RESEARCH ALS TODAY

THE ALS ASSOCIATION | VOLUME 2 | FALL 2007

INSIDE

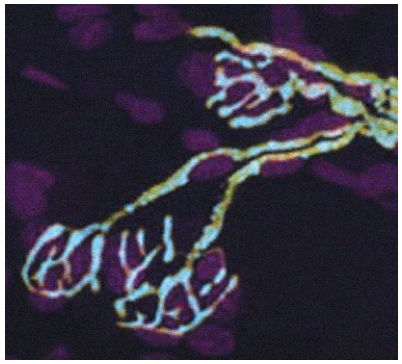
ALS Research: Model Systems Drive Progress

With the discovery more than ten years ago that mutations in the antioxidant enzyme, copper-zinc superoxide dismutase (SOD1) produce ALS in some inherited cases, construction of transgenic rodent models enabled researchers to begin to ask about disease mechanism. The transgenic animals also provide a test system for potential therapeutics. Over the succeeding decade, ALS researchers were able to show a modest effect in the mutant SOD1 models of several candidate treatments. The most dramatic effects so far have been achieved by genetic alterations rather than small molecules.

The transgenic SOD1 rat and mouse are important tools. The rat is providing a larger format for tests of gene and stem cell therapies as well as RNAi, all promising routes towards effective treatment that requires delicate and accurate targeting within the spinal cord. Important caveats to using these rodent models are that tests should be properly blinded and controlled, and that genetic drift and different disease susceptibility by sex be taken into account.

New transgenic models of the disease are being designed. One focus is on the angiogenin gene, with variants that appear to associate with ALS in some populations. A transgenic worm is serving as a screen for therapeutics, and a zebrafish model is being developed. This year, the team of Jeff Lichtman, M.D., Ph.D., at Harvard collaborating with The Jackson Laboratories, published on a mouse with mitochondria tagged with a fluorescent probe. These MitoMice will help show the exact roles of these cellular organelles implicated in ALS. The mice are available from Jackson Laboratories (MitoMouse (stock number 6614 (MitoC) or 6617 (MitoS) see Resources, pg. 2). Robert Burghes, Ph.D., has collaborated with this effort and will be helping to see how mitochondria are affected in mutant SOD1 mice, by crossing these with MitoMice, through funding by The Alan L. Phillips Discovery Grant Award, made possible through support from Morton and Malvina Charlestein.

Through its TREAT ALS initiative, The ALS Association has forged collaborations with the biotech industry to screen for new therapeutics using motor neurons derived from stem cells (see Spring 07 issue of Research ALS Today). In addition, efforts are underway to use nuclear reprogramming with the goal of a pluripotent cell operating with the genetic instructions obtained from cells of ALS patients. This should prove to be a powerful model system to discover potential new therapeutics (see Stem Cell article, pg. 2).



Mitochondria in nerve endings on muscle glow blue in transgenic mice. Cell nuclei are purple.
–Image courtesy Thomas Misgeld, Ph.D.

Di Gorgio FP, et al., 2007 Nature Neurosci. 10:608-614.
Schmymick JC, et al., 2007 Lancet Neurol. 6:322-328.
Misgeld T, et al., 2007 Nature Methods 4:559-561.

FTD and ALS Conference: Challenges for Consensus

The second international conference on frontotemporal dementia and ALS convened in London, Ontario, Canada, June 10 through 13, 2007 cosponsored by The ALS Association and the ALS Society of Canada. The conference was attended by clinicians, neuropsychologists and pathologists, each bringing their perspectives to the table. A focus was the newly identified protein, TDP-43, apparently common to both ALS and FTD (see guest article, pg. 3). Presenters also discussed newly identified genes that could provide clues. Through the fruitful discussions that took place around the formal presentations, experts are developing guidelines that will help clinicians and caregivers meet the challenges posed by this complex disorder.

Murphy J, et al., 2007 Arch Neurol. 64:330-334
Valdmanis P, et al., 2007 Arch Neurol. 64:240-245
Strong MJ, et al., 2007 Mol Cell Neurosci. 35:320-327

ALS Association™

Investigators Embark on Exciting New Avenues of Research

The landscape of ALS research is changing as recent discoveries and improved technologies open new areas for exploration. This edition features TAR-DNA-binding protein 43 (TDP-43) identified in association with ubiquitinated inclusions in disease tissue. Whether this protein plays an integral role in familial and/or sporadic ALS will become evident as we begin to understand more about the protein's function. Efforts continue to identify new genes linked to familial ALS and in particular a region on chromosome 9 associated with both ALS and frontotemporal dementia (FTD). Although the role of mutant Cu/Zn superoxide dismutase 1 (SOD1) remains unclear and accounts for only 2 % of ALS, investigators recently published data to suggest that normal SOD1 can become altered and may be associated with sporadic ALS.

Lucie Bruijn, Ph.D.
Science Director and Vice President
The ALS Association

As new genes emerge from genome wide association studies in sporadic ALS patients, the importance of collaboration and data sharing becomes paramount so that findings can be validated and the field does not focus solely on avenues that may initially appear of importance but cannot be replicated and bear no relevance for the disease. The ALS Association is working with several groups to compare data arising from these studies.

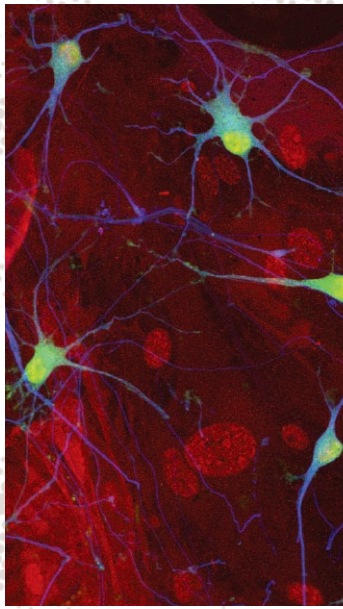
With increasing focus on translational studies, important basic research must continue in parallel to provide the necessary tools and targets for down stream drug development. The ALS Association encourages such efforts through our international grant programs and requires researchers to make resources and data available so that more rapid advances are made through participation of the broader community.

Congratulations to four new Milton Safenowitz Postdoctoral Fellows who embark on important studies to further ALS research and bring new ideas to the field.

–Lucie Bruijn, Ph.D.

Promise of Stem Cell Research for ALS Therapies

Stem cell research for ALS encompasses not only applications for regenerative medicine but also provides a powerful tool for drug development.



Traditional cell-based assays for ALS drug discovery rely on surrogates for motor neurons such as immortalized or tumor cell lines. Primary cultures of motor neurons take time and have limited expansion capacity, hampering high-throughput screening. The capacity of embryonic stem cells to self-renew and differentiate into motor neurons make these a powerful source of cellular models for drug development, from target discovery, target validation to lead optimization. The identification of genetic and molecular factors guiding development of motor neurons has helped provide assays using motor neurons derived from stem cells.

Obtaining adequate numbers of motor neurons is a key factor for cell replacement therapies and for drug development. Researchers are creating models from both mouse and human embryonic stem cells. Motor neurons can be obtained in large quantities from embryonic stem cells obtained from mice without the use of feeder layers. These cells are already in use for high-throughput screening (search www.alsa.org for Lee Rubin). Motor neurons can be derived from human embryonic stem cells[5,7], but their slow expansion rate impedes high-throughput screening.

Other challenges relate to the pathophysiological features of ALS disease. For

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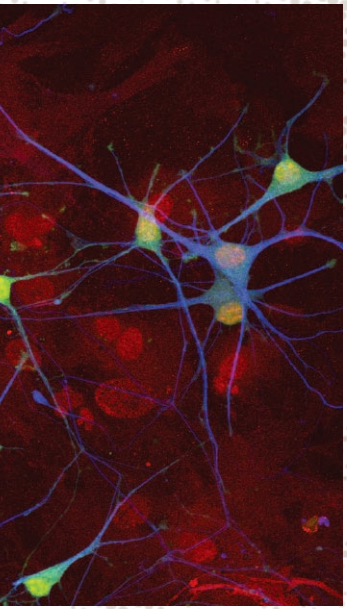
RESOURCES

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

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

Stem Cell Research cont.



In vitro model of human motor neurons derived from embryonic stem cells co-cultured with glia. Motor neurons expressing H9-GFP (in green) are labeled with the neuronal marker Tuj1 (in blue). Glia is labeled with the anti S-100 antibody (in red).

–Image courtesy of Monica Carrasco, Ph.D., a Milton Safenowitz Post-Doctoral Fellow for ALS research, Maniatis Lab, Harvard University, Cambridge, MA.

Continued from Page 2

example, efforts to obtain homogenous motor neuron cultures derived from stem cells for high-throughput screening assays is at odds with the discovery that glial cells surrounding motor neurons are critical for supporting motor neuron health[1,2,3,6]. Nevertheless, with rapid progress in science and technology, assays are emerging that model ALS more closely.

A recent study[4] suggests the possibility of a customized ALS cell-based assay using somatic cell nuclear transfer. The researchers show in the mouse that fertilized eggs containing an extra set of chromosomes, normally discarded by *in vitro* fertilization clinics, can be used as recipients for chromosome transfer. If applicable to humans, this approach would overcome technical and ethical issues in the effort to obtain a sufficient quantity of oocytes from female donors. Discarded fertilized eggs would be suitable recipient cells to produce tailored human embryonic stem cells containing the genetic materials of patients with familial or sporadic forms of ALS. The hope is that embryonic stem cells will differentiate into sick and dying motor neurons reproducing in a faster manner what is happening during the life-time of an ALS patient, enabling accelerated drug screening.

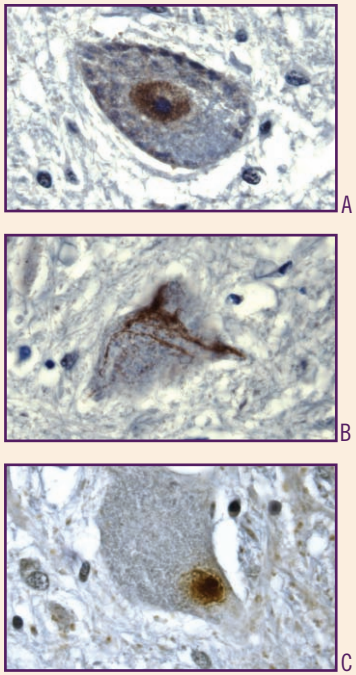
1 Boillée S, et al., 2006 Science 312:1389-1392.
2 Clement AM, et al., 2003 Science 302:113-117.
3 Di Gorgio FP, et al., 2007 Nature Neurosci 10:608-614.
4 Egli D., et al., 2007 Nature 447:679-685.
5 Li XJ, et al., 2005 Nature Biotechnology 23:215-221.
6 Nagai M, et al., 2007 Nature Neurosci 10:615-622.
7 Shin S, et al., 2005 Stem Cells Dev 14:266-269.
8 Wichterle H, et al., 2002 Cell 110:385-397.

TO KEEP CURRENT with the ALS field, read the monthly journal news reports at www.alsa.org under the research tab.

New Disease Protein Found in ALS

Guest article by Janice Robertson, Ph.D.

The pathological hallmark of ALS is the presence of ubiquitinated inclusions within the cytoplasm of affected motor neurons, comprising of skein-like inclusions, round inclusions and Lewy body-like inclusions. Ubiquitinated inclusions are also present within a subtype of frontotemporal lobar degeneration (FTLD-U) in which there is known to be a clinical overlap with ALS4. In a recent breakthrough, a major component of the ubiquitinated inclusions in ALS and FTLD-U was identified as the TAR-DNA-binding protein 43 (TDP-43) [2, 6]. This finding lent further support that ALS and FTLD-U represent spectrums of the same underlying disorder. TDP-43 is a 43 kDa protein normally present within the nucleus, where it functions as a transcriptional repressor or as a regulator of alternative splicing [3]. However, in ALS and FTLD-U, TDP-43 is mislocalized from the nucleus and is associated with ubiquitinated inclusions within the cytoplasm of affected neurons[6]. Whether there is a movement of TDP-43 from the nucleus to the cytoplasm, or if TDP-43 synthesized in the cytoplasm is blocked from entering the nucleus is unknown. Using biochemical fractionation of disease tissue, a pathological signature of TDP-43 was identified, comprising of an abnormally phosphorylated species of 45 kDa that resolves to the correct molecular weight of 43 kDa upon dephosphorylation; species of ~25 kDa that correspond to a C-terminal fragment(s) of TDP-43 that resolve to 4 distinct bands of 23-27 kDa after dephosphorylation; and a higher molecular weight smear that represents ubiquitinated TDP-43 [6]. This pathological signature for TDP-43 occurred only in diseased tissue and not in unaffected areas. There may not be absolute specificity for TDP-43 abnormalities in ALS and FTLD-U, as pathological inclusions labeled with TDP-43 antibodies have recently been described in Alzheimer's disease and Lewy body related diseases [1, 5]. Nevertheless, the identification of TDP-43 as a disease-relevant protein in ALS has opened new avenues of research that have until recently focused almost exclusively on SOD1. It is conceivable that abnormalities of TDP-43 actively contribute to the neurodegenerative cascade, perhaps acting through a loss of normal TDP-43 function in the nucleus or a gain of cytotoxic function in the cytoplasm, or perhaps a combination of both. Whatever the outcome, the identification of TDP-43 has provided great excitement, and this can only mean good things for ALS research.



TDP-43 antibody labeling of normal and ALS motor neurons. Note localization of TDP-43 to the nucleus in healthy motor neurons (A) and the association with ubiquitinated skein-like inclusions (B) and round inclusions (C) in diseased motor neurons.

–Images courtesy Janice Robertson PhD and Teresa Sanelli PhD

1 Amador-Ortiz C, et al., 2007 Ann Neurol 61:435-445.
2 Arai T, et al., 2006 Biochem Biophys Res Commun351:602-611.
3 Buratti E, et al., 2001 Embo J 20:1774-1784.
4 Lomen-Hoerth C, et al., 2002 Neurology 59:1077-1079.
5 Nakashima-Yasuda H, et al., 2007 Acta Neuropathol (Berl). 114:221-229.
6 Neumann M, et al., 2006 Science 314:130-133.

Investigator-Initiated Research Grants

2 Calls for Abstracts Per Year: In June (Autumn) and December (Spring)

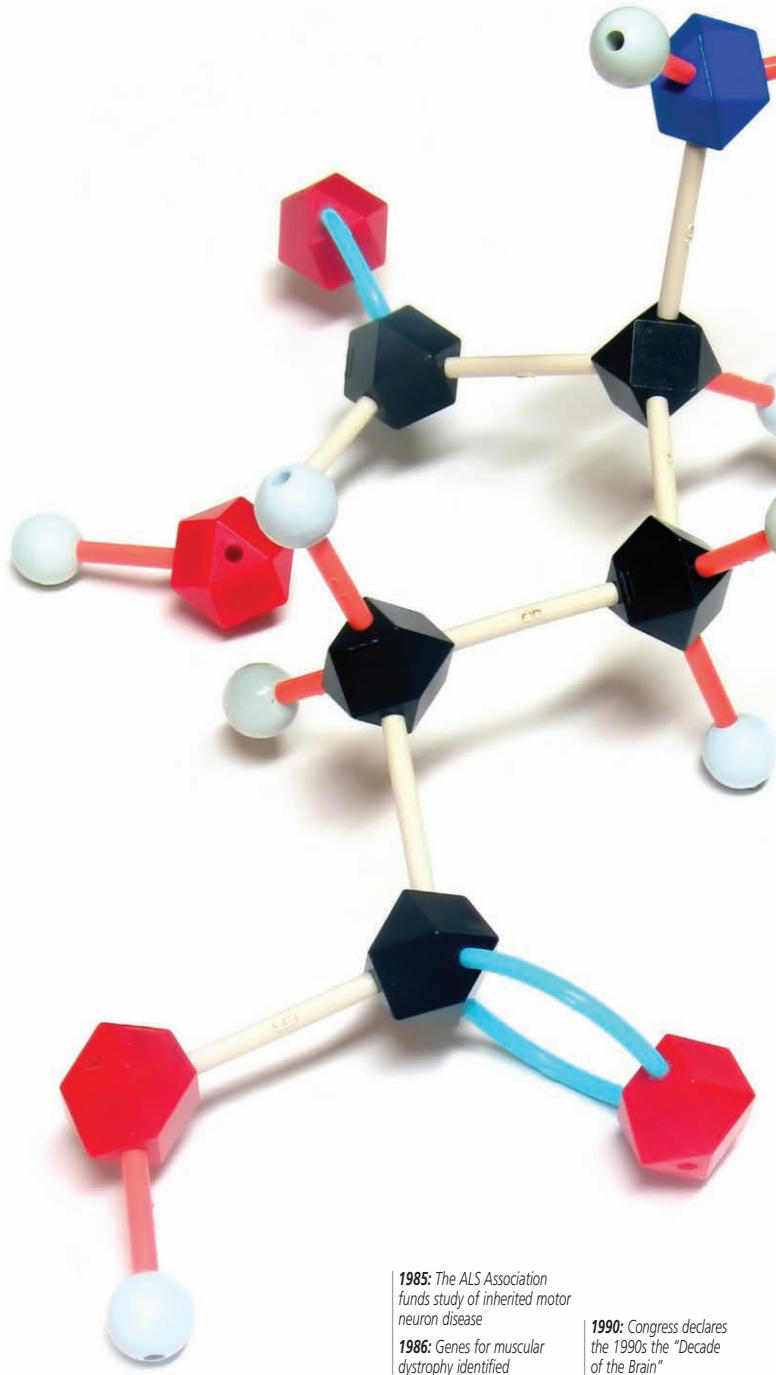
The ALS Association's INVESTIGATOR-INITIATED RESEARCH GRANT PROGRAM supports innovative research of high scientific merit and ALS in areas of ***stem cell research, disease mechanism, therapeutic approaches, model systems and genetics.*** *The ALS Association encourages international applications.*

Multi-year Grants are offered twice a year *to ESTABLISHED ALS INVESTIGATORS. The ALS Association will support research that is projected for periods of one (1) up to three (3) years. Funding is committed for one (1) year only, with noncompetitive renewals conditioned upon receipt of satisfactory interim progress reports. Awards will be in an amount of* ***$80,000 per year****.*

Starter Grants are offered twice a year *for NEW INVESTIGATORS ENTERING THE FIELD OF ALS, proposing innovative and novel projects likely to provide important results relevant to ALS research. Alternatively, they can be PILOT STUDIES BY ESTABLISHED ALS INVESTIGATORS or STUDIES BY SENIOR POST-DOCTORAL FELLOWS IN THE ALS FIELD. These applications do not require strong preliminary data but must emphasize novelty, feasibility, innovation and relevance to ALS. The maximum amount awarded is* ***$40,000 for 1 year****.*

The Milton-Safenowitz Post-Doctoral Fellowship for ALS Research is awarded annually *each spring. The call for abstracts is part of the Investigator Initiated Research call announced each December. The award is* ***$40,000 annually for 2 years****. Applicants who are eligible are new post-doctoral fellows or those that have been a fellow for no more than one year.*

CONTACT *For grant information or to be added to our mailing list, please contact researchgrants@alsa-national.org.*



timeline

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

1869: *French neurologist Jean-Martin Charcot identifies ALS*

50s: *DNA structure solved*

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

1968: *SOD1 enzyme identified*

70s: *Programmed cell death in motor neurons demonstrated*

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

1986: *Genes for muscular dystrophy identified*

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

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

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

The Milton Safenowitz Post-Doctoral Fellowship for ALS Research

Four young investigators funded by The Milton Safenowitz Post-Doctoral Fellowship for ALS Research are engaged in innovative projects to accelerate progress in the field. The ALS Association is especially committed to bringing new concepts and methods into ALS research and young scientists play an important role in this process. Funding is by the generosity of the Safenowitz family through the Greater New York Chapter of The ALS Association, in memory of Milton, who died in 1998 of the disease.

Mitochondria and ALS

Sandrine Da Cruz, Ph.D., with Don Cleveland, Ph.D., University of California, San Diego, is investigating the role of mitochondria in the disease. She will use mice that over express or lack genes for mitochondrial function. Da Cruz will breed each of these types of mice to two different transgenic mice having a different change to the SOD1 protein responsible for some inherited cases of ALS. These mice should be able to show if enhancing mitochondrial function will change motor neuron loss. Da Cruz will also see whether mitochondria are compromised in motor neurons or in muscle.

Understanding the mechanism underlying the premature degeneration and death of neurons during ALS remains critical. I really hope that determining whether mitochondria, which are the "power-house" of the cell, contribute to the pathogenesis will provide potential directions for therapies.

–Sandrine Da Cruz, Ph.D., Ludwig Institute for Cancer Research at UCSD, San Diego, CA

ALS Biomarkers

Gurudutt Pendyala, Ph.D., working with Howard Fox, M.D., Ph.D., at The Scripps Research Institute, La Jolla, California, is building on prior success with HIV biomarkers. He will use mass spectroscopy to uncover metabolic products in cerebrospinal fluid changing specifically with ALS that could reflect altered physiology. A reliable and reproducible set of metabolic biomarkers would allow faster diagnosis, streamlined clinical trials, and a window into the disease process that could provide therapeutic targets. The team plans to compare findings in mice and in normal humans to the SOD1 mutant mouse.

Analyzing the metabolome of the cerebrospinal fluid holds great promise for biomarker identification for ALS.

–Gurudutt Pendyala, Ph.D., The Scripps Research Institute, La Jolla, CA

Stem Cells Steered to Cortico-Spinal Motor Neurons

Caroline Rouaux, Ph.D., working with Paola Arlotta, Ph.D., at Massachusetts General Hospital, will build on progress achieved under the direction of Jeffrey Macklis, Ph.D., at Harvard. These investigators have found some of the molecular control signals that guide stem cells in the developing brain to send their axons down the spinal cord, targeting the lower motor neurons that contract muscles. Rouaux will use genetic engineering to confirm if these signal molecules indeed direct certain stem cells to become the cortico-spinal motor neurons. The information should give strategies to produce upper motor neurons to replace those dying in ALS.

ALS is unfortunately still diagnosed very late during disease progression, at a stage when the majority of the neurons that are vulnerable have already degenerated. I believe that parallel strategies aimed at replacing lost motor neurons appear extremely promising as they may ultimately result in recovery. This complementary research direction is challenging but has great potential if we can progressively understand the peculiar molecular mechanisms that specify development of corticospinal and spinal motor neurons.

–Caroline Rouaux, Ph.D., Massachusetts General Hospital and Harvard Medical School, MA

Cellular Defense: Nuclear Factor-E2 Related Factor 2 (Nrf2)

Marcelo Vargas, Ph.D., working with Jeffrey Johnson, Ph.D., at the University of Wisconsin, Madison, will examine the role of the Nrf2 defense system present in the glial cells that surround the motor neurons. Astrocytes buffer the motor neurons from products of normal cell chemistry that are toxic in excess. A protein, Nrf2 initiates a defense system in astrocytes. With mice that produce excess Nrf2 in astrocytes, Vargas will see if this defense system might be reinforced for ALS, by crossing Nrf2 over-expressing mice with those making the mutant SOD1 protein. This should define whether the Nrf2 system is indeed a therapeutic avenue into the disease process.

Compelling evidence shows that different cell types are involved in the disease; the most challenging issue will be whether onset and progression are determined by the same or different factors and how the different cell types involved contribute to each stage.

–Marcelo Vargas, Ph.D., University of Wisconsin, WI

1991
- Researchers link familial ALS to chromosome 21

1992
- The ALS Association begins workshops
- Glutamate transporter shown to be defective in ALS
- Growth factor BDNF found to increase survival of motor neurons

1993
- SOD1 gene mutation (chromosone 21) discovered in familial ALS
- Trials using glutamate blocker riluzole begin

1994
- Animal studies combining CNTF and BDNF demonstrate decreased motor neuron loss
- GDNF rescues degenerating motor neurons during development in an in vitro experiment
- Transgenic animals carrying mutated human SOD1 gene exhibit ALS-like symptoms and pathology

1995
- FDA approves riluzole

1996
- Toxic properties of the SOD1 enzyme discovered and linked to familial ALS

1997

active Research Projects cont.

Continued from Back Cover

GENETICS OF ALS

Al-Chalabi, PhD, FRCP, Ammar / *Institute of Psychiatry, King's College, London, UK*
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Methner, MD, Axel / *University Hospital, Dusseldorf, GERMANY*
Niu PhD, Li / *State University of New York (SUNY), Albany, NY*
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Rothstein, MD, PhD, Jeffrey / *Johns Hopkins University, Baltimore, MD*
Schubert, PhD, Dave / *Salk Institute, La Jolla, CA*
Van Broeckhoven, PhD, DSc, Christine / *University of Antwerp, NETHERLANDS*

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Carroll, PhD, Michael / *The CBR Institute for Biomedical Research, Inc., Boston, MA*
Cunningham, PhD, Timothy / *Drexel University, Philadelphia, PA*
Enikolopov, PhD, Grigori / *Cold Spring Harbor Laboratory, NY*
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Heiman-Patterson, MD, Terry / *Drexel University, Philadelphia, PA*
Moeller, PhD, Thomas / *University of Washington, Seattle, WA*
Prather, PhD, Paul / *University of Arkansas, Little Rock, AR*

LABORATORY MODELS OF ALS

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Silverman, PhD, Richard / *Northwestern University, Chicago,IL*

Continued on Page 7

timeline cont.

1998

RNAi discovered by Craig Mello and Andrew Fire

1999

2000

The ALS Association co-sponsors workshop on high-throughput drug screening with NINDS

NINDS issues first ever RFA (request for applications) specifically for ALS research

2001

A transgenic rat is designed; efforts start on fly model

Attention turns to support cells of nerve tissue to find role in ALS

Inflammation and programmed cell death gather research interest

ALS2 gene (alsin protein) linked to juvenile ALS

The ALS Association/NINDS collaborative effort begins screening drugs

2002

The ALS Association holds scientific workshop on "Environmental Factors and Genetic Susceptibility"

Aggressive search for new ALS genes funded by The ALS Association

Scientists complete map of mouse genome

Agency of Toxic Substances and Disease Registries awards 5 grants focused on ALS

Department of Defense approves funding for ALS-specific research

2003

Study shows surrounding support cells play key role in ALS

Study shows that human embryonic stem cells can be stimulated to produce motor neurons

Gulf War study shows that vets deployed to Persian Gulf in 1991 developed ALS at twice the rate of those not deployed there

IGF-1 gene therapy study proves beneficial in mice with ALS

VEGF gene abnormalities shown to be potential factor in ALS

The ALS Association collaborates with U.S. Department of Veterans Affairs to enroll all vets with ALS in registry

Early tests of ceftriaxone appear to increase survival in mice with ALS

Combination of creatine and minocycline prove more effective together in mouse model than either drug alone

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MITOCHONDRIA
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Robertson, PhD, Janice / *University of Toronto, Ontario, CANADA*
Roos, MD, Raymond / *University of Chicago, IL*
Thomas, PhD, Philip / *University of Texas Southwestern Medical Center, Dallas, TX*
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Urushitani, MD, PhD, Makoto / *Laval University, Quebec, CANADA*
Walter, PhD, Peter / *University of California, San Francisco, CA*
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grants

2004
Study implicates smoking as likely risk factor in sporadic ALS
Study releases evidence that mitochondrial malfunction may play an important role in ALS

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

2005
Ceftriaxone increases levels of the glutamate transporter GLT1 in a mouse model of ALS
RNAi treatment to silence the mutant SOD1 gene yields increased survival in mice
First international workshop on frontotemporal dementia discusses link to ALS
Stem cells engineered to make GDNF survive when transplanted into rats modeling ALS
Publication identifies potential biomarkers for ALS
Early data suggests that mutant SOD1 may be secreted by and may activate microglia

*Launch of TREAT ALS initiative (**T**ranslational **Re**search **A**dvancing **T**herapies for ALS) to accelerate clinical trials in ALS*
VEGF increases survival in a rat model of ALS while improving motor performance

2006
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

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

2007
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

First genome screening data published based on NINDS ALS Repository

active

Research Projects of The ALS Association Fall 2007

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