to chromosome 21

The ALS Association begins workshops

1992

Glutamate transporter shown to be defective in ALS

Growth factor BDNF found to increase survival of motor neurons

1993

SOD1 gene mutation (chromosome 21) discovered in familial ALS

Trials using glutamate blocker riluzole begin

1994

Transgenic animals carrying mutated human SOD1 gene exhibit ALS-like symptoms and pathology

Animal studies combining CNTF and BDNF demonstrate decreased motor neuron loss

GDNF rescues degenerating motor neurons during development in an in vitro experiment

1995

FDA approves riluzole

1996

Toxic properties of the SOD1 enzyme discovered and linked to familial ALS

1997

Clinical Trials

Continued from page 5

How You Can Help

Many dedicated clinicians and researchers are involved in the trials described on the previous pages. However, we cannot complete these trials without participation by patients with ALS. Benefits of participation include the ability to help others by answering important questions, “positive feelings” of hope and altruism, and more frequent monitoring throughout the disease which by itself may be associated with a more optimal course. The bottom line is that the faster patients enroll, the faster we complete these and all future studies, and the faster we get to a cure for ALS.

If you are interested in learning more about a specific clinical trial, search the clinicaltrials.gov website. This website is a central database of virtually all clinical trials in the United States, and even contains information from other countries. The site is easy to search and will provide you with detailed information about trials in ALS and study contact information to help you find trials that may be right for you. Provided in this overview are the clinicaltrials.gov identifiers to assist you with your search.

Additionally, you should ask your doctor and ALS study team about clinical trials. They may be able to tell you about new trials starting in your treatment center or a site nearby.

You may also contact the Northeast ALS Consortium (NEALS), a clinical trial consortium dedicated to ALS clinical research. Visit its website at: www.aslconsortium.org or contact by phone at **617-724-7398**.

The ALS Association supports NEALS and the **Translational Research Advancing Therapy for ALS (TREAT ALS)** program.

The information provided above is supplied by The Northeast ALS Consortium (NEALS). NEALS is a non-profit organization that supports high-quality clinical research and clinical trials in ALS, also known as Lou Gehrig’s Disease. NEALS provides research support systems to our member-researchers, the ALS research community, and people with ALS. Most information provided here can also be found on the NEALS website, www.aslconsortium.org.



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 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

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 five grants focused on ALS

Department of Defense approves funding for ALS-specific research

FTLD-ALS Spectrum

Continued from page 1

How did you get started researching ALS and FTLD?

One of the major research interests in our center is FTLD because there are neurofibrillary tangles in the brains of these patients comprised of tau, similar to what is seen in Alzheimer’s Disease. Other FTLD patients have tangles that do not contain tau and until recently the proteins were unknown. The center’s interests have now expanded to all diseases containing tangles, including corticobasal degeneration and progressive supranuclear palsy, clinical subtypes of FTLD. We have a particular interest in understanding how FTLD is linked with ALS as they often occur together.

What do all of these diseases have in common?

A large percentage of FTLD patients have tau pathology, including the mutated, misfolded form of tau protein in tangles of patients with familial FTLD. Indeed, of particular interest to us is the fact that tau mutations were identified in FTLD patients. This is very important because these mutations are inherited in an autosomal dominant manner, suggesting a genetic link to the tau pathology, despite the fact that the majority of the patients seem to have sporadic disease.

What happened next?

We continued looking at brain tissue from FTLD patients and found that many of the so-called clinical FTLD cases don’t actually have tau pathology. They are tau-negative and synuclein negative meaning that disease in these patients is not caused by tau or synuclein, which is the disease protein associated with Parkinson’s disease.

FTLD actually is a very broad spectrum of seemingly different diseases, which include disorders characterized by symptoms such as a profound loss of executive functions, behavioral deficits, and language problems. In addition to that, patients may also have parkinsonism and motor neuron disease similar to ALS. Thus, FTLD is a very heterogeneous group of diseases. There are also a number of FTLD families whose disease was known to be linked to a gene on chromosome 17 where the tau gene resides, but they don’t have tau pathology. In 2006 Michael Hutton showed that progranulin is another FTLD gene on chromosome 17 that harbors many disease causing mutations. Two months later we identified TDP-43 as a disease protein for FTLD and ALS.

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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

timeline cont.

1998

RNAi discovered by Craig Mello and Andrew Fire

1999

2000

2001

2002

2003

FTLD-ALS

Continued from page 6

How did your lab and the Hutton lab rectify all of these differences?

We showed that FTLN patients with mutations in the progranulin gene develop TDP-43 pathology, suggesting that a defective progranulin gene somehow leads to accumulation of TDP-43.

What is the difference between the normal function of tau in the brain versus TDP-43?

Tau is predominantly found in neurons and its function is to stabilize microtubules, so offsetting the loss of tau function with microtubule stabilizing drug is a therapeutic strategy for tau diseases or tauopathies. TDP-43 is a DNA-binding protein that regulates the stability of many genes and aids in the splicing of many genes. Thus, offsetting the loss of nuclear TDP-43 due to the formation of TDP-43 inclusions could be a therapeutic strategy for ALS and FTLN cause by abnormal TDP.

How did you find out FTLN and ALS are related?

Since some FTLN patients also have motor neuron disease we looked at their spinal cord to see whether they had TDP-43 pathology. Then, low and behold, we saw TDP-43 pathology in the FTLN patients' spinal cord tissue. Then we said, wait a second, some FTLN patients have motor

neuron disease and some ALS patients have a form of dementia. We began to think that maybe they are related. Then we stained for TDP-43 in brain and spinal cord tissues from patients with ALS alone and basically we found it in all the sporadic ALS cases we looked at and also in some familial cases.

Didn't geneticists identify mutations in TDP-43 familial ALS cases shortly after that?

Yes. That's how that story evolved. We then did a study comparing the pathology in the brain and spinal cord of ALS and FTLN patients and verified our hunch that these diseases are really along a spectrum of disease presentations from FTLN to ALS and intermediate or mixed conditions. In FTLN, there is more brain pathology and less in the spinal cord. In ALS, there is more TDP-43 pathology in the spinal cord and less brain pathology.

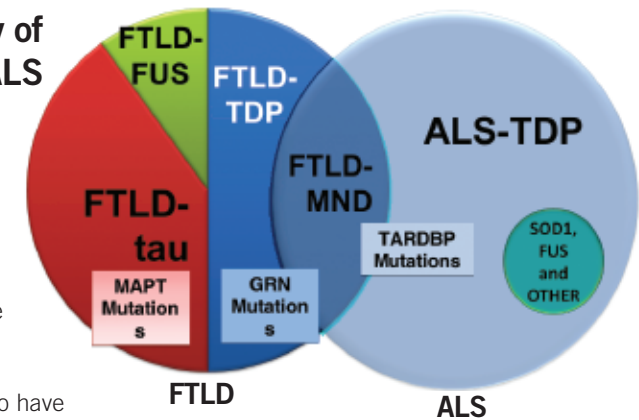
What we found was that in the spinal cord, TDP-43 accumulations are mostly comprised of the full-length molecule, whether it is ALS or FTLN. In the brain, a fragment of TDP-43 accumulates, but in the spinal cord it is the full-length protein that accumulates. We do not understand why yet, but we think this maybe a clue that could lead to the discovery of new therapeutic drugs for ALS and FTLN.

Neuropathology of FTLN and ALS

So how do you differentiate between ALS and FTLN?

There's a tremendous overlap. Patients with clinical evidence of pure ALS may have very little pathology in the brain, which is termed ALS without dementia. There are ALS patients who also have dementia, and these patients have a lot more TDP-43 pathology in brain tissue and vice versa for FTLN, while patients with FTLN have almost no spinal cord pathology. However, when there is more TDP-43 pathology in the spinal cord of FTLN patients, this usually correlates with clinical evidence of motor weakness.

From a genetic point of view there are probably several genes that are involved in both ALS and FTLN. However, another reason, other than the TDP-43 pathology, that links ALS and FTLN together, is the families that have inherited disease, in which one family member may have ALS and another family member may have FTLN and perhaps a third member could have both. That type of evidence suggests that what we are dealing with here is a spectrum of the same disease, which is a TDP-43 proteinopathy.



What does this mean for patients and their families who are trying to grapple with this?

It is still early in our research, but it's our understanding that there are at least two major categories of disease pathology. Let's assume that FTLN, based on pathology and genetics, has two flavors, tau and TDP-43. They are extremely different proteins with different functions. The treatment for each is going to be very different, even though they have the same clinical manifestation. The first step then is to distinguish patients with FTLN with tau versus patients with FTLN with TDP-43. Right now there is no good way to do that. However, the biomarker research we are doing now offers hope we can find chemicals in spinal fluid or plasma to be able to make this distinction. Then we will need tau and TDP-43 focused therapies. In the case of tau, these are now just emerging, such as microtubule stabilizing therapies, including those that are coming from our drug discovery program. In the case of TDP-43, there is far more work to be done.

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

Ceftriaxone increases levels of the glutamate transporter GLT1 in a mouse model of ALS
First international workshop on frontotemporal dementia discusses link to ALS
Stem cells engineered to make GDNF survive when transplanted into rats modeling 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.

2004

2005

2006

2007

2008

2009

2010

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

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

RESEARCH WEBINARS

Tuesday, April 19, 2011 / 4:00 - 5:00 p.m. EDT

Ashkan Javaherian, Ph.D. / iPierian, San Francisco, Calif.

Using Induced Pluripotent Stem Cells to Identify New Treatments for ALS

Adult skin cells can be manipulated to generate induced pluripotent stem cells to produce motor neurons and astrocytes, cells at risk in ALS. The ALS Association has awarded a one-year grant to iPierian to support the identification of a “cellular phenotype,” which represents differences in motor neurons or astroglial cells derived from ALS patients versus healthy controls. This phenotype would be the basis for drug screening to identify potential disease-modifying drug candidates for ALS.

Tuesday, May 17, 2011 / 4:00 - 5:00 p.m. EDT

Seward Rutkove, M.D. / Beth Israel Deaconess Medical Center, Boston, Mass.

Electrical Impedance Myography as a Biomarker for ALS

Dr. Seward Rutkove’s biomarker, a method called electrical impedance myography (EIM), sensitively measures the flow of a tiny, painless electrical current through muscle tissue. As the disease progresses, ALS patients’ muscles atrophy, and the more their muscles weaken and shrink, the greater the change detected as the current moves through the muscle. By comparing the size and speed of the electrical current as it passes through healthy and diseased tissue, EIM can accurately measure the progression of the disease.

Tuesday, June 14, 2011 / TBD

Tom Maniatis, Ph.D. / Columbia Medical School, New York, N.Y.

The Role of TDP-43 in ALS

Identification of mutations in TDP-43 linked to familial ALS has opened up new avenues for research. Using novel technologies, Dr. Tom Maniatis’ laboratory is attempting to understand how TDP-43 causes ALS, enabling the identification of new approaches to treat ALS.

Tuesday, July 19, 2011 / 4:00 - 5:00 p.m. EDT

Nicholas Maragakis, M.D. / Johns Hopkins School of Medicine, Baltimore, Md.

Exercise Clinical Trial for ALS

Despite decades of discussion over the potential benefit or harm of exercise in ALS, no study has compared these two forms of exercise, resistance and endurance, with the current standards of ALS care—stretching and range of motion exercise. The ALS Association is funding Drs. Nicholas Maragakis and Merit Cudkowicz to address these questions in a randomized, controlled study with the long-term goal of establishing a larger efficacy study and eventually a consensus statement on the potential benefits (or detriments) of exercise in this neurodegenerative disease.



Clinical Research Pilot Study Request for Proposals

Deadline for brief study outline: May 28, 2011

Email researchgrants@alsa-national.org for study outline form.

- The ALS Association’s scientific research program TREAT ALS (T**ranslational R**esearch **A**dvancing **T**herapy for ALS) encourages translational research to bring new treatments to patients.
- Currently there is only one FDA-approved drug for ALS, Riluzole, which has a modest effect on patient survival.
- This request for proposals (RFP) seeks to fund pilot clinical studies to obtain preliminary clinical data that will support applications to the National Institutes of Neurological Disorders and Stroke (NINDS) for subsequent larger clinical trials of an intervention to treat or prevent ALS.
- The proposed study must address questions that, when answered, will optimize the design of more definitive clinical trials rather than simply addressing the clinical question with lower power. The research proposal should directly address how the preliminary study will advance the design of a subsequent definitive clinical trial for efficacy.

Budget:

A maximum of \$150,000/per year for a maximum of two years
No indirect costs will be paid in conjunction with these awards

Application Receipt Dates:

Brief study outline	May 28, 2011
Request to submit full application	July 17, 2011
Submission of full application	September 1, 2011
Notification of award	October 31, 2011

Funding begins upon receipt of all relevant signatures.



The ALS Association National Office
1275 K. Street NW, Suite 1050
Washington, DC 20005
www.alsa.org