

**Amyotrophic Lateral Sclerosis**  
**(ALS/MND/Lou Gehrig's)**

**CALIFORNIA**

**Irvine - University of California**

**John H. Weiss M.D., Ph.D.**

RG Motor neuron ROS, glutamate transport disruption and amyotrophic lateral sclerosis (ALS)

\$100,000.00	7/1/2004	6/30/2005	Year 1
\$100,000.00	7/1/2005	6/30/2006	Year 2
\$100,000.00	7/1/2006	6/30/2007	Year 3

*Summary:* Using simple models, researchers have found that glutamate stimulation causes MNs to produce unusually large quantities of injurious free radicals. Furthermore, these free radicals can leave the MNs and disrupt nearby astrocyte glutamate pumps. These observations provide the basis for a new vicious cycle model of ALS. The proposed project aims to further test this model, and to examine therapeutic interventions suggested by the model that may slow disease progression.

**La Jolla - Ludwig Institute for Cancer Research**

**Christine Van de Velde Ph.D.**

DG The contribution of mitochondria to mutant SOD1-mediated motor neuron degeneration in ALS

\$45,000.00	7/1/2005	6/30/2006	Year 1
\$45,000.00	7/1/2006	6/30/2007	Year 2
\$45,000.00	7/1/2007	6/30/2008	Year 3

*Summary:* Amyotrophic lateral sclerosis is a fatal neurodegenerative disease characterized by the selective loss of motor neurons. The biological basis for this selective killing remains unknown. The investigator intends to determine the basis for this specificity and determine the role of mitochondria (the energy centers within cells) in this form of motor neuron degeneration.

**La Jolla - University of California**

**Koji Yamanaka M.D., Ph.D.**

DG The role of ALS2 in the post-natal survival of human motor neurons

\$45,000.00	7/1/2004	6/30/2005	Year 1
\$45,000.00	7/1/2005	6/30/2006	Year 2
\$45,000.00	7/1/2006	6/30/2007	Year 3

*Summary:* Two genetic causes of ALS are now known, including a mutation (named ALS2) which generates a motor neuron disease in infants and juveniles that progresses. The Researchers will focus on identifying how the loss of the ALS2 protein gives rise to the selective death of the motor neurons.

**Martina Wiedau-Pazos M.D., Ph.D.**

RG Motor neuron specific gene expression profile in amyotrophic lateral sclerosis (ALS)

\$98,349.00	1/1/2006	12/31/2006	Year 1
\$72,489.00	1/1/2007	12/31/2007	Year 2

*Summary:* Mechanism-based therapies of amyotrophic lateral sclerosis are unavailable because cell mechanisms that underly selective motor neuron vulnerability remain a mystery. To discover early triggers of neurodegeneration, the investigators propose to identify key gene expression changes specific to motor neurons before disease onset from two mouse models of motor neuron disease. Consequently, early genetic markers and pathways specific for motor neuron disease will be identified. Further functional assessment of identified genes may provide the framework of candidates therapeutic targets for ALS prevention and treatment.

**David Pleasure M.D.**

RG Neuropilin-2 facilitates axonal regeneration in PNS

\$95,064.00	7/1/2003	6/30/2004	Year 1
\$95,064.00	7/1/2004	6/30/2005	Year 2
\$95,064.00	7/1/2005	6/30/2006	Year 3

*Summary:* Investigators have shown that neuropilin-2 (NP2) facilitates axonal regeneration. They will investigate the mechanism of this trophic effect of NP2, and its relevance to therapy for motor neuron diseases.

**San Francisco - California Pacific Medical Center**

**Robert G. Miller M.D.**

TRA MDA/ALS Web-based Database  
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\$146,959.00	8/1/2003	7/31/2004	Year 1
\$158,515.00	8/1/2004	7/31/2005	Year 2
\$160,848.00	8/1/2005	7/31/2006	Year 3

*Summary:* The information retrieved from the MDA/ALS Web-based Database will help determine the cause of ALS and aid patients and physicians in managing ALS.

**Stanford - Stanford University**

**Lorene M. Nelson Ph.D.**

RG Cholesterol-lowering medication as risk and prognostic factors for ALS

\$99,035.00	1/1/2006	12/31/2006	Year 1
\$102,352.00	1/1/2007	12/31/2007	Year 2
\$93,915.00	1/1/2008	12/31/2008	Year 3

*Summary:* The primary objective of this study is to investigate whether the use of cholesterol-lowering medications increases the risk of developing ALS or influences the rate of disease progression among individuals who have ALS. If cholesterol or cholesterol-lowering medications are shown to play a role in development or prognosis of ALS, this will contribute to knowledge about the biological mechanisms of motor neuron disease.

**FLORIDA**

**Miami - University of Miami**

**Walter Bradley DM, FRCP**

PPG Hyperbaric oxygen therapy in amyotrophic lateral sclerosis (ALS)

\$256,770.00 1/1/2006 12/31/2006 Year 1

*Summary:* This study will determine if Hyperbaric Oxygen therapy is of benefit with a double blind placebo controlled trial of HBO versus sham hyperbaric treatment. Preliminary studies suggest that HBO improves strength in the disease. This project is of relevance to the mission of MDA to find effective treatments for ALS. A positive outcome in this trial would lead to the development of more practical ways of administering high dose oxygen for the treatment of ALS patients.

**Alison Grossman Ph.D.**

DG Impact of psychosocial factors on ALS onset and disease progression

\$45,000.00 7/1/2003 6/30/2004 Year 1  
\$45,000.00 7/1/2004 6/30/2005 Year 2  
\$45,000.00 7/1/2005 6/30/2006 Year 3

*Summary:* There is a widespread belief among ALS physicians that those patients who "fight the disease" have a slower rate of progression, and that the disease preferentially affects "nice" people. Investigators study will provide scientific evidence on these beliefs that at present are based on anecdotal observations, using novel approaches. Part A of the study will investigate how psychosocial variables related to "fighting spirit" impact upon ALS progression, adherence to medical recommendations, forced vital capacity and functional status. Part B will examine how "niceness," or premorbid personality characteristics are associated with development of ALS. They will analyze family members' ratings of sporadic ALS patients' premorbid personality traits.

**Carlos Moraes Ph.D.**

RG Mitochondrial dysfunction in amyotrophic lateral sclerosis (ALS)

\$85,686.00 7/1/2003 6/30/2004 Year 1  
\$97,824.00 7/1/2004 6/30/2005 Year 2  
\$98,906.00 7/1/2005 6/30/2006 Year 3

*Summary:* Several lines of evidence showed that mitochondria is involved in the pathogenesis of ALS. A transgenic model harboring a mutated SOD1 gene also showed mitochondrial abnormalities. Investigators plan to explore this concept and produce transgenic mice that express the mutant protein in the mitochondria. If the disease is also observed in these models, they will have gained valuable information on the mechanisms related to the pathogenesis of ALS.

**Spiridon Papapetropoulos M.D., Ph.D.**

RG Cyanobacterial toxin (BMAA) in postmortem brain tissue and hair samples of ALS patients

\$110,000.00 1/1/2006 12/31/2006 Year 1  
\$110,000.00 1/1/2007 12/31/2007 Year 2

*Summary:* Exposure to high concentrations of a naturally occurring, non-protein amino acid called beta-N-methylamino-L-alanine (BMAA) has been associated with a rare form of ALS found in the south pacific island of Guam. Recently, examination of brain tissue of ALS patients in Guam and a very small number of sporadic ALS and Alzheimer's disease cases in the US and Canada revealed high concentrations of BMAA. The objective of this application is to study this association by measuring BMAA concentration in brain tissue and hair samples of ALS, Alzheimer's disease and Parkinson's disease patients. The results may have an impact on prevention, etiology and treatment of ALS.

**ILLINOIS**

**Chicago - Northwestern University**

**Jianhua Yan M.D.**

DG A molecular target for amyotrophic lateral sclerosis (ALS) therapy: A gene for ALS/FTD

\$45,000.00	7/1/2003	6/30/2004	Year 1
\$45,000.00	7/1/2004	6/30/2005	Year 2
\$45,000.00	7/1/2005	6/30/2006	Year 3

*Summary:* Identification of the causative gene of ALS/FTD will lead to the development of specific therapy. They can establish animal models to study mechanism of the disease, to identify molecular targets to develop therapy which can be tested on the animal models. It will also be possible to offer highly accurate diagnostic tests and provide clinical screening and genetic counseling to patients with ALS/FTD. These experiences could also be utilized in studying other forms of ALS.

**Chicago - University of Chicago**

**James R. Brorson M.D.**

RG Glutamate receptors on corticospinal motor neurons and amyotrophic lateral sclerosis (ALS)

\$38,125.00	7/1/2003	6/30/2004	Year 1
\$38,125.00	7/1/2004	6/30/2005	Year 2
\$38,125.00	7/1/2005	6/30/2006	Year 3

*Summary:* The corticospinal neurons, carrying the brain's directions for motor activity to the spinal centers innervating the muscles, are essential to all coordinated movement. These cells are a vulnerable population in diverse conditions ranging from the motor neuron degeneration of ALS to spinal cord traumatic injuries. Nevertheless, little is known about their functional properties. Through a fluorescence labeling technique and application of electrical recording techniques, we can characterize in detail their possession of the receptors activated by the neurotransmitter glutamate, and discover whether overactivation of these receptors is an important cause of toxicity in these neurons.

**Chicago - University of Illinois**

**David Featherstone Ph.D.**

RG Molecular mechanisms regulating extracellular glutamate

\$71,479.00	1/1/2004	12/31/2004	Year 1
\$74,179.00	1/1/2005	12/31/2005	Year 2
\$80,985.00	1/1/2006	12/31/2006	Year 3

*Summary:* All forms of amyotrophic lateral sclerosis (ALS) seem to involve abnormally high levels of extracellular glutamate. Glutamate is the major excitatory neurotransmitter in the central nervous system, and high extracellular levels of glutamate have long been known to be neurotoxic and are implicated in many neurodegenerative diseases. It is likely that abnormal extracellular glutamate levels cause or contribute to ALS. Using *Drosophila* genetics, researchers will relatively quickly identify the molecular mechanisms by which extracellular glutamate is regulated in the neuromuscular system. This will help us understand what causes ALS and also identify potential new drug targets.

**INDIANA**

**Muncie - Ball State University**

**Derron Bishop Ph.D.**

RG Axon loss in a mouse model of amyotrophic lateral sclerosis (ALS)

\$97,367.00	7/1/2003	6/30/2004	Year 1
\$82,289.00	7/1/2004	6/30/2005	Year 2
\$83,867.00	7/1/2005	6/30/2006	Year 3

*Summary:* This project will resolve the cellular defects within degenerating motoneurons in a mouse model of ALS using three-dimensional confocal and electron microscopy.

**MARYLAND**

**Baltimore - Johns Hopkins University**

**Kazim Sheikh M.D.**

RG Quantitative MRI of the muscle in SOD1 mice

\$100,000.00	1/1/2006	12/31/2006	Year 1
\$100,000.00	1/1/2007	12/31/2007	Year 2

*Summary:* This grant proposes to examine the utility, specificity, and sensitivity of muscle MRI as a tool to monitor disease course and as an outcome measure for preclinical drug screening in a well characterized animal model of amyotrophic lateral sclerosis. These experimental studies could potentially help in the development of imaging techniques and protocols that can be directly applicable to patients with neuromuscular disorders such as ALS and neuropathies. The working model and rationale of such an approach is supported by the immense impact of brain MRI disease management and drug screening in multiple sclerosis.

**MASSACHUSETTS**

**Boston - Harvard University**

**Tiffany Reiter Ph.D.**

DG Heme oxygenase in motor neuron resistance to NO toxicity

\$45,000.00	1/1/2005	12/31/2005	Year 1
\$45,000.00	1/1/2006	12/31/2006	Year 2
\$45,000.00	1/1/2007	12/31/2007	Year 3

*Summary:* Nitric oxide (NO) and its chemical by-products have been implicated for a role in the development of ALS. Heme oxygenase-1 (HO-1), an enzyme, has recently been implicated for a role in motor neuron resistance to NO toxicity. Researchers propose to study the mechanism(s) by which HO-1 prevents NO toxicity. Further understanding of the mechanism(s) of NO-resistance in motor neurons will contribute to the design of therapeutic agents to treat ALS.

**Charlestown - Massachusetts General Hospital**

**Susanna Benn Ph.D.**

DG Studies of the therapeutic effect of Hsp27 in amyotrophic lateral sclerosis (ALS) mice

\$45,000.00	1/1/2004	12/31/2004	Year 1
\$45,000.00	1/1/2005	12/31/2005	Year 2
\$45,000.00	1/1/2006	12/31/2006	Year 3

*Summary:* Investigators aim to breed mice that express a small heat shock protein known as Hsp27, which both prevents protein clumping and inhibits apoptosis, in the ALS mice. This information may support the exploitation of Hsp27 for the treatment of patients with ALS.

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

RG High throughput drug screening in SOD1-mediated amyotrophic lateral sclerosis

\$88,110.00	1/1/2005	12/31/2005	Year 1
\$85,228.00	1/1/2006	12/31/2006	Year 2

*Summary:* ALS is a progressive neurodegenerative disease involving loss of large motor neurons in the brain and spinal cord. The goal of this study is to identify small molecules able to reduce the production of toxic proteins in SOD1-mediated ALS.

**Davide Trotti Ph.D.**

RG Symoylation of the glutamate transporter EAAT2 in the pathology of ALS

\$96,701.00	7/1/2005	6/30/2006	Year 1
\$96,811.00	7/1/2006	6/30/2007	Year 2
\$95,161.00	7/1/2007	6/30/2008	Year 3

*Summary:* The goal of this study is to understand the pathophysiological mechanisms responsible for EAAT2 impairment in ALS. The investigators believe that this impairment not only leads to excitotoxic cell death by glutamatergic overstimulation of motor neurons in the spinal cord, but also that fragments of the EAAT2 protein generated by pathological reactions occurring in ALS sustain or worsen this disease.

**Clifford Woolf M.D., Ph.D.**

RG Hsp27 and motor neuron survival

\$84,954.00	7/1/2003	6/30/2004	Year 1
\$87,977.00	7/1/2004	6/30/2005	Year 2
\$91,109.00	7/1/2005	6/30/2006	Year 3

*Summary:* This study will test if lack of expression of heat shock protein 27 (Hsp27) contributes to an increased susceptibility for motor neurons to die, and if gene therapy with Hsp27 has potential benefit for preventing or delaying neuron loss in motor neuron diseases such as ALS.

## MICHIGAN

### Ann Arbor - University of Michigan

#### **Denise A. Figlewicz Ph.D.**

RG New models of familial amyotrophic lateral sclerosis (FALS): Unmasking modifier genes

\$80,274.00	1/1/2004	12/31/2004	Year 1
\$84,713.00	1/1/2005	12/31/2005	Year 2
\$85,446.00	1/1/2006	12/31/2006	Year 3

*Summary:* The mutant Cu-Zn superoxide dismutase gene, which leads to adult-onset progressive loss of spinal motor neurons both in FALS patients and in transgenic mouse models, will be bred into 6 genetically distinct mouse strains. Variations will appear in the clinical course of the disease in the new mouse models of ALS. These mice will then be used to identify important ALS modifier genes i.e., genes that either accelerate or delay the degeneration of motor neurons. Such genes will provide new insights into the pathways involved in motor neuron degeneration, and may also provide new targets for therapeutic intervention in ALS.

### Detroit - Wayne State University

#### **William S. Brusilow Ph.D.**

RG Effect of methionine sulfoximine and ketoacids on the amyotrophic lateral sclerosis (ALS) mouse

\$91,520.00	1/1/2006	12/31/2006	Year 1
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*Summary:* ALS is a fatal neurodegenerative disorder that results, in part, from defects in the brain metabolism of the molecule glutamate. This research will treat a mouse model of ALS with compounds known to lower brain glutamate, to determine if altering glutamate levels directly will have an impact on the onset or progression of the disease.

## MINNESOTA

### Rochester - Mayo Clinic

#### **Bruce Horazdovsky Ph.D.**

RG Regulation of IGF-1 receptor signaling and trafficking in ALS2

\$100,000.00	1/1/2006	12/31/2006	Year 1
\$100,000.00	1/1/2007	12/31/2007	Year 2
\$100,000.00	1/1/2008	12/31/2008	Year 3

*Summary:* Amyotrophic lateral sclerosis (ALS) is characterized by the progressive death of neurons that control muscles. The gene mutated in ALS2 codes for a protein called Alsin that plays an important role in preventing neurons from dying. The researchers hope that by dissecting Alsin function they will gain new insights into the causes of ALS and in doing so identify new targets for treatment.

## MISSOURI

### St. Louis - Washington University

**Jeffrey Milbrandt M.D., Ph.D.**

RG Treatment of axonopathy in ALS by increased NAD synthesis and Sirt1 activation

\$100,000.00	7/1/2005	6/30/2006	Year 1
\$100,000.00	7/1/2006	6/30/2007	Year 2
\$100,000.00	7/1/2007	6/30/2008	Year 3

*Summary:* The investigators have found that increased levels of an enzyme involved in cellular energy metabolism can protect against axonal degeneration. This protection requires an additional protein that is important for regulating lifespan. The investigators will determine whether axonal degeneration caused by defective mitochondria, powerplants of the cell that are frequently defective in neurological diseases, can be blocked by this pathway. The investigators will explore the therapeutic utility of activating this axonal protective pathway in a mouse model of ALS.

**NEW YORK**

**New York - Columbia Presbyterian Medical Center**

**Hiroshi Mitsumoto M.D.**

EMG Restricted funds for the Eleanor and Lou Gehrig MDA/ALS Center

\$512,828.00	4/1/2004	3/31/2005	Year 3
\$438,949.00	4/1/2005	3/31/2006	Year 4

*Summary:* Ear-marked gift

**New York - Columbia University**

**Hiroshi Mitsumoto M.D.**

RG Genetic-environmental epidemiology in amyotrophic lateral sclerosis (ALS)

\$136,690.00	1/1/2004	12/31/2004	Year 1
\$137,628.00	1/1/2005	12/31/2005	Year 2
\$141,398.00	1/1/2006	12/31/2006	Year 3

*Summary:* Investigators will develop an effective, reliable patient questionnaire, establish a method of selecting and recruiting subjects for study, investigate environmental exposure and risk factors, and establish a DNA and plasma banking system for future investigation of genetic make-up and biochemical profiles in ALS. The proposed study will be the first project of the MDA initiated National ALS Study Group. Gene-environment interaction in ALS is critical in identifying potential causes of ALS as well as approaches for prevention and treatment.

**Hiroshi Mitsumoto M.D.**

SG MDA/ALS Multidisciplinary Care Conference

\$15,000.00	2/1/2006	11/30/2006	Year 1
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*Summary:* This conference is designed for neurologists, advanced practice nurses, rehabilitation therapists, nutritionists, social workers and other health professionals involved in the management of ALS. Participants will be provided with up to date information regarding ALS research and current clinical management practices related to respiratory issues, symptom management, nutrition, communication, rehabilitation, caregiver support and end of life in ALS.

## **New York - Cornell University**

### **M. Flint Beal M.D.**

RG	Testing novel therapeutics in a transgenic mouse model of amyotrophic lateral sclerosis (ALS)				
	\$73,058.00	7/1/2004	6/30/2005	Year 1	
	\$73,058.00	7/1/2005	6/30/2006	Year 2	
	\$73,058.00	7/1/2006	6/30/2007	Year 3	

*Summary:* The investigators have obtained evidence that treatment with a drug which inhibits inflammation, as well as another which acts as an antioxidant, both exert significant neuroprotective effects in a transgenic mouse model of ALS. These studies have the promise of developing novel new therapies to slow or halt the progression of ALS.

### **M. Flint Beal M.D.**

RG	Targeting new therapeutics in a transgenic mouse model of ALS				
	\$82,042.00	1/1/2006	12/31/2006	Year 1	
	\$82,042.00	1/1/2007	12/31/2007	Year 2	

*Summary:* The present studies are devoted to developing new effective treatments for ALS. The investigators will determine whether 2 agents, which block damage to mitochondria, exert therapeutic effects in a transgenic mouse model of ALS. They also intend to test a novel compound, which activities pathways, which protect against inflammation and oxidative damage. These studies have the promise of developing novel new thereapies to slow or halt the progression of ALS.

## **New York - Mount Sinai School of Medicine**

### **Giulio Pasinetti M.D., Ph.D.**

RG	The role of cyclooxygenase-2 inhibitors in a model of ALS neurodegeneration				
	\$87,698.00	7/1/2003	6/30/2004	Year 1	
	\$87,698.00	7/1/2004	6/30/2005	Year 2	
	\$87,698.00	7/1/2005	6/30/2006	Year 3	

*Summary:* Researcher's will generate a profile of protein biomarkers that represent the therapeutic benefit of cyclooxygenase in ALS and study these proteins as a function of the clinical and pathological progression of this disease.

## **NORTH CAROLINA**

### **Chapel Hill - University of North Carolina**

#### **Nikolay V. Dokholyan Ph.D.**

RG	Uncovering the origins of mutant SOD1 toxicity in familial ALS				
	\$108,738.00	1/1/2004	12/31/2004	Year 1	
	\$107,735.00	1/1/2005	12/31/2005	Year 2	
	\$110,819.00	1/1/2006	12/31/2006	Year 3	

*Summary:* To understand mutant-mediated SOD1 toxicity, investigators must uncover how the SOD1 physical properties - thermal stabilities of SOD1 monomers and naturally occurring dimers - are affected by mutations. It is challenging and time consuming to experimentally estimate the effect of a large number of these mutations. Investigators propose to computationally determine whether FALS associated SOD1 mutations (i) destabilize SOD1, (ii) increase SOD1 dimer dissociation rates, and/or (iii) alter SOD1 metallation. Each of these scenarios promotes SOD1 misfolding/aggregation, and aggregates, in turn, may be toxic. They also propose to employ newly developed computational tools to reconstruct the structure of SOD1 aggregates, a crucial step in the development of drugs that inhibit SOD1 aggregate formation.

**Winston-Salem - Wake Forest University**

**Oswaldo Delbono M.D., Ph.D.**

RG IGF-1 regulation of calcium signaling in ALS

\$100,000.00	7/1/2005	6/30/2006	Year 1
\$100,000.00	7/1/2006	6/30/2007	Year 2
\$100,000.00	7/1/2007	6/30/2008	Year 3

*Summary:* The main goal of this proposal is to determine whether the increased expression of targeted insulin-like growth factor-1 (IGF-1) to the central nervous system delays the fatal outcome of familial, and some cases, of sporadic Amyotrophic Later Sclerosis (ALS). In addition, the investigators will test the hypothesis that IGF-1 prevents the downregulation of the calcium signaling cascade - gene expression involved in ALS motor neuron apoptosis.

**PENNSYLVANIA**

**Hershey - Pennsylvania State University**

**James R. Connor Ph.D.**

RG Genotyping analysis for Hfe mutations in amyotrophic lateral sclerosis

\$102,020.00	7/1/2003	6/30/2004	Year 1
\$80,032.00	7/1/2004	6/30/2005	Year 2
\$83,190.00	7/1/2005	6/30/2006	Year 3

*Summary:* Investigators propose to: (i) perform a prospective genotyping analysis using blood samples, (ii) determine the effect of the Hfe mutation on age of onset and rate progression of ALS, and (iii) determine the cellular distribution at which the Hfe mutation may be influencing ALS (e.g. muscle versus motoneurons).

**Philadelphia - University of Pennsylvania**

**Hong Lin Ph.D.**

DG Role of NF-L RNA-binding protein in protein aggregation and neurodegeneration in amyotrophic lateral sclerosis (ALS)

\$44,550.00	7/1/2004	6/30/2005	Year 1
\$44,550.00	7/1/2005	6/30/2006	Year 2
\$44,550.00	7/1/2006	6/30/2007	Year 3

*Summary:* This research proposal will seek to explore the role of p190RhoGEF in triggering aggregation if NF-L and mutant SOD1 proteins in motor neurons of mutant SOD1 transgenic mice, in cultured motor neurons and in neuronal cell lines. The study may provide important insights into pathogenetic mechanisms of motor neuron degeneration and identify potential targets for therapeutic intervention.

## TEXAS

### Houston - University of Texas Health Center

#### **Vasanthi Jayaraman Ph.D.**

RG High throughput screening for AMPA receptor antagonists for ALS

\$100,000.00	1/1/2005	12/31/2005	Year 1
\$100,000.00	1/1/2006	12/31/2006	Year 2

*Summary:* Glutamate toxicity mediated through a class of proteins called AMPA receptors is currently thought to be the major trigger for motor neuron death. Inhibitors of this protein have been consistently effective in animal models but not in humans mainly because of their low water solubility leading to their deposition in the liver resulting in necrosis. There is hence, a need for water soluble AMPA receptor inhibitors as drugs for ALS and investigators propose to address this need by screening for RNA ligands as inhibitors, since these are water soluble, using a high throughput screening assay developed in the lab.

### San Antonio - University of Texas

#### **Holly Van Remmen Ph.D.**

RG Alterations in mitochondrial function in the initiation and progression of ALS

\$100,000.00	1/1/2005	12/31/2005	Year 1
\$100,000.00	1/1/2006	12/31/2006	Year 2
\$100,000.00	1/1/2007	12/31/2007	Year 3

*Summary:* To further delineate the role of oxidative stress in ALS, investigators will mutant SOD mice with mouse models that have decreased oxidative stress due to increased levels of the protective antioxidant enzymes, MnSOD, Catalase PHGpx and Thioredoxin. The results of this study will provide a better understanding of the role of mitochondria in ALS and potentially lead to new options for interventions and therapies aimed at preventing mitochondrial oxidative stress.

## WASHINGTON

### Seattle - University of Washington

#### **Patrick Weydt M.D.**

DG VEGF gene delivery strategies for motor neuron disease

\$45,000.00	7/1/2005	6/30/2006	Year 1
\$45,000.00	7/1/2006	6/30/2007	Year 2
\$45,000.00	7/1/2007	6/30/2008	Year 3

*Summary:* VEGF-replacement therapy has yielded encouraging successes in transgenic animal models. However, VEGF also has effects on many other tissues, e.g. tumor growth. Therefore, targeting of VEGF to the motor neurons may be mandatory to fully realize its therapeutic potential. The investigators propose to generate 2nd generation viral vectors and then to test if VEGF delivery to motor neurons or muscle can successfully treat mice with ALS and SBMA, while limiting untoward off-target effects.

## Belgium

## Leuven - VIB

### **Peter Carmeliet Ph.D., M.D.**

RG Therapeutic potential of VEGF for amyotrophic lateral sclerosis (ALS)

\$120,452.00	1/1/2004	12/31/2004	Year 1
\$124,482.00	1/1/2005	12/31/2005	Year 2
\$118,000.00	1/1/2006	12/31/2006	Year 3

*Summary:* Accumulating evidence indicates that reduced VEGF levels negatively influence ALS both in humans and in animal models of ALS. This project investigates in preclinical mouse and rat models of ALS, whether and how VEGF can be used to prevent or attenuate neurodegeneration and neuromuscular disease.

## Canada

### London - University of Western Ontario

#### **Christen Shoemith BSc, MD**

TRA Clinical Research Training  
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\$74,200.00	7/1/2005	6/30/2006	Year 1
\$69,910.00	7/1/2006	6/30/2007	Year 2

*Summary:* The Clinical Research Training Grant is designed to provide promising young physicians the research training opportunities that are needed to become productive clinical investigators in neuromuscular diseases. Grantees will receive training in the diagnosis and management of adults and children with neuromuscular diseases, complete formal coursework in clinical research methodologies, and complete a clinical research project during the two years of fellowship training.

#### **Michael Strong M.D, FRCPC**

RG The regulation of microglial activation in amyotrophic lateral sclerosis (ALS)

\$81,846.00	7/1/2004	6/30/2005	Year 1
\$86,782.00	7/1/2005	6/30/2006	Year 2
\$89,702.00	7/1/2006	6/30/2007	Year 3

*Summary:* The Researchers are proposing that the nature of the motor neuron injury is a critical determinant in whether this microglial response is neuroprotective or neurotoxic, and that this delicate balance between neuroprotection and neurotoxicity is disturbed in ALS. In these experiments, they will determine whether the nature of the motor neuron interaction with microglial cells, following neuronal injury, can be modified to shift the balance in favor of neuroprotection.

## Montreal - McGill University

**Heather Durham Ph.D.**

RG Mechanisms of motor neuron vulnerability to disease

\$89,419.00	7/1/2004	6/30/2005	Year 1
\$86,185.00	7/1/2005	6/30/2006	Year 2
\$88,715.00	7/1/2006	6/30/2007	Year 3

*Summary:* This research project will investigate how mutant proteins responsible for familial motor neuron diseases alter the interaction between two important normal functions that must occur in motor neurons: receiving information through excitation of receptor proteins by the neurotransmitter, glutamate, and disposal of both normal and damaged proteins through the proteasome.

**Eric A. Shoubridge Ph.D.**

RG Assembly of cytochrome c oxidase in mitochondrial encephalomyopathy

\$88,554.00	7/1/2005	6/30/2006	Year 1
\$88,554.00	7/1/2006	6/30/2007	Year 2
\$88,554.00	7/1/2007	6/30/2008	Year 3

*Summary:* The enzymes responsible for energy production are large protein complexes composed of many subunits. The proper coordination and assembly of these components is essential to deliver the energy required for muscle work. The investigators are investigating the role of two different proteins which, when mutated, result in loss of activity of one of the enzyme complexes in skeletal muscle and nerve, due to a failure of complex assembly, and fatal neuromuscular disease.

**Montreal - Montreal General Hospital**

**Guy Rouleau M.D., Ph.D.**

RG Identification and characterization of the ALS3 gene

\$100,000.00	1/1/2005	12/31/2005	Year 1
\$100,000.00	1/1/2006	12/31/2006	Year 2

*Summary:* Investigators are examining the sequence of the entire 4 mega-base pair region from the disease bearing allele of an affected individual. When all of the patient's DNA sequence variations in this region are known, they will identify which variant is the causative mutation. This will be done by testing for the variation's absence in control individuals and by searching for other mutations in the same gene from our panel of sporadic and familial ALS samples. A thorough characterization of the causative gene will ensue.

**Montreal - University of Montreal**

**Guy Rouleau M.D., Ph.D., FRCPC**

RG Screening genes critical for the development of motor neurons in ALS patients

\$100,000.00	1/1/2006	12/31/2006	Year 1
\$100,000.00	1/1/2007	12/31/2007	Year 2
\$100,000.00	1/1/2008	12/31/2008	Year 3

*Summary:* Recently, a group of researchers have identified a set of 30 genes specifically expressed in a subset of motoneurons. Identifying mutations in these genes will have a significant impact on our understanding of the pathogenic mechanisms in ALS as well as provide new insights into potential treatment strategies and therapeutic targets.

### **Quebec - Laval University**

#### **Francois Berthod Ph.D.**

RG Development of a tissue-engineered model of spinal cord to study amyotrophic lateral sclerosis (ALS)

\$71,569.00	7/1/2004	6/30/2005	Year 1
\$75,240.00	7/1/2005	6/30/2006	Year 2
\$80,240.00	7/1/2006	6/30/2007	Year 3

*Summary:* A model of reconstructed spinal cord will permit the study of various combinations of cells overexpressing the mutant and wild type human SOD1, in order to determine which non-neuronal cell type could induce or participate in MN death and the mechanism responsible.

### **Italy**

### **Rome - University of Rome**

#### **Antonio Musaro Ph.D.**

RG Study of the molecular and functional interplay between muscle and nerve in a mouse model of ALS

\$73,700.00	7/1/2005	6/30/2006	Year 1
\$73,700.00	7/1/2006	6/30/2007	Year 2
\$73,700.00	7/1/2007	6/30/2008	Year 3

*Summary:* ALS is considered a motor neuron disease. However, in light of recent experimental evidences it is clear that the accumulation of SOD1 mutants in postnatal motoneurons does not cause motoneuron pathology or motoneuron disease. The innovative aspects of this project are to disclose the role exerted by the untested skeletal muscle system on the pathogenesis of ALS and to define the molecular connection between muscle and nerve regulating tissue remodeling.

### **United Kingdom**

### **London - University College London**

#### **Linda Greensmith Ph.D.**

RG Treatment of ALS with Arimoclomol, a novel inducer of heat shock proteins

\$7,140.00	1/1/2005	12/31/2005	Year 1
\$100,000.00	1/1/2005	12/31/2005	Year 1
\$100,000.00	1/1/2006	12/31/2006	Year 2
\$100,000.00	1/1/2007	12/31/2007	Year 3

*Summary:* Arimoclomol belongs to a new category of molecules that up-regulate the expression of heat shock proteins. In the proposed study, investigators would like to investigate the mechanism of action of these novel molecules and characterize the heat shock response in motor neurons, in order to optimize human clinical trials of this compound and possibly identify other potential novel therapeutic targets.