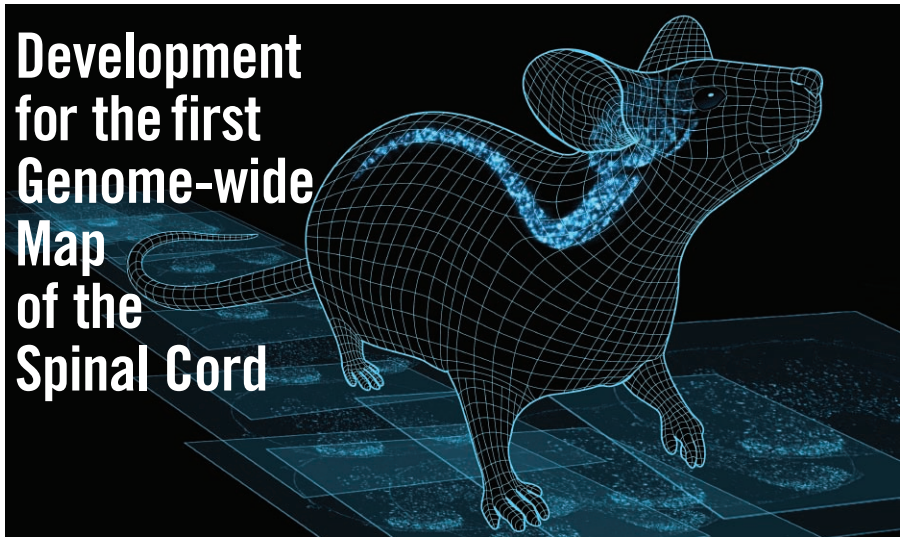
RESEARCH ALS TODAY

THE ALS ASSOCIATION | VOLUME 4 | FALL 2008

INSIDE



Source:
Allen Institute for Brain Science
www.brain-map.org

The ALS Association is supporting the design and development of the first genome wide spinal cord atlas. The initial data set of 2000 genes can be accessed immediately at www.brain-map.org. When completed the Allen Spinal Cord Atlas will detail approximately 18,000 genes in all segments of the cord including data from juvenile (postnatal day four) and adult (postnatal day fifty six) developmental stages. Access to this information will be invaluable for scientists focused on understanding disease mechanisms for ALS. The initial phase is to develop an atlas from normal mouse spinal cord tissue (C57BL/6J male) so that this could be used as a reference to compare tissue from mouse models of ALS and spinal cord injury. These studies will provide the exact localization of known and unknown genes and may give insight into changes in expression levels of various genes providing clues to pathways involved in the disease process.

The study led by Ralph Puchalski, Ph.D. at the Allen Institute was funded by a consortium of public, private and foundation funds. Scientists in the ALS and the spinal cord injury field established an advisory team and worked together to develop the most appropriate design to provide researchers with the most meaningful data. The project will be completed within 12 months, and all data will be made publicly available. Gene expression is mapped at cellular resolution by a technique called RNA in situ hybridization (ISH), a semi-quantitative measure of gene expression. For more details visit http://mousespinal.brain-map.org/spinal/common/content/Overview.

ALS Association™
TREAT ALS
Translational Research Advancing Therapy for ALS

Advances in ALS Genetics

by Ammar Al-Chalabi, Ph.D., F.R.C.P.

Gene-hunting technology now allows us to find ALS genes faster than ever before. One of the first genes identified as causing any disease was copper/zinc superoxide dismutase, SOD1, identified in 1993 using a technique that was new at the time: linkage. SOD1 mutations are now thought to be responsible for between 2 and 7% of ALS and about 20% of familial ALS. About 12 more ALS gene addresses have been identified and four new ALS genes found. Because linkage works best when there are at least three generations of a family to study, the ALS genes (apart from SOD1) discovered using this technique have been for young onset or slowly progressive ALS, but in the last year a second gene for the more common form of ALS has been found. The discovery of this gene, TDP43, is exciting because although our understanding of ALS has improved since the finding of SOD1 mutations, we still do not know how they cause disease. A second window on this process may make things clearer. TDP43 belongs to a class of proteins involved in RNA processing. This is a step the cell machinery takes in converting a gene sequence into protein. As will be seen shortly, although it is a basic cell function, it seems particularly important to motor neurons.

Continued on Page 2

"Replication by independent researchers or evidence from other scientific techniques can be used to add confidence to any genetic association with sporadic ALS."

ALS Research Brings New Insights

The last few months have been an exciting time for ALS research. Researchers are generating new model systems for ALS with the recent knowledge that mutations in TDP43 are linked to the disease; new genes for ALS are on the horizon, the first stem cells were generated from ALS patients, and new clinical trials are underway. With all this excitement, the question remains: why are there still no meaningful therapies for ALS?

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

ALS is a complex disorder. No two patients manifest the disease in exactly the same way. For this reason, it is possible that some people with ALS respond differently to treatments. Early diagnosis remains challenging and is essential for therapies to be effective in the disease. There are likely to be many different causes for the disease; the best understood at this time are the genetic causes for which the gene mutations are known. As it is not just a genetic disorder and likely an individual's predisposition in combination with environmental exposures, it is a challenging puzzle.

Despite this, scientists are committed to finding the answers, and new insights are continually unfolding. There is increased interest from the industry sector, critical for the development of therapies. There is also increased awareness of the disease through media opportunities, advocacy efforts and the dedicated ALS community. For all these reasons and the increasing number of collaborative efforts, I am confident that we are going to move forward in ALS research to find the meaningful therapies so desperately needed in this disease.

- Lucie Bruijn, Ph.D.

ALS Genetics cont.

Continued from Page 1

Most people with ALS do not have a family history, but our specific genetic make-up can make us more likely to develop ALS in certain circumstances. Because this takes a combination of multiple mildly deleterious genetic variations, environmental exposures and probably a random element too, the susceptibility is not transmitted to the next generation. The result is sporadic ALS. Because the genes are of small effect, the signal to detect them in genetic studies is also small, and a comparison of genetic variants from hundreds or thousands of people with ALS and similar numbers of unaffected, unrelated people (controls) is needed. For various statistical reasons, the results are not as reliable as those in a linkage study, and it can be more difficult to be certain of a true finding. Replication by independent researchers or evidence from other scientific techniques can be used to add confidence to any genetic association with sporadic ALS.

"The main barrier to finding ALS genes, the small numbers of samples, is now being overcome."

Because of technological limitations, early association studies could only concentrate on examining one gene at a time. This was chosen by the researcher as being a likely candidate as an ALS-causing gene. Because association studies are not completely reliable, many of these genetic associations have not been convincing as true ALS-causing genes. Perhaps the most widely accepted are genetic variations in the heavy neurofilament gene (NFH), vascular endothelial growth factor (VEGF), angiogenin (ANG), and the survival motor neuron gene (SMN). If we include genetic associations and linkage findings from other motor neuron diseases such as spinal muscular atrophy, there is a theme to many of the

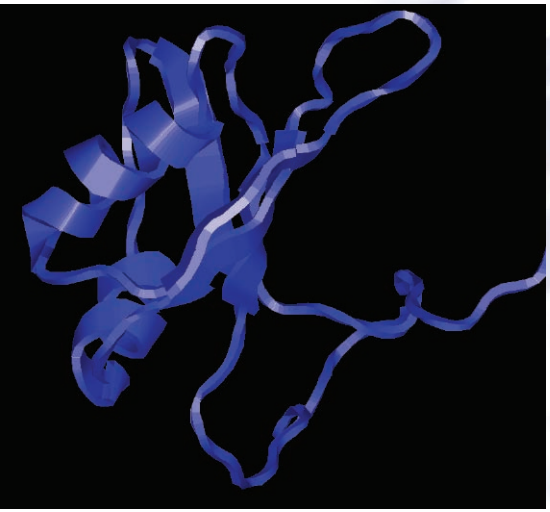
Continued on Page 3

ALS Genetics cont.

Continued from Page 2

genes: RNA processing. RNA processing is what happens when a gene, encoded in DNA, is copied by the cellular machinery into a related molecule, RNA. The RNA message is then cut up, spliced back together, sequence-edited and generally processed into a form that can be used for making protein.

ANG was chosen as a candidate ALS gene because it is related to systems for coping with low oxygen. It has a second, less well known role in RNA processing. SMN, which causes spinal muscular atrophy and is involved in ALS, is also an RNA processing gene. The SETX gene, which causes a form of familial ALS, is involved in RNA processing, as are the GARS and IARS genes for some rarer forms of spinal muscular atrophy. Taken with the TDP43 gene linkage in some families with ALS, there is increasing evidence for RNA processing problems causing motor neuron degeneration. Why this should be is not yet clear but is the focus of ongoing research.



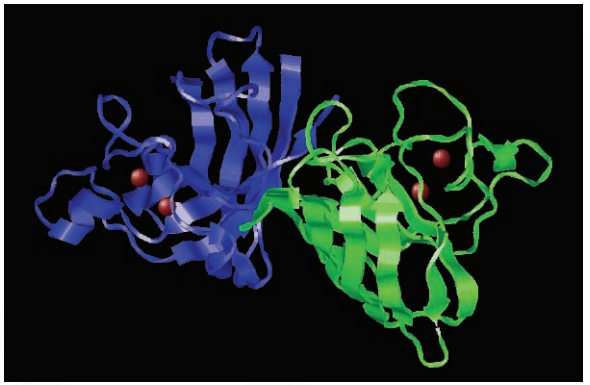
A model of the TDP43 protein structure in which mutations have recently been identified as causing ALS.

Although candidate gene studies can be useful, the ideal gene-hunting strategy would be a quick way of testing every gene simultaneously. This is now one step closer with new technology using microchips and laser scanning. The microchips contain tests for up to a million genetic variants. More than 200 DNA samples can be tested fairly easily by a single researcher in one week. (Only 14 years ago the rate of progress was one ten millionth of this).

International collaborations and consortia have now tested thousands of ALS and control samples in these genome-wide association studies. Although three possible disease genes have been found, as is common with association studies, the signals are not strong or repeatable. The first reported association was with a gene of unknown function, FLJ10986. This has not been detected by other studies. A second study identified ITPR2, a receptor involved in the glutamate pathway. Again, this has not been found in other studies. An alternative analysis from the same group identified a different gene, DPP6, which was also the top hit in a study from a third group but only when the analysis included the original study samples. The result was not statistically significant, and the signal was weakened by the new samples casting doubt on the finding. Although there are several more groups waiting to report their results, initial studies are therefore a little disappointing. This is probably because ALS is not a single condition but multiple different similar syndromes all with different causes, weakening an already small signal. Genes for diabetes were only found when tens of thousands of samples were analyzed together, and the same is likely to be true for ALS. There are also many other forms of genetic variation than is detectable with a microchip and these will become easier to study as time goes on.

The main barrier to finding ALS genes, the small numbers of samples, is now being overcome. Laboratory technology has improved even further and continues to do so. It is now possible to produce a human genome sequence in a few days rather than thirty years. The remaining obstacles are therefore the statistical methods needed to analyze the data, the huge computing resources needed to handle billions of DNA results in thousands of people, and the money required to finance the research. All of these can be overcome with time and effort.

One of the first steps in this process was begun in the late 1990s with the establishment of the ALSOD database (http://alsod.iop.kcl.ac.uk/als). The aim was to allow researchers to combine genetic mutation and clinical information in a way that would provide new insights into the relationship between the two. This database has recently been given a new lease of life with fresh funding from The ALS Association. It has already been rewritten to provide a more user-friendly interface and has links to predictions of how mutations affect proteins. It will soon be expanded further with the ultimate aim of combining all current ALS genetic knowledge in an automatically updating format.



Two SOD1 proteins combine to make a functioning enzyme. The copper and zinc are shown as red spheres.

RESOURCES

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

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

The ALS Association Research Staff

Lucie Bruijn, Ph.D.
Senior Vice President, Research and Development
***Research ALS Today** Editor*

Mark Yard
Director, Operations and Programs

Stem cells and

Stem cells hold an almost mystical place in medicine and are regularly touted by the media as a panacea for diseases of the heart, blood and brain. Not too surprising. After all, we are made up from billions of separate cells – all of which originated from primitive stem cells. So, if we could reactivate our own, or produce and transplant new ones, stem cells could possibly replace our old and dying tissues forever. But each tissue is unique. Each disease has its own challenges. And each stem cell its own flavor.

What are Stem Cells?

The term "stem cell" is used very widely, but there are in fact many different types. Embryonic stem cells can only be generated from very early embryos (in humans at about five days of development when the embryo is the size of a pin head). These stem cells can expand for long periods and be stored in banks. They are called "pluripotent" which means that they can make all the cells of the human body under the right conditions. They can also make all of the cells found in the brain including neurons, astrocytes and oligodendrocytes (Figure 1). Importantly, under the right conditions they can also produce the motor neurons lost in ALS. Adult stem cells can be generated from the bone marrow and some other tissues. Generally, adult stem cells can only make a few cells of the body associated with where they were taken from and certainly not motor neurons. However, there is a new twist to this story at the end of this article.

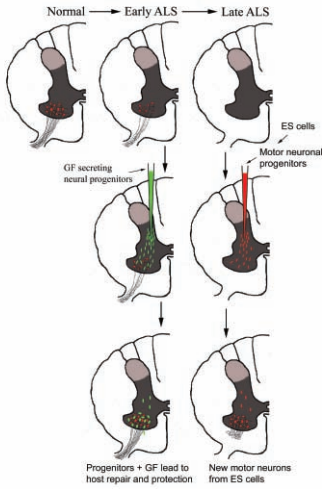


Figure 2. Schematic showing the different approaches to replacing lost motor neurons or protecting dying motor neurons using stem cells.

Stem Cell Therapy for ALS?

The most obvious use for stem cells would be to make new motor neurons to replace those that are lost in ALS (Figure 2). In fact, this has been done by Dr. Kerr and his colleagues at Johns Hopkins University using mouse embryonic stem cells to replace lower motor neurons in the spinal cord in a mouse model of motor neuron degeneration. However, moving this type of research to the human is daunting. A large number of different and complex strategies were needed for the motor neurons to grow out successfully in the mouse studies, and the distance the new axon has to grow to connect to the muscle in humans is very long. In addition, we have to also consider the upper motor neuron located within the brain that projects down to the spinal cord which is also affected in ALS. However, while currently a long way from the clinic, research in this area is moving forward and technical hurdles are breaking down with time.

A more practical (and immediate) approach may be to protect the motor neurons within patients that are undergoing degeneration using stem cells (Figure 2). This may be possible, as recent studies from the Cleveland laboratory in San Diego have shown that in addition to the motor neuron being sick, some of its important cellular neighbors called astrocytes are also dysfunctional. Stem cells can make new astrocytes after transplantation to the spinal cord, and these may then be able to help slow down the death of motor neurons that are still connected to the muscle. Furthermore, work from our group (supported by The ALS Association for more than five years) has shown that stem cells can be modified to make powerful growth factors such as GDNF and IGF-1, which are normally hard to deliver into the brain and spinal cord. When these cells are transplanted into rat models of ALS, they differentiate into cells with astrocyte like properties, continue to release GDNF and IGF-1 and protect the dying motor neurons. While this is exciting, the animals in these studies did not show a reduction in their paralysis. We feel that this may be due, in part, to the human cells not acquiring mature astrocyte features. However, Dr. Nick Maragakis and his team from Johns Hopkins have shown that rat astrocytes may work better in this same model. Another possibility may be that while the motor neurons survived, they

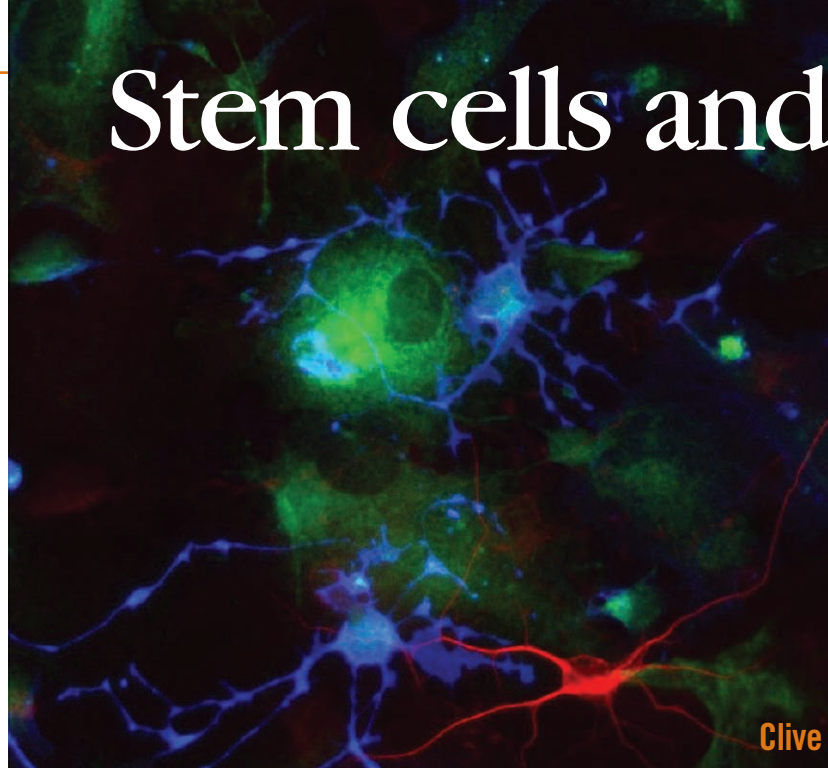
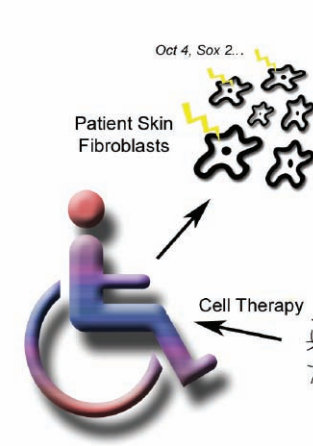


Figure 1. Neuron (red), astrocyte (green) and oligodendroctye (blue) that were derived



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

ALS: Where are we now?

Svendsen, Ph.D.

from neural stem cells.

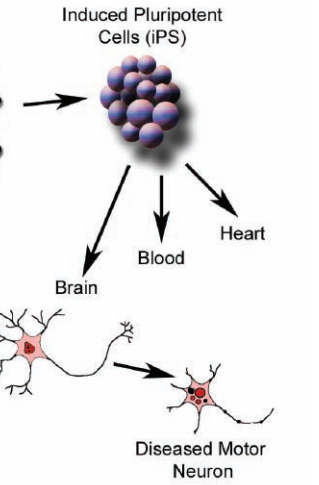


Figure 3. The cycle of iPS cells. The skin of a patient can be transformed into pluripotent stem cells that can then be pushed into neural tissue for use in drug screening or cell therapy.

lost contact with their muscles and could no longer activate them. Indeed, when we looked at the muscle tissue of these animals they had very few connections to neuromuscular junctions.

To address this issue, we have now modified adult human stem cells from the bone marrow to produce GDNF and transplanted these cells into the muscle of the ALS rat. Interestingly, the cells survive, release GDNF and can prevent the degeneration neuromuscular junctions. These animals also showed a significant slow down in their rate of paralysis. We are currently working hard to develop adult human stem cells releasing GDNF for human use to see if this might work in ALS. Perhaps both spinal cord injections of neural stem cells and muscle injections of adult stem cells releasing GDNF will have the most powerful effect – and these studies are currently underway in our animal models.

There are of course ethical issues with using stem cells derived from embryo's or fetal tissues to treat ALS, and there are also other challenges associated with physically transplanting the cells and the possibility of their being rejected by the recipients immune system. But in the next section, a possible solution is discussed.

The Future of Stem Cells

The pace of advancement in the stem cell field is relentless. Last November, teams in Japan and at the University of Wisconsin showed that you could take human adult skin cells (that are normally only able to make one type of cell – or unipotent) and turn them into cells that look almost identical to pluripotent human embryonic stem cells. For the scientists in this field, this is akin to alchemy where lead can be turned into gold. And in one stroke, the controversy over using cells derived from human embryos is removed. The trick was rather simple. Make the adult skin cells artificially turn on genes that are normally switched on in embryonic stem cells. Then they are tricked into going back in time to an embryonic state. These cells are called induced pluripotent stem (iPS) cells (Figure 3). Very recently Kevin Eggan and his colleagues from Harvard took skin cells from an 82-year-old patient with late onset ALS associated with the SOD1 mutation and made iPS cells which then generated motor neurons. Why are they important for ALS patients'? In the future these cells may be used to create new astrocytes, motor neurons or even muscle cells in the culture dish which could subsequently be transplanted back into patients with ALS. There would be little rejection of the cells as they would be the patients own. Furthermore, they are derived from adult tissues and so there would be no ethical issues.

However, as with all scientific breakthroughs, the devil is often in the details. In order to make iPS cells, a number of powerful pluripotentcy genes have to be expressed in the DNA of the cells. This makes them potentially liable to become cancerous after grafting. In addition, this type of "personalized medicine" is clearly going to be very expensive (if we have to make a separate stem cell line for each patient) in the early days. Finally, the cells may not function well after grafting as they might carry the ALS deficit which made the patient sick to begin with. Interestingly, very new unpublished data are suggesting new ways to make iPS cells without using viruses or inserting genes into the DNA. So hold on tight – this is going to be a rollercoaster ride over the next few years.

However, the final legacy of iPS cells may not be cell therapy – but a new tool to understand how and why ALS develops and how to slow it down through drug screening. As iPS cells can be derived from the skin cells of ALS patients, they should carry with them any genetic information that led to the disease in the first place. Generating motor neurons from ALS – iPS cells could therefore provide a brand new model of the disease to work on. If the ALS motor neurons are more vulnerable to toxins or other insults than non ALS motor neurons, it will be possible to screen new drugs to prevent this process. Given the lack of drugs found using the mouse model of ALS to date, it is certainly time to add other human models such as this to the mix in order to increases our chances of success.

Conclusion

Stem cells may be able to help in the battle against ALS in many different ways - from cell therapy to disease modeling, drug delivery and drug screening. While there is much hype in the media and a number of false promises abroad, there is also a solid base of experiments and ideas that will lead the field carefully forward over the next few years. With quality science, an energetic approach, thoughtful movement towards clinical trials and responsible financial support and advocacy, we have hope.

"The pace of advancement in the stem cell field is relentless... However, as with all scientific breakthroughs, the devil is often in the details."

–Clive Svendsen, Ph.D.

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 (chromosome 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

Investigator-Initiated Research Grants

The ALS Association's INVESTIGATOR-INITIATED RESEARCH GRANT PROGRAM supports innovative research of high scientific merit and ALS relevance 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 *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 *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 one 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 two years****. Applicants who are eligible are new post-doctoral fellows or those that have been a fellow for no more than one year.*

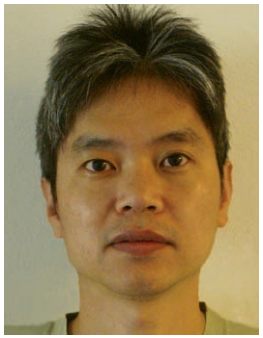
The ALS Association sponsors a Clinical Management Research Grant Program *to improve care and quality of living with ALS. The program funds starter grants for research into the clinical, psychological and/or social management of ALS. The projects are funded in the range of a total of* ***$40,000 - $50,000 for up to two years****.*

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

The Milton Safenowitz Post-Doctoral

Three 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 Safenowitz, who died in 1998 of the disease.

ROLE OF AUTOPHAGY IN ALS



Taiji Tsunemi, M.D., Ph.D.
University of Washington
Seattle, WA, USA

Taiji Tsunemi, M.D., Ph.D., working with Albert LaSpada, M.D., Ph.D., at University of Washington, Seattle, is investigating the role of autophagy in ALS. He will use primary cortical neurons from transgenic mice that ubiquitously express GFP - tagged LC3. These neurons displayed a striking punctate LC3 distribution when autophagy is induced. He will observe autophagy status when wild-type or mutant SOD1 are transfected into the neurons. He will also see the spinal cord of double transgenic mice which have mutant SOD1 mice and GFP-LC3. Then he will activate autophagy in the primary cortical neurons and the mice. This will clarify whether activating autophagy is the therapeutic target of motor neuron degeneration of ALS.

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

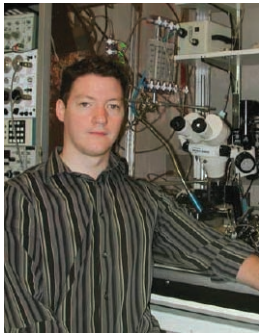
2001
- A transgenic rat is designed; efforts start on fly model
- Attention turns to support cells of nerve tissue to find role in ALS
- Inflammation and programmed cell death gather research interest
- ALS2 gene (alsin protein) linked to juvenile ALS
- The ALS Association/NINDS collaborative effort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

Fellowship for ALS Research

MOTOR UNIT PROPERTIES IN MOUSE MODEL OF ALS



Marin Manuel, Ph.D.
Northwestern University
Chicago, IL, USA

"The relationship between motoneurons and the muscle fibers they innervate is a subject that has often been overlooked in ALS research. My new technique will provide significant insight on the respective role of these two partners in the onset of the disease."

ROLE OF TDP 43 IN ALS

Teresa Sanelli, Ph.D.
University of Toronto,
Toronto, ON, Canada

"The Milton Safenowitz Post-Doctoral Fellowship for ALS research will enable us to tackle the role of TDP-43, which was recently discovered as a potentially important protein in ALS, in motor neurons. The financial and moral support that the Milton Safenowitz Fellowship and The ALS Association bring is immense, and we are grateful as it allows us to pursue complex questions with regards to ALS, bringing us ever closer to a cure."

active Research Projects cont.

grants

Continued from Back Cover

Beattie, Ph.D., Christine / *Ohio State University, Columbus, OH*
Burden, Ph.D., Steven / *Skirball Institute, NYU, NY*
Burghes, Ph.D., Arthur / *Ohio State University, Columbus, OH*
Callaerts, Ph.D., Patrick / *University of Leuven, BELGIUM*
Carri, Ph.D., Maria, Teresa / *University of Rome, Rome, ITALY*
Cox, Ph.D., Gregory / *The Jackson Laboratory, Bar Harbor, ME*
Deng, M.D., Ph.D., Han-Xiang / *Northwestern University, Chicago, IL*
Dupuis, Luc / *INSERM, Strasbourg, FRANCE*
Lweis, Ph.D., Jada / *Mayo Clinic, Jacksonville, FL*
Manuel, Ph.D., Marin / *Northwestern University, Chicago, IL,*
Morton, Ph.D., David / *Oregan Health and Science University, Portland, OR*
Petrucelli, Ph.D. / *Mayo Clinic, Jacksonville, FL*
Norga, Ph.D., Koen / *University of Leuven, BELGIUM*
Raoul, Ph.D., Cedric / *INMED, FRANCE*
Sanelli, Ph.D., Teresa / *University of Toronto, Toronto, CANADA*
Seburn, Ph.D., Kevin / *The Jackson Laboratory, Bar Harbor, ME*
Tennore, Ramesh Ph.D. / *Ohio State University, Columbus, OH*
Tsuda, Ph.D. / *Baylor College of Medicine, Houston, TX*
Xu, Zuoshang M.D., Ph.D. / *University of Massachusetts, Worcester, MA*

MITOCHONDRIA

Da Cruz, Ph.D., Sandrine / *Ludwig Institute for Cancer Research, La Jolla, CA*
Cassina, M.D., Ph.D., Patricia, Maria / *Universidad de la Republica, Montevideo, URUGUAY*

SOD1 (COPPER ZINC OXIDE DISMUTASE 1)

Beckman, Ph.D., Joseph / *Oregon State University, Corvallis, OR*
Bosco, Ph.D., Daryl / *Massachusetts General Hospital, MA*
Hayward, M.D., Ph.D., Lawrence / *University of Massachusetts, Worcester, MA*
Julien, Ph.D., Jean-Pierre / *Laval University, Quebec, CANADA*
Marklund, M.D., Stefan / *Umea University, Umea, SWEDEN*
McLaurin, Ph.D., JoAnne / *University of Toronto, Ontario, CANADA*
Robertson, Ph.D., Janice / *University of Toronto, Ontario, CANADA*
Thomas, Ph.D., Philip / *University of Texas Southwestern Medical Center, Dallas, TX*
Urushitani, M.D., Ph.D., Makoto / *Laval University, Quebec, CANADA*

STEM CELLS

Macklis, M.D., D.HST, Jeffrey / *Massachusetts General Hospital, Boston, MA*
Maniatis, Ph.D., Tom / *Harvard University, Cambridge, MA*
Rouaux, Ph.D., Caroline / *Massachusetts General Hospital, Cambridge, MA*
Svendsen, Ph.D., Clive / *University of Wisconsin, Madison, WI*
Strittmatter, M.D., Stephen / *Yale University, New Haven, CT*
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2004	2005	2006	2007	2008
Study implicates smoking as likely risk factor in sporadic ALS	*Ceftriaxone increases levels of the glutamate transporter GLT1 in a mouse model of ALS*	*ALS patient samples collected to NINDS ALS Repository*	*Stem cell study shows SOD1 mutant support cells can kill any motor neuron*	*Stem cells generated from ALS patients*
Study releases evidence that mitochondrial malfunction may play an important role in ALS	*RNAi treatment to silence the mutant SOD1 gene yields increased survival in mice*	*Repository samples allow genome analysis for sporadic ALS*	*ALS U.S. registry efforts gaining ground in Congress*	*Discovery of DPP6 in two genome-wide association studies in ALS*
	First international workshop on frontotemporal dementia discusses link to ALS	*First TREAT ALS clinical trials funded*	*Fish model of ALS: Progress reported*	*Mutations in TDP-43 linked to familial and sporadic ALS*
	Stem cells engineered to make GDNF survive when transplanted into rats modeling ALS	*First TREAT ALS clinical trials begun*	*SOD1 in altered form common to both sporadic and inherited ALS*	
	Publication identifies potential biomarkers for ALS		*Engineered stem cells making GDNF help motor neurons survive in SOD1 mutant rats*	
	Early data suggests that mutant SOD1 may be secreted by and may activate microglia			
Study funded by The ALS Association to find biomarkers in cerebrospinal fluid and blood	*Launch of TREAT ALS initiative (**T**ranslational **Re**search **A**dvancing **T**herapies for ALS) to accelerate clinical trials in ALS*	*TDP-43 discovered as a common link in FTD, ALS*	*First genome screening data published based on NINDS ALS Repository*	*Induced Pluripotent Stem Cell Technology opens up new avenues for ALS*
	VEGF increases survival in a rat model of ALS while improving motor performance	*Chromosome 9 region intense focus for FTD, ALS*		

active

Research Projects of The ALS Association Fall 2008

ALS Association

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