



New Research. New Treatments. New Hope.

2009/2010 Annual Report



“ The ALS Therapy Alliance board members are profoundly grateful to CVS/pharmacy for its ALS fundraising campaign, which has been invaluable in the effort to develop an international consortium of ALS researchers. ”

Robert H. Brown, Jr., D.Phil., M.D.

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Our Mission

The ALS Therapy Alliance, Inc. (ATA), established in 2002, partners with corporations, biotech and pharmaceutical firms, manufacturers and the media to create awareness and raise funds for research of Amyotrophic Lateral Sclerosis (ALS), also known as Lou Gehrig's disease. Our board of directors consists of esteemed researchers, scientists and Nobel Prize winners who are affiliated with top institutions such as Massachusetts General Hospital, Harvard Medical School, Massachusetts Institute of Technology, Harvard University, Tufts University, Children's Hospital Boston, Brigham and Women's Hospital, Beth Israel Deaconess Hospital, Columbia University, Boston University, Brandeis University, and the University of Massachusetts Medical School.

In 2002, ATA invited CVS/pharmacy to join the fight against ALS by asking its customers to donate to the cause at the checkout counters. Nine years later, that partnership is still thriving and CVS/pharmacy is an integral part of the annual ALS fundraising campaign. The organization and funding of the ATA have been structured so that more than 90% of the money generated through CVS/pharmacy is committed to funding ALS research.

To date, nearly \$24 million has been raised and great strides are being made towards finding a cure for this devastating disease.



Members of the CVS/pharmacy team present a check to the ALS Therapy Alliance's Researching a Cure Campaign for \$4.4 million. Pictured from left to right are Hannah Miller; Wally the Green Monster; Kyle Miller; Tom Ryan, Chairman of the Board and Chief Executive Officer for CVS Caremark Corporation; Dr. Robert Brown, Director and organizer of the ALS Therapy Alliance; Troy Brennan, Executive Vice President and Chief Medical Officer for CVS Caremark Corporation; Jon Roberts, Executive Vice President, Rx Purchasing, Pricing and Network Relations for CVS Caremark Corporation, Bill Miller, 2009 Co-spokesperson (with wife Dana Miller who has ALS, not pictured); Marley Miller; Spencer Miller.

The Facts on ALS



ALS: what the name really means

ALS is a rapidly progressing neurological disorder that attacks motor nerve cells responsible for voluntary movement. The meaning of the name amyotrophic lateral sclerosis is Greek in origin. “A” means “no” or “negative,” “myo” refers to “muscle,” and “trophic” stands for “nourishment.” So, amyotrophic means “no muscle nourishment.” Lateral sclerosis refers to the fact that the sides of the spinal cord appear scarred, or sclerosed, in late-stage ALS.

ALS: the initial onset and symptoms

Initially, symptoms of ALS may include twitching, cramping and stiffness of muscles, unusual fatigue and clumsiness, or difficulty swallowing and speaking. Although the sequence of emerging symptoms and the progression rate for the disease differ from person to person, an ALS patient’s muscles will ultimately weaken and become paralyzed. A patient’s thinking ability, bladder and bowel function, sexual function and senses — sight, hearing, smell, taste and touch — however, are unaffected. When the muscles in the diaphragm and chest wall fail, patients cannot breathe and most will die from respiratory failure, usually three to five years after the symptoms begin.

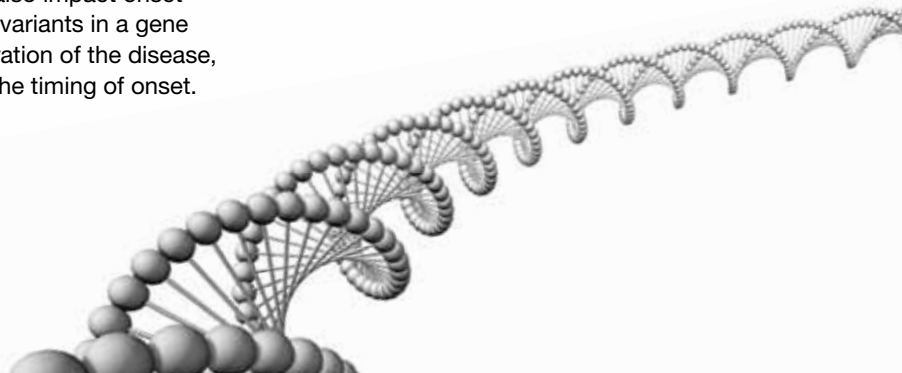
ALS: the real cause remains a mystery

The cause of ALS is not known, except in the rare case of familial ALS. These cases arise because of mutations in several genes. One gene makes a free radical absorbing protein, known as superoxide dismutase (SOD1); mutations in this gene render the SOD1 protein toxic. Mutations in two other genes, known as FUS/TLS and TDP43, cause proteins produced by these genes to be sequestered in abnormal locations in motor neurons, and probably also adversely impact genetic material known as RNA. Causes proposed for non-familial (sporadic) ALS include: high levels of the neurotransmitter glutamate; exposure to adverse environmental factors such as infections or poisons; insufficient energy generation by brain cells; inflammation in the spinal cord; and slowing of the transport of substances in long neuron processes, known as axons.

It has now been determined that variations in some genes also impact onset and survival in ALS. Thus some normally occurring genetic variants in a gene that makes a motor protein known as KIFAP3 affect the duration of the disease, while variants in a gene known as chromogranin influence the timing of onset.

“ It is remarkable that nearly 20 genetic factors are now known to be involved in ALS. Each factor points to pathways by which motor neurons die in ALS, and thus highlights possible targets for therapy. Many of these genes have led to the development of petri dish and animal models with which new drug treatments can be tested, accelerating the rate of discovery of human treatments. ”

Robert H. Brown, Jr.
D.Phil., M.D., Chair of the Dept. of
Neurology, University of Massachusetts
Medical School



Committed to Finding a Cure

No cure: But new treatments are being developed

There is no cure for ALS. Currently, only a single drug, called Riluzole, is FDA-approved for use in ALS patients. At best, this drug slows the disease only modestly. Members of the ALS Therapy Alliance's scientific board, and grantees of the Alliance, are currently pursuing several new therapies.


In a collaboration with Knopp Neurosciences, the Northeast ALS Consortium (NEALS) conducted a phase II trial of pramipexole (KNS 760604) in ALS. Pramipexole is a novel, oral neuroprotective therapy. We happily report that the phase II trial showed promising, positive data that the drug had a dose-dependent affect on slowing ALS disease progression. Now, Biogen Idec and Knopp Neurosciences have entered into an exclusive worldwide license agreement to further the development of pramipexole for the treatment of ALS. An international phase III trial (the true test of a drug's efficacy) will begin enrollment this spring.

In addition to promising small molecules, which are traditional drugs, researchers are investigating therapies that silence expression of toxic genes, such as the SOD1 gene, whose mutations can cause ALS. This is an innovative new approach, which represents tremendous progress. One such approach, developed by colleagues at Isis Pharmaceuticals, is currently in trials in ALS.

In addition to Riluzole and experimental treatments, other interventions, such as feeding, breathing and ambulation aids, can substantially relieve some of the symptoms and clinical problems caused by ALS. Some of these symptoms (such as fatigue, muscle cramps, depression, sleep disturbance) are at least partially helped by medications that do not treat the primary process of motor nerve degeneration in ALS.

Can your genetic makeup cause ALS?: The role of DNA

The ALS Therapy Alliance is committed to using state-of-the-art genetic testing techniques to identify why certain people have the disease. Scientists believe that susceptibility to ALS is strongly influenced by genetic makeup and, recently, several genes have been implicated in ALS. There has been substantial progress in identifying new genetic variants that make people susceptible to the disease. In an integral project funded in large part by the ATA, scientists in Boston, Atlanta, London and Chicago are conducting studies of DNA variants that may be associated with enhanced risk of developing ALS.



“
... an awful lot to live for ...
Lou Gehrig's farewell speech”

“
Creating a network of
scientists working together,
sharing data and
expediting therapy
development is critical
to finding a
cure for ALS.”
Merit E. Cudkowicz, M.D., M.Sc.

ALS Therapy Alliance-funded research is being conducted in other countries, including Australia, China, England, Belgium and Germany.

A large consortium study recently spotlighted in *Lancet Neurology* has demonstrated that about 10% of sporadic ALS cases are associated with variants in a genetic marker that may also be related to familial ALS and a type of dementia (fronto-temporal dementia). This underscores the importance of finding this ALS-FTD gene and also highlights the important potential overlap between inherited and non-inherited forms of ALS.

An ALS Therapy Alliance-funded state-of-the-art genomic center at the University of Massachusetts will allow application of the latest gene identification technology in the search for new ALS genes. The center is conducting a variety of research, including DNA sequencing of ALS patients' genomes. Importantly, members of the ALS genomics center are collaborating with researchers at Duke University to fully sequence the entire complement of DNA molecules in the genome of individuals with familial and sporadic ALS.

The role of motor nerve cells: Early evidence of degeneration

The ALS Therapy Alliance has funded studies by leading scientists worldwide. This research has resulted in numerous findings, including early evidence of degeneration. In their research, these scientists have studied ALS mice, finding electrical abnormalities in their motor neurons long before the disease begins. The motor nerve cells are electrically overactive in a pattern that is likely to be injurious after many months.

Early evidence of degeneration was discovered by scientists at the Massachusetts Institute of Technology and Australian researcher Brigitte van Zundert. When studying motor neurons in brain slices of one week old ALS mice, there was evidence of abnormal behavior – excessive firing and abnormal circuitry and sprouting of motor neurons.

ALS is difficult to diagnose because the symptoms are similar to those of other neuromuscular disorders. The neurological exam usually shows evidence of muscle weakness and atrophy. In ALS, non-motor functions such as feeling, memory and cognition remain normal.

ALS knows no boundaries: ALS studies across cultures

The ALS Therapy Alliance has galvanized experts from around the globe in the fight against ALS. For instance, the ATA has used a portion of the proceeds from the annual CVS/ pharmacy fundraising campaign to recruit ALS investigators in Mexico. Mexican neurologists and clinical scientists have been collecting demographic data and both serum and DNA samples from ALS patients within Mexico. This has facilitated the development of a clinical database and accelerated programs to identify genetic variants in sporadic and familial ALS.

The ATA has also funded studies of a pediatric form of a motor neuron disease, which commonly occurs in southern India. ATA funding has allowed clinicians to acquire DNA samples from affected individuals and is presently supporting efforts at gene identification.

The ALS Therapy Alliance, together with the Israeli Science Fund (ISF), recently co-funded two international symposia on ALS; these meetings attracted ALS investigators from many countries.

ATA-funded research is also being conducted in other countries, including Australia, China, England, Belgium and Germany.

“

Only by collaborating and approaching the problem from many different perspectives can we overcome obstacles to the development of truly effective therapies.

”

Lawrence J. Hayward, M.D., Ph.D.

“ With the wonderful support of CVS/pharmacy, the ATA has been able to develop several parallel ALS research projects that are unprecedented and extremely promising. ”

Robert H. Brown, Jr.,
D.Phil., M.D.

“ CVS/pharmacy and the ALS Therapy Alliance share a common goal of helping people achieve their highest possible quality of life and ATA’s doctors bring a tremendous amount of passion, determination and intellect to this cause... By bringing together the very best minds in the field of ALS research, the ATA has focused funds and resources to make great strides in the battle against this disease. ”

Jonathan Roberts, CVS/pharmacy

A meeting of the minds: Sharing discoveries

Scientists and clinicians from an array of ALS networks meet at regular intervals to discuss their findings and implement new trials; many of these meetings have received funding from the ALS Therapy Alliance and CVS/pharmacy partnership. These groups include the country’s largest clinical trials network, known as the Northeast ALS Consortium (NEALS), the ALS Research Group, and the International Consortium on ALS and Superoxide Dismutase (ICOSA). The ATA believes that financial support for NEALS is critical, as NEALS is the world’s most active ALS clinical research and trials consortium. In one current study, NEALS is conducting a comparison trial of creatine (an energy-enhancing substance) and tamoxifen (an estrogen receptor blocking drug). It is also assisting in trials of pramipexole (jointly with Biogen Idec) and gene silencing (with Isis Pharmaceuticals).

A faster diagnosis: Tools to help diagnose ALS

ALS is difficult to diagnose because its symptoms are similar to those of other neuromuscular disorders. The diagnosis is often based on a full neurological examination and clinical tests, which can take months to complete.

To assist in solving this problem, the ALS Therapy Alliance has used funds raised by CVS/pharmacy to help investigators discover molecules that distinguish ALS from non-ALS body fluids. It is hoped that molecules like these, sometimes designated as “biomarkers,” will speed up diagnosis at early stages of the disease and accelerate treatment.

Animals in the fight against ALS: Animals aid research

Animals are powerful tools in the study of ALS, and in recent years the diversity of animal models has expanded substantially. With every gene defect that is identified, it has been possible to generate animal models of ALS caused by the corresponding defect. These animal models have involved mice and rats and, more recently, fruit flies and fish. Each animal offers its own particular advantages as an experimental model.

Discoveries

By studying animals with ALS, scientists can learn more about the process of degeneration of motor nerves in the brain and spinal cord. New discoveries and new ALS treatments can be tested very efficiently in the ALS animal models. Funds provided by the ALS Therapy Alliance and CVS/pharmacy help scientists conduct this research.

Mini-models of ALS: Drug screening

A new research technique implemented in many laboratories, and supported in part by the ALS Therapy Alliance, is a method called high-throughput drug screening. In this approach, scientists test drugs in tiny petri dish models of ALS, which increases efficiencies and reduces costs. Compounds that appear helpful in high-throughput tests can then be examined more definitively in the animal models.

Stem cell therapy: Reversing cell death

There has been extraordinary progress in the application of stem cell biology to studying neurodegeneration in ALS, which has significant implications for processes such as drug screening. Stem cell biology has made huge advances in the last five years, which have clearly accelerated ALS research and the quest for therapy.

Stem cells may offer a variety of benefits for a disease like ALS. In present studies, they permit sophisticated analyses of different types of interactions between motor neurons and surrounding cells, some of which contribute to cell death in motor neuron disease. In the long term, stem cell technologies may facilitate replacement of lost motor neurons, although this is many years away. Stem cells may also be useful as vehicles for delivering drugs to the nervous system.

It is now possible to generate stem cells and then motor neurons from skin biopsies of living patients, which means that, for the first time, scientists are able to study motor neurons derived from living ALS patients. This is especially significant because such motor neurons possess the genetic makeup of the patients

who provided the skin biopsies. Such cultures of human motor neurons are highly advantageous, both as a biological tool and because it bypasses ethical issues surrounding fetal-derived stem cell research.

Drug delivery to the brain: Crossing the iron curtain

A major problem in treating brain disorders is getting treatments across the blood brain barrier (BBB), an iron curtain that normally prevents proteins and toxins from entering the central nervous system. To be effective in brain diseases, drugs must go from the bloodstream to the brain and spinal cord. New investigations, funded in part by the ALS Therapy Alliance, are looking for ways to engineer molecules that will navigate through the BBB.

Axonal transport

Axons are the long appendages that extend from the cell body of a motor neuron to muscle. Transport of materials along the length of the motor neuron axon (so-called axonal transport) is an important cellular process that is critical for normal motor neuron function and viability. Genetic or toxic defects that impair axonal transport can compromise the viability of motor neurons.

Recent studies of axonal transport proteins within axons have suggested the hypothesis that defective axonal transport may be a critical element in ALS motor neurons. Some of the pivotal studies in axonal transport and ALS have been funded by the ALS Therapy Alliance.

Moreover, new findings indicate that in some cases of sporadic ALS (with no mutations in the SOD1 gene or protein), the SOD1 protein gets misfolded and can directly inhibit axonal transport.

“ The goal is to stop ALS before it ever starts. ”

H. Robert Horvitz, Ph.D.

Board of Directors



Alan Abraham

Alan Abraham is the president of Granite State Development, a private, not-for-profit company established in 1982 to administer the Small Business Administration's 504 Loan Program. It operates throughout New Hampshire, Maine, Massachusetts and Vermont. Abraham graduated from Tulane University with a bachelor of science degree in history and earned his master of business administration in finance and investments from George Washington University. After losing a family member to ALS, he joined the ATA and developed the CVS/pharmacy campaign jointly with Jonathan Roberts of CVS/pharmacy.



Robert H. Brown, Jr., D.Phil., M.D.

Robert H. Brown, Jr., D.Phil., M.D., earned his bachelor's degree in biophysics at Amherst College, a doctorate of philosophy in neurophysiology at Oxford University, and a medical degree at Harvard Medical School. He is presently the chair of the Department of Neurology at the University of Massachusetts Medical School.

Dr. Brown's primary research interest has been inherited, paralytic neuromuscular disorders with a focus, since 1980, on ALS. He currently serves as the director and organizer of the ALS Therapy Alliance and is a non-voting member on the board.

As part of a consortium of investigators, Dr. Brown played a central role in the discovery of mutations or genetic variants in several ALS-related genes, including cytosolic superoxide dismutase, alsin, dynactin, KIFAP3 and FUS/TLS.

Dr. Brown has also identified gene defects causing three other diseases known as Miyoshi myopathy (dysferlin), hyperkalemic periodic paralysis (skeletal muscle sodium channel), and familial sensory neuropathy (serine palmitoyltransferase).



Merit E. Cudkowicz, M.D., M.Sc.

Dr. Merit Cudkowicz is a professor of neurology at Massachusetts General Hospital (MGH) and Harvard Medical School. Dr. Cudkowicz earned her bachelor's of science degree in chemical engineering at the Massachusetts Institute of Technology and completed medical training at the Health Science and Technology Program of Harvard Medical School. She obtained

a master's degree in clinical epidemiology from the Harvard School of Public Health. She was a resident and chief resident in neurology at MGH. She was a fellow in the MGH/ Massachusetts Institute of Technology Clinical Investigator Training Program from 1994 to 1996.

Dr. Cudkowicz's research and clinical activities are dedicated to the study and treatment of patients with neurodegenerative disorders, in particular amyotrophic lateral sclerosis (ALS). Dr. Cudkowicz directs the MGH ALS clinic and the MGH Neurology Clinical Trials Unit. She is one of the founders and co-directors of the Northeast ALS Consortium, a group of 92 clinical sites in the United States and Canada dedicated to performing collaborative academic led clinical trials in ALS. In conjunction with the NEALS consortium, she planned and completed seven multi-center clinical trials in ALS and is currently leading three new trials in ALS. Dr. Cudkowicz received the American Academy of Neurology 2009 Sheila Essay ALS award.

She has been a pioneer in promoting and developing more efficient methods of testing new therapies in people with ALS. She is actively mentoring young neurologists in clinical investigation in ALS and related neurodegenerative disorders. Dr. Cudkowicz is on the medical advisory board for the Muscular Dystrophy Association and the Amyotrophic Lateral Sclerosis Association.



Robert J. Ferrante, Ph.D., M.Sc.

Robert J. Ferrante, Ph.D., M.Sc., is a professor of neurology, pathology and laboratory medicine, psychiatry and behavioral neuroscience at the Boston University School of Medicine. He is the director of the Experimental Neuropathology Unit and Translational Therapeutics Laboratory at the Bedford Veterans Affairs Medical Center in Bedford, Mass. Dr. Ferrante has a wide-range of knowledge about the neuropathology and mechanisms of neurodegeneration in adult-onset neurological diseases, especially ALS, with more than 30 years experience in clinical and experimental neurology. He is considered an expert in the application of experimental models of disease and in bench-to-bedside translational studies. Dr. Ferrante is a member of the Northeast ALS Consortium and is a steering committee member on six current human clinical trials using therapeutic agents that were developed in his laboratories. He is currently the director and co-principal proponent of a multi-center phase one clinical trial in ALS for the Veterans Administration.

Over the past 10 years, Dr. Ferrante has developed one of the premier translational programs for developing and characterizing

therapeutic strategies for neurological diseases. His laboratory has been a driving force in completing pre-clinical drug trials in mice for direct translation to human clinical trials in ALS patients.



Lawrence J. Hayward, M.D., Ph.D.

Lawrence J. Hayward, M.D., Ph.D., received his doctorate degrees in neuroscience and medicine from Baylor College of Medicine in Houston, Texas. He completed a neurology residency and neuromuscular disease fellowship at Massachusetts General Hospital. During that time, his research focused on neuromuscular conditions caused by defective ion channels. In 2000, Dr. Hayward started his own laboratory at the University of Massachusetts Medical School as an assistant professor of neurology. Dr. Hayward became an associate professor in 2003 and serves as joint faculty in the departments of physiology, biochemistry and molecular pharmacology, and the program in neuroscience. He sees patients regularly in the Neuromuscular Clinic and on the wards, contributes to medical school and resident teaching, and serves as a mentor for graduate students and fellows in the laboratory.

In 1998, Dr. Hayward initiated biochemical studies with Dr. Robert Brown to identify toxic properties of mutant SOD1 enzymes that cause familial ALS.

Dr. Hayward's group and collaborators have shown that impaired zinc binding and other vulnerabilities produce misfolded forms of the SOD1 protein that are prone to aggregation or other abnormal interactions. Since 2008, the lab has focused upon establishing new in vivo models using mouse and zebrafish systems to investigate mechanisms by which mutant forms of nucleic acid binding proteins cause ALS.



H. Robert Horvitz, Ph.D.

H. Robert Horvitz, Ph.D., received the Nobel Prize in Physiology or Medicine in 2002 and is the David H. Koch Professor of Biology at the Massachusetts Institute of Technology, an investigator of the Howard Hughes Medical Institute, a neurobiologist at the Massachusetts General Hospital, and a member of the MIT McGovern Institute for Brain Research and the MIT Koch Institute for Integrative Cancer Research. Dr. Horvitz received bachelor's degrees in mathematics and economics from the Massachusetts Institute of Technology and performed his Ph.D. studies in biology at Harvard University.

Dr. Horvitz was a postdoctoral scientist at the Medical Research Council Laboratory of Molecular Biology in Cambridge, England, and has been an assistant, associate and full professor in the Department of Biology at the Massachusetts Institute of Technology. Dr. Horvitz has received numerous awards for his accomplishments. Some of these honors include: Charles A. Dana Award for Pioneering Achievement in Health (1995); General Motors Cancer Research Foundation, Sloan Prize (1998); Gairdner Foundation International Award (1999); March of Dimes Prize in Developmental Biology (2000); the Genetics Society of America Medal (2001); the Bristol-Myers Squibb Award for Distinguished Achievement in Neuroscience (2001); the Wiley Prize in the Biomedical Sciences (2002); the Peter Gruber Foundation Genetics Prize (2002); the American Cancer Society Medal of Honor (2002); and the Alfred G. Knudson Award of the National Cancer Institute (2005). He has also received several honorary degrees and has served on many editorial boards and committees.

Dr. Horvitz has achieved world-wide recognition for his discoveries of cell death genes and his delineation of the molecular pathways through which these genes operate. These discoveries continue to have new and compelling implications across basic cell biology and much of medicine, including the fields of cancer and neurodegenerative diseases, like ALS.

“CVS and the ALS Therapy Alliance share a common goal of helping people achieve their highest possible quality of life and ATA's doctors bring a tremendous amount of passion, determination and intellect to this cause...By bringing together the very best minds in the field of ALS research, the ATA has focused funds and resources to make great strides in the battle against this disease.”

Jonathan Roberts, CVS/pharmacy

Board of Directors



Tom Maniatis, Ph.D.

Tom Maniatis, Ph.D., is the Isidore S. Edelman Professor and chairman of biochemistry and molecular biophysics at the Columbia University Medical Center. He received his bachelor's degree from the University of Colorado at Boulder and a doctorate in molecular biology from Vanderbilt University. His

postdoctoral studies were carried out at Harvard University and at the Medical Research Council for Molecular Biology in Cambridge, England.

Dr. Maniatis has held research and academic positions at the Cold Spring Harbor Laboratory in New York and the California Institute of Technology in Pasadena, and he recently retired from Harvard University after 30 years on the faculty.

Dr. Maniatis' research has been recognized by numerous awards, including the Eli Lilly Award in Microbiology and Immunology, the Scientific Achievement Award of the American Medical Association, the Richard Lounsbery Award for Biology and Medicine, and the Jacob Heskell Gabbay Award in Biotechnology and Medicine, as well as membership in the U.S. National Academy of Sciences.

Dr. Maniatis is best known for pioneering the development and application of recombinant DNA methods to the study of gene regulation. His research has impacted a broad spectrum of biomedical fields, from basic mechanisms of gene expression to advances in understanding human genetic and inflammatory diseases. Dr. Maniatis' laboratory is currently using both mouse and human pluripotent stem cells to study ALS disease mechanisms.



Craig C. Mello, Ph.D.

Dr. Craig C. Mello is an investigator at Howard Hughes Medical Institute, the Blais University Chair in Molecular Medicine, and co-director of the RNA Therapeutics Institute at the University of Massachusetts Medical School in Worcester.

He received his B.Sc. degree in biochemistry from Brown University in 1982 and received his Ph.D. from Harvard University in 1990.

From 1990 to 1994, he conducted postdoctoral research at the Fred Hutchinson Cancer Research Center in Seattle, Wash. Dr. Mello's pioneering research on RNAi, in collaboration with Dr. Andrew Fire, has been recognized with many prestigious awards culminating with the 2006 Nobel Prize in Physiology or Medicine.

Dr. Mello, along with his colleague Dr. Fire, discovered the process by which a particular form of ribonucleic acid – RNA, the cellular

material responsible for the transmission of genetic information – can silence targeted genes. This RNAi process offers astounding potential for understanding and manipulating the cellular basis of human disease, and RNAi is now the state-of-the-art method by which scientists can “knock out” the expression of specific genes to thus define the biological functions of those genes. Just as important has been the finding that RNAi is a normal process of genetic regulation that takes place during development, opening a new window on developmental gene regulation.



Jonathan C. Roberts

Jonathan C. Roberts is Executive Vice President and COO for CVS Caremark Pharmacy Services. In his current position he is responsible for PBM Trade and Retail Pharmaceutical Purchasing, New Product Development, Underwriting and PBM Networks.

Roberts is a seasoned retail pharmacy executive with more than 30 years of experience in retail pharmacy, 18 of those with CVS Caremark. He is a results-driven, experienced leader with a diverse mix of field management, business operations and information systems integration experience. He most recently served as chief information officer for CVS Caremark, where he spearheaded several key initiatives, including the Pharmacy Service Initiative (PSI). PSI has enhanced pharmacy performance at CVS/pharmacy and has been highlighted in business case studies at the Harvard Business School and Yale School of Management.

Roberts is a member of the SureScripts Executive Advisory Council and the eHealth Initiative's Leadership Council. He earned his degree in pharmacy from the Virginia Commonwealth University School of Pharmacy and is a graduate of the Wharton Executive Management Program.

Auditor's Letter

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INDEPENDENT AUDITOR'S REPORT

To the Board of Directors
ALS Therapy Alliance, Inc.

I have audited the accompanying statement of financial position of ALS Therapy Alliance, Inc. (a nonprofit organization), as of December 31, 2009, and the related statement of activities and statement of cash flows for the year then ended. These financial statements are the responsibility of the Organization's management. My responsibility is to express an opinion on these financial statements based on my audit.

I conducted my audit in accordance with auditing standards generally accepted in the United States of America. Those standards require that I plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatements. The audit included examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. I believe that my audit provides a reasonable basis for my opinion.

In my opinion, the financial statements referred to above present fairly, in all material respects, the financial position of ALS Therapy Alliance, Inc., as of December 31, 2009, and the changes in net assets, and its cash flows for the year then ended, are in conformity with accounting principles generally accepted in the United States of America.



Cindy Courtney, CPA, CFP
North Hampton, NH
December 13, 2010

Financial Statements

Balance Sheet

ASSETS	
Cash and cash equivalents (Note #1)	\$ 5,501,156
Accrued interest	16,260
Short-term investments (Note #3)	4,193,877
Long-term investments (Note #3)	499,706
TOTAL ASSETS	10,210,999
LIABILITIES	
Research grants payable	484,632
TOTAL LIABILITIES	484,632
NET ASSETS	
Unrestricted net assets	9,726,367
TOTAL NET ASSETS	9,726,367
TOTAL LIABILITIES & NET ASSETS	10,210,999

Cash Flows

CASH RECEIPTS FROM OPERATING ACTIVITIES	
Contributions	\$ 4,405,211
Interest Income	190,964
TOTAL CASH RECEIPTS FROM OPERATING ACTIVITIES	4,596,175
CASH DISBURSEMENTS FROM OPERATING ACTIVITIES	
Bank Charges	77
Contract Administrator	7,000
Licensing Fees	19
Insurance	2,820
Office Supplies	74
Research Grants	1,886,069
TOTAL CASH DISBURSEMENTS FROM OPERATING ACTIVITIES	1,896,059
NET CASH RECEIVED FROM OPERATING ACTIVITIES	2,700,117

Income Statement

REVENUE	
Contributions	\$ 4,694,736
Net Interest Income (Note #3)	45,470
TOTAL REVENUE	4,740,205
EXPENSES & LOSSES	
Program Services	
Research Grants	1,381,831
Supporting Services	
Management and general	10,780
Fundraising	288,734
Unrealized holding loss on investments (Note #3)	40,237
TOTAL EXPENSES & LOSSES	1,721,582
CHANGES IN NET ASSETS	3,018,624
NET ASSETS AT BEGINNING OF YEAR	6,707,743
NET ASSETS AT END OF YEAR	9,726,367

CASH FROM INVESTING ACTIVITIES	
Sale of investments	5,200,000
Purchase of investments	(4,755,149)
NET CASH RECEIVED FROM INVESTING ACTIVITIES	444,851
TOTAL INCREASE IN CASH & CASH EQUIVALENTS	3,144,968
CASH & CASH EQUIVALENTS BEGINNING OF YEAR	2,356,188
CASH & CASH EQUIVALENTS END OF YEAR	5,501,156
NON-CASH ITEMS	
Donated fundraising expenses	288,734
Donated professional services	790

The ALS Therapy Alliance, Inc., (the Organization) is a not-for-profit corporation organized to raise funds from individual donors to fund ALS (Amyotrophic Lateral Sclerosis) research. The Organization provides a vehicle for a diverse group of scientists and clinicians to coordinate research related to ALS. Applications for research grants solicited from research hospitals and other organizations are reviewed by the board of directors and selected for funding. Those projects funded are required to present their findings to the Organization. The Organization is supported primarily through donor contributions from a three-week joint fundraising campaign with CVS/pharmacy. Approximately 98% of the Organization's support for the current and prior years came from the CVS/pharmacy joint fundraising campaign.



Note 1: Significant Accounting Policies

- A. The Organization is exempt from taxation under section 501(c)(3) of the Internal Revenue Code and is classified as other than a private foundation.
- B. Method of accounting: The Organization uses the accrual method of accounting for financial reporting and tax basis for federal income tax purposes. Calendar year reporting has been adopted.
- C. Contributions: In-kind contributions and contributed services requiring specific expertise are recorded at the estimated fair value of the contribution. Since its inception, the Organization's fundraising expenses have been donated by an unrelated organization. The Organization recognizes income to the extent of the fair value of these donated expenses and services as well as an expense for the corresponding amount.
- D. Investments: Investments in U.S. Treasury Securities are reported at their fair values in the statement of financial position. Unrealized gains and losses are included in the change in net assets.
- E. Cash and Cash Equivalents: For the purposes of the statement of cash receipts and disbursements, the Organization considers all short-term U.S. Treasury Securities with an original maturity of three months or less to be cash equivalents.
- F. Use of estimates: The preparation of financial statements using generally accepted accounting principles requires management to make estimates and assumptions that affect certain reported amounts and disclosures. Accordingly, actual results could differ from those estimates.
- G. Property and Equipment: The Organization capitalizes property and equipment over \$1,000. Lesser amounts are expensed. Purchased property and equipment is capitalized at cost. Donations of property and equipment are recorded as contributions at their estimated fair value and reported as unrestricted contributions unless the donor has restricted the asset for a specific purpose. As of the date of these financial statements, the Organization owned no property and equipment.

Note 2: Excess Deposits

The Organization had deposits with banks and brokerages on December 31, 2009, that exceeded the federal insurance limits by \$4,602,443 and \$648,713 respectively.

Note 3: Investments

The Organization held short-term investments in U.S. Treasury notes totaling \$4,193,877 that mature within one year and long-term investments in U.S. Treasury notes totaling \$499,706 with a maturity date of greater than one year. These investments are reported at fair value. Fair value is determined by using quoted prices in active markets for identical assets (Level 1) at the close of the business day. Temporary fluctuations in fair value are reported as unrealized gains and losses. Substantially, all securities are held to their maturity, resulting in no realized gain or loss.

The following schedule summarizes the investment return and its classification in the statement of activities for the year ended December 31, 2009:

Unrestricted interest income	\$	190,964
Decrease in accrued interest		(35,816)
Less: Accrued interest paid on purchase		(27,872)
Less: Amortized bond premium paid		(81,806)
Net interest income		45,470
Net unrealized loss		(40,237)
Total investment return	\$	5,233

Note 4: Commitments

As of December 31, 2009, the Organization had approved research grant commitments in the amount of \$484,632 to be paid in 2010 for year two of ongoing multi-year research projects.

Note 5: Related Party Transactions

Several of the board members of the Organization are highly trained research scientists with expertise in the area of ALS research. As scientists, some have submitted research grant applications following the Summary of Guidelines for Application requirements as approved by the board. When a grant proposal submitted by a board member is reviewed by the board, that board member is not allowed to vote or remain in the room when such proposal is discussed and voted upon. During the year ended December 31, 2009, \$553,750 of board member research projects were funded.

Note 6: Subsequent Events

The Organization has evaluated subsequent events through December 13, 2010, the date that the financial statements were issued.



Grant Summaries

Project: Genome-wide association study of samples from the UK National Motor Neuron Disease DNA Bank

Investigator: Ammar Al-Chalabi, Ph.D., F.R.C.P. Dip.Stat.
King's College London, United Kingdom (UK)

About 5% of people with amyotrophic lateral sclerosis (ALS), known as a motor neuron disease in the UK, have a family history of ALS. For the remainder, who have so-called sporadic ALS, we know from studies of identical and non-identical twins that genetic factors contribute to disease risk. One way to find gene variations that might increase the risk of someone developing sporadic ALS is to compare the genetic makeup of large numbers of people with sporadic ALS with the genetic makeup of large numbers of people without ALS to see if there is any consistent difference.

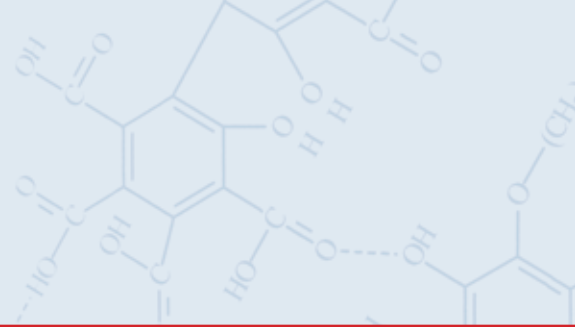
In this study, about 600 samples from a national bank of ALS DNA samples in the UK were compared with results from about 4,000 samples from the general UK population. The signal of a genetic contribution to sporadic ALS was seen on chromosome 9. These results were then combined with information from seven other countries to make the largest genetic study of ALS ever - 4,000 people with ALS and 8,000 people without. The association signal became even stronger. This means that people who carry the risky genetic variant at this gene address have a slightly higher risk of ALS than people who do not, and it accounts for about 10% of people with sporadic ALS. At this gene address, there are only three genes, called MOBKL2B, IFNK and C9orf72. Efforts are underway to find out which gene is the problem. The results have been published in the prestigious journal *Lancet Neurology*.

Project: Phase III: Production Four Version III ATLAS Devices

Investigator: Patricia Andres, M.S., D.P.T.
Massachusetts General Hospital (MGH), United States

In response to a critical need for improved outcome measures in ALS clinical research, to accurately and efficiently measure strength in small groups of patients, we developed a new device called Accurate Test of Limb Isometric Strength (ATLIS). ATLIS tests 12 muscle groups in the limbs using a fixed, wireless load cell. A validation study, supported by MDA, demonstrated excellent reliability and very positive user acceptance.

Last year, ATA provided funding for two new production-ready strength measurement prototypes (Version III). Funds from the Neurology Clinical Trials Unit at MGH were used to build two additional prototypes. A total of five ATLIS III prototypes are in use in clinical research sites throughout the country to collect ATLIS data from 500 healthy adults that will be used to allow raw ATLIS data to be converted to a percent of predicted normal values. Use of percent of normal will mitigate differences between subjects and enable disease progression rates to be calculated based on a 100 point scale. These five ATLIS prototypes will also be used in the tamoxifen/creatine trial to directly compare ATLIS with HHD in this longitudinal study.



We are extremely grateful for the support that ATA has provided through various stages of ATLIS prototype development. We feel that ATLIS will prove to be an efficient and practical method to measure disease progression in ALS and enable candidate drugs to be screened quicker and with less expense.

Project: Multicenter Study for Validation of ALS Biomarkers
Investigator: Merit E. Cudkowicz, M.D., M.Sc.
Massachusetts General Hospital (MGH), United States

Twenty-five Northeast ALS Consortium (NEALS) Centers are currently participating in a Multicenter Study for the Validation of ALS Biomarkers with the primary objective of identifying factors that contribute to the pathogenesis of ALS. Development of disease biomarkers and diagnostic laboratory tests would facilitate earlier treatment intervention, help monitor treatment efficacy and, ultimately, lead to the identification of targets that could be used in therapy development. Sponsored by ALSA, ATA and the NIH, and working in conjunction with Metabolon, Inc., blood and cerebrospinal fluid (CSF) is collected for metabolomic testing. Metabolomics provides a new approach to evaluate global biochemical defects in ALS and to establish characteristic and unique metabolic patterns for ALS and its different phenotypic forms. It is believed that these signatures and knowledge of the corresponding molecular structures will provide diagnostic markers for the disease and provide insights into disease mechanisms.

A total of 650 blood and 300 CSF samples will be collected from healthy individuals, ALS disease mimics and people with ALS. In addition, up to 600 blood samples from all groups will be collected for a sub-study for DNA analysis.

Currently, there are 445 total volunteers enrolled. A total of 411 blood samples have been collected along with 226 longitudinal blood samples, 190 CSF samples and 246 DNA samples.

Specific biomarkers for ALS would be valuable because they may point to new hypotheses in the pathogenesis, allow earlier and more accurate disease diagnosis, and serve as surrogate indices of disease activity that enhances monitoring for therapeutic effect in treatment trials.

Project: Analysis of mTOR and Synaptic Activity in Amyotrophic Lateral Sclerosis
Investigator: Eric Frank, Ph.D.
Tufts University, United States

In this project, we characterized the synaptic connectivity between various types of sensory neurons and the motoneurons that they innervate in hSOD1 mutant mice during early postnatal stages. Our goal was to determine whether this mutation altered neural circuits in the spinal cord at early postnatal stages, well before the loss of motoneurons that is a hallmark of the ALS phenotype.

Synaptic connections were assessed by making electrical recordings from motoneurons. This was in response to stimulation of sensory nerves in isolated spinal cord preparations from nine-day-old mice pups expressing the hSOD1G93A or hSODwt genes. We found that the specificity of synaptic inputs from sensory neurons was abrogated in mutant mice. Normally, inputs from a motoneuron's own muscle afferents are more than 10 times as large as those from unrelated muscles.

In contrast, these connections are much less specific in hSOD1G93A mice; inputs from unrelated muscles were more than twice their normal amplitude. There was also an increase in the excitation of motoneurons caused by stimulation of cutaneous nerves. Stimulation of the saphenous nerve elicited synaptic potentials that were twice as large as in hSODwt mice. Intracellular recordings suggested that cutaneous axons were often projecting to inappropriate motoneurons, again suggesting a loss of synaptic specificity.

Taken together, our results show that although many of the direct synaptic pathways are intact in neonatal hSOD1 mutant mice, the selectivity of these pathways is appreciably reduced. This reduction in specificity may contribute to the loss of motor coordination noted in earlier investigations at times prior to the outright loss of motoneurons.

Project: Transgenic Mouse Models of FUS/TLS-mediated ALS
Investigator: Lawrence J. Hayward, M.D., Ph.D.
University of Massachusetts Medical School, United States

Genetic defects that affect proteins involved in the regulation of RNA processing or transport have been linked to both familial and sporadic forms of ALS. Mutant variants of one of these proteins, FUS, have been estimated to cause ~5% of familial ALS. Mutations near the C-terminus of the FUS gene cause motor neuron loss, but the mechanism(s) of toxicity have not yet been identified.

Grant Summaries

In this project, we are establishing transgenic mouse models that express either normal or mutant human FUS protein in the brain and spinal cord. We are characterizing 15 independent transgenic lines to detect altered FUS sub-cellular localization and other neuropathological features and to assess quantitative motor function and survival. These results will indicate whether the FUS mutations trigger dominant gain-of-function, loss-of-function, or dominant-negative mechanism(s) affecting motor neurons. Moreover, these insights will enable the identification of novel targets for slowing the neuronal degeneration and will accelerate rapid preclinical testing of treatment strategies for ALS.

Project: Zebrafish Models of FUS-ALS

Investigator: Lawrence J. Hayward, M.D., Ph.D.

University of Massachusetts Medical School, United States

Over the past four years, gene defects that may alter the function of several proteins involved in the processing of RNA have been linked to both familial and sporadic forms of ALS. Mutant variants of one of these proteins, FUS, have been estimated to cause ~5% of familial ALS. FUS normally helps to coordinate important cellular reactions such as splicing of nascent RNA in the nucleus and translation of the RNA message into protein in the cytoplasm. Initial studies suggest that mutant FUS may be localized abnormally in the cytoplasm of affected motor neurons in ALS, but the mechanism(s) by which dominant expression of the mutants injures motor neurons is not known.

The goal of this project is to establish and characterize zebrafish models of FUS-mediated ALS based on transgenic knock-in and knock-out manipulation of the zebrafish FUS gene. Zebrafish are increasingly being used to study mechanisms related to neurodegenerative diseases because of their small size and the ability to produce hundreds of eggs per day. Zebrafish embryos develop a functional motor system within three days after fertilization, and because zebrafish embryos are optically transparent, their morphology and physiology can be directly visualized. Experiments using fluorescent molecules to report back on the health of the nervous system can be designed, and hundreds of drugs can be tested in large numbers of individual animals over a few days. Our long-term goal is to use these genetic zebrafish models to identify novel drug targets and screen for their effectiveness in treating ALS.

Project: Analysis of mTOR & Synaptic Activity in ALS

Investigator: Zhigang He, Ph.D.

Children's Hospital Boston, United States

In ALS, available evidence suggests that motoneurons become dysfunctional very early in this disease. Electrophysiological studies reveal substantial increases in neuronal excitability and synaptic activity as early as the first postnatal week. These changes may be paralleled by alterations in synaptic connectivity with motoneurons, a possibility that has not been explored previously. These early changes are apparent well before the onset of neuromuscular degeneration and motoneuron loss, suggesting that it may be critical to understand the functional alterations in motoneurons during postnatal development.

In addition, the molecular mechanisms for these and other abnormalities in the motoneurons of ALS models and patients remain unclear. Our preliminary results suggest that the mammalian target of rapamycin (mTOR) activity is prematurely down-regulated in both upper and lower motoneurons of ALS mice at 10 weeks. This pathway is known to be a central regulator of cell survival and growth and remodeling of axons and dendrites as well as synaptic structures. We thus hypothesize that alterations of mTOR activity in motoneurons may be an important underlying mechanism in the development of motoneuron dysfunction and death in ALS models and perhaps in human patients.

In this application, we propose to utilize a combination of electrophysiological, behavioral, genetic and pharmacological means to test this hypothesis. We are in the process of determining the time course of the down-regulation of mTOR in ALS mice and its correlation with the development of ALS pathology, testing the hypothesis that synaptic inputs to motoneurons are affected in ALS mice at early postnatal stages, and assessing the potential therapeutic effects of modifications in the mTOR pathway on slowing or halting the progression of ALS.

Project: Characterization of Three Novel ALS Genes

Investigator: John Landers, Ph.D.

University of Massachusetts Medical School, United States

Amyotrophic lateral sclerosis (ALS) is an adult-onset neurodegenerative disease caused by the selective loss of motor neurons. It is ultimately lethal with a typical patient survival of two to five years. Although most ALS cases are sporadic in nature, ~10% are familial.

In recent years, the identification of genetic causes of familial amyotrophic lateral sclerosis (FALS) has greatly contributed to understanding the pathogenesis of ALS in general. Unfortunately,



only one-third of the underlying genetic causes of FALS have been explained to date. Through our efforts, we have identified novel genes, which contribute to the development and progression of ALS.

Using a candidate gene approach, we have discovered that mutations in the Paraoxonase gene cluster contribute to familial and, to a lesser extent, sporadic ALS. Through a whole genome association study, we have identified a variant in the Kinesin-Associated Protein 3 (KIFAP3) gene that acts as a modifier of survival in sporadic ALS.

Lastly, we are focused on the identification of a gene causal for FALS within a genomic region determined by linkage analysis. This project is focused on understanding how each of these contributes to ALS and other neurodegenerative diseases. Understanding how these genes influence the process of neurodegeneration will aid in the development of novel strategies to interfere or prevent this process.

Project: Regulation of Alternative Splicing by TDP43

Investigator: Tom Maniatis, Ph.D. (and Brad Friedman, Ph.D.)
College of Physicians and Surgeons, Columbia University,
United States

TDP43 is an RNA processing factor that is mislocalized and abnormally processed in neurons and glia of a majority of SOD1-unrelated ALS patients. Rare mutations in TDP43 segregate with the disease in certain ALS families, suggesting that it plays a causative role. However, neither the pathway by which TDP43 abnormalities can lead to neuron death nor the normal function of TDP43 is understood. Two new genomic technologies will be used to study its activity in mouse embryonic spinal cord cultures.

First, RNA-Seq will be performed to analyze RNA from TDP43-depleted and control embryonic spinal cord cultures in order to detect TDP43-regulated RNA processing. This technique can uncover differential nucleic acid processing at all levels – transcription, splicing, poly-adenylation and RNA editing. In addition, this method can be used to detect DNA mutations.

Second, CLIP-Seq will be used to identify the RNA binding sites of TDP43 in the same cells. CLIP-Seq is a method by which total cellular RNA directly bound to a specific protein can be purified and massively sequenced. Analysis of the binding sites determined by CLIP-Seq and the regulated exons determined by

RNA-Seq will provide important insights into the role of TDP43 in RNA processing. This comparison may also identify genes or pathways altered by the loss of function of TDP43 that lead to motor neuron death.

If successful, the proposed studies will shed light on a previously unexplored aspect of the ALS disease mechanisms, and in the process identify novel therapeutic strategies.

Project: Blockade of Integrin-mediated Peripheral Nervous System inflammation in ALS.

Investigator: Tom Maniatis, Ph.D. (and Isaac Chiu, Ph.D.)
College of Physicians and Surgeons, Columbia University,
United States

Amyotrophic lateral sclerosis (ALS) is a fatal, neuro-degenerative disease characterized by the selective death of motor neurons in the brain and spinal cord. Denervation of the neuromuscular junction and pathology at the axon is an early and significant feature of ALS disease progression. However, the mechanisms governing motor axon degeneration are not well defined.

We have characterized the prominent infiltration of activated macrophages within peripheral nerves and axons of transgenic mouse models of ALS. These cells accumulated over time within ventral roots, sciatic nerves and muscles of SOD1G37R and SOD1G93A transgenic mice, but not in SOD1WT or non-transgenic controls.

We hypothesize that interactions between peripheral macrophages and distal axons of motor neurons may aberrantly alter neuronal function and survival. During inflammation, immune cells utilize a specific set of surface integrin receptors for recruitment into affected tissues. Antibody mediated blockade of integrins has been utilized in acute and chronic disease models to inhibit macrophage and lymphocyte influx into inflamed tissues in vivo.

In this project, we propose to use anti-integrin antibodies to chronically inhibit macrophage entry into the peripheral nervous system of SOD1G93A transgenic mice during motor neuron degeneration. These experiments will potentially lead to insights on the molecular mechanisms of macrophage entry and activation, immune-axonal interactions, and direct therapeutic applications in ALS.

Grant Summaries

Project: Modulating Disease Progression in ALS Mice Using Conditional RNAi

Investigator: Michele M. Maxwell, Ph.D.
MassGeneral Institute for Neurodegenerative Disease,
Massachusetts General Hospital and Harvard Medical School,
United States

The primary goals of this research project are to develop and test a flexible system for regulatable RNAi-mediated gene silencing in vivo and to use this system to evaluate the therapeutic potential of gene knockdown approaches for the treatment of ALS. For dominantly inherited neurodegenerative diseases such as mutant SOD1-mediated familial ALS, the disease-causing mutant protein itself is an important therapeutic target. For this reason, efforts aimed at reducing the cellular load of mutant proteins via gene knockdown have become a major focus of therapy development for ALS. This approach has shown considerable promise, and previous studies have shown that RNAi-based silencing of mutant SOD1, if achieved early enough in life and in a widespread manner, can ameliorate disease in ALS mice. In most cases, however, treatments were administered to young animals long before they exhibit symptoms of disease, and these studies could not address whether knockdown of mutant SOD1 could be beneficial at later stages of disease.

In order to evaluate mutant SOD1 as a therapeutic target in both pre- and early-symptomatic stages of disease, we devised a flexible transgenic expression system for RNAi that permits ubiquitous, but temporally regulatable, knockdown of SOD1. When introduced into existing ALS mice via genetic crosses, these regulatable RNAi transgenes permit knockdown of mutant SOD1 upon administration of a small molecule inducer. This conditional system for RNAi may aid in identifying an appropriate window for treatments designed to reduce mutant SOD1 levels in familial ALS. In addition, the transgenic expression system was designed to be readily adaptable for silencing of any desired target gene in any mouse model of motor neuron degeneration. This system will therefore provide a valuable resource for future studies designed to identify or confirm additional putative therapeutic targets for ALS.

Project: Misregulation of TDP43 and FUS mRNA in ALS

Investigator: Melissa J. Moore, Ph.D.
HHMI/Univ. of Massachusetts Medical School, United States

Misense mutations in the RNA/DNA binding proteins TDP-43 and FUS/TLS have been shown to be causative of familial amy-

trophic lateral sclerosis (FALS). The mutant proteins accumulate in the cytoplasm and exhibit decreased abundance in the nucleus of affected neurons. Similar cytoplasmic accumulation and nuclear clearance of TDP-43 and FUS/TLS is also observed in sporadic ALS (SALS). Thus ALS could result in part from a loss of nuclear function. We are investigating the possibility that homeostatic levels of both TDP-43 and FUS/TLS are maintained by a negative feedback loop in which alternative splicing of the mRNAs encoding these proteins is linked to nonsense mediated mRNA decay (AS-NMD). NMD is a translation-dependent degradation pathway that eliminates mRNAs whose open reading frames terminate upstream of one or more exon-exon junctions (the sites where introns were removed). Many RNA binding proteins keep their expression in check by targeting their own mRNAs to NMD via alternative splicing when intracellular protein concentrations rise. Since such a feedback loop critically depends on protein function in the nucleus, cytoplasmic sequestration of TDP-43 and FUS/TLS could lead to a self-perpetuating cascade of protein overexpression that may be a causative event for disease.

To date, we have shown that TDP-43 mRNA contains introns in its 3'-UTR and is subject to NMD. We have also demonstrated that a significant fraction of FUS/TLS transcripts are degraded in a translation-dependent manner. We are currently investigating the effects of TDP-43 or FUS/TLS transgene overexpression on endogenous protein levels, using both wild type proteins and ALS-causative mutations. We hope that these experiments will prove illuminative as to the effects of ALS-causing mutations on TDP-43 and FUS/TLS protein levels.

Project: FUS/TLS in FALS by Studies in a Model Organism and Yeast modeling of FUS ALS

Investigator: Gregory Petsko, Ph.D.
Brandeis University, United States

The aim of this project was to develop a model in a simple, genetically tractable organism for the role of the human gene FUS/TLS in familial amyotrophic lateral sclerosis (FALS). Mutations in FUS/TLS have been shown to cause inheritable ALS, but the connection with the cell death of spinal motor neurons is not understood.

In humans, the disease is associated with mislocalization of FUS/TLS from the nucleus to the cytoplasm, combined with the formation of discrete clumps of aggregated protein. We therefore attempted to create a model that recapitulated these phenotypes

plus cell death. We chose for our model organism budding yeast because it has most of the cellular machinery found in complex organisms and has been used successfully to model Parkinson's and Huntington's diseases in the past.

We over expressed both wild-type and mutant human FUS/TLS in yeast and found that high levels of expression of either caused the protein to mislocalize from the nucleus to the cytoplasm and to form punctuate aggregates; over expression also caused cell death. We systematically deleted various parts of the FUS/TLS gene and found that the reason both wild-type and mutant protein caused these phenotypes was that the nuclear localization signal contained in the C-terminal part of the protein is not effective in yeast, so high levels of expression of even the wild-type form cannot be retained in the nucleus. This observation suggested that the disease-causing variants in humans act by disrupting this signal, and we were able to show that this is indeed the mechanism.

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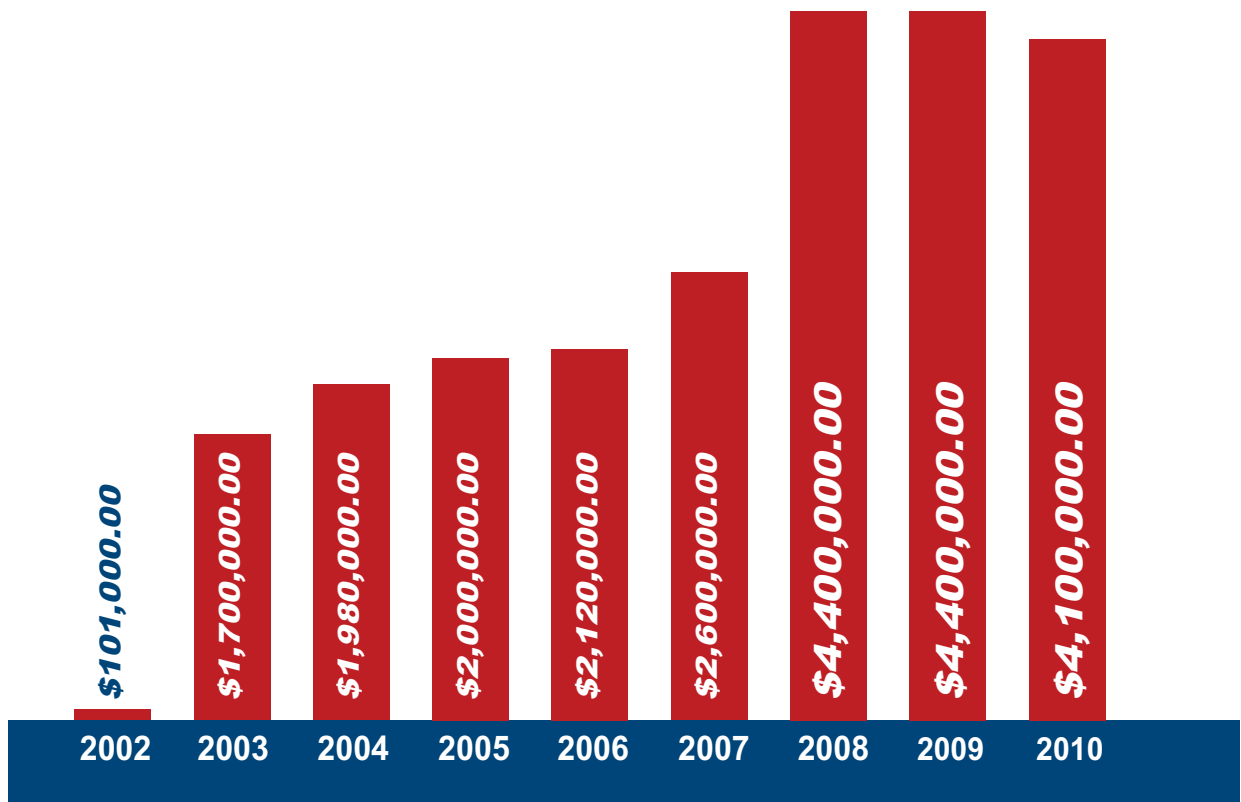
The ALS Therapy Alliance has also co-sponsored projects with Project ALS, the Angel Fund, the ALS Association and the Northeast ALS Consortium.



Hope for the Future

By stimulating new ALS research projects, the ALS Therapy Alliance partnership with CVS/pharmacy has provided the ALS community with renewed hope that meaningful ALS treatments will be discovered.

How this fundraising campaign has grown over the years:





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