August 11, 2014

THE ALS ASSOCIATION’S GLOBAL RESEARCH AWARDS 2014

The ALS Association’s latest research awards include funding commitments of $3,472,079 to scientists in laboratories in nine states in the United States as well as in the U.K., France, Canada, Switzerland, Israel and Australia. These awards, which support 21 new projects, are part of its Translational Research Advancing Therapies for ALS (TREAT ALS™) portfolio, a diverse portfolio of amyotrophic lateral sclerosis (ALS) research to find treatments and a cure for Lou Gehrig’s Disease. These new awards include Investigator-Initiated Awards and the Milton Safenowitz Post-Doctoral Fellowship for ALS Research Awards.

These awards are made possible through generous donors and from chapters of The ALS Association, which provide ongoing and generous support to fund ALS research. Chapters continually work with certified centers and clinics to provide the best care to people living with ALS.

INVESTIGATOR-INITIATED AWARDS

Investigators submit a proposed line of inquiry covering diverse areas of research, and The ALS Association convenes a scientific review committee to discuss proposals and make selections based on the merits of each. There are two types of Investigator-Initiated Awards: innovative discovery awards and multi-year awards.

Researcher: Luc Dupuis, Ph.D., INSERM, Strasbourg, France
Clotilde Lagier-Tourenne, M.D., Ph.D., University of California, San Diego, California

Topic: Understanding the genetic mechanisms of FUS-mediated ALS through a conditional knock-in mouse model

Description: Mutations in the FUS gene are responsible for a subset of familial ALS cases with young onset and very rapid disease progression. The protein encoded by the FUS gene accumulates in the cytoplasm of neurons in individuals with FUS mutations and also in many with sporadic forms of the disease. The researchers recently generated a mouse model with a targeted mutation in the FUS gene that leads to the truncation of the FUS protein and its exclusive cytoplasmic localization, a situation
closely mimicking what is happening in people with the disease. Mice with two copies of this mutant gene die at birth, like animals completely devoid of FUS. However, the team has obtained preliminary data supporting that loss of FUS and expression of a truncated FUS protein do not drive a similar phenotype. In particular, the neurons innervating muscles, called motor neurons, are strikingly lost in presence of mutant FUS but not in mice devoid of FUS protein. Hence, the new ALS mouse model that they have built will be a useful tool to understand the adverse property gained by the mutant FUS protein. The objective of this project is to determine whether mice with one copy of the mutant gene develop symptoms of ALS and to understand whether FUS mutations lead to ALS through direct toxic effects in motor neurons. This project has the potential to markedly impact our knowledge on the pathophysiological function of FUS in ALS and provide the ALS community with a novel animal model of the disease.

**Researcher: Mary-Louise Rogers, Ph.D., Flinders University, Adelaide, Australia**

**Topic: A urinary biomarker to track progression of ALS in humans**

**Description:** Amyotrophic Lateral Sclerosis is a devastating illness with no effective way to objectively measure disease when testing new treatments. The researchers have found a protein shed from motor nerves that can be detected in urine by a simple enzyme based assay. They propose to help validate this test in larger numbers of samples. They will do this by showing the biomarker can track disease progress in people with ALS. They will also test urine samples from individuals who carry a known ALS-causing mutation for this marker, from pre-symptomatic to symptomatic disease. The overall significance of the project is that the marker has the potential to be used in clinical trials, testing the effectiveness of new treatments for this devastating disease.

**Researcher: Su-Chun Zhang, M.D., Ph.D., Waisman Center, University of Wisconsin, Madison**

*The study is generously funded by the Wisconsin Chapter of The ALS Association*

**Topic: Identifying drugs that promote neurofilament and axonal integrity in ALS patient motor neurons**

**Description:** ALS is a devastating motoneuron (MN) disease with no effective treatment. Its pathological feature is the presence of abnormal protein inclusions, especially neurofilament (NF) aggregates, in MNs and nerve (axonal) degeneration. These pathological hallmarks are replicated in model animals that express ALS-causing genes. The researchers have recently discovered that MNs derived from people with ALS exhibit a reduced level of neurofilament light polypeptide (NF-L), followed by NF aggregation, axonal degeneration, and cell death. In animal models, when the NF-L is restored by genetic means, it prevents NF aggregation and mitigates axonal degeneration of MNs, suggesting that NF misregulation and aggregation are important targets for therapeutic intervention. They therefore propose to build a drug-screening platform using ALS patient MNs to identify drugs that restore NF-L levels and/or prevent
NF aggregation in MNs. The initially identified compounds will be validated in cells derived from different individuals with the disease, including those from people with the sporadic form (without family history), as well as in ALS transgenic mice. Identification of drugs that delay or prevent ALS MN degeneration using ALS patient MNs will likely facilitate translation to clinical application and open new options for treating ALS.

**Researcher: Giovanni Manfredi, M.D., Ph.D., Weill Medical College of Cornell, New York, New York**

*This study is generously funded by the Greater Philadelphia Chapter of The ALS Association*

**Topic:** Metabolic biomarkers in skin fibroblasts of sporadic ALS patients

**Description:** The goal of this study is to identify metabolic signatures in sporadic ALS fibroblasts (skin cells) that correlate with clinical characteristics of the disease. The researchers will investigate energy metabolism properties in a large series of fibroblasts directly derived from skin biopsies of individuals affected by sporadic ALS. Their preliminary data indicate that sporadic ALS fibroblasts have different energy metabolism settings than fibroblasts from unaffected individuals. They will aim at correlating metabolic patterns with crucial disease characteristics, such as age of onset and progression. These studies aim at establishing fibroblast metabolism as a predictive factor for the evolution of ALS, and most importantly, they could help to predict the individual responsiveness to therapies. Because fibroblasts’ changes could be reflective of systemic changes in people with ALS, the metabolic signature in fibroblasts could serve as a systemic disease biomarker, which will be investigated in plasma from the same individuals from whom the skin biopsies were taken. In this study, they will also investigate the mechanisms underlying the metabolic changes observed in ALS fibroblasts. Since mitochondrial dysfunction and metabolic unbalance have been consistently associated with ALS, these studies could provide new insights in the pathogenesis of the disease.

**Researcher: Nicholas J. Maragakis, M.D., Johns Hopkins University School of Medicine, Baltimore, Maryland**

**Topic:** Investigating astrocyte-mediated degeneration of upper motor neurons in ALS

**Description:** Amyotrophic Lateral Sclerosis results in the impairment of upper motor neurons (MNs) in the motor cortex and lower MNs in the spinal cord. A fundamental shortcoming of the ALS community’s research is the small number of basic science and clinical investigations into upper MN dysfunction in ALS patients. However, the discovery of novel markers to reliably identify upper MNs now allows for these investigations. One of the major disease pathways influencing lower MN death in ALS is through non-neuronal glial cells such as astrocytes. Recently, astrocytes derived from familial and sporadic post-mortem ALS patients were shown to cause the death of lower MNs in culture. In this study, the researchers will investigate whether upper MNs are
also pathologically influenced by astrocytes. They will use astrocytes taken from ALS mouse models as well as astrocytes derived from stem cells created from individuals with the disease. The results may begin to offer critical insight into whether upper MNs degenerate through similar or divergent mechanisms as lower MNs in ALS. Further understanding of these mechanisms can guide the development of therapies targeting upper MNs specifically or therapies which may be beneficial for upper and lower MNs.

**Researcher: Thomas Lloyd, M.D., Ph.D., Johns Hopkins University, Baltimore, Maryland**

**Topic:** The role of nuclear transport defects in the pathogenesis of ALS/FTD

**Description:** The entry and exit of biomolecules into the cell nucleus is tightly regulated, a process called nuclear transport. The researchers have recently discovered that a protein called Ran-GAP, known to control nuclear transport, is altered in both human cell models and in a fruit fly model of ALS that contains the disease-causing expansion of the C9orf72 gene. Importantly, in this fly model, nuclear transport is severely altered. The goal of this study is to understand why and how such problems occur in ALS and whether they can be reversed with small molecule inhibitors.

**Researcher: Professor Elizabeth Fisher, Ph.D., UCL Institute of Neurology, London, United Kingdom**

**Topic:** A new humanized delta-14 mutant mouse model for dissecting the pathobiology of FUS-ALS

**Description:** One route to understanding ALS is to look at the relatively rare cases caused by defects in specific genes. One such gene, FUS, causes an early-onset, rapidly progressive form of ALS. To understand more about how FUS mutations cause ALS, the researchers have developed a new animal model carrying the gene mutation, which they will study to gain new insights into disease pathogenesis. The model will be made freely available to other researchers as well.

**Researcher: Eliahu Heldman, Ph.D., Lauren Sciences LLC, Beer-Sheva, Israel**

*This study is generously funded by the Greater Philadelphia Chapter of The ALS Association*

**Topic:** Treatment of ALS by Targeted Delivery of GDNF to Motoneurons using Novel V-Smart™ Nanovesicles

**Description:** The goal of this project is to utilize the researchers’ proprietary V-Smart™ drug delivery system for targeted delivery of GDNF-loaded V-Smart™ nanovesicles, administered systemically, to brain regions where motoneurons degenerate in ALS and test efficacy in protecting against neurodegeneration and inducing neurorestoration. GDNF (glial-cell derived neurotrophic factor) is a growth factor for neurons. Preclinical
studies show that GDNF provides beneficial effects in SOD1 ALS mouse models, but GDNF does not penetrate the blood-brain barrier and has limited diffusion within the brain after direct injection because of tight binding to brain tissue. The researchers will develop GDNF-loaded V-Smart™ vesicles that target areas of motoneuron degeneration to maximize GDNF delivered there. They will also test efficacy in restoring motor neuron deficits and prolonging the lifespan of ALS mice. These experiments will set the stage for development of a similar approach for people with ALS. This approach is currently being evaluated for Parkinson’s disease.

**Researcher: Jeffrey Rothstein M.D., Ph.D., Johns Hopkins University, Baltimore, Maryland**

**Topic:** Glial Metabolic Connectivity in Amyotrophic Lateral Sclerosis

**Description:** Axons are specialized extensions of neurons that are critical for the organization of the nervous system. In order to maintain function in axons that often extend some distance from the cell body, specialized mechanisms of energy delivery are likely necessary. In recent years the researchers and others have generated data that suggest that oligodendroglia, the cells that wrap around the long axons in the nervous system, are critical for maintaining the function of axons. This pathway has important implications both for the basic biology of the nervous system as well as for ALS. Their studies have shown these cells are injured early in ALS, and their loss of metabolic support has tremendous influence on ALS disease progression. This new study will examine the connections between the brain glia, astrocytes and oligodendroglia, that make this critical process operate and how dysfunction of this process leads to disease—as well as potential future drug targets.

**Researcher: Masatoshi Suzuki, Ph.D., University of Wisconsin, Madison**

*The study is funded supported by the Wisconsin Chapter of The ALS Association*

**Topic:** Application of human skeletal muscle stem cells to treat and understand ALS

**Description:** The researchers will use a rat model of ALS to test new treatments based on stem cells. Specifically, they will test the effects on skeletal muscles of transplanting cells that produce and secrete trophic factors. Their study will determine whether a newly established line of skeletal muscle progenitor cells can improve established strategies for stem cell or viral delivery of genes in skeletal muscles. Furthermore, they propose to generate muscle cells using stem cells derived from ALS patients. Those muscle cells can be used for ALS disease modeling and drug screening.

**Researcher: Tania Gendron, Ph.D., Mayo Clinic, Jacksonville, Florida**

**Topic:** Mechanisms of c9RAN protein-induced neurodegeneration in c9FTD/ALS
Description: An expansion mutation in the C9orf72 gene causes ALS and frontotemporal dementia (FTD) through unknown means. The researchers have found that the expansion leads to the expression of proteins that would otherwise not exist within neurons. In this study, they will investigate whether and how these so-called c9-RAN proteins contribute to the disease. A better understanding of this could ultimately lead to development of therapeutics to reduce these proteins or their effects. The proteins may also serve as a biomarker for ALS development, and the team will investigate the utility of this approach.

**Researcher: Ann Hart, Ph.D., Brown University, Providence, Rhode Island**

**Topic:** Precise C. elegans models of ALS

Description: It remains unclear why changes in SOD1, TDP-43, FUS, and other proteins cause ALS. Virtually all animal models for ALS rely on overproduction of disease proteins resulting in rapid degeneration and death. However, the researchers suggest 1) that models that avoid overexpression are critical for understanding ALS and 2) that the early stages of dysfunction in slowly progressing disease must be delineated to understand why neurons die. They use the nematode C. elegans to precisely model early events in ALS. The C. elegans neuromuscular system resembles that of vertebrates, and most genes whose mutation causes ALS are present in C. elegans. The short lifespan of C. elegans and simple genetics allow the researchers to order ALS disease genes into functional pathways, so they know which genes act early, and which act late in the disease. They have taken a new approach to modeling early stages of ALS, inserting ALS disease-causing mutations into the corresponding C. elegans gene. Precise insertion has less dramatic consequences than overexpression of human disease proteins. The new precise models likely more accurately reflect early stage disease ALS and will allow the team to determine what goes wrong at early stages of ALS.

**Researcher: Muralidhar L. Hegde, M.D., Houston Methodist Hospital Research Institute, Houston, Texas**

**Topic:** TDP-43 pathology–mediated DNA repair deficiency in ALS

Description: TDP-43 is a protein that binds to both DNA and RNA. Mutations in the TDP-43 gene are a cause of ALS, through unknown mechanisms. The researchers' preliminary data demonstrate that TDP-43 is required for efficient DNA double strand break (DSB) repair in neurons, where it is recruited to interact with other repair proteins, and that depleting TDP-43 increases the number of DSBs in DNA, including those in ALS patients. Based on these results, the researchers hypothesize that loss of nuclear TDP-43 in ALS causes deficient repair of DNA in neurons, promoting cell death and thus contributing to disease. The team will test this hypothesis using state-of-the-art technology, potentially opening up new avenues therapeutic interventions.
Researcher: Christine E. Beattie, Ph.D., The Ohio State University, Columbus, and John P. Manfredi, Ph.D., Sfida Biologic, Inc., Salt Lake City, Utah

Topic: Evaluation of Novel γ-Secretase Modulators in a Zebrafish ALS Model

Description: The researchers have identified a new class of small molecules that exhibit extraordinary effects on motor neurons, whose dysfunction accounts for the devastating symptoms of ALS. The principal goal of the project is to determine if these novel small molecules have promise as therapeutics for ALS. Accordingly, they propose to test in an economical animal model of ALS three representative members of this class of compounds, examining their capacity to restore normal growth of motor neurons, to restore normal structure to the region of the motor neuron that interacts with muscle, and to restore normal movement of the animal. Results from this pilot project will indicate if any of the three tested compounds exhibit the potential for development as a pharmaceutical treatment for ALS. If so, the findings will necessarily suggest the possibility that other members of the class of compounds may have even greater potential. Results will also indicate if a protein complex that has never been considered to participate in the etiology of ALS provides a target for ALS treatments. Thus, the project may introduce new pharmaceuticals to treat ALS and new approaches to identifying yet more promising pharmaceuticals.

Researcher: Hanna Rosenmann, Ph.D., Hadassah Hebrew University, Jerusalem, Israel

This study is generously funded by the Greater Philadelphia Chapter of The ALS Association

Topic: CSF exchange therapy in ALS: removal of endogenous CSF and replacement with biologically enriched artificial CSF

Description: ALS is a complex disease and is not fully understood. Treatment is likely to be more effective when is directed to both the elimination of harmful agents from the central nervous system (CNS) and to the support/enrichment of the CNS with protective agents. The researchers will develop a novel approach to achieve such a goal by exchange of cerebrospinal fluid (CSF), the fluid that circulates within the whole CNS. This exchange will include the removal of the endogenous CSF of a diseased animal and the infusion of CSF enriched with active biological molecules possessing protective features. As potential sources for the enrichment of CSF the team will use cell secretions of stem cells and platelet extracts, sources which have been shown to contain beneficial and protective agents for the CNS. They will test the ability of this approach to alter the disease course in the animal model.
Researcher: Elijah Stommel, M.D., Ph.D., Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire

Topic: Environmental risk factors for ALS: The northern New England database, cyanobacteria, and methylmercury

Description: The researchers will expand upon a pilot case-control study of the role of environmental toxins in ALS, using people with ALS and clinic controls from their extensive database at Dartmouth College and the University of Vermont. They will use spatial analysis techniques and a questionnaire, plus databases of water quality and environmental contamination, to determine whether exposure to environmental neurotoxins and toxicants near places of residence and work increases the risk of developing ALS. They will focus this study on environmental exposure to mercury and cyanobacteria toxins and will compare biomarkers of exposure to mercury and beta-methylamino-l-alanine (BMAA) in human tissues and biological samples from adjacent water bodies with questionnaire-derived data regarding environmental exposures. This study will lay the groundwork for a larger case-control study of gene-environment interactions and environmental risk factors for ALS.

MILTON SAFENOWITZ POST DOCTORAL FELLOWSHIPS
The Association also offers The Milton Safenowitz Postdoctoral Fellowship for ALS Research Award. Founded by the Safenowitz family through the Greater New York Chapter of The ALS Association and in memory of Mr. Safenowitz, who died of ALS in 1998, these awards are to encourage and facilitate promising young scientists to enter the ALS field.

Researcher: Philip McGoldrick, Ph.D., University of Toronto, Canada

Topic: Pathomechanisms of C9orf72 in real time

Description: A repeat expansion in C9orf72 is the most common cause of ALS and frontotemporal dementia (FTD), which are now recognized as a spectrum of the same underlying disease mechanism. Currently three pathways have been suggested to contribute to disease in C9orf72 patients; 1) RNA toxicity, associated with the formation of nuclear RNA foci composed of the repeat expansion; 2) expression and aggregation of proteins generated from the repeat expansion; and 3) reduced C9orf72 protein levels. The hypothesis to be tested here is that each potential pathomechanism contributes to disease. Using cultured motor neurons and cortical neurons, the cell types affected in disease, the researchers will test whether they act alone or in concert with one another. In a novel set of experiments, they plan to use live cell imaging to directly examine RNA foci and proteins formed from the repeat to examine their dynamics in neurons to determine how they may be toxic. From these experiments, they aim to separate the different toxicities associated with these mechanisms. Importantly, they plan to do this in both motor neurons and cortical neurons, to see whether differences in these cell types may reflect disease vulnerability. This knowledge will inform us on how the repeat
expansion causes disease, allowing development of therapeutic strategies to abrogate these effects.

Rechercheur: Florent Laferriere, Ph.D., University of Zurich, Switzerland

Topic: Contribution of protein aggregation in the pathogenesis of ALS: seeding, spreading, and toxicity

Description: ALS, like other neurodegenerative diseases such as Alzheimer’s or Parkinson’s disease, is associated with the accumulation of misfolded proteins in neuronal and glial cells in the central nervous system. The major misfolded proteins linked with ALS pathology are SOD1, FUS/TLS and TDP-43. The latter, a DNA/RNA-binding protein, is the main component of cytoplasmic inclusions in almost all sporadic cases of ALS (>90 percent of all ALS), accompanied by its nuclear depletion. Moreover, mutations in this protein are associated with inherited ALS, and the affected neurons of those with the disease present abnormal localization and aggregation of TDP-43. This protein has an intrinsically high propensity to aggregate and has the ability to propagate its misfolding and aggregation, in a prion-like manner. Despite intensive research, the contribution of TDP-43 aggregation in the pathogenesis of ALS remains poorly understood. To shed light to this crucial issue, the researchers will separate the TDP-43 aggregates present in ALS patients’ brains according to their size. Then they will be able to determine the relationship between protein aggregation and its pathogenic properties.

Rechercheur: Ke Zhang, Ph.D., Johns Hopkins University, Baltimore, Maryland

This study is generously funded by the Greater Philadelphia Chapter of The ALS Association

Topic: The role of nuclear transport defects in the pathogenesis of ALS/FTD

Description: Biological molecules are tightly controlled to enter and exit the nucleus in cells, a process called nuclear transport. The precise regulation of such processes is essential for physiological functions and is disrupted in many human diseases, including neurodegenerative disease. The researchers' recent data show that nuclear transport is severely disrupted in the most common inherited form of ALS, caused by mutations in the C9orf72 gene. Using a fruit fly model, they have found that the machinery that drives molecules to enter the nucleus in neurons is defective and appears to be due to abnormal function of a protein called RanGAP. This leads to redistribution of proteins that are very important for the nerve cells to survive. The team’s goal is to understand why and how such problems occur in ALS and whether these abnormalities can be corrected by drug therapies. They will first address the key molecular mechanisms and then will test drugs that potentially keep these proteins inside the nucleus.
Researcher: Claudia Fallini, Ph.D., University of Massachusetts Medical School, Worcester

Topic: Characterizing the pathogenic role of TDP-43 in PFN1-linked ALS

Description: Mutations in the gene encoding Profilin1 (PFN1) are the cause of ALS in 1-2 percent of familial cases. Mutant PFN1 protein aggregates in the cell body of motor neurons, the cells that degenerate in ALS. The researchers found that PFN1 sequesters TDP-43 into these aggregates. Mutations in the gene encoding TDP-43 itself are a cause of ALS, and the aggregation of the TDP-43 protein is a common phenomenon in degenerating motor neurons in both sporadic and familial ALS. Together, these observations suggest that TDP-43 may be responsible for motor neuron degeneration in PFN1-associated ALS. In this project the team will investigate the link between mutations in PFN1 and the aggregation of TDP-43 and whether mutant PFN1 toxicity depends on alteration in TDP-43 functions in motor neurons. The results from this project will help the understanding of the processes that are altered in ALS motor neurons, thus paving the way to the identification of therapeutic targets for the treatment of this disease.

Researcher: Veronique Belzil, Ph.D., Mayo Clinic, Jacksonville, Florida

Topic: Characterizing the contributions of epigenetic changes in c9FTD/ALS

Description: ALS and frontotemporal dementia (FTD) are two devastating conditions seen together in up to 50 percent of individuals affected with either disease. ALS and FTD are believed to result from the same or overlapping defective biological processes, with recent findings demonstrating that a mutation in the C9orf72 gene is present in a significant number of ALS and FTD patients. Much effort is now being dedicated to identifying how the mutation impairs biological processes, leading to reduced gene expression levels and abnormal cell functioning. The researchers recently showed that epigenetic changes, or modifications in gene expression that occur independently of the gene’s structure, are responsible for the abnormal reduction in C9orf72 gene expression. They also demonstrated these epigenetic changes, which are unique to patients carrying the mutation, are detectable in blood. In the current study, they aim to generate a full epigenetic and expression profile of C9orf72 mutants, evaluate whether epigenetic variation also contributes to mRNA-mediated toxicity, and assess whether these changes may be used as biomarkers of disease. Considering that epigenetic variation, a common theme in neurodegeneration, can be targeted by therapeutics, this study may be very important to the future development of treatments for ALS and FTD.

For questions on these and other research grants, please email: researchgrants@alsa-national.org.