

CALENDAR YEAR(s): 2009,2010,2011,2012

**FUNDING PROGRAM LEGEND**

(DRG)	Designated Research Grant
(RRG)	Restricted Research Grant
(RF)	Research Fellowship
(RG)	Research Grant
(SG)	Special Grant
(DG)	Research Development Grant
(TCL)	Tall Cedars of Lebanon
(CRTG)	Clinical Research Training Grant
(TRAC)	Translational Research Grant
(TR-IG)	Infrastructure Grant
(TR-CG)	Corporate Grant

**ARIZONA**

**Phoenix - St. Joseph's Hospital & Medical Center**

**Fu-Dong Shi M.D., Ph.D.**

RG	CD4+CD25+ regulatory T cells in experimental myasthenia gravis			
	\$120,000.00	1/1/2009	12/31/2009	Year 3

*Summary* Two new approaches to enhance a key regulatory element of the immune system and define the feasibility of these approaches for myasthenia gravis (MG) therapy.

**Tempe - Arizona State University**

**N. Jeanne Wilson-Rawls Ph.D.**

RG	The Role of the Notch/Numb interaction in promoting skeletal muscle repair.			
	\$121,538.00	1/1/2009	12/31/2009	Year 1
	\$123,318.00	1/1/2010	12/31/2010	Year 2
	\$128,456.00	1/1/2011	12/31/2011	Year 3

*Summary* Before any stem cell therapy can be incorporated into clinical practice it will be necessary to characterize the genetic and biochemical regulators of signals which drive stem cells to survive and self-renew. An understanding of the regulation of these events will represent an important step for enhancing the self-renewal of engrafted cells, and thus their regenerative potential as therapies for myopathies. The studies that are proposed ask important questions to determine the role of Numb regulation of Notch signaling and whether it creates a molecular switch between these two processes in myogenesis. Using inducible mutants of Numb we will examine the impact of this gene on satellite cell proliferation and differentiation. Muscle repair will be measured following experimentally induced injury by examining the rate and extent of muscle fiber regeneration and the number and distribution of active and reserve satellite cells. The establishment of genetically corrected populations of satellite cells represents a viable approach to treating some forms of muscular dystrophy. Enhancing the self-renewal capabilities of engrafted satellite cells will significantly contribute to the regenerative potential of this therapeutic approach.

**Tucson - University of Arizona**

**Ronald E Allen Ph.D.**

RG	Satellite cells stimulate angiogenesis in skeletal muscle			
	\$100,000.00	1/1/2009	12/31/2009	Year 3

*Summary* Researchers will study how muscle precursor cells regulate new vessel development and how these cells can stimulate vessel growth in dystrophic muscle. This may lead to therapy to maintain muscle mass and strength.

**David Hartshorne Ph.D.**

RG	Role of the calpain system in human muscular dystrophy			
	\$98,778.00	7/1/2008	6/30/2009	Year 3

*Summary* The loss of muscle mass in the muscular dystrophies is due to a greatly increased rate of muscle protein degradation. This degradation may be initiated by a variety of physiological events, but it ultimately is mediated by two proteolytic enzymes belonging to the calpain system. This project will determine how the calpains are changed in human dystrophic muscle and how these changes lead to increased and/or unregulated muscle protein degradation.

**CALIFORNIA****Davis - University of California****Sue C. Bodine Ph.D.**

RG	Function and regulation of muscle E3 ligases, MuRF1 and MAFbx			
	\$122,826.00	7/1/2008	6/30/2009	Year 3

*Summary* This proposal will investigate the physiological role of two recently discovered genes, MuRF1 and MAFbx, that are selectively expressed in muscle tissue and upregulated under numerous atrophy conditions including myopathies and neural degeneration.

**Ricardo Anibal Maselli M.D.**

RG	Congenital myasthenic syndromes: Refining newer tools for diagnosis and treatment			
	\$100,000.00	1/1/2009	12/31/2009	Year 3

*Summary* Researchers will develop new DNA sequencing technology for treatment of congenital myasthenic syndromes based on interference of RNA expression.

**Craig McDonald M.D.**

CRNG	MDA Clinical Research Network at UC Davis			
	\$100,000.00	8/1/2008	7/31/2009	Year 1
	\$100,000.00	8/1/2009	7/31/2010	Year 2
	\$.00		7/31/2010	Year 3

*Summary* The MDA Neuromuscular Disease Clinic at UC Davis will be a regional clinical research center as part of a MDA Clinical Research Network that supports studies of Duchenne muscular dystrophy (DMD). The UC Davis center will work with the MDA Clinical Research Network to: 1) Assume a leadership role in the development of a DMD clinical registry that will facilitate the conduct of clinical studies aimed at optimizing and standardizing clinical care; 2) Develop and optimize standardized and comprehensive outcome measures for DMD to be used in clinical studies and trials; 3) Refine and validate an innovative self-report health-related quality of life measure (NeuroQoL) which will be employed across the lifespan of children and adults with DMD; 4) Assess the relationship of candidate clinical endpoints to health-related quality of life measures in DMD to facilitate and expedite the testing of new therapies through clinical trials; 5) Coordinate activities which enhance communication and collaboration with MDA clinics in the western United States by engaging MDA clinics in training activities, regional education conferences, and collaborative clinical research activities.

**David Paul Richman M.D.**

RG	Pathogenesis of Anti-MuSK Myasthenia			
	\$125,000.00	1/1/2009	12/31/2009	Year 1
	\$125,000.00	1/1/2010	12/31/2010	Year 2
	\$125,000.00	1/1/2011	12/31/2011	Year 3

*Summary* The majority of, but not all, patients with myasthenia gravis (MG) have antibodies (Abs) that attack the acetylcholine receptors (AChR) at their nerve-muscle junctions and block the signaling between the nerves and muscles. Other MG patients, many of whom have significant muscle wasting, have a different set of autoantibodies targeting another protein component of the nerve-muscle junction: muscle-specific kinase (MuSK). The role of Abs to MuSK in this form of MG is not known, in contrast to the role of Abs to the AChR in standard MG which are known to block the signaling between nerve and muscle. It is not even clear if the MuSK autoantibodies play any role in the myasthenia that develops in these patients. This project is aimed at determining whether these Abs are important

and, if they are, precisely what effect they have on nerve-muscle signaling. We have successfully engineered tissue culture cells to produce MuSK and have purified the large amounts of the protein required for immunization of experimental animals to produce an animal model of this disease. We have recently immunized laboratory rats with the purified MuSK and have succeeded in producing a very severe form of this disease. We are now proposing to study the mechanisms by which the Abs cause this severe muscle weakness and wasting. This information will have a high likelihood of providing the types of information needed to develop treatments of this very severe and poorly understood form of MG.

**Irvine - California Stem Cell, Inc**

**Chris N Airriess PhD, Cardiovascular Physiology**

**TR-CG** Cell Transplantation Strategy For the Treatment of Amyotrophic Lateral Sclerosis

\$200,000.00                      7/1/2008                      6/30/2009                      Year 1

*Summary* Amyotrophic lateral sclerosis (ALS) results in motor function loss because the cells within the spinal cord that control muscles are destroyed. California Stem Cell (CSC) has developed technology to make those cells in unlimited quantity, using human embryonic stem cells (hESCs). The goal of this research is restoration of function to the muscles that control breathing in ALS patients. The greatest challenge of hESC research is to generate large amounts of one cell type in high purity for use in disease. Our company Founder was the first researcher to make large amounts of high purity cells from hESCs, which were used for treating spinal cord injuries in rats and are currently being developed for use in humans. Here, we propose to conduct safety and functional studies of this new ALS treatment. It is essential to use larger animal models to better reflect the human condition. We will also work closely with the Food and Drug Administration to ensure our studies are relevant to humans.

**Irvine - University of California**

**Jouni Vesa Ph.D.**

**DG** Characterization of Molecular Pathogenesis of IBMPFD

\$60,000.00                      1/1/2009                      12/31/2009                      Year 1

\$60,000.00                      1/1/2010                      12/31/2010                      Year 2

\$60,000.00                      1/1/2011                      12/31/2011                      Year 3

*Summary* IBMPFD (Inclusion Body Myopathy associated with Paget's disease of bone and Frontotemporal Dementia) is a progressive condition causing weakness and atrophy of the skeletal muscle. Muscle weakness begins in 20s to 40s, and the disease is characterized by accumulation of storage material in the muscles. Paget's disease is caused by excessive osteoclastic activity and increased bone turnover. Frontotemporal dementia begins in the middle of 50s showing degeneration of the frontal and temporal lobes of brain. Affected individuals die from progressive muscle weakness, and cardiac and respiratory failure in their 40s to 60s. IBMPFD is caused by mutations in the VCP (Valosin Containing Protein)-gene. The majority of disease mutations change a conserved amino acid 155 (R155H/P/C/S) suggesting an important role for this residue. Entire protein is also highly conserved suggesting that VCP is necessary for normal development and survival of the muscle, bone and brain cells. VCP is involved in several cellular activities including membrane fusion, transcription activation, cell cycle control, apoptosis, and protein degradation. The aim of this proposal is to characterize those pathological cascades that result in muscle weakness in IBMPFD patients, using molecular and cellular approaches. In our experiments, we aim to clarify the pathological mechanisms of IBMPFD using cells and tissues from patients and control subjects, as well as from our recently generated mouse model for IBMPFD.

**Sara T. Winokur Ph.D.**

**RG** Developmental gene expression in FSHD mesoangioblast stem cells

\$95,000.00                      7/1/2008                      6/30/2009                      Year 2

*Summary* Researchers will test mesangioblasts from FSHD and normal tissues to learn of alterations in developmental gene expression forming muscle.

**Kyoko Yokomori Ph.D.**

RG	Identification of D4Z4 target genes critical for FSHD pathogenesis			
	\$122,738.00	1/1/2009	12/31/2009	Year 2

*Summary* We hypothesize that the heterochromatin structure spreads a silencing effect to target genes, but in FSHD this effect is lost and these genes may be abnormally expressed. We would therefore like to make transgenic mice overexpressing a specific gene in a muscle-specific manner to test whether it leads to muscular dystrophy. The successful outcome of this project will provide a valuable opportunity to understand FSHD pathogenesis by generating a mouse model, which could lead to development of therapeutic interventions.

**La Jolla - Burnham Institute for Medical Research****Rolf Bodmer Ph.D**

RG	Cardiac Dystrophin Model in Drosophila			
	\$121,240.00	1/1/2009	12/31/2009	Year 2
	\$121,240.00	1/1/2010	12/31/2010	Year 3

*Summary* In this proposal we plan to utilize the genetic tools available in the fly model (1) to study potential downstream effectors of Dystrophin in cardiac performance and morphology, (2) to utilize the Drosophila dystrophin model to examine the ability of micro- or mini-versions of human dystrophin gene to correct the dystrophin mutant defects, and (3) to carry out genetic screens to identify new gene candidates that may contribute to the cardiomyopathies observed in human Muscular Dystrophy patients. The outcome is to elucidate the genetic pathways associated with dystrophic heart defects, and to point to potential therapeutic targets for dilated cardiomyopathy.

**La Jolla - Ludwig Institute****Don Cleveland Ph.D.**

RG	Determining the contribution of mitochondrial dysfunction in ALS pathogenesis			
	\$125,000.00	1/1/2009	12/31/2009	Year 2
	\$125,000.00	1/1/2010	12/31/2010	Year 3

*Summary* Abnormal mitochondrial morphology have consistently been reported in ALS patients and mouse models that are genetic mimics of an inherited form of ALS. Genetic methods in ALS model mice will be used to increase mitochondrial biogenesis and function, decrease production of damaging, highly reactive forms of oxygen, and increase the ability of mitochondria to control an intracellular signaling chemical (calcium). This three pronged approach should determine the contribution of specific mitochondrial dysfunctions and provide potential directions for therapies.

**La Jolla - University of California****Ju Chen Ph.D.**

RG	The functional role of nebulin in nemaline myopathy			
	\$110,000.00	1/1/2009	12/31/2009	Year 3

*Summary* Mutations in nebulin protein causes nemaline myopathy. Researchers will determine if thin filament length correlates with nebulin isoform expression. It will also be determined what role nebulin has in signaling at the Z-line when a subdomain is deleted.

**Stephan Lange Ph.D. (Dr. sci.nat.)**

DG	The role of novel M-band associated proteins in LGMD2J.			
	\$45,000.00	1/1/2009	12/31/2009	Year 2
	\$45,000.00	1/1/2010	12/31/2010	Year 3

*Summary* Several mutations at the very end of titin have been identified to cause the LGMD2J-form of muscular dystrophy. We identified two structural muscle proteins that interact with the end-region of titin. We will characterize these binding partners of titin and delineate their biological role for muscle formation and function. Ultimately, these studies may lead to a better understanding and treatment of this muscular dystrophy.

**G. Diane Shelton D.V.M, Ph.D.**

RG	Canine Model of Inflammatory Myopathies: Molecular Mechanisms			
	\$103,693.00	7/1/2008	6/30/2009	Year 1
	\$100,813.00	7/1/2009	6/30/2010	Year 2
	\$104,711.00	7/1/2010	6/30/2011	Year 3

*Summary* One of the problems hindering the advancement of new treatments for human inflammatory myopathies is the lack of suitable animal models. Canine IMs occur spontaneously, have reliable clinical signs, and are treated similarly to human IMs. As in human IM patients, autoantibodies are found in canine IMs; however, unlike in humans to date, autoantibodies in canine IMs are muscle specific. We believe that further studies of the muscle specific autoantibodies found in both CMMM and CPM may offer insight into mechanisms of development of autoimmunity in both human and canine inflammatory myopathies. Such autoantibodies are potentially also present in human IM patients. The results of this project may generate a new understanding of IMs and lead to new tools for the diagnosis and treatment of IMs in humans as well as dogs.

**La Jolla - The Salk Institute for Biological Studies****Jiefei Yang Ph.D**

DG	The role of nestin in the formation of neuromuscular junctions			
	\$45,000.00	1/1/2009	12/31/2009	Year 3

*Summary* Researchers will study the role of nestin protein in regulating the stability of acetylcholine receptor (AChR) clusters and the integrity of the neuromuscular junction (NMJ). This may represent a target for therapeutic development.

**La Jolla - The Scripps Research Institute****Ya Wen Liu Ph. D.**

DG	Dynamin-2 cellular function and the consequences of mutations linked to CMT			
	\$60,000.00	1/1/2009	12/31/2009	Year 1
	\$60,000.00	1/1/2010	12/31/2010	Year 2
	\$60,000.00	1/1/2011	12/31/2011	Year 3

*Summary* Genetic analysis of families with heritable Charcot Marie Tooth neuropathies has revealed several mutations in the large GTPase dynamin-2 to be associated with the disease. It is not known how these mutations change the activity of dynamin-2 and affect its function in living cells. We are experts in dynamin biochemistry and cell biology and we propose to determine exactly how these mutations affect dynamin function so that we can determine the underlying cause of disease. This information may be useful in designing therapeutic interventions to prevent the onset of disease or to lessen its severity.

**Markus W. Zeeb Ph.D.**

DG	Structure determination of muscleblind and its complexes with ss/dsRNA by NMR spectroscopy			
	\$45,000.00	7/1/2008	6/30/2009	Year 3

*Summary* This proposal aims to study the structure of free MBNL and its interactions with its physiological binding partners as well as the disease associated binding target. These studies will reveal insights into the disease mechanisms at a molecular level, which will provide the basis for development of specific drug therapies for the fight against DM.

**Los Angeles - University of California****Carmen Bertoni Ph.D.**

RG	Gene correction for Duchenne muscular dystrophy mediated by modified single stranded oligonucleotide			
	\$126,500.00	7/1/2008	6/30/2009	Year 2
	\$126,500.00	7/1/2009	6/30/2010	Year 3

*Summary* Mouse models will be developed to study the effects of oligonucleotides on correcting dystrophin DNA for DMD.

**Bennett Novitch Ph.D.**

RG	Role of FoxP Transcription Factors in Spinal Motor Neuron Development			
	\$120,000.00	7/1/2008	6/30/2009	Year 1
	\$120,000.00	7/1/2009	6/30/2010	Year 2
	\$120,000.00	7/1/2010	6/30/2011	Year 3

*Summary* Motor neurons (MNs) are essential for all muscle movements, and the loss of their function underlies many devastating neurodegenerative diseases such as spinal muscular atrophy, spinal bulbar muscular atrophy, and amyotrophic lateral sclerosis. While few therapies currently exist to treat these conditions, great hope has been raised by the possibility of using stem cells to replace damaged MNs and restore motor functions. To achieve this goal, it is vital to first understand how MNs are normally formed. During embryonic development, distinct classes of MNs are generated, each dedicated to the innervation of particular groups of muscles. The recovery of movement is likely to require the regeneration of all types of MNs. However, the methods that are currently being used to make MNs from stem cells appear to generate only one of these classes, raising the following questions: Can other classes of MN be generated, and if so, will each class have a different therapeutic potential? In our preliminary work, we have found that members of the Foxp gene family are expressed by subsets of developing MNs, suggesting that these genes may contribute to the process of MN diversification. We will examine how Foxp genes participate in MN development, and test whether their function can be manipulated to create different classes of MNs from stem cells and advance the development of MN disease therapies.

**Melissa Spencer Ph.D.**

RG	Investigation of Trim32 using biochemistry and mouse models to understand LGMD2H and SMA			
	\$109,450.00	1/1/2008	6/30/2009	Year 3

*Summary* The investigators are investigating the protein mutated in limb girdle muscular dystrophy 2H and sarcotubular myopathy to gain insight into disease mechanisms.

**Peter Stoilov Ph.D.**

DG	High throughput screening for small molecules affecting alternative splicing: A search for drugs to t			
	\$45,000.00	1/1/2009	12/31/2009	Year 3

*Summary* A novel reporter assay will screen for compounds that modulate the splicing of SMN2 exon 7 to compensate for the loss of SMN1 in spinal muscular atrophy (SMA).

**David W. Walker Ph.D.**

DG	Modeling hereditary mitochondrial complex I deficiency in Drosophila			
	\$45,000.00	7/1/2008	6/30/2009	Year 3

*Summary* This research proposes to develop a model of hereditary mitochondrial encephalomyopathy in Drosophila, which will allow a powerful genetic approach to study the basic mechanisms of neuromuscular disease.

**Los Angeles - University of Southern California****Chien-Ping Ko Ph.D.**

RG	Synaptic Defects in Spinal Muscular Atrophy			
	\$89,840.00	7/1/2008	6/30/2009	Year 1
	\$93,189.00	7/1/2009	6/30/2010	Year 2
	\$96,707.00	7/1/2010	6/30/2011	Year 3

*Summary* The long-term goal of this research is to develop novel therapies for SMA by targeting the sites of defects contributing to motor impairments. In this investigation, we will use a mouse model mimicking type II SMA to characterize two potential sites of defects at nerve connections (synapses): nerve-muscle contacts and synaptic contacts on spinal motor neurons. We will test a novel concept that motor impairment is primarily attributed to defects in the synaptic contacts on spinal motor neurons, rather than in the nerve-muscle contacts, as suggested by the prevailing thinking. In addition, we will examine whether the activation of glial cells called microglia may contribute to synapse loss in spinal motor neurons. The research will provide a new fundamental

understanding on the mechanisms of SMA and other motor neuron diseases. The findings could also lead to novel therapies by focusing on drugs that can promote formation, maintenance and function of synapses on motor neurons in the spinal cord.

## Menlo Park - Stanford University

### Helen M. Blau Ph.D.

RG	A novel mouse model for Duchenne muscular dystrophy			
	\$100,000.00	7/1/2008	6/30/2009	Year 2
	\$100,000.00	7/1/2009	6/30/2010	Year 3

*Summary* Researchers will develop a new mouse model incorporating telomerase activity to more closely mimic the human DMD.

### Stephane Boutet Ph.D.

DG	Regulation of Pax3 and Pax7 during postnatal myogenesis			
	\$45,000.00	1/1/2009	12/31/2009	Year 3

*Summary* Researchers will elucidate the mechanisms of Pax3 expression during post-natal myogenesis. This will help to understand Pax3 role in muscle stem cells and may lead to therapies in muscular dystrophy.

### Michele Calos Ph.D.

RG	Non-viral gene therapy for Duchenne muscular dystrophy using phiC31 integrase			
	\$100,000.00	1/1/2009	12/31/2009	Year 2

*Summary* We have developed a simple, non-viral gene transfer system that uses an integrase enzyme to correct cells genetically in a safe manner. The integrase places the therapeutic gene into defined locations in the chromosomes, minimizing the risk of activating cancer genes. Our approach will take advantage of a type of adult stem cell called mesoangioblasts from blood vessels isolated, corrected by using integrase, and reintroduced, eliminating the need for immune suppression and providing a potential cure for the disease.

### Hans Katzberg MD

CRTG	Effect of Diaphragm Pacing Stimulation on Sleep Quality in Patients with ALS			
	\$90,000.00	7/1/2008	6/1/2009	Year 1
	\$90,000.00	7/1/2009	6/1/2010	Year 2

*Summary* Investigators believe that studying the effects of conditioning the diaphragm on sleep quality in patients with ALS will help us better understand sleep dysfunction in this group of patients and also represents a potential novel therapeutic intervention for treating sleep dysfunction in patients with ALS and neuromuscular disease.

### Lorene Marie Nelson Ph.D.

RG	Gene-Environment Interactions in the Etiology of ALS			
	\$98,209.00	1/1/2009	12/31/2009	Year 1
	\$96,955.00	1/1/2010	12/31/2010	Year 2
	\$98,415.00	1/1/2011	12/31/2011	Year 3

*Summary* Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease, and very little is known about factors that predispose to the development of ALS. Only 5-10% of ALS patients have a familial (genetic) form of the disease. Among the remaining 90% of patients with sporadic ALS, the cause is unknown. It is likely that a multifactorial process causes ALS, with contributions from both environmental and genetic factors. Using data from a recently completed epidemiologic study of ALS, we propose to investigate whether exposure to metals or pesticide chemicals is associated with the risk of developing ALS, and whether certain genetic factors either increase or decrease the risk associated with these exposures. By determining whether genetic factors modify the risk associated with these environmental agents, we hope to provide insight regarding the biological basis for the development of ALS. If these factors are shown to play a role in the cause of ALS, this will contribute to knowledge about the mechanisms of disease. With this knowledge, strategies could be developed to prevent ALS or to slow disease progression among affected individuals.

**William Talbot Ph.D.**

RG	A novel neuronal protein that triggers myelination in Schwann cells			
	\$97,984.00	7/1/2008	6/30/2009	Year 1
	\$99,000.00	7/1/2009	6/30/2010	Year 2
	\$99,000.00	7/1/2010	6/30/2011	Year 3

*Summary* Myelin is the insulation that allows axons to rapidly transmit nervous impulses. Disruption of myelin insulation causes the symptoms of Charcot-Marie-Tooth disease and other debilitating peripheral neuropathies. Our goal is to use the zebrafish to identify new genes in the formation of myelin and their associated axons. We have recently identified a novel membrane-associated protein that is essential for cells to form myelin. Researchers will test that this protein is an axon-associated signal that triggers myelin formation by Schwann cells that when lacking may be a new model of Charcot-Marie-Tooth disease. Researchers will investigate if this protein may be signal activating another gene called Krox20 known to be disrupted in some CMT cases. These experiments will be an important step toward remyelination therapies for peripheral neuropathies and other diseases of myelin.

**Ching H. Wang M.D., Ph.D.**

RG	A pilot therapeutic trial of hydroxyurea on type 1 spinal muscular atrophy (SMA)			
	\$100,000.00	7/1/2005	6/30/2009	Year 3
	\$40,000.00	1/1/2009	6/30/2009	Year 5

*Summary* Investigators propose to study the safety of a novel treatment for type I SMA using hydroxyurea. They will measure the treatment efficacy by using three clinical indicators and two biochemical markers.

**Mountain View - iZumi Bio, Inc.****John Dimos Ph.D.**

DG	A human embryonic stem cell based model of spinal muscular atrophy.			
	\$60,000.00	7/1/2008	6/30/2009	Year 1
	\$60,000.00	7/1/2009	6/30/2010	Year 2
	\$60,000.00	7/1/2010	6/30/2011	Year 3

*Summary* To study the root cause of SMA and its early progression, it is essential to observe motor neurons degenerating over time. Patient-specific induced pluripotent stem (iPS) cells, like embryonic stem cells, have the ability to form any of the body's specialized cells. Unlike embryonic stem cells, SMA-specific iPS cells contain all the genetic information that leads to SMA in patients, and can generate diseased motor neurons. Motor neurons made from healthy and SMA iPS cells can be compared in a reproducible fashion to uncover root causes of SMA. Billions of spinal cord motor neurons can be generated from iPS cells, making this system useful for discovering and testing new therapeutics. We have established SMA-specific embryonic stem cell lines previously, and our preliminary observations suggest that motor neurons made from these cells exhibit aspects of SMA. Here we propose to use a similar iPS cell-based approach to characterize fundamental events underlying SMA onset and progression, and to validate this approach for drug screening.

**Palo Alto - Palo Alto Institute for Research & Education, Inc.****Thomas Rando M.D., Ph.D.**

RG	Mechanisms of Fibrosis in Muscular Dystrophies			
	\$125,000.00	7/1/2008	6/30/2009	Year 1
	\$125,000.00	7/1/2009	6/30/2010	Year 2
	\$125,000.00	7/1/2010	6/30/2011	Year 3

*Summary* Fibrosis refers to the development of scar-like tissue in place of functional cells of that tissue. In skeletal muscle, fibrosis develops as muscles waste from degenerative disorders such as muscular dystrophies, and muscle cells are replaced by connective tissue. This is associated not only with progressive weakness as functional muscle cells are lost, but also by progressive muscle stiffness since connective tissue is not as elastic as muscle tissue. The goals of the experiments in this study are to understand why fibrosis occurs in the muscular dystrophies and to determine the biochemical mechanisms that lead to that fibrosis. We have preliminary data that suggest that a specific biochemical pathway, known as the "Wnt signaling pathway," is overactive in dystrophic muscle and

affects the cells in a way that leads to the development of fibrosis. We will directly test whether blocking this pathway leads to a reduction of the fibrosis that develops in the mdx mouse. These studies have the potential to lead directly to new therapies that will reduce the amount of fibrosis in the muscles of boys with Duchenne muscular dystrophy.

#### **Pasadena - California Institute of Technology**

##### **Frederique Murielle Ruf Ph.D.**

DG	In toto single-cell imaging of somitogenesis and muscle formation			
	\$60,000.00	1/1/2009	12/31/2009	Year 1
	\$60,000.00	1/1/2010	12/31/2010	Year 2
	\$60,000.00	1/1/2011	12/31/2011	Year 3

*Summary* In this proposal I plan to investigate the mechanisms underlying somite and muscle formation using the zebrafish as a model. Somites are conserved structures among vertebrates and give rise to skeletal structures and muscles. The goal is to develop a complete digital reconstruction of these processes in wildtype and muscular dystrophy mutant embryos with single-cell resolution. We will combine two powerful techniques in intact living and developing embryos: 1) in toto single-cell imaging, and 2) a fliptrap genetic screen to isolate mutations and study endogenously the role of muscle-related proteins. Overall, this should give us an unprecedented opportunity to understand how muscles are built during development, maintained throughout life, and degenerate during diseases.

#### **Redlands - LLVARE**

##### **Xuezhong Qin Ph.D**

RG	Therapeutic Potential of PAPP-A for Muscular Dystrophy			
	\$116,875.00	7/1/2008	6/30/2009	Year 1
	\$105,380.00	7/1/2009	6/30/2010	Year 2

*Summary* Duchenne muscular dystrophy (DMD) is a lethal disease caused by a mutation in the dystrophin gene. Although the eventual cure for DMD must rely on systemic delivery of a functional dystrophin gene to all muscles, alternative strategies that improve the quality of life in DMD patients are crucial until genetic treatments are available. Insulin-like growth factors (IGFs) represent an ideal candidate for improving muscle function in DMD. However, IGF-I therapy also has limitations mainly because an effective and safe IGF-I concentration is difficult to achieve, and frequent IGF-I injections must be given to patients. Instead of increasing the amount of IGF-I in the body through IGF-I injection, we will increase the activity of IGF-I produced by patients themselves by inactivating IGF inhibitors, namely, the inhibitory IGF binding proteins (IGFBPs). This can be achieved by the use of pregnancy-associated plasma protein (PAPP)-A, which is a potent protease that specifically destroys IGFBP-2, -3, and -5. If this proof of principle is confirmed by our studies, novel therapeutic strategies to defend against the secondary symptoms of DMD could be developed in the future.

#### **San Diego - San Diego State University Research Foundation**

##### **Sanford I. Bernstein Ph.D.**

RG	Disease mechanism and therapy development for inclusion body myopathy type 3			
	\$150,021.00	1/1/2009	12/31/2009	Year 2
	\$153,059.00	1/1/2010	12/31/2010	Year 3

*Summary* Our studies will test the hypotheses that: 1) specific functional defects in myosin cause hereditary Inclusion Body Myopathy type 3 (hIBM3), 2) defective myosin leads to specific cell biological and physiological abnormalities, and 3) manipulation of molecular chaperone levels or other gene products can prevent myosin dysfunction/degradation/aggregation and thereby improve muscle structure and performance.

#### **San Francisco - California Pacific Medical Center**

##### **Robert G Miller MD**

TR-IG	MDA/ALS web-based database			
	\$144,750.00	8/1/2008	7/31/2009	Year 3

*Summary* The ongoing ALS CARE program is a voluntary multicenter registry that has provided a unique source of information that may be used to improve the care of patients with ALS. The major focus of the new Web-based initiative will be to obtain long-term follow-up data and information about quality of life as well as survival. These data will be used to evaluate variations in patient care, adherence to standards of care and published practice parameters and also to help design clinical trials and epidemiological studies in ALS. An additional important focus of the Web-based ALS database will be to educate participating patients and visitors to the home page about ongoing clinical trials and clinical research studies, as well as to present an ongoing example of the role of the MDA/ALS division in the care of ALS patients nationwide.

**Robert G Miller MD**

RG	Multicenter Screening Trial of Safety and Efficacy of Lithium Carbonate in ALS			
	\$638,604.00	3/1/2008	2/28/2009	Year 1
	\$130,393.00	3/1/2009	2/28/2010	Year 2
	\$.00		2/28/2010	Year 3

*Summary* The purpose of the study is to respond to the recent claim that a common drug, lithium carbonate, can slow the progression of Lou Gehrig's disease (ALS). Lithium carbonate appeared to have benefit in a small study of Italian patients and in a mouse model of ALS. We propose a new and efficient trial design to quickly confirm these results.

**Robert G Miller MD**

CRNG	Infrastructure for a Small Screening Trial Consortium			
	\$100,000.00	8/1/2008	7/31/2009	Year 1
	\$100,000.00	8/1/2009	7/31/2010	Year 2
	\$100,000.00	8/1/2010	7/31/2011	Year 3

*Summary* We propose to establish a network of leading ALS centers to perform small drug trials that can screen for promising new agents in ALS. We plan to perform open label trials that can streamline the search for agents that have a large enough benefit that we can see it in small novel screening trial designs and to avoid placing too many resources into treatments that will turn out to be ineffective.

**San Francisco - University of California**

**Marc Diamond M.D.**

RG	AR oligomerization and proteolytic cleavage in SBMA			
	\$100,000.00	7/1/2008	6/30/2009	Year 3

*Summary* The investigators propose to use several mouse models to test the idea that protein aggregation is tightly linked to pathology, and identify the site of cleavage in androgen receptor (AR) that generates the toxic fragment in vivo. The answers to this work could lead to novel therapies based on inhibiting aggregation or proteolytic cleavage of AR.

**Steven L. McIntire M.D., Ph.D.**

RG	A C. elegans model of muscular dystrophy			
	\$110,000.00	1/1/2009	12/31/2009	Year 3

*Summary* Researchers have developed a means to identify genes whose mutations cause muscle degeneration or ameliorates muscle degeneration in the C. elegans animal model of dystrophic animals

**Louis J. Ptacek MD**

RG	Molecular and clinical characterization of Andersen-Tawil syndrome			
	\$100,000.00	7/1/2008	6/30/2009	Year 3

*Summary* ATS is a rare disorder that is caused by mutations in a potassium channel in 70% of patients. After the researchers have cloned this channel, they have shown it to be expressed in the brain. Thus, they are looking for a cognitive phenotype in ATS subjects.

## San Mateo - Innolyst, Inc.

### Kyle Brown BS

TR-IG MDA/DRCI Research Clearinghouse  
\$25,000.00 11/1/2008 10/31/2009 Year 3

*Summary* Drug discovery foundations have scientists and CROs conducting research around the globe. Innolyst will deploy a web-based portal focused on the needs of Duchenne Muscular Dystrophy foundations. Innolyst will integrate collaboration tools and data together into an easy-to-use portal interface, and manage the hardware, perform backups, upgrades, content loading and routine maintenance. Innolyst will be responsible for the entire solution from inception to on-going end user support. The Research Portal will be deployed to DRCI affiliated researchers of four MD research foundations: 1) Muscular Dystrophy Association (MDA); 2) Association Francaise Contre Myopathy (AFM); 3) Parent Project Muscular Dystrophy (PPMD); 4) United Parent Project Muscular Dystrophy (UPPMD)

## Santa Barbara - University of California

### Carol Vandenberg Ph.D.

RG Regulation of inward rectifier potassium channels in dystrophic skeletal muscle  
\$90,000.00 7/1/2008 6/30/2009 Year 3

*Summary* This research will investigate the role of dystrophin in the mechanisms that control the function of potassium channels in skeletal muscle fibers using a mouse model of the disease (mdx) and in vitro gene transfer.

## Sepulveda - Sepulveda Research Corporation

### Babak Darvish M.D.

RG Development of Muscle-Specific Mouse Model for HIBM  
\$.00 1/1/2009 12/31/2009 Year 2  
\$.00 1/1/2010 12/31/2010 Year 3

*Summary* We are proposing to produce a mouse model of hIBM that will mimic the human disease. Like humans, this mouse model will lack a specific sugar-like molecule (N-glycolylneuramate) that is normally produced in mice. We can further clarify why the genetic defect leads to muscle damage, develop therapeutic ideas, and we can test if the therapeutic ideas are safe and effective. If the ideas prove safe and effective in the mice, then we can consider testing the same therapy on human patients.

## COLORADO

## Aurora - University of Colorado Denver, Anschutz Medical Campus

### Roger A. Bannister Ph.D.

DG Regions of the skeletal muscle DHPR alpha1S subunit involved in coupling with RyR1  
\$45,000.00 7/1/2008 6/30/2009 Year 3

*Summary* The goal of this proposal is to characterize the basic mechanisms in which electrical signals produced by the nervous system trigger muscle contraction.

### William J. Betz Ph.D.

RG 'Hot spots' of secretion and exocytosis of 'empty' vesicles at the neuromuscular junction  
\$53,240.00 1/1/2009 12/31/2009 Year 3

*Summary* Researchers will study a newly created mouse model to study vesicle processing at the neuromuscular junction in order to shed light on diseases affecting this system.

**Mair E Churchill B.A., M.Sc, Ph.D.**

RG	Molecular Characterization of Mitochondrial Transcription Complex Assembly			
	\$113,138.00	1/1/2009	12/31/2009	Year 2
	\$115,852.00	1/1/2010	12/31/2010	Year 3

*Summary* A mouse that lacks one of the components of the transcription machinery (called mtTFA) has many features of severe skeletal muscle degeneration, similar to those found in severe human muscular dystrophies. By obtaining three-dimensional pictures of these proteins and the machinery that they form, we will learn how these systems work. This will give us new ideas into how to overcome deficits of mitochondrial function caused by genetic disorders and disease states that result in muscular dystrophy.

**Martin Gartz Hanson Ph.D.**

DG	Exploring a New Ryr1 Mouse model Important in Neuromuscular Disease			
	\$45,000.00	1/1/2009	12/31/2009	Year 2
	\$45,000.00	1/1/2010	12/31/2010	Year 3

*Summary* The goal of this proposal is to show that at least one gene, essential in muscle contraction, is also crucial at the neuromuscular junction (NMJ). Information obtained through a combination of electrophysiological and molecular biology methods will lead to a better understanding of the fundamental mechanisms required in the formation, connectivity and communication between the central nervous system and the muscle, which can be applied to the study and potential therapies of neuromuscular diseases.

**Matthew Taylor MD**

RG	Genetic and cellular mechanisms of Danon Disease (x-linked vacuolar myopathy)			
	\$98,926.00	1/1/2009	12/31/2009	Year 2
	\$97,378.00	1/1/2010	12/31/2010	Year 3

*Summary* Muscle diseases like Danon disease that are complicated by cardiac involvement carry a high morbidity and mortality. Currently, no effective therapy, other than heart transplantation, exists for Danon disease and there is an urgent need to advance understanding of this under-studied disease. This project will create human cell lines from patients with Danon disease with the goal of understanding the basic biological mechanisms causing pathology in Danon disease. A second effort will use gene therapy to 'cure' the disease in a human cellular model and will provide a foundation for future therapeutic studies in intact animals and eventu

**Boulder - The Regents of the University of Colorado****Kurt Beam Ph.D.**

RG	Dynamic rearrangements of the DHPR and RyR1 during excitation of normal and diseased muscle			
	\$105,600.00	7/1/2008	6/30/2009	Year 2
	\$105,600.00	7/1/2009	6/30/2010	Year 3

*Summary* Researchers will study how mutations in DHPR and RyR1 cause CCD, MH, and HYOPP. Experiments will determine how mutations affects the interactions between DHPR and RyR1 which affect the excitation-contraction coupling for voluntary control of skeletal muscle.

**Bradley Olwin Ph.D.**

RG	Identification and Characterization of a Satellite Stem Cell			
	\$112,440.00	1/1/2009	12/31/2009	Year 2
	\$112,658.00	1/1/2010	12/31/2010	Year 3

*Summary* Recent data from our lab and others suggests that satellite cells are heterogeneous, suggesting that different subpopulations of cells self-renew by asymmetric cell division to maintain the satellite cell pool, while others are responsible for regenerating the muscle fibers. We plan to determine if the subpopulation of cells we have identified undergoes asymmetric cell division to replenish the quiescent satellite cell pool.

**David C. Sheridan Ph.D.**

DG	Bi-directional signaling between Ca <sup>2+</sup> channels in skeletal muscle EC coupling		
\$45,000.00	7/1/2008	6/30/2009	Year 2
\$45,000.00	7/1/2009	6/30/2010	Year 3

*Summary* Researchers will study how the receptors DHPR and RyR1 communicate for normal EC-coupling altered in disease.

**Fort Collins - Colorado State University**

**Carol J. Wilusz Ph.D.**

RG	The effects of CUG-repeat expansion in myotonic dystrophy on cytokine mRNA stability		
\$98,029.00	7/1/2008	6/30/2009	Year 2
\$98,029.00	7/1/2009	6/30/2010	Year 3

*Summary* Researchers will study effect of CUG-BP on cytokines in DM1.

**CONNECTICUT**

**New Haven - Yale University**

**Lynn Cooley Ph.D.**

RG	Genetic analysis of muscle function and muscle disease at the single-cell level		
\$120,000.00	1/1/2009	12/31/2009	Year 1
\$100,000.00	1/1/2010	12/31/2010	Year 2
\$100,000.00	1/1/2011	12/31/2011	Year 3

*Summary* Although many genes associated with muscular dystrophy have been identified in recent years, how mutations in these genes cause illness is still poorly understood. The use of simple animals as models for human disease is a powerful way to increase our understanding of disease progression. The fruit fly, *Drosophila melanogaster*, is particularly well suited for genetic analyses. Many genes in fruit flies are very similar to human genes, including those associated with human muscular dystrophies. We have discovered a unique *Drosophila* muscle type in which we can perform genetic experiments on single muscle cells. We plan to study the effect of several muscular dystrophy-associated genes in these fly muscles with the goal of understanding how they contribute to muscle function and coordination. Importantly, we can observe muscles in live preparations and compare muscle function in young and old flies to see how muscle function changes with age. In addition, we will study the ability of the *Drosophila* muscle to renew itself from a pool of precursor cells. This project will provide important information for creating new therapeutic approaches for treating muscular dystrophy in people.

**Antonio Giraldez PhD**

RG	The Role of microRNAs in muscle development and muscular dystrophy			
	\$134,054.00	1/1/2009	12/31/2009	Year 1
	\$131,899.00	1/1/2010	12/31/2010	Year 2
	\$135,347.00	1/1/2011	12/31/2011	Year 3

*Summary* Muscular dystrophies cause progressive weakness and degeneration of skeletal muscle. Despite the diverse genetic origins, muscular dystrophies are characterized by a failure to maintain normal muscle homeostasis. MicroRNAs (miRNAs) encode ~21nt RNAs that regulate gene expression in animals and plants, but their functions are largely unknown. Several miRNAs (miR-1, miR-206, miR-133) are conserved in all animals and are highly expressed in skeletal muscle during embryonic development and adulthood. These observations suggest the hypothesis that these and other miRNAs regulate muscle development and homeostasis in animals. To investigate the role of miRNAs during skeletal muscle development we have (i) generated zebrafish embryos mutant in the miRNA-processing enzyme (Dicer), which lack mature miRNAs, (ii) have developed antisense oligonucleotides to inhibit miRNA processing and (iii) to inhibit the regulation of individual target mRNAs. This proposal focuses on the functional analysis of microRNAs in skeletal muscle going from the experimental identification of their targets in vivo (Aim 1) to the analysis of the physiological role of individual miRNA-target interactions (Aim 2), with the long-term objective of understanding how miRNAs regulate gene expression during muscle development and disease. This project will provide fundamental knowledge to develop a therapy that aims to restore normal muscle homeostasis and growth during muscular dystrophy.

**Noam Y. Harel MD., Ph.D.**

DG	The nogo-ALS connection: Effects on axon transport			
	\$45,000.00	7/1/2008	6/30/2009	Year 3

*Summary* Nogo protein enhances survival in a mouse model of ALS. Further evidence suggests that Nogo's protective effect against ALS may derive from its ability to regulate transport. By learning more about how Nogo regulates transport, this study could lead to new targets for therapy against the transport defect in ALS.

**DISTRICT OF COLUMBIA****Washington - Children's Research Institute (CNMC)****Terence Partridge Ph.D.**

RG	Role of the Nuclear Envelope in Muscle Satellite Cell Activity.			
	\$140,000.00	1/1/2009	12/30/2009	Year 1
	\$140,000.00	1/31/2010	1/30/2011	Year 2
	\$140,000.00	1/31/2011	12/31/2011	Year 3

*Summary* Maintenance and repair of muscle is performed by muscle satellite cells, which proliferate and differentiate into muscle at sites of damage. It has been found that some myopathies such as Emery-Dreyfuss and Limb-Girdle muscular dystrophies arise because of mutations in nuclear membrane proteins such as lamins and other components of the nuclear membrane collectively called NETs. Here, we propose to investigate how mutations in NETs disturb maintenance of muscle and contribute to the development of disease. Our preliminary data has identified NETs that are regulated by satellite cell activation, proliferation and differentiation. We propose to study how these satellite cell activities are altered when we prevent production of these NETs. This will be performed both in tissue culture and in satellite cells grafted into living muscles of recipient mice. We have also developed a mouse line that lacks Lap2alpha and lamin, two components that, via their interactions with Rb/MyoD transcription factors, have been implicated in control of cellular proliferation. We propose to examine satellite cells derived from these mice to better understand proliferation and differentiation processes. Finally, we propose to examine how the NETs are affected in other dystrophies such as mdx and dysferlin-deficient mice. We expect these studies to shed light on disease processes, characterize novel regulatory factors involved in muscle regeneration, and identify novel targets for therapy.

**Susan Sparks M.D., Ph.D.**

RRG	Evaluation of Limb-Girdle Muscular Dystrophy			
	\$35,000.00	12/1/2008	11/30/2009	Year 1

*Summary* Limb-girdle muscular dystrophy (LGMD) is a group of muscular dystrophies with onset of weakness in childhood or adulthood. One form of LGMD (LGMD2I, or FKRP deficiency) is caused by a defect in glycosylation (the process of adding sugar units to proteins). Our central hypothesis is that glycosylation (The process of adding sugar units to proteins) adjust the environment in muscle both by allowing flexibility of the extracellular matrix (that is the part of the tissue that provides structural support to the cells) and influencing how the cells communicate with each other. Defects in glycosylation alter both of these processes. There is evidence that patients that have defects in glycosylation may have less expression of certain proteins (TGF- $\alpha$  and IGF-II signaling network proteins). In order to test this hypothesis, we would like to measure the levels of these proteins. We expect the levels of the tested proteins are higher in patients with glycosylation defects as compared to patients with other muscular dystrophies. We also want to learn more about LMGD, so we can use this information in future studies

**Washington - Children's Research Institute****Robert T Leshner M.D.**

RRG	Inter-rater reliability of Quantitative Muscle Testing vs Hand Held Myometry			
	\$70,000.00	2/1/2008	1/31/2009	Year 1

*Summary* With increases in the numbers of experimental therapies and clinical trials in DMD, it is important to define reliable and sensitive endpoints that fulfill FDA requirements for relevance to quality of life. The aim of this study is to compare two commonly utilized pediatric strength testing measures: hand-held myometry (HHM) and the CINRG Quantitative Measurement System (CQMS). The goal is to identify a sensitive and valid tool for measuring muscle strength in children with Duchenne Muscular Dystrophy. The data obtained from this study will be used to make recommendations for strength measurement endpoints in prospective muscular dystrophy trials and provide more reliable and accurate recommendations in the clinic for strength assessment.

**FLORIDA****Gainesville - University of Florida****Lucia Notterpek PhD**

RG	HSP90 modulators, as potential therapeutics for Charcot-Marie-Tooth neuropathies			
	\$100,000.00	7/1/2008	6/30/2009	Year 2
	\$100,000.00	7/1/2009	6/30/2010	Year 3

*Summary* Researchers will investigate the effect of HSP90 as a potential therapy for CMT1A.

**Maurice Swanson Ph.D.**

RG	Mechanisms of RNA-Mediated CNS pathogenesis in myotonic dystrophy			
	\$122,517.00	1/1/2009	12/31/2009	Year 3

*Summary* Researchers will investigate how the impaired RNA processing in myotonic dystrophy may affect structural and possibly cognitive abilities in the central nervous system.

**Maurice Swanson Ph.D.**

RG	Regulation of MBNL3 in Muscle Development and Disease			
	\$123,688.00	1/1/2009	12/31/2009	Year 1
	\$125,973.00	1/1/2010	12/31/2010	Year 2
	\$128,327.00	1/1/2011	12/31/2011	Year 3

*Summary* Myotonic dystrophy (DM) is the most common form of muscular dystrophy in adults. Recent studies from our lab and others have indicated that DM is an RNA-mediated disease caused by the expansion DNA repeats which are subsequently transcribed into pathogenic RNA repeats. These repetitive RNAs are toxic because they inhibit the activities of RNA splicing factors, the muscleblind-like (MBNL) proteins, which are essential for the development of adult tissues. While we have successfully created mouse models for DM which fail to express the Mbnl1 protein, these mice do not develop either the severe muscle wasting characteristic of adult-onset DM or the impaired development of muscles in infants with congenital DM. This proposal is designed to test the hypothesis that another member of the Mbnl gene family, MBNL3, is sequestered in DM tissues and loss of this protein is required for disease-associated alterations in muscle development and maintenance.

**Krista Vandeborne PhD, PT**

RG	Validation of MR imaging for clinical trials in muscular dystrophy			
	\$133,916.00	7/1/2008	6/30/2009	Year 3

*Summary* The goal of this project is to develop a way to observe whether or not gene or drug therapies have corrected the problem in the muscles of boys with Duchenne muscular dystrophy without the need to take muscle biopsies.

**Lizi Wu Ph.D.**

RG	Roles of the MAML1 co-activator in myogenesis and muscular dystrophy			
	\$126,861.00	7/1/2008	6/30/2009	Year 2
	\$126,861.00	7/1/2009	6/30/2010	Year 3

*Summary* Researchers will study a stem cell factor called Maml1 which has a dual role in stem cell generation and differentiation.

**Miami - University of Miami School of Medicine****John Barrett Ph.D.**

RG	Long-term consequences of motor terminal stress in mouse models of familial ALS			
	\$94,226.00	7/1/2008	6/30/2009	Year 2
	\$90,000.00	7/1/2009	6/30/2010	Year 3

*Summary* Researchers will determine if defective post-stress restoration of NMJ is due to inability to regenerate or to maintenance of regenerated NMJs.

**Antoni Barrientos Ph.D.**

RG	Understanding the molecular basis of Leigh's syndrome associated to cytochrome c oxidase deficiency			
	\$108,000.00	7/1/2008	6/30/2009	Year 2
	\$99,000.00	7/1/2009	6/30/2010	Year 3

*Summary* Cytochrome C oxidase (COX) deficiency is the most frequent cause of mitochondrial neuromyopathies in humans. Patients afflicted with these diseases present heterogeneous clinical phenotypes, including Leigh syndrome (LS), muscle weakness and encephalomyopathy. Mutations in surf1 is the most frequent cause of COX deficiency. A better understanding of COX biogenesis is essential for elucidating the molecular basis underlying this group of diseases. The main objective of the proposed research is to investigate the role of Shy1p, the yeast homologue of Surf1p, using the yeast *Saccharomyces cerevisiae* as a model complemented with studies in cell cultures from LS patients.

**Lisa Baumbach Ph.D.**

RG	XL-SMA Mutations - Genotype: Phenotype Correlations & Biological Implications			
	\$86,736.00	7/1/2008	6/30/2009	Year 1
	\$84,471.00	7/1/2009	6/30/2010	Year 2
	\$63,675.00	7/1/2010	6/30/2011	Year 3

*Summary* Our research group has spearheaded an international effort to identify and collect families with X-linked lethal infantile spinal muscular atrophy (XL-SMA), a lethal infantile neurodegenerative disorder similar to Type I SMA, but with additional features of congenital contractures and fractures. Genetic mapping studies allowed the first identification of a candidate disease gene interval (Xp11.3-q11.2), while more recent studies narrowed the gene region. Within the last year, we have collected strong evidence supporting identification of a known gene, UBE-1, as the XL-SMA disease gene. UBE-1 catalyzes the first step in protein ubiquitination-proteasome pathway, which targets numerous proteins for degradation. Our long-term goal is to apply knowledge gained from XL-SMA disease gene discovery to both prenatal and antenatal disease detection, and implementation of therapeutic strategies. The project short-term goals are: (i) to identify and collect additional XL-SMA patients and patients with overlapping clinical phenotypes; (ii) to complete mutation screening studies in these patients; (iii) to complete preliminary investigations concerning disease pathogenesis. Identification of the causal XL-SMA disease gene allows for the first advance in many years. The combined study results will allow for the first understanding and eventual treatment of this devastating illness, as well as insight into its relationship to other motor neuron and neurodegenerative disorders.

**Gavriel David Ph.D., M.D.**

RG	Calcium handling in peripheral motor axons - role in CMT disease			
	\$113,694.00	1/1/2009	12/31/2009	Year 1
	\$111,213.00	1/1/2010	12/31/2010	Year 2
	\$108,073.00	1/1/2011	12/31/2011	Year 3

*Summary* In Charcot-Marie-Tooth disease type 1 (CMT1) the major symptoms of muscle weakness and atrophy arise from degeneration of motor axons, which breaks the link between motor neuron activity and muscle contraction. The reason why disruption of myelin in this disease leads to degeneration of axons is not known, but recent studies in animal models of CMT1 show that the type and spatial distribution of sodium and potassium channels undergo extensive reorganization at the sites of abnormal myelination. We discovered that physiologically-activated healthy motor axons display localized calcium elevations in the close vicinity of their nodes of Ranvier, and these calcium elevations are much more extensive in the Trembler-J mouse model of CMT1 disease. Thus we hypothesize that calcium overload contributes to axonal degeneration and motor dysfunction in CMT1A. We propose to apply state-of-the-art calcium imaging techniques to Trembler-J axons, to reveal the pathways of these pathological calcium elevations, identify the optimal agents that suppress them without interfering with normal motor function, and then test if treating Trembler-J model mice with these agents will improve their axonal survival and motor performance.

**Carlos Moraes Ph.D.**

RG	Increased mitochondrial biogenesis as therapy to mitochondrial myopathies			
	\$117,533.00	1/1/2009	12/31/2009	Year 3

*Summary* Researchers have discovered a protein that controls expression of genes related to mitochondrial function that improves cellular health by upregulating respiration. This may have application to mitochondrial disorders.

## Tampa - University of South Florida

### Svitlana Garbuzova-Davis Ph.D., D.Sc.

RG	Blood-Brain Barrier Evaluation in ALS Patients			
	\$110,000.00	7/1/2008	6/30/2009	Year 1
	\$110,000.00	7/1/2009	6/30/2010	Year 2

*Summary* Impairment of the blood-brain barrier (BBB), blood-spinal cord barrier (BSCB), or blood-cerebrospinal fluid barrier (BCSFB) may be involved in amyotrophic lateral sclerosis. In the spinal cord and brain of both ALS patients and animal models, immune cells were observed that may be critical in motor neuron damage. Also, compounds found in the cerebrospinal fluid of ALS patients suggest that barrier permeability may be affected. Recently, we showed disruption of the BBB/BSCB in areas of motor neuron degeneration in ALS mice. To our knowledge, no direct examinations have been undertaken to verify BBB or BSCB dysfunction in ALS patients. It is our hypothesis that the BBB and BSCB are compromised in ALS patients. These studies will determine competence of these barriers by a microscopic examination of post-mortem brain and spinal cord samples from ALS patients. We will first examine tissue from the brain and spinal cord of former ALS patients for visible barrier damage using an electron microscope. Second, we will examine the integrity of barrier vascular elements using immunohistochemical tests for various blood vessel markers. The results of this study may provide a basis for improved therapeutic strategies for the treatment of ALS.

## GEORGIA

### Atlanta - Emory University

#### Gary Bassell Ph.D.

RG	Axonal mRNA regulation by hnRNP-Q1 and SMN			
	\$100,679.00	1/1/2009	12/31/2009	Year 1
	\$103,742.00	1/1/2010	12/31/2010	Year 2
	\$106,900.00	1/1/2011	12/31/2011	Year 3

*Summary* Spinal Muscular Atrophy (SMA) is the most common inherited cause of infant mortality. SMA is a neurodegenerative disease affecting primarily motor neurons that is caused by the inherited loss of the Survival of Motor Neuron protein (SMN). An important objective of SMA research is to understand the normal functions of SMN in the nervous system. SMN is transported in RNA granules which appear to contain mRNAs that are locally translated within axons. Local protein synthesis within axons provides an important mechanism for the axon to control its own structure and function during development and possibly also within mature nerves. Thus, it has been hypothesized that SMN may play some role in the mechanism of mRNA transport and local protein synthesis. A major objective of this proposal is to identify SMN protein partners in axons. Preliminary data presented here indicate that the SMN interacting protein, hnRNP-Q1, is co-transported with SMN in motor neuron axons. hnRNP-Q is a known component of mRNA transport granules and has been previously shown to be involved in various aspects of mRNA regulation. Here we will use cultured neurons from mouse embryos to test the hypotheses that hnRNP-Q1 is required for mRNA localization and that interactions with SMN can influence this trafficking. These studies will provide new insight into the pathomechanism involved in SMA and should identify new targets for therapeutic intervention.

#### Michael Benatar PhD

RG	The predict and prevent amyotrophic lateral sclerosis (PAPALS) study			
	\$160,000.00	7/1/2008	6/30/2009	Year 2
	\$159,999.00	7/1/2009	6/30/2010	Year 3

*Summary* Investigators will study ALS population over time to assess epidemiological markers, disease onset and biomarkers.

**Jonathan D. Glass MD**

**RRG** Models and treatments in motor neuron diseases  
 \$88,894.00 3/1/2008 2/28/2009 Year 1

*Summary* Animal models of Amyotrophic Lateral Sclerosis demonstrate that the pathological progression of disease may begin at nerve terminals, where motor neurons connect to skeletal muscles (the neuromuscular junction). Additionally, experimental interventions in animals with ALS have shown that protection of motor neuron cell bodies does not provide significant protection against weakness and death, which is explained by the lack of protection for motor nerve fibers (axons) and neuromuscular junctions. This research investigation focuses on the mechanisms underlying axonal degeneration in models of ALS. We will specifically investigate the role of oxidative stress in axonal degeneration, a hypothesis that is supported by experimental data from animal models and from humans.

**Jonathan D. Glass MD**

**CRNG** Emory MDA/ALS Clinical Research Center  
 \$100,000.00 8/1/2008 7/31/2009 Year 1

*Summary* We are committed to work with other Clinical research centers to investigate treatment interventions in ALS.

**Madhuri R Hegde B.S, M.S, Ph.D**

**TR-IG** Microarray based mutation detection in genes associated with inherited NMDs  
 \$200,000.00 9/1/2008 8/31/2009 Year 1

*Summary* We propose to design a set of microarray-based tools that will enable the high-throughput comprehensive identification of genetic variants underlying inherited neuromuscular disorders (inherited NMDs) including Congenital Muscular Dystrophies (CMDs), Duchenne and Becker Muscular Dystrophy (DMD and BMD), Emery Dreifuss Muscular Dystrophy (EDMD), Limb-Girdle Muscular Dystrophies (LGMD), and Spinal Muscular Atrophy (SMA). This project will develop the technology and protocols leading to a novel highly sensitive, rapid and reliable diagnostic tool for enhanced molecular testing for inherited NMDs.

**Kimberly Kafadar Long Ph.D.**

**DG** Mechanisms of Sca-1 regulation by TGFb  
 \$60,000.00 7/1/2008 6/30/2009 Year 1  
 \$60,000.00 7/1/2009 6/30/2010 Year 2

*Summary* Whether induced by exercise, trauma, or disease, the regenerative ability of skeletal muscle is largely dependent on satellite cells, a population of stem cells that resides in skeletal muscle along the myofibers. In response to growth stimuli, satellite cells are induced to proliferate, differentiate, and fuse to form new myofibers or fuse into existing myofibers. We are interested in how Sca-1, a protein present in numerous stem cell populations, affects muscle growth and regeneration. Transforming growth factor-beta 1 (TGF-b1) is highly upregulated in response to muscle injury. TGF-b1 dysregulation in multiple muscular dystrophies results in extensive connective tissue deposition. This increase in fibrosis greatly inhibits the full recovery of the muscle. Modulation of TGF-b1 in dystrophic patients may be of great therapeutic value. We have shown that TGF-b1 is a novel negative regulator of Sca-1 expression in myoblasts, although the mechanism of this action is unknown. The goal of this study is to identify the pathway through which TGF-b1 regulates Sca-1 expression, including transcriptional activators of Sca-1. We believe that these studies may uncover novel therapeutic means by which to ameliorate the poor regeneration in dystrophic muscle.

**Grace Pavlath Ph.D.**

**RG** OPMD: Role of PABPN1 in mRNA Biogenesis and Myogenesis (NIH RFA)  
 \$99,990.00 7/1/2008 6/30/2009 Year 2

*Summary* The goal of these studies is to understand why people with mutations in the PABPN1 protein develop a disease called oculopharyngeal muscular dystrophy (OPMD) where eyelid, pharyngeal, and limb muscles are primarily affected. Our experiments will study the role of PABPN1 in the muscle cells that are affected in the disease. Understanding the role of PABPN1 specifically in these muscle cells will lead to a greater understanding of the pathogenesis of OPMD as well as possible new therapeutic strategies for this disease.

## Augusta - Medical College of Georgia

### Laxman D. Gangwani Ph.D.

RG      Function of the zinc finger protein ZPR1 in spinal muscular atrophy (SMA)  
\$139,328.00      1/1/2009      12/31/2009      Year 3

*Summary* Researchers will determine the function of zinc-finger protein 1 (ZPR1) in the pathogenesis of spinal muscular atrophy (SMA) in a mouse model of the disorder.

## ILLINOIS

### Chicago - Illinois Institute of Technology

#### Nick Menhart Ph.D.

RG      Domain structure of the dystrophin rod in relation to STR motifs and exon structure  
\$77,217.00      1/1/2009      12/31/2009      Year 3

*Summary* Studies will determine how to modify the rod domain of the dystrophin gene without perturbing its structure and function.

### Chicago - Rush University Medical Center

#### Jingsong Zhou Ph.D.

RG      Abnormal interactions of mitochondria and sarcoplasmic reticulum in ALS muscle  
\$100,000.00      7/1/2008      6/30/2009      Year 2  
\$100,000.00      7/1/2009      6/30/2010      Year 3

*Summary* Investigators will study the alteration in mitochondrial and calcium levels during progression of ALS.

### Chicago - University of Illinois

#### Scott Brady

RG      Kinases and fast axonal transport in SBMA  
\$110,000.00      7/1/2008      6/30/2009      Year 3

*Summary* Proposed studies will evaluate pathogenic mechanisms in a mouse model of SBMA, using a combination of pharmacological, biochemical, and cell biological experiments to define a novel pathogenic pathway that is affected in SBMA and results in compromised FAT.

#### Ken-ichiro Fukuchi M.D., Ph.D.

RG      Therapeutic delivery of anti-amyloid antibody for inclusion-body myositis  
\$100,000.00      7/1/2008      6/30/2009      Year 2  
\$100,000.00      7/1/2009      6/30/2010      Year 3

*Summary* AAV vector with antibody to AB-aggregates seen in IBM patients will be tested on IBM mouse models as potential therapy.

#### Jesus Garcia-Martinez M.D., Ph.D.

RG      Function of the alpha2/delta1 subunit in skeletal muscle  
\$128,708.00      7/1/2008      6/30/2009      Year 3

*Summary* This project will determine the role of the a2/d1 subunit in excitation-contraction coupling and its possible involvement in cell adhesion. The results will help identify new potential targets for therapy in conditions where calcium release or cell recognition mechanisms are altered.

## Chicago - The University of Chicago

### Elizabeth M. McNally M.D., Ph.D.

RG	NIH-RFA Nuclear Membrane Protein Interaction in Muscle Disease			
	\$99,921.00	7/1/2008	6/30/2009	Year 2
	\$99,980.00	7/1/2009	6/30/2010	Year 3

*Summary* Mutations in genes that encode proteins of the nuclear membrane are a common cause of muscular dystrophy. My laboratory is interesting in determining how changing the nuclear membrane leads to muscle disease.

### Elizabeth M. McNally M.D., Ph.D.

RG	Stem cell therapy for limb-girdle muscular dystrophy			
	\$101,749.00	7/1/2008	6/30/2009	Year 3

*Summary* Muscle has the ability to regenerate itself. Because of this, muscle cell transplantation may be an effective therapy for LGMD. This research works on isolating the most effective stem cells from muscle that will restore sarcoglycan expression.

### Raymond Philip Roos M.D.

RG	Non-cell autonomous degeneration and ALS			
	\$110,000.00	7/1/2008	6/30/2009	Year 3

*Summary* The researchers plan to use transgenic mice to clarify how different neural cell types interact to lead to MND. These studies may provide insights into MN death and new treatment directions.

### Raymond Philip Roos M.D.

RG	Transgenic mouse studies and therapeutic directions in ALS			
	\$90,000.00	7/1/2008	6/30/2009	Year 2
	\$90,000.00	7/1/2009	6/30/2010	Year 3

*Summary* AIS is a neurodegenerative disease characterized by the selective loss of motor neurons (MNs). Approximately 10% of ALS cases are familial (known as FALS), and ~25% of FALS cases are caused by mutations in Cu/Zn superoxide dismutase type 1 (SOD1). We plan to use transgenic mice that express mutant SOD1 to clarify the reasons for MN cell death. We will examine whether decreasing MTSOD1 expression prior to disease onset delays its onset or slows its duration, whether increasing the normal form of SOD1 expression accelerates disease, and whether stopping a normal cellular response to misfolded proteins slows disease onset. These studies may provide insights into MN death and new treatment directions.

## Hines - Hines VA Hospital

### Craig J. Serpe Ph.D.

DG	The immune systems role in motoneuron survival: Potential ALS therapy			
	\$40,110.00	1/1/2009	12/31/2009	Year 3

*Summary* Researchers will test the effects of a BDNF-producing CD4+T cell on motoneuron survival after injury.

## INDIANA

### Indianapolis - Indiana University

#### Tatiana M. Foroud Ph.D.

TR-IG	International Spinal Muscular Atrophy Patient Registry			
	\$33,112.00	7/1/2008	6/30/2009	Year 1
	\$34,105.00	7/1/2009	6/30/2010	Year 2
	\$35,129.00	7/1/2010	6/30/2011	Year 3

*Summary* The International Spinal Muscular Atrophy Patient Registry was founded in 1986 to provide a link between patients and families interested in participating in research and researchers interested in studying SMA. The registry currently contains 1,568 families with 18,221 family members. The purpose of this application is to seek funds to continue the expansion and development of the International Spinal Muscular Atrophy Patient Registry and to: Implement new initiatives to identify, recruit and retain SMA patients and families. Collect more extensive and uniform clinical and epidemiological data. Track research study participation including enrollment, withdrawal, and completion. Establish international collaborations to develop and maintain a database of uniform, de-identified data in collaboration with the organization, Translational Research in Europe for the Assessment and Treatment of Neuromuscular Diseases. Expand awareness and use of the registry by SMA researchers.

### West Lafayette - Purdue University

#### Shihuan Kuang Ph. D.

RG	Enhancing satellite cell self-renewal in dystrophic muscle			
	\$120,655.00	1/1/2009	12/31/2009	Year 1
	\$118,212.00	1/1/2010	12/31/2010	Year 2
	\$116,842.00	1/1/2011	12/31/2011	Year 3

*Summary* Growth and repair of skeletal muscle depend on a sustained supply of satellite cells, whose number is normally maintained through a self-renewal process. In Duchenne muscular dystrophy, a lethal degenerative disease that affects some 250,000 Americans, even normal bouts exercise cause extensive muscle damage, accompanied by rapid exhaustion of satellite cells and failure in the repair of damaged muscles. In this project, we aim to investigate why satellite cells are depleted, and to explore novel approaches to restore satellite cells and the intrinsic regenerative capacity of dystrophic muscles. We address these questions using a mouse model (mdx) of Duchenne muscular dystrophy. First, the self-renewable satellite cells will be genetically tagged to assess whether they are depleted in mdx mouse. Meanwhile, mdx satellite cells will be cultured to determine whether their self-renewal capacity is impaired. Next, we will investigate whether depletion of satellite cells in mdx is due to disruption of signaling events controlling stem cell self-renewal. In this regard, the 'Notch' signaling will be examined using a transgenic mouse in which all the Notch positive cells exhibit green fluorescence. Lastly, we will genetically boost the Notch signaling in mdx mice and investigate whether stem cell self-renewal and muscle regeneration will be improved. These studies may lead to potential therapeutic approaches to improve muscle repair and delay disease onset of muscular dystrophies.

## IOWA

### Iowa City - The University of Iowa

#### Aaron Beedle Ph.D.

DG	Role of Muscle Development/Regeneration in the Pathology of Dystroglycanopathy		
\$60,000.00	1/1/2009	12/31/2009	Year 1
\$60,000.00	1/1/2010	12/31/2010	Year 2

*Summary* Dystroglycan is an essential link between structural components inside and outside of cells to maintain the integrity of tissues like muscle and heart. In dystroglycanopathies the bond between dystroglycan and the extracellular matrix is disturbed. Sugars that normally decorate the outer region of dystroglycan are lost so that it can't bind to proteins outside of cells, increasing susceptibility to damage. To date, mutations have been identified in five different genes as causing this disease in patients. The genes encode proteins that are known or suspected to add or regulate sugars on dystroglycan. Although the number of dystroglycanopathy patients is rising, there are no treatment options available. We have generated a new mouse model to study dystroglycanopathies and develop therapeutic options. Our early data suggest that loss of dystroglycan glycosylation in muscle development leads to severe, clinically relevant features of muscular dystrophy whereas when disruption is later (mature muscle), mice are mild or asymptomatic. Our research goal is to study mouse models with abnormal dystroglycan during development and regeneration, but restored glycosylation in mature muscle. We expect these experiments to identify a critical time frame for loss of dystroglycan glycosylation in disease severity and assess the potential for therapeutic strategies that rescue dystroglycan in mature muscle.

#### Shawn Flanagan Ph.D.

RG	Role of reactive oxygen species in ALS-associated mutant SOD1 toxicity		
\$52,857.00	1/1/2009	12/31/2009	Year 3

*Summary* It is known that mutant SOD1 in familial ALS causes an increase in reactive oxygen species (ROS) known to be detrimental to tissues. We will attempt to learn the source of the increased ROS in order to develop therapies.

#### Pamela Kent Geyer Ph.D.

RG	The role of Drosophila LEM domain proteins on nuclear function: Implications for EDMD		
\$85,000.00	1/1/2009	12/31/2009	Year 3

*Summary* Studies in the fly model will determine function of nuclear lamina proteins which are affected in Emery-Dreifuss muscular dystrophy (EDMD)

#### Erik Paul Rader Ph.D.

DG	Efficacy of LARGE as a therapeutic strategy for limb-girdle muscular dystrophy		
\$45,000.00	1/1/2009	12/31/2009	Year 2
\$45,000.00	1/1/2010	12/31/2010	Year 3

*Summary* I will test whether overexpression of LARGE anchors the dystroglycan complex to the surface membrane and minimizes the pathology in mouse models of sarcoglycan deficiency. I will study skeletal muscle structure and function following LARGE overexpression in mice that lack alpha-, beta-, gamma-, or delta-sarcoglycan. The results will shed light on the molecular pathogenesis of sarcoglycanopathy but also on the therapeutic potential of pharmacological strategies that modulate expression and/or activity of LARGE.

## LOUISIANA

### Baton Rouge - Louisiana State University A&M College (LSU)

#### Eric A. First Ph.D.

RG	Understanding the connection between the protein synthesis and Charcot-Marie-Tooth disorder		
\$110,000.00	1/1/2009	12/31/2009	Year 3

*Summary* Researchers will study mutations in the genes causing CMT-2D and DI-CMTC, two types of Charcot-Marie-Tooth (CMT) disorder.

## New Orleans - Louisiana State University Health Sciences Center

### Jakob Reiser PhD

RG	Remote therapeutic gene delivery for SMA				
	\$99,305.00	7/1/2008	6/30/2009	Year 1	
	\$105,972.00	7/1/2009	6/30/2010	Year 2	
	\$100,239.00	7/1/2010	6/30/2011	Year 3	

*Summary* This study seeks to identify a practical means of gene therapy in Spinal Muscular Atrophy (SMA). SMA, the leading inherited cause of death in children under two years of age, results from the progressive loss of lower motor neurons. While the disease lacks any validated treatments, recent advances confirm that loss of function in one of the survival of motor neuron genes (SMN1) causes SMA. The availability of defined genetic (SMN gene) and anatomical (motor neurons) targets has prompted enthusiasm for rapid translation of experimental therapies for this disease. SMA has also been recognized as a model for the development of translational therapies in a wide range of neurodegenerative disease. Finally, the identification of SMN loss of function as the key cause of SMA has focused attention on gene transfer as an optimal approach to this disorder.

## MAINE

### Bar Harbor - The Jackson Laboratory

#### Laurent Bogdanik Ph.D.

DG	A new mouse model for agrin-related congenital myasthenic syndromes.				
	\$60,000.00	7/1/2008	6/30/2009	Year 1	
	\$60,000.00	7/1/2009	6/30/2010	Year 2	
	\$60,000.00	7/1/2010	6/30/2011	Year 3	

*Summary* We have found a new mouse mutation causing a severe myasthenia that will serve as an animal model for human diseases in which the function of the proteins MuSK and rapsyn are altered by genetic mutations or autoimmunity. This mutation affects a protein called agrin that acts upstream of both MuSK and rapsyn; it should, therefore, recapitulate the features of both MuSK and rapsyn mutations. It also more closely resembles human disease-causing mutations than the previous mouse mutations available for agrin, MuSK and rapsyn. We will complete the characterization of this mutation so that it can be used to study human myasthenia mechanisms and treatments. Our finding that agrin mutation causes a myasthenia suggests that agrin itself is involved in human diseases; further, the mutation seems to modify agrin interactions with other, undetermined proteins. We will identify these new partners of agrin, which could be responsible for orphan myasthenic syndromes in humans. Using this new myasthenia model, we will pursue a pharmacological study to determine how neurotransmitter release impacts disease progression. Under certain circumstances, neurotransmitter release can disrupt neuromuscular junctions, an effect that is counteracted by agrin. However, myasthenia therapies often increase neurotransmitter activity. We will test whether these treatments may actually worsen the defects caused by deficiencies in agrin, MuSK or rapsyn.

#### Kimberly Huebsch Ph.D.

DG	Function of titin's N2A domain in a murine model of human muscular dystrophy				
	\$45,000.00	7/1/2008	6/30/2009	Year 3	

*Summary* Understanding the molecular mechanisms of the muscular dystrophy with myositis (MDM)(LGMD2J) will provide important insight into the biological pathways of muscular dystrophies leading to potential therapies for human diseases.

## MARYLAND

### Baltimore - Johns Hopkins University

#### Ronald Cohn M.D.

RG	Therapeutic potential of TGF-beta antagonism in muscular dystrophies			
	\$87,433.00	7/1/2008	6/30/2009	Year 2
	\$87,433.00	7/1/2009	6/30/2010	Year 3

*Summary* Losartan, a TGF-B blocker will be tested for therapeutic importance in DMD and possible forms of LGMD.

#### Vassilis Koliatsos M.D.

RG	Human neural stem cells as tools in reconstructing motor circuits			
	\$150,000.00	1/1/2009	12/31/2009	Year 3

*Summary* Researchers will explore clinical benefits of multiple grafts of neural stem cells in primary motor and motor relay areas of the brain and spinal cord in achieving restoration of circuitry.

#### Brett Morrison M.D., Ph.D.

DG	Increasing muscle size and strength by reducing myostatin in mouse models of ALS			
	\$45,000.00	7/1/2008	6/30/2009	Year 2
	\$45,000.00	7/1/2009	6/30/2010	Year 3

*Summary* Studies are to use both genetic and pharmacologic methods to increase muscle size and strength in different ALS mouse models.

#### Jeffrey Rothstein M.D., Ph.D.

RG	Drug screening program for motor axons in amyotrophic lateral sclerosis (ALS)			
	\$109,286.00	1/1/2009	12/31/2009	Year 3

*Summary* Researchers will explore drugs essential for selective growth of motor nerves to aid recovery of damaged motor nerves as in ALS.

#### Shanthini Sockanathan PhD

RG	Molecular mechanism of motor neuron differentiation			
	\$125,000.00	7/1/2008	6/30/2009	Year 3

*Summary* The aim is to understand how GDE2, a protein essential for the initial production of motor neurons, mediates its function through its interaction with three other proteins that impact distinct cellular processes. Interestingly, motor neurons maintain high levels of GDE2 throughout life. It will be investigated if GDE2 is important for motor neuron differentiation, function and survival using mouse genetics.

### Baltimore - Johns Hopkins University School of Medicine

#### Elizabeth H. Chen Ph.D.

RG	Regulation of WASP-Interacting Protein During Myoblast Fusion			
	\$84,000.00	1/1/2009	12/31/2009	Year 2
	\$88,000.00	1/1/2010	12/31/2010	Year 3

*Summary* This project will investigate the regulation of an important factor required for myoblast fusion. These studies may lead to insights into certain muscle diseases and effective modulation of the fusion process in therapeutic settings in the future.

#### Se-Jin Lee M.D., Ph.D.

RG	Identification of new modulators of muscle growth			
	\$115,000.00	7/1/2008	6/30/2009	Year 1
	\$115,000.00	7/1/2009	6/30/2010	Year 2
	\$115,000.00	7/1/2010	6/30/2011	Year 3

*Summary* We previously identified myostatin as a secreted protein that normally acts to suppress muscle growth. Considerable effort has been directed at developing drugs capable of blocking myostatin activity, as such drugs could have widespread applications for treating patients with muscle degenerative diseases. In recent work, we have demonstrated the existence of other signaling proteins that cooperate with myostatin to block muscle growth. The goal of this proposal is to begin to identify these other proteins and their receptors, as such proteins would be attractive targets for drug development.

**Maureen A. Lefton-Greif Ph.D.**

RG	Coordination of Respiration with Deglutition/Phonation in DMD and SMA			
	\$82,606.00	1/1/2009	12/31/2009	Year 2

*Summary* We propose to study an innovative approach to assessment of dysphagia in children with DMD and SMA by using a respirodeglutometer (RDG) to record several channels of biophysical responses (nasal airflow, laryngeal motion and pharyngeal sound) during swallows. RDG may provide a practical means for early detection and characterization of dysphagia, reducing the associated pulmonary morbidities, for children with DMD, SMA and other neurologic disorder

**Jeffrey Rothstein M.D., Ph.D.**

RRG	Robert Packard Center for ALS Research (Wings Over Wall Street & Regency Homes)			
	\$532,748.00	8/1/2008	7/31/2009	Year 1

*Summary* Funding received from MDA (as directed by Wings Over Wall Street & the Regency Homes Golf Classic) will be used to help fund research projects through the Packard Center for ALS Research. Each project is affiliated with a Johns Hopkins-based researcher, who will participate in the Packard Center's collaborative process, and has been reviewed and approved by the Center's scientific advisors. Any additional funding required by these projects beyond that awarded by MDA will be covered by the Robert Packard Center. Money received from MDA Wings Over Wall Street and Regency Homes MDA Golf Classic will not be used to support Dr. Rothstein or his lab.

**Hiroimi Sesaki Ph.D.**

RG	Understanding the Biochemical Basis of CMT Type 2A			
	\$126,970.00	1/1/2009	12/31/2009	Year 2
	\$140,637.00	1/1/2010	12/31/2010	Year 3

*Summary* We are investigating the functions of mitofusin 2 using the yeast homolog Fzo1p at the molecular level. We have shown that Fzo1 directly mediates mitochondrial fusion using purified proteins. In this proposal, we will determine the molecular function of mitofusin 2/Fzo1p in mitochondrial fusion. Outcomes of this proposal will significantly enhance our understanding of the biochemical role of mitofusin 2/Fzo1p, and provide novel insights into the pathogenesis of Charcot-Marie-Tooth neuropathy type 2A.

**Kathryn R. Wagner M.D., Ph.D.**

RG	Reducing fibrosis in muscular dystrophy			
	\$104,357.00	1/1/2009	12/31/2009	Year 2
	\$108,981.00	1/1/2010	12/31/2010	Year 3

*Summary* The purpose of the proposed research is to determine the mechanisms by which various growth factors influence muscle fibrosis and to attempt to reduce fibrosis through modulation of these factors. Identifying the cells involved with fibrosis formation and attempting to reverse fibrosis by regulating these cells with a myostatin inhibitor in animal models of muscular dystrophy. Since a variety of myostatin inhibitors are in pharmaceutical development, information regarding their anti-fibrotic effects can be put into clinical practice imminently.

**Yongjie Yang Ph.D.**

DG	Dysregulation of astroglial glutamate transporter EAAT2/GLT1 in ALS				
	\$60,000.00	7/1/2008	6/30/2009	Year 1	
	\$60,000.00	7/1/2009	6/30/2010	Year 2	
	\$60,000.00	7/1/2010	6/30/2011	Year 3	

*Summary* Glutamate-induced excitatory toxicity is one of the major pathogenic pathways in the motor neuron diseases. Severe loss of the astroglial excitatory amino acid transporter 2 (EAAT2, rodent analog GLT1), the primary transporter responsible for removing >90% of extracellular glutamate, has been found in animal models of various motor neuron diseases and postmortem patients. So far, the regulation of GLT1/EAAT2 expression and mechanisms of loss of the GLT1/EAAT2 in motor neuron diseases are very poorly understood. The proposed study aims to better understand the dysregulation mechanisms of EAAT2/GLT1 in the animal model of ALS by identifying the critical EAAT2 promoter elements and by investigating the function of a novel target protein in the regulation of EAAT2/GLT1 expression. The knowledge from these studies will help to better understand the disease pathogenesis and also provide new target for novel drug discovery.

**Baltimore - University of Maryland****Robert J. Bloch Ph.D.**

RG	Intermediate Filament Proteins in Skeletal Muscle				
	\$120,000.00	1/1/2009	12/31/2009	Year 2	
	\$120,000.00	1/1/2010	12/31/2010	Year 3	

*Summary* We are studying the special roles of two filaments, desmin and keratin, both termed "intermediate", to learn how they work together to link the contractile structures to each other and to dystrophin at the cell membrane, and how the absence of these proteins, alone or together, compromises the structure and function of skeletal muscle.

**Diana Ford Ph.D.**

DG	Obscurin Signaling through RhoA in Skeletal Muscle				
	\$60,000.00	1/1/2009	12/31/2009	Year 1	
	\$60,000.00	1/1/2010	12/31/2010	Year 2	
	\$60,000.00	1/1/2011	12/31/2011	Year 3	

*Summary* Dystrophic muscle is much more susceptible to injury, so it is important to determine not only what the mechanisms underlying muscle repair and regeneration are, but also how the missing components in dystrophic muscle lead to perturbations of these recovery pathways. The primary goal of the proposed research is to examine the role of rhoA in these pathways, in particular through its interaction with obscurin. Obscurin is a giant scaffolding protein in muscle that not only serves a structural role, but also mediates signaling. Concentrated around each contractile unit of muscle, obscurin is well positioned to sense force transmission. RhoA is a small signaling protein that has been shown to mediate muscle growth and differentiation and that, I have shown, may be activated by obscurin when muscle contracts forcefully. Here I propose to study how obscurin and rhoA regulate muscle fibers, and how their pathways are altered in dystrophic muscle.

**Aikaterini Kontrogianni-Konstantopoulos Ph.D.**

RG	M-band proteins and their role in thick filament assembly				
	\$75,000.00	1/1/2009	12/31/2009	Year 3	

*Summary* Researchers will study the protein obscurin involved with the contractile apparatus in muscle. It is hypothesized that this protein has a role in organization of the contractile apparatus proteins.

**Richard M. Lovering Ph.D.**

DG	Sarcolemmal recovery after damage in dystrophic muscle				
	\$45,000.00	1/1/2009	12/31/2009	Year 3	

*Summary* Researchers will investigate the roles of dystrophin, delta sarcoglycan and dysferlin in membrane damage and repair.

**Patrick W. Reed Ph.D.**

DG	Analysis of changes in the proteome in facioscapulohumeral muscular dystrophy			
	\$45,000.00	7/1/2008	6/30/2009	Year 2
	\$45,000.00	7/1/2009	6/30/2010	Year 3

*Summary* Researchers will attempt to discover gene products altered in FSHD muscle to determine how such a change may effect FSHD.

**MASSACHUSETTS**

**Boston - Beth Israel Deaconess Medical Center**

**Maria Chiara Manzini Ph.D.**

DG	Identification of genes involved in severe CMD associated with brain defects			
	\$45,000.00	1/1/2009	12/31/2009	Year 2
	\$45,000.00	1/1/2010	12/31/2010	Year 3

*Summary* We have collected a large group of patients affected with WWS, MEB or CMD with milder eye and brain malformations. By combining clinical and genetic analyses, we will determine the impact of the known genes and identify novel genes responsible for these diseases. In the short term, this work will provide additional diagnostic tools, and in the future, it will help understand the biology of these disorders on the path to a cure.

**Boston - Brigham and Women's Hospital, Inc.**

**Steven A Greenberg MD**

RG	Lymphocyte maturation within muscle in the inflammatory myopathies			
	\$85,000.00	7/1/2008	6/30/2009	Year 2
	\$85,000.00	7/1/2009	6/30/2010	Year 3

*Summary* Researchers will study inflammatory myopathies to understand the immune system attack in these disorders.

**Mohammad Salajegheh M.D.**

DG	The Identification of Antigens in Inclusion Body Myositis			
	\$60,000.00	7/1/2008	6/30/2009	Year 1
	\$60,000.00	7/1/2009	6/30/2010	Year 2
	\$60,000.00	7/1/2010	6/30/2011	Year 3

*Summary* None of the known immune therapies have proven to be effective for treating inclusion body myositis (IBM). While both inflammatory and degenerative mechanisms are implicated in the disease process, the relationship between the two remains unclear. Studies have shown that the inflammation present in IBM muscle is antigen driven, and that it involves both cell-mediated (cytotoxic T cells) and humoral (B cells, plasma cells and antibodies) immunity. However, the nature of these antigens is unknown, and their identification will allow us to better understand the disease process and lead to the development of more specific diagnostic methods and effective therapies. Previous studies have demonstrated the feasibility of using antibodies for the identification of antigens in other inflammatory diseases. We have developed similar strategies aimed at identifying antigens in IBM, using a combination of immunologic and proteomics techniques, as well as advanced mass spectrometry. Our preliminary results have suggested that alpha B crystallin may act as an autoantigen in certain IBM patients. We propose to perform a systematic approach to further identify antigens in IBM, determine their localization within muscle and their relationship to degenerative components.

## Boston - Children's Hospital Boston

### Basil T. Darras M.D.

CRNG	Children's Hospital Boston MDA Clinical Research Center			
	\$100,000.00	8/1/2008	7/31/2009	Year 1
	\$100,000.00	8/1/2009	7/31/2010	Year 2
	\$100,000.00	8/1/2010	7/31/2011	Year 3

*Summary* As a participating MDA Clinical Research Network site, we propose to conduct a natural history study that will examine the longevity of DMD patients and will take into account for the first time the molecular genetics of dystrophinopathies. We will relate clinical outcome to both molecular defect and treatment modality to assess the impact on survival and outcome of the more interventional, aggressive treatments that have been developed for our patients by medical, orthopedic, pulmonary, cardiology, and gastrointestinal disciplines over the past 15-20 years.

### Emanuela Gussoni Ph.D

RG	BMP4 pathway in human muscle SP/MP cells			
	\$124,635.00	7/1/2008	6/30/2009	Year 3

*Summary* The project will study specific interactions among cells isolated from human skeletal muscle. Such interactions are thought to generate signals that promote cell division and differentiation. After understanding the effects of these interactions on purified cells, they will inject selected cell populations in mice with muscular dystrophy, to test their ability to repair damaged muscle.

## Boston - Harvard Medical School

### Marcia Haigis Ph.D.

RG	Regulation of Mitochondria by SIRT3			
	\$109,122.00	1/1/2009	12/31/2009	Year 1
	\$114,128.00	1/1/2010	12/31/2010	Year 2
	\$119,901.00	1/1/2011	12/31/2011	Year 3

*Summary* Mitochondrial function is essential for ATP production in tissues that consume energy, such as the muscle. Dysfunction of mitochondria can lead to loss of energy production, build up of harmful oxidants and tissue decline. The goal of this study is to examine the effect of a mitochondrial enzyme, SIRT3, on mitochondrial energy production in the skeletal muscle, and to see how these parameters are affected by diet and age. SIRT3 is interesting because it is homologous to a conserved regulator of aging SIR2. In fact, the SIR2 family of proteins is hypothesized to control aspects of metabolism, obesity, and muscle mass in mammals. We have discovered that SIRT3 interacts with critical components of energy production in the mitochondria. We propose to use chemical assays to measure how SIRT3 regulates ATP and oxidants. We propose to use biological assays to measure how SIRT3 regulates muscle function by using a mouse model that lacks SIRT3 protein. We also propose to investigate how mitochondrial acetylation and SIRT3 affect a mouse model of muscular dystrophy. These experiments will provide us with new information about how mitochondrial SIR2 protein works to regulate energy in the muscle, and how it may be dysregulated during muscular dystrophies.

## Boston - Massachusetts General Hospital

### Merit Ester Cudkowicz MD

RG	Validation of a new device to measure neuromuscular disease progression			
	\$75,000.00	7/1/2008	6/30/2009	Year 2
	\$75,000.00	7/1/2009	6/30/2010	Year 3

*Summary* Clinicians will test ATLAS to determine isometric strength assessments in ALS patients to establish a more accurate and faster method for drug evaluations.

**Merit Ester Cudkowicz MD**

<b>CRNG</b>	MDA ALS Clinical Research Network : Massachusetts General Hospital ALS Center			
	\$100,000.00	8/1/2008	7/31/2009	Year 1
	\$100,000.00	8/1/2009	7/31/2010	Year 2
	\$100,000.00	8/1/2010	7/31/2011	Year 3

*Summary* The process of developing new drugs for ALS is particularly challenging because of relative rarity of this disorder. Low enrollment rates and high study participant withdrawal add further challenges. Due to advances in our understanding of ALS pathogenesis, there is potentially a large pipeline of therapies to bring forward for patients with ALS. The current strategy is to test one drug at a time against placebo. However, if multiple active drugs are tested against each other and then only best of that group is compared against placebo, the time required to develop an effective ALS therapy could be cut-down considerably. We propose that the MDA ALS Clinical Research Network establish a protocol and system to perform selection design studies on treatments that are ready for phase 2 testing. The Network will collaborate with regional centers to improve study enrollment and retention.

**Anne-Marie Wills M.D.**

<b>CRTG</b>	Trial of high fat/high calorie diet versus optimal calorie replacement in ALS			
	\$90,000.00	7/1/2009	6/30/2010	Year 1
	\$90,000.00	7/1/2010	6/30/2011	Year 2

*Summary* I am a board-certified neurologist at Massachusetts General Hospital specializing in amyotrophic lateral sclerosis (ALS). I will conduct a Phase II safety and feasibility study of high fat/high calorie diet versus optimal calorie replacement in ALS. People with ALS are generally instructed to increase their calorie intake; however, the ideal amount and type of calories has not been studied. Several studies in an animal model of ALS have shown that a high fat/high calorie diet can increase survival by as much as 38%. This clinical trial will measure feasibility, compliance and serious adverse events on high fat/high calorie, versus high calorie, versus normal calorie diet. We anticipate that the data from this study will aid in the design of a larger efficacy study and eventually the inclusion of dietary recommendations in an ALS practice parameter.

**Boston - Boston University****Mahasweta Girgenrath Ph.D**

<b>DG</b>	A combinatorial strategy to treat the pathology of congenital muscular dystrophy			
	\$45,000.00	1/1/2009	12/31/2009	Year 3

*Summary* Congenital muscular dystrophy type 1A (MDC1A) due to loss of laminin, will be studied to determine mechanisms to improve skeletal muscle growth, repair and survival in this disorder.

**Francisco J. Naya Ph.D.**

<b>RG</b>	Role of the MEF2-regulated gene myospryn in striated muscle			
	\$94,477.00	7/1/2008	6/30/2009	Year 3

*Summary* The aim of this project is to understand in greater detail the role of Myospryn in muscle using genetics and molecular biology techniques. These studies will provide us with a better understanding of muscle function and will ultimately help in the development of new drugs for the treatment of muscle disease.

## Cambridge - ALS Therapy Development Foundation Inc.

### Steven Perrin Ph.D.

TRAC	Identification and validation of therapeutic targets for ALS clinical development			
	\$6,000,000.00	3/1/2008	2/28/2009	Year 2
	\$6,000,000.00	3/1/2009	2/28/2010	Year 3

*Summary* The Muscular Dystrophy Association and ALS Therapy Development Institute (ALS-TDI) are collaborating on a program to comprehensively characterize disease progression in ALS using animal models of neurodegeneration and ALS clinical samples. The unbiased approaches of genomics, proteomics, and genetics will assist in understanding biological mechanism associated with disease susceptibility, onset, and progression. An unparalleled secondary validation process will be implemented using in vivo and in vitro technologies to prioritize the most relevant molecules associated with disease biology. Proof-of-concept studies will be evaluated in murine models of neurodegenerative disease to assess the effects of putative therapeutics on surrogate markers of disease as well as survival. From these studies the ALS-TDI will develop validated therapeutic targets ready for pre-clinical and clinical development and deliver diagnostic and prognostic disease biomarkers for use in clinical applications.

## Cambridge -Harvard College

### Alfred L. Goldberg Ph.D.

RG	Protein breakdown in muscle in normal and disease states			
	\$122,692.00	1/1/2009	12/31/2009	Year 3

*Summary* Researchers will study FoxO to determine its control over atrophy-related genes (atrogenes) which induce degradation in muscle atrophy.

### Deepak Kumar Ph.D.

DG	Identification of Pax3/Pax7 target genes in satellite cells			
	\$45,000.00	1/1/2009	12/31/2009	Year 3

*Summary* Researchers will identify targets of Pax7 and Pax3 in satellite cells to understand maintenance and differentiation of satellite cells into myofibers.

### Malcolm Whitman PhD

RG	Regulation of myostatin in the extracellular matrix and the control of muscular dystrophy			
	\$87,515.00	1/1/2009	12/31/2009	Year 3

*Summary* Myostatin can be stored in the body in an inactive state which can be activated by a novel mechanism. Therapies may be developed to block this activation and enhance muscle growth.

## Waltham - Repligen Corporation

### James Rusche Ph.D.

TR-CG	HDAC Inhibitors for Friedreich's Ataxia and Myotonic Dystrophy			
	\$414,724.00	12/1/2008	11/30/2009	Year 2
	\$.00		11/30/2009	Year 3

*Summary* Friedreich's ataxia and myotonic dystrophy are diseases with no current treatments. Recent finds of compounds that can activate critical genes provides an opportunity for new drugs. Work has begun to see if compounds can be made suitable for treating adolescent patients and deliver a safe therapy. Most often, lead compounds must be chemically modified to find a derivative potent on the target but safe enough to use in humans. A library of compounds derived from the chemical leads is being synthesized. With this library and researchers skilled in models of these diseases, we will hopefully identify a compound that is potent, safe, and active in models of FRDA and DM1. These are the objectives of the program: i) identify the optimal compound for development ii) evaluate the compounds in animal models of the human disease iii) complete pharmacology and toxicology to support human clinical testing. The conclusion will be compounds ready for clinical research in FDRA and DM1 patients.

## Watertown - Boston Biomedical Research Institute

### Jeffrey Boone Miller PhD

RG	MDC1A therapeutic mechanisms: Model studies.			
	\$100,925.00	1/1/2009	12/31/2009	Year 1
	\$103,591.00	1/1/2010	12/31/2010	Year 2
	\$106,310.00	1/1/2011	12/31/2011	Year 3

*Summary* One type of Congenital Muscular Dystrophy is caused by mutations that prevent the proper function of a protein called laminin-alpha2. One result of the loss of laminin-alpha2 function is that muscle cells die so that muscle mass and strength are greatly reduced. In model studies, we have identified methods that slow muscle cell death and ameliorate disease symptoms. These methods depend on modifying a particular molecular pathway that centers on the protein called Bax. In the studies proposed here, we will analyze additional molecular pathways that interact with and regulate Bax. By understanding how these pathways regulate Bax in diseased muscle, we will learn how loss of muscle cells occurs upon mutations of laminin-alpha2. Furthermore, it may prove possible to manipulate these additional pathways with drugs in a way that will prove therapeutically useful for congenital muscular dystrophy.

## Worcester - University of Massachusetts Medical School

### Elliot J. Androphy MD

RG	Vesicular transport factor interacts with SMN and the pathogenesis of SMA			
	\$109,644.00	1/1/2009	12/31/2009	Year 2
	\$110,375.00	1/1/2010	12/31/2010	Year 3

*Summary* Our goal is to uncover the specialized functions of the SMN protein in the motor neuron, loss of which lead to progressive muscle weakness. We have identified a novel SMN binding protein that is involved in transport of proteins in other parts of the cell and hypothesize its interaction with SMN may be used for a different type of transport in motor neurons.

### Zuoshang Xu Ph.D.

RG	Transgenic models of ALS caused by VAPB mutation			
	\$95,000.00	7/1/2008	6/30/2009	Year 2

*Summary* Researchers will study how mutant VAPB causes ALS in animal models which may lead to new therapeutic approaches.

### Jianhua Zhou Ph.D.

RG	Protecting against SMN defects by stress response proteins and biological molecules			
	\$82,856.00	1/1/2009	12/31/2009	Year 3

*Summary* Researchers will test if stress response proteins or small molecules may compensate for the loss of SMN protein providing a therapy for Spinal Muscular atrophy (SMA).

## MICHIGAN

### Ann Arbor - The Regents of the University of Michigan

#### Mohammed Akaaboune

RG	Studies of receptor recycling at neuromuscular junction from mice deficient in alpha dystrobrevin an			
	\$75,000.00	7/1/2008	6/30/2009	Year 3

*Summary* This research focuses on better understanding the ways in which the number and density of acetylcholine receptors are maintained in normal neuromuscular junctions and how they are disrupted in diseases.

**James Dowling M.D., Ph.D.**

DG	Characterization and rescue of a murine model of myotubular myopathy			
	\$45,000.00	7/1/2008	6/30/2009	Year 2
	\$45,000.00	7/1/2009	6/30/2010	Year 3

*Summary* A mouse model of myotubular myopathy will be used to understand relationship of myotubularin mutations and disease.

**Daniel Goldman Ph.D.**

RG	Epigenetic control of muscle activity-dependent gene expression			
	\$121,008.00	7/1/2008	6/30/2009	Year 2
	\$121,008.00	7/1/2009	6/30/2010	Year 3

*Summary* Muscle atrophy may be due to disruption of NMJ signalling. The role of HDACs in this pathway will be studied.

**Detroit - Wayne State University****Gyula Acsadi M.D., Ph.D.**

RG	The effects of SMN depletion on the expression of genes participating in axonal growth and transport			
	\$93,985.00	1/1/2008	3/31/2009	Year 3

*Summary* Studying the functions of the SMN protein, as well as the consequences of its decrease in neurons, would extend current knowledge about the disease mechanism. This proposal aims to investigate the effects of SMN loss on nerve cell development and function which will promote the developemnt of effective therapies for SMA.

**John Kamholz PhD**

RG	The structure and function of myelin protein zero mutations causing CMT1B			
	\$117,000.00	7/1/2008	6/30/2009	Year 1
	\$117,000.00	7/1/2009	6/30/2010	Year 2
	\$117,000.00	7/1/2010	6/30/2011	Year 3

*Summary* Myelin protein zero (MPZ) is the major protein of myelin in the peripheral nervous system (PNS). Mutations in MPZ cause an inherited demyelinating neuropathy, called CMT1B, which has associated muscle weakness, sensory loss, and difficulty walking. In this study we will investigate the structure of human MPZ and several mutations that cause CMT1B. We have already determined the three dimensional structure of the normal human MPZ, and its analysis, including molecular modeling, suggests several ways that mutations could alter its structure to cause neuropathy. We will extend these studies to include analysis of the three dimensional structure and function of several mutations in MPZ that cause either early or late onset neuropathy. These studies will provide a basis for designing specific and novel treatments for this neurodegenerative disease.

**Richard Lewis M.D.**

PPG	High dose ascorbic acid treatment of Charcot Marie Tooth Disease type 1A.			
	\$230,000.00	7/1/2008	6/30/2009	Year 3

*Summary* Currently there are no cures or medical treatments available for the most common inherited peripheral neuropathy; Charcot-Marie-Tooth disease type 1A. Recent studies have shown that nerve damage in an animal model of CMT1A improves with high dose ascorbic acid (vitamin C). Investigators propose to undertake a multicenter clinical trial to determine whether it is feasible to further investigate the potential benefits of treating CMT1A patients with high dose ascorbic acid.

**Jun Li M.D., Ph.D.**

RG	Neurodegeneration in Loss of Function of Fig4			
	\$100,000.00	1/1/2009	12/31/2009	Year 1
	\$100,000.00	1/1/2010	12/31/2010	Year 2
	\$100,000.00	1/1/2011	12/31/2011	Year 3

*Summary* We have recently described a novel recessively inherited disease, Charcot-Marie-Tooth type 4J (CMT4J) that is caused by mutations in the Fig4 gene (Chow et al, Nature 2007). This mutation eliminates the expression of Fig4 in mice, namely pale temor (plt) mice that manifest weakness, neuronal loss and excessive vacuoles (like tiny membrane-bound 'bubbles' when visualized under the microscope) in neurons. Our subsequent studies in the plt mice and patients with CMT4J showed severe axonal loss and impaired trafficking of organelles (small cargos in the cells) in the mutant cells (Zhang et al, Brain 2008). These findings suggest that Fig4 is essential for neuronal survival. Moreover, we found a robust increase of mTOR activity in plt mice. Increased mTOR activity is known to play an important role in some neurodegenerative disorders. In this proposal, we will first determine whether mTOR inhibitor protects neurons from degeneration in plt mice. Second, we will evaluate whether a combined treatment of lithium and inositol reduces vacuoles and restores organelle trafficking in Fig4 deficient cells. Therefore, this project may provide important insights into the pathogenesis of neuronal degeneration and potential therapeutic targets.

**Samia Ragheb Ph.D.**

RG	Baff and the B-Cell in myasthenia gravis (MG)			
	\$125,783.00	1/1/2009	12/31/2009	Year 3

*Summary* A newly discovered molecule, Baff, helps B-cells of the immune system to survive and multiply. Understanding this relationship will allow development of therapies for myasthenia gravis (MG)

**Michael Shy M.D.**

RG	Treating the mouse model of early onset CMT1B			
	\$116,259.00	7/1/2008	6/30/2009	Year 1
	\$119,075.00	7/1/2009	6/30/2010	Year 2
	\$121,975.00	7/1/2010	6/30/2011	Year 3

*Summary* Charcot Marie Tooth disease type 1B is one of the most common inherited peripheral neuropathies. Patients develop leg and arm weakness, develop balance problems and have difficulty feeling pain and temperature. Many cases of CMT1B are particularly severe and prevent children from walking until they are several years old and confine patients to wheelchairs before adulthood. We have generated a mouse model of the severe forms of CMT1B and are now trying to develop treatments for these mice that can then be tried in patients.

**Michael Shy M.D.**

TR-IG	NORTH AMERICAN CMT NETWORK			
	\$292,572.00	1/1/2009	12/31/2009	Year 1
	\$.00	1/1/2010	12/31/2010	Year 2
	\$.00	1/1/2011	12/31/2009	Year 3

*Summary* The CMT North American Database currently includes a large number of well studied patients with different types of CMT to be available for clinical trials and clinical investigations. To improve the Database, ensure that patients are evaluated in a uniform fashion and to provide an infrastructure that will lead to high quality research for patients throughout the United States we are extending the Database and creating the North American CMT Network. Patients within the Network will be evaluated at one of six Centers of Excellence throughout the United States, DNA samples will be banked, and scoring systems for children with CMT will be established. This CMT Network will provide the infrastructure for CMT research within the United States and throughout the world.

## MINNESOTA

### Minneapolis - University of Minnesota - Twin Cities

#### Atsushi Asakura Ph.D.

RG	Muscle stem cell transplantation for muscular dystrophy			
	\$100,000.00	7/1/2008	6/30/2009	Year 1
	\$100,000.00	7/1/2009	6/30/2010	Year 2
	\$100,000.00	7/1/2010	6/30/2011	Year 3

*Summary* Possible approaches to restoring muscle fiber degeneration in Duchenne muscular dystrophy patients include cell therapy, gene therapy or a combination of the two. Muscle contains a type of stem cell called satellite cells that give rise to newly formed muscle fibers. We demonstrate that genetically modified satellite cell-derived myoblasts, isolated from mice lacking MyoD, a muscle-specific master transcription factor, display significantly higher engraftment compared to wild-type myoblasts when injected into injured muscle. Importantly, these genetically modified myoblasts were revealed to possess remarkable resistance to cell death and increased survival after stress induction, compared to wild-type myoblasts. In addition, these genetically modified myoblasts were detected underneath the basal lamina of muscle fibers after transplantation, indicating the self-renewal property of the myoblasts. Therefore, MyoD<sup>-/-</sup> myoblasts may preserve stem cell characteristics following transplantation, including resistance to cell death, efficient engraftment and contribution to satellite cells. In addition, we noticed that MyoD negatively regulates cell survival factors. Our data offer evidence for improved therapeutic stem cell transplantation for muscular dystrophy, in which suppression of MyoD in myogenic progenitors would be beneficial to therapy by providing a selective advantage for the expansion of stem cells.

#### Darko Bosnakovski Ph.D.

DG	Molecular analysis of DUX4 and gene therapy for FSHD			
	\$45,000.00	7/1/2008	6/30/2009	Year 2
	\$45,000.00	7/1/2009	6/30/2010	Year 3

*Summary* In FSHD, DUX4 gene expression is expressed only in myoblasts of affected patients. Studies will attempt to understand DUX4 effects on downstream target genes.

#### John West Day MD, PhD

CRNG	University of Minnesota Duchenne Muscular Dystrophy Clinical Research Center			
	\$100,000.00	8/1/2008	7/31/2009	Year 1

*Summary* We are eager to participate and involve the MDA DMD Clinical Research Network in approaches we are developing, which involve behavior, physical therapy, and nutritional methods, in addition to novel cell-based, protein-based and pharmacological treatments currently under development.

#### James M. Ervasti Ph.D.

RG	TAT-Utrophin as a Protein Therapy for Dystrophinopathy			
	\$125,000.00	7/1/2008	6/30/2009	Year 1
	\$125,000.00	7/1/2009	6/30/2010	Year 2
	\$125,000.00	7/1/2010	6/30/2011	Year 3

*Summary* These studies will continue to develop a novel protein replacement therapy in dystrophin-deficient mdx mice that may ultimately be used to stop or slow the progression of Duchenne muscular dystrophy. We will also investigate the capability of a novel targeted TAT-utrophin construct to specifically transduce dystrophic skeletal muscle, which could potentially increase efficacy, decrease the effective dosage, and further minimize the potential side effects of TAT-utrophin transduction into non-muscle tissues. Our approach complements other strategies, particularly utrophin upregulation approaches, which may potentially be combined to provide optimal benefit to patients.

#### Michael Koob Ph.D.

RG	Towards gene therapy of mitochondrial disease			
	\$100,000.00	11/1/2008	10/31/2009	Year 1
	\$100,000.00	11/1/2009	10/31/2010	Year 2

*Summary*

**Dawn A. Lowe Ph.D.**

RG Benefits of exercise to dystrophic muscle without compromising regenerative capacity  
\$64,868.00 7/1/2008 6/30/2009 Year 3

*Summary* This proposal is directed at determining the cellular responses of dystrophic muscle of young mice to endurance (voluntary wheel-running) and resistance (strength-training) exercises. The long-term goal is to show that exercise can improve skeletal muscle function and enhance the quality of life of individuals with muscular dystrophy.

**Dawn A. Lowe Ph.D.**

RG A bone-sparing strategy for muscular dystrophies  
\$98,841.00 1/1/2009 12/31/2009 Year 1  
\$90,520.00 1/1/2010 12/31/2010 Year 2  
\$88,964.00 1/1/2011 12/31/2011 Year 3

*Summary* The rate of bone fractures is on the rise in individuals with Duchenne Muscular Dystrophy (DMD) and there is little progress being made toward remediation. There are many underlying causes of bone degradation in DMD with a major one being the low stresses placed on bone by weak muscles. Because muscles and bones work together, the first aim of our project is to determine the simultaneous functional changes of these two tissues in dystrophic mice. This is essential so that treatment strategies that are optimal for both muscle and bone can be devised and evaluated. The second aim of our project is to determine the efficacy of low-level, mechanical vibration to increase the quantity and quality of bone in DMD. This intervention is non-invasive, non-pharmacological, involves short treatment sessions, and has been shown to improve bone, decrease fractures, and increase mobility in several populations of disabled children. However, mechanical vibration has not been studied in individuals with muscle disease and before it can be considered as a therapy for DMD, it must irrefutably be determined to be non-damaging to the fragile muscle. The third aim of our project is to work with clinicians and therapists at the University in order to relate our findings on mechanical vibration of mouse bone and muscle to a therapy for individuals with DMD.

**Rita R. Perlingeiro Ph.D.**

RG Approaches to recover the stem cell niche and promote neurogenesis in ALS  
\$129,616.00 1/1/2009 12/31/2009 Year 3

*Summary* Researchers will use stem cells from umbilical cord blood or bone marrow to promote neurogenesis as well as neuroprotection for existing neurons in ALS.

**Laura P.W. Ranum Ph.D.**

RG Multisystemic Model of RNA Toxicity for DM1 and DM2  
\$110,000.00 1/1/2009 12/31/2009 Year 2  
\$110,000.00 1/1/2010 12/31/2010 Year 3

*Summary* The proposed research will better define the molecular causes and potential reversibility of the multisystemic features of myotonic dystrophy (DM1). Analysis of new mouse models we have developed will allow us to better define the underlying causes of these diseases and the potential to reverse the disease when the transgene is turned off. Understanding the specific molecular changes that occur is important for developing future treatments to stop disease progression.

**Laura P.W. Ranum Ph.D.**

SG	6th International Conference on Unstable Microsatellites and Human Disease			
	\$7,500.00	1/1/2009	1/31/2009	Year 1

*Summary* I am writing to apply for support for the 6th International Conference on Unstable Microsatellites and Human Disease. This meeting occurs approximately every 2 years and has alternated between Europe and N. America. We expect about 140 scientists to attend. This meeting brings together an interdisciplinary group of investigators studying all of the microsatellite expansion disorders which fosters productive discussions on what is common and what is different about these diseases as a group. Featured prominently this year will be sessions on RNA gain of function effects (DM1/DM2, SCA8, SCA10, FXTAS), bi-directional expression of triplet expansion disorders (HDL2, SCA7, FXTAS and DM1), repeat instability, protein gain and loss of function and treatment strategies (SCA1, SBMA and FA). Because Dr. Muhlrud mentioned that the Costa Rica venue has raised concern, I want to take a moment to address this issue. As you can see from our website [www.microsatellites.ca](http://www.microsatellites.ca), the list of invited speakers is world class and the format, which will follow previous meetings, is ambitious. Second, because this is an international meeting which has been held in Europe and North America it made sense to pick a location west of the Atlantic that would encourage scientists from Central, South and North America to attend. Finally, the Guanacaste Airport has direct, affordable flights from many major cities in the US & Europe and the conference site is extremely affordable.

**David D. Thomas Ph.D.**

RG	Interaction of actin with dystrophin and utrophin			
	\$100,000.00	7/1/2008	6/30/2009	Year 2
	\$100,000.00	7/1/2009	6/30/2010	Year 3

*Summary* Researchers will investigate the interactions of dystrophin and utrophin with actin filaments.

**DeWayne Townsend D.V.M., Ph.D.**

DG	Understanding cardiac dystrophin: Critical to improving gene therapy for DMD			
	\$45,000.00	1/1/2009	12/31/2009	Year 2
	\$45,000.00	1/1/2010	12/31/2010	Year 3

*Summary* This proposal will examine the ability of a truncated dystrophin to replace dystrophin in the heart. Cardiac function will be assessed in several animal models of DMD. These studies will provide critical information for developing the next generation of truncated dystrophins that will improve the treatment of the heart in DMD.

**Rochester - Mayo Clinic Rochester****Michael A Barry Ph.D.**

RG	Cell Targeting Vectors for Muscular Dystrophy			
	\$109,671.00	7/1/2008	6/30/2009	Year 1
	\$109,137.00	7/1/2009	6/30/2010	Year 2
	\$107,679.00	7/1/2010	6/30/2011	Year 3

*Summary* This project will develop technologies towards the use of "smart" gene therapy vectors that can seek out and target gene delivery to neuromuscular muscle cells in the body for the treatment of Duchenne and other muscular dystrophies.

**Andrew George Engel M.D.**

RG	Congenital myasthenia syndrome			
	\$116,563.00	1/1/2009	12/31/2009	Year 3

*Summary* Studies of congenital myasthenic syndromes will be conducted to improve diagnosis, treatment and prevention.

**Bruce Horazdovsky Ph.D.**

RG	Cellular Defects Associated with ALS2			
	\$125,000.00	1/1/2009	12/31/2009	Year 1
	\$125,000.00	1/1/2010	12/31/2010	Year 2
	\$125,000.00	1/1/2011	12/31/2011	Year 3

*Summary* Amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease) is a complex disorder characterized by the progressive death of neurons that control muscles. A person with ALS suffers increasing paralysis and usually dies within 3 to 5 years of diagnosis due to respiratory complications. Though little is known about what actually causes ALS in most people, approximately 10% of these cases have a genetic link. For the past five years, we have been examining one gene that is mutated in a genetic form of ALS, called ALS2. Unlike the classical ALS described above, this juvenile form of the disease appears very early in life (leading to paralysis), but is not quite as severe as the classical form of the disease. The gene mutated in these children codes for a protein called Alsin that plays an important role in preventing neurons from dying. Though we have discovered some of the key processes that are regulated by Alsin, our analysis is just beginning, and there are many new discoveries to be made. It is our hope that by dissecting Alsin function we will gain new insights into the causes of ALS and in doing so identify new targets for treatment.

**MISSOURI****Columbia - University of Missouri****Dawn DW Cornelison Ph.D.**

RG	The role of syndecan-4 in extracellular signal transduction by muscle satellite cells			
	\$117,812.00	1/1/2009	12/31/2009	Year 3

*Summary* Syndecan-4 is critical for success of satellite cell-mediated muscle regeneration. Researchers will try to determine the molecular basis for the cellular phenotype comparing growth factor binding and growth factor signaling in satellite cells with and without syndecan-4. We will determine which activities of the protein are needed for specific cell functions.

**Dongsheng Duan PhD**

RG	Local injection of the intron 60 trans-AAV vectors in dystrophic dog			
	\$169,052.00	1/1/2009	12/31/2009	Year 3

*Summary* AAV is promising in gene therapy but not large enough to carry the full dystrophin gene. We have developed a dual vector system to allow for splicing two parts of the gene together.

**Dongsheng Duan PhD**

RG	Systemic AAV gene therapy in a Duchenne dog model			
	\$115,000.00	7/1/2008	6/30/2009	Year 1
	\$115,000.00	7/1/2009	6/30/2010	Year 2
	\$115,000.00	7/1/2010	6/30/2011	Year 3

*Summary* Adeno-associated virus-mediated gene therapy has shown great promise to ameliorate Duchenne muscular dystrophy. In this study we will apply our novel techniques to achieve whole body gene transfer in newborn DMD dogs. The majority of DMD patients can be diagnosed through neonatal screening. Our study will open the door for neonatal gene therapy in human patients in the future.

**Christian Lorson PhD**

RG	The role of enhanced muscle in SMA			
	\$120,758.00	1/1/2009	12/31/2009	Year 1
	\$123,658.00	1/1/2010	12/31/2010	Year 2
	\$126,658.00	1/1/2011	12/31/2011	Year 3

*Summary* Spinal Muscular Atrophy is the leading genetic cause of infantile death, yet there currently is no treatment or cure. This proposal is designed to test a muscle-enhancing compound and a SMN-inducing compound in a mouse model of disease. These results have the potential to identify novel therapeutic avenues for SMA patients.

**Great Falls - McLaughlin Research Institute**

**John R. Bermingham Ph.D.**

RG	Lgi4 signaling mechanisms in Schwann cell development
\$94,943.00	7/1/2008 6/30/2009 Year 3

*Summary* This project will reveal novel genetic mechanisms by which the timing of peripheral myelination is controlled, and thereby identify potential novel therapies for the treatment of myelin disease.

**St. Louis - Saint Louis University****Jindrich Soltys Ph.D., D.V.M.**

RG	Role of Complement and its Regulatory Proteins in EAMG Pathogenesis
\$121,735.00	7/1/2008 6/30/2009 Year 1
\$122,884.00	7/1/2009 6/30/2010 Year 2
\$124,553.00	7/1/2010 6/30/2011 Year 3

*Summary* Myasthenia gravis (MG) is an autoimmune disease that compromises how well a skeletal muscle responds to transmission from a nerve. The abnormality is caused by the breakdown of the AChR due to complement activation. Complement represent about 30 serum proteins, which interact with the cellular immune response. The ultimate purpose of our investigation is to understand how humoral (complement fixing antibodies) and cellular immunity (T and B cells) respond in the absence of the complement regulatory proteins or when the activity of complement is completely inhibited. Our investigation will provide a rationale for application of complement inhibition as a therapeutic intervention in patients with MG. Complement inhibitors are already used in various disorders, and we believe that similar application in neuromuscular disorders will provide an efficient and alternative way of treatment.

**St. Louis - Washington University in St. Louis****Robert Baloh M.D., Ph.D.**

DG	Mechanism of peripheral neuropathy from mitofusion 2 mutations
\$25,000.00	7/1/2008 6/30/2009 Year 3

*Summary* This proposal outlines experiments to investigate the mechanisms of disease-associated MFN2 mutants in sensory neurons to produce a model of the disease in a dish, as well as to produce a mouse model of CMT due to mitofusion 2 mutations.

**Anne M Connolly M.D.**

RG	Synergistic effects of steroids, ACE inhibitor, and exercise in mdx mice
\$99,764.00	1/1/2008 3/31/2009 Year 3

*Summary* This proposal will look at long-term effects including strength, fatigue, and amount of voluntary exercise in this well characterized mouse model.

**Anne M Connolly M.D.**

CRNG	MDA-DMD Center at Washington University
\$100,000.00	8/1/2008 7/31/2009 Year 1
\$100,000.00	8/1/2009 7/31/2010 Year 2
\$100,000.00	8/1/2010 7/31/2011 Year 3

*Summary* We present three clinical proposals that a clinical trials network could rapidly address. First, establish clinical outcome measures in infants, young boys and wheelchair-bound boys and men with DMD. There is a pressing need now to establish outcomes for very young who may be unreliable for testing and for older, weaker boys and men. Second, we propose to establish standard of care for treatment of osteoporosis in boys and men with DMD. A careful prospective trial is needed to determine what and when treatment should be given. Third, we propose to determine if angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) are comparable in treatment of cardiomyopathy in DMD. While two trials now show that ACE inhibition delays the onset of cardiomyopathy and prolongs the life of boys with DMD, no human trials of ARBs have been done. This second class of drugs shows beneficial skeletal muscle benefit in mdx mice. Therefore a randomized trial comparing the two would have immediate clinical implications.

**Aaron DiAntonio M.D., Ph.D.**

RG	Synaptic defects in a Drosophila model of congenital muscular dystrophy
\$105,527.00	7/1/2008 6/30/2009 Year 3

*Summary* This research will use powerful genetic techniques to identify genes that bypass the requirement for POMT1 in that identification of such genes will provide a deeper understanding of CMD and identify candidate genes that could ameliorate the disease.

**Paul T. Golumbek M.D., Ph.D.**

RG	Prednisolone's Therapeutic Site of Action in Mdx Mice
\$150,000.00	7/1/2008 6/30/2009 Year 1
\$150,000.00	7/1/2009 6/30/2010 Year 2
\$150,000.00	7/1/2010 6/30/2011 Year 3

*Summary* Prednisolone improves the strength and lifespan of mdx mice and boys with DMD, but we still don't understand how it works. Some believe it works by suppression of the immune system, others think the effect is on muscle directly, while others support a combination of these effects. We have previously investigated the role of three key immune players (complement, T-cells, and B-cells) in order to pinpoint which might worsen muscle strength and which respond to steroid treatment. We showed these players do not worsen the strength of mdx mice and do not account for prednisolone's action. Finding an immune response that worsens strength would allow us to arrest it. By ruling out the immune system we can avoid focusing research on innocent bystanders. Using depletion and genetics approaches, similar to the previous study, we plan to investigate the remaining immune suspects and test for direct muscle effects. Using strength tests as outcome measures (as are used in clinical trials with DMD boys), we will test muscle and immune components, macrophages, granulocytes and Natural killer cells. We will either deplete or disable the immune cells or disable the direct muscle response to steroid in mdx mice, and then assess steroid's clinical actions. Independently, each of the immune cells is capable of attacking sick muscle fibers and each is capable of steroid responsiveness. This work will define steroid's therapeutic mechanism in mdx mouse (and thus DMD) muscle disease.

**Didier Hodzic Ph.D.**

RG	Involvement of the LINC Complex in Emery-Dreifuss Muscular Dystrophy
\$125,000.00	1/1/2009 12/31/2009 Year 2
\$125,000.00	1/1/2010 12/31/2010 Year 3

*Summary* We hypothesize that mutations of A-type lamins related to EDMD compromise the integrity of the LINC complex, which, in turn, induces a mechanical failure of the whole cell and possibly of muscle tissues. We will test this hypothesis and further examine the in vivo consequences of the disruption of the LINC complex. These results could provide a molecular etiology of muscle pathologies linked to A-type lamin mutations.

**Jeffrey D. Milbrandt MD, PhD**

RG	Increased Nmnat activity as treatment for hereditary neuropathies
\$110,000.00	7/1/2008 6/30/2009 Year 1
\$110,000.00	7/1/2009 6/30/2010 Year 2
\$110,000.00	7/1/2010 6/30/2011 Year 3

*Summary* Disease progression in many neuropathies and neurodegenerative conditions like CMT and ALS is correlated with abnormalities in axons, the neuronal extensions that connect neurons to their targets. We have found that increased levels of an enzyme that synthesizes a molecule involved in cellular energy metabolism can protect against axonal degeneration by decreasing the accumulation of naturally occurring toxic substances generated by cellular processes. We will now investigate the cellular pathways that are involved in protecting axons from damage by this enzyme. We will also explore whether altering this enzyme and/or energy pathways can protect against axonal degeneration and slow disease progression caused by mutations associated with hereditary neuropathies.

**Alexander Parsadanian Ph.D.**

RG	Therapeutic potential of Neurturin in the G93A mouse model of ALS			
	\$112,000.00	7/1/2008	6/30/2009	Year 1
	\$112,000.00	7/1/2009	6/30/2010	Year 2
	\$112,000.00	7/1/2010	6/30/2011	Year 3

*Summary* Neurotrophic factors (NF) have been considered as potential agents for the treatment of motoneuron diseases (MND), including ALS, based on their in vitro and in vivo ability to promote the survival of motoneurons (MN). We focused primarily on members of GDNF Family Ligands (GFLs): GDNF, Neurturin (NTN), Artemin (ART) and Persephin (PSP), which have overlapping but distinct effects on MNs. The in vivo effects of NTN on MNs are not studied in detail. As a proof of concept, we have selected a transgenic approach to address this question. We generated transgenic mice overexpressing NTN in skeletal muscle (Myo-NTN) and in neurons (Thy1-NTN). Based on our preliminary data demonstrating that overexpression of NTN in neurons promotes complete and long-term survival of axotomized MNs, we propose that NTN will have significant beneficial effects in a mouse model of familial ALS. We will study the neuroprotective effects of NTN in G93A-SOD1 mice cross-bred with our transgenic mice overexpressing NTN either in skeletal muscles or in neurons both at anatomical and behavioral levels. We will study the effects of NTN on MN, motor axon, NMJ and terminal Schwann cell degeneration. We will elucidate the mechanisms of NTN action and signaling pathways activated by NTN in vivo. Understanding the mechanisms by which NTN acts on normal and degenerating MNs may give insight into how this NF can be used for treatment of MNDs.

**Conrad Weihl M.D., Ph.D.**

RG	ERAD and the unfolded protein response IBMPFD muscle disease			
	\$111,139.00	1/1/2009	12/31/2009	Year 1
	\$110,036.00	1/1/2010	12/31/2010	Year 2
	\$111,717.00	1/1/2011	12/31/2011	Year 3

*Summary* Inclusion body myopathies (IBM) are a group of disabling skeletal muscle disorders. Mutations in the protein p97/VCP that cause the autosomal dominant multisystem syndrome, IBMPFD, inclusion body myopathy associated with paget's disease of the bone (PDB) and fronto-temporal dementia (FTD). One clear role for p97/VCP is as a facilitator of protein degradation via the ubiquitin-proteasome system (UPS). p97/VCP is essential for the degradation of cytosolic proteasome substrates as well as for endoplasmic reticulum associated degradation (ERAD) of misfolded secreted or transmembrane proteins. It likely performs this role by selectively binding with ubiquitinated substrates via co-factors and transferring them to the 26S proteasome machinery. Currently it is unclear how mutations in p97/VCP cause disease. We plan to explore the role of IBMPFD mutations in p97/VCP on the UPS in skeletal muscle using cultured and a transgenic mouse model.

**NEW JERSEY****Newark - UMDNJ-New Jersey Medical School****Diego Fraidenaich Ph.D.**

RG	Embryonic stem cells prevent Duchenne muscular dystrophy in mdx mice			
	\$100,000.00	1/1/2009	12/31/2009	Year 2
	\$100,000.00	1/1/2010	12/31/2010	Year 3

*Summary* We seek to prevent muscular dystrophy from occurring by supplying wild type embryonic stem cells before the muscle forms. We will inject wild type mouse embryonic stem cells into early mouse embryos predisposed to DMD. Preliminary analyses found that low numbers of embryonic stem cells incorporated into the mouse are sufficient to prevent disease from occurring. We will investigate further the underlying molecular mechanisms whereby the embryonic stem cells exert corrections in skeletal muscle.

**Piscataway - UMDNJ--Robert Wood Johnson Medical School**

**Sarah Ellen Hitchcock-DeGregori Ph.D.**

RG	Tropomyosin in health and disease: Bioinformatics and biophysical approaches			
	\$109,157.00	1/1/2009	12/31/2009	Year 2
	\$107,913.00	1/1/2010	12/31/2010	Year 3

*Summary* Mutations in tropomyosin cause a number of myopathies, including cardiomyopathies, nemaline myopathies, distal arthrogyryposis, and Cap disease. We will carry out a bioinformatics analysis of the evolution of tropomyosin structure. We will create a phylogenetic tree and the measure the evolutionary rate of each amino acid. This will identify the most conserved residues and lead to new models that will be experimentally tested with the aim of understanding how disease-causing mutations lead to cellular dysfunction and disease.

**NEW YORK**

**Albany - Research Foundation of SUNY - University at Albany**

**Zhen Huang Ph.D.**

DG	Developing aptamer-based anti-excitotoxic drugs for ALS			
	\$45,000.00	7/1/2008	6/30/2009	Year 3

*Summary* Discover new and powerful inhibitors and explore the possibilities of using them to control the hyperactive receptor proteins involved in ALS.

**Albany - University at Albany**

**Li Niu Ph.D.**

RG	Rapid Kinetic Studies of GYKI Compounds as Neuroprotective Agents for ALS			
	\$110,000.00	7/1/2008	6/30/2009	Year 1

*Summary* Excessive activity of AMPA receptors is linked to motor neuron degeneration in ALS. Developing inhibitors to control the excessive activity of AMPA receptors has been a long pursued therapeutic strategy for ALS. GYKI compounds are a group of the most promising inhibitors developed to date. However, how these compounds work is not clear. This is because the inhibitor-receptor interaction must be studied when the AMPA receptor is in functional states, which only exist for a split second. Conventional methods of studying these receptors and inhibitors are not fast enough. In contrast, a laser technology will allow us to study the biological functions of an inhibitor in the required time frame. We will characterize 23 representative GYKI compounds by defining the inhibition constants and the relationship between the chemical structure and the inhibitory property. We will also determine whether it is productive to use two inhibitors at the same time. We will further test these compounds in an ALS animal model. Our study will provide valuable assessment of whether these compounds are potentially useful (1) to control AMPA receptor activity under neurodegenerative conditions, and (2) to be tested in clinical trials. Furthermore, we will provide useful information on how newer and more potent GYKI compounds can be synthesized in the future.

**Bronx - Albert Einstein College of Medicine of Yeshiva University**

**Jennifer Troncales Aguilan Ph.D.**

DG	The role of LARGE in the glycosylation of alpha-dystroglycan			
	\$45,000.00	7/1/2008	6/30/2009	Year 1
	\$45,000.00	7/1/2009	6/30/2010	Year 2
	\$45,000.00	7/1/2010	6/30/2011	Year 3

*Summary* The discovery of the dystrophin gene, which is the cause of Duchenne Muscular Dystrophy, led to the discovery of additional gene mutations that give rise to other muscular dystrophies. These genes encode proteins that form a large complex with dystrophin called the dystrophin glycoprotein complex (DGC). Alpha-dystroglycan (a-DG) is a glycoprotein in the DGC that serves to maintain mechanical stability and function of skeletal muscle. a-DG links the cytoskeleton under the cell membrane to matrix proteins on the cell surface including laminin. Laminin binds to the sugars on a-DG. Abnormalities in the structure or loss of these sugars lead to congenital muscular dystrophies known as dystroglycanopathies. The sugars are transferred to a-DG by enzymes called glycosyltransferases. Six genes thought to encode glycosyltransferases or chaperones that mediate sugar transfer to a-DG have been identified. One of these genes, LARGE, is the basis of MDC1D. Overexpression of LARGE bypasses defects in several dystroglycanopathies by restoring a-DG function. However, the biochemical reactions catalysed by LARGE are unknown. The aim of this proposal is to determine how LARGE modifies a-DG in order to understand the biochemical basis of MDC1D and to determine how LARGE may be used in the treatment of dystroglycanopathies.

**Chi-Wing Chow PhD**

RG	Exosomal Trafficking and CMT1C Disease			
	\$90,000.00	1/1/2009	12/31/2009	Year 1
	\$90,000.00	1/1/2010	12/31/2010	Year 2
	\$90,000.00	1/1/2011	12/31/2011	Year 3

*Summary* Charcot-Marie-Tooth (CMT) disease is an inherited neurological disorder in which patients display demyelination in the peripheral nervous system. The high prevalence (1:2500) of CMT diseases brings enormous burdens onto our health-care system and severely affects the economy of the United States. Mutations in protein SIMPLE account for the etiology in CMT1C patients. Duplication of PMP22 in CMT1A patients exhibit similar electrophysiological parameters and histopathological observations as in CMT1C, suggesting molecular interaction between SIMPLE and PMP22. The molecular basis of SIMPLE, however, is not known. My laboratory recently discovered that SIMPLE participates in vesicular trafficking to EXTRACELLULAR space. Indeed, secreted SIMPLE is found in exosomes, unique extracellular fractions that contain 50-90 nm microvesicles. Major function of the exosome is to facilitate cell-cell autocrine/ paracrine communications and genetic exchanges by delivering/ disposing endosomal cargos to extracellular milieu. Our recent data further demonstrated that missense mutations found in CMT1C patients abolished the ability of SIMPLE to localize to the extracellular exosomes. Expression of PMP22, mimicking duplication of PMP22 in CMT1A, also reduced exosomal secretion of SIMPLE, supporting genetic interaction of CMT1C and CMT1A. Here, we propose that Schwann cells containing CMT1C SIMPLE mutants cause defects in myelination, in part, due to the lack of exosome-mediated communication.

**Amber Wells Ph.D.**

DG/TCL	Investigating the effects of mRNA targeting and translation on muscle adhesion			
	\$45,000.00	1/1/2009	12/31/2009	Year 2
	\$45,000.00	1/1/2010	12/31/2010	Year 3

*Summary* We propose to investigate how CMA (cell-matrix attachments) mRNAs are localized to CMAs and how the localized synthesis of protein affects CMA adhesion.

## Cold Spring Harbor - Cold Spring Harbor Laboratory

### Adrian R. Krainer Ph.D.

RG	Correction of the SMN2 splicing defect in SMA mice using antisense oligonucleotides			
	\$254,000.00	7/1/2008	6/30/2009	Year 2
	\$254,000.00	7/1/2009	6/30/2010	Year 3

*Summary* Researchers will use antisense oligos to SMN2 for correct splicing to form SMN1 the form missing in SMA.

## Hawthorne - Taro Pharmaceuticals USA, Inc.

### Jacob Levitt MD

TR-CG	Dichlorphenamide for Periodic Paralysis			
	\$525,050.00	9/1/2008	8/31/2009	Year 1
	\$270,800.00	9/1/2009	8/31/2010	Year 2
	\$270,800.00	9/1/2010	8/31/2011	Year 3

*Summary* Acetazolamide (ACZ) and dichlorphenamide (DCP) have been used off-label for periodic paralysis (PP). Patients may respond initially to ACZ but then develop progressive weakness. Case reports suggest that DCP prevents and may even reverse this progressive weakness, returning patients to independence. DCP, approved by FDA for glaucoma, is no longer available anywhere because it is no longer used for that indication. After his initial study of DCP showed it was effective short term in reducing PP attacks, Dr. R. C. Griggs is conducting a yearlong study of ACZ vs DCP for attack and weakness prevention to develop standard treatment and provide data for FDA approval of DCP for PP. Taro Pharmaceuticals is making the ACZ and DCP for the study and has agreed to make DCP commercially for PP. It has obtained the rights from Merck to manufacture DCP to 2008 standards. Dr. Griggs will provide safety/outcome data for FDA filings. We expect to return DCP to the market soon after study completion.

## Ithaca - Cornell University

### Marilena D'Aurelio Ph.D.

DG	Pathogenesis of ATP6 mutations: Towards a pharmacological therapy for mitochondrial disease			
	\$45,000.00	7/1/2008	6/30/2009	Year 2

*Summary* ATPase 6 mutations in mitochondria cause a variety of diseases. How this mutation affects various pathways will be studied.

### Jordi Magrane Ph.D.

DG	Mitochondrial axonal transport defects in amyotrophic lateral sclerosis (ALS) motorneurons			
	\$44,990.00	1/1/2009	12/31/2009	Year 3

*Summary* Researchers will use mitochondrially-targeted fluorescent protein to visualize mitochondria for anterograde or retrograde transport. This study should determine if there are mitochondrial transport deficits in ALS.

### Giovanni Manfredi M.D., Ph.D.

RG	Modulation of the mitochondrial permeability transition pore to ameliorate ALS			
	\$96,775.00	1/1/2009	12/31/2009	Year 3

*Summary* Researchers will generate a mutant SOD1 mouse model lacking cyclophilin D, important for membrane permeability transition of mitochondria which may indicate a role in ALS.

## New York - Columbia University Medical Center

### Jinsy Andrews M.D.

CRTG David A. Gardner Neuromuscular Research Fellow  
\$90,000.00 7/1/2008 6/30/2009 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.

### Veronica Hinton Ph.D.

RG Development of Language Skills Among Boys with Duchenne Muscular Dystrophy  
\$107,097.00 7/1/2008 6/30/2009 Year 1  
\$101,840.00 7/1/2009 6/30/2010 Year 2  
\$104,214.00 7/1/2010 6/30/2011 Year 3

*Summary* The objective of this study is to examine development of language skills in boys with Duchenne muscular dystrophy (DMD). Children with DMD have been shown to be at risk for having delayed language skills, and many have a limited ability to listen to and hold verbal information in immediate memory. For the child with DMD, little attention has been given to the real-life issues associated with cognitive deficits. Most clinical attention is aimed at treating the physical aspects of the disease and slowing the progressive muscular weakness. Children with DMD may struggle at learning academics, and have poor social skills. Although these concerns are not life-threatening, they may compromise a child's optimal enjoyment of his life, yet can be mediated and improved, especially if identified early. This research aims to clarify the nature of the development of these issues. The study will build on our ongoing work that has already identified language skills in two groups of children with DMD. Younger boys who have been followed over two years will be followed longer to examine the the acquisition of academic skills. Older school-aged boys who have had detailed assessment of their language skills will be tested on academic tests and questioned about their social skills and quality of life. This study offers an exceptional opportunity to investigate ways to ameliorate an area of potentially considerable stress in children with DMD.

### Michio Hirano M.D.

RG/TCL Molecular pathogenesis of scapulo-peroneal myopathy due to FHL1 mutations  
\$136,170.00 1/1/2009 12/31/2009 Year 1  
\$117,758.00 1/1/2010 12/31/2010 Year 2  
\$117,795.00 1/1/2011 12/31/2011 Year 3

*Summary* Scapulo-peroneal (SP) myopathy (sometimes called scapulo-peroneal muscular dystrophy) is an inherited condition characterized by weakness initially in the upper back (scapula) and lower leg (peroneal) region. We have been studying a large Italian-American family with SP myopathy and have identified the causative mutation in a gene called FHL1. Our goal is to understand how mutations in FHL1 cause degeneration of muscle. Through a careful analysis of defects of FHL1, we hope to develop a rational therapy for SP myopathy and expand our understanding of normal muscle function.

### Hiroshi Mitsumoto D.Sc.

CRNG MDA Clinical Research Network  
\$100,000.00 8/1/2008 7/31/2009 Year 1  
\$100,000.00 8/1/2009 7/31/2010 Year 2  
\$100,000.00 8/1/2010 7/31/2011 Year 3

*Summary* The Eleanor and Lou Gehrig MDA/ALS Research Center at Columbia University has been a leader in providing state-of-the-art multidisciplinary care and management for patients with ALS and their families. We propose to develop a scale for clinically meaningful changes. The Network will be instrumental in developing a research biobank and effective educational activities for patients with ALS and their families.

**Hiroshi Mitsumoto D.Sc.**

RRG	WOWS ALS Research at the Eleanor & Lou Gehrig MDA/ALS Research Center at CUMC			
	\$402,512.00	8/1/2008	7/31/2009	Year 1

*Summary* The MDA Wings Over Wall Street (WOWS) fund has enormously helped initiate and maintain a high output of clinical and translational research activity in ALS at the Eleanor and Lou Gehrig MDA/ALS Research Center, Columbia University since 2002. In fact, this fund has turned our ALS Center into one of the most prominent ALS Centers in the Nation and led to the subsequent establishment of the Center for Motor Neuron Biology and Disease at Columbia University. We had a number of breakthroughs and important contributions in the ALS clinical and basic science fields. With continued support from the MDA Wings, we will continue clinical and translational research projects to make every effort to find the cause and cure of ALS.

**New York - Memorial Sloan-Kettering Cancer Center****Mary Baylies Ph.D.**

RG	Investigation of mechanisms underlying Myonuclear positioning			
	\$105,092.00	1/1/2009	12/31/2009	Year 1
	\$107,574.00	1/1/2010	12/31/2010	Year 2
	\$110,548.00	1/1/2011	12/31/2011	Year 3

*Summary* Critical to the performance of muscle is its correct formation, maturation and interaction with both the nervous system and tendons. During normal development, myonuclei localize in the center of myofibers and subsequently migrate to the fiber surface, becoming located beneath the sarcolemma and distributed evenly along the length of myofiber. Many myopathies and dystrophies are characterized by a redistribution of these myonuclei from the external positions to central positions within a myofiber. Despite the importance of nuclear positioning for proper muscle function and clinical diagnosis, very little is known about this process. To address this gap in knowledge, we conducted a forward genetic screen in the model organism *Drosophila melanogaster* to find genes responsible for nuclear positioning. Our screen has revealed a class of mutants that show defects in nuclear positioning. We have investigated one member of this class and have mapped this mutation to a gene that we named swoosh. Live imaging analysis indicates that, in contrast to wildtype muscle nuclei, swoosh mutant nuclei fail to migrate and position. In this proposal we will investigate the swoosh protein and its role in correctly positioning myonuclei. Based on our preliminary data, we hypothesize that swoosh functions to correctly move nuclei along microtubules to their final position, and that it accomplishes this by serving as an adaptor between the microtubule motor kinesin and the nuclear protein lamin.

**New York - Mount Sinai School of Medicine****Dale Lange M.D.**

RG	Safety and Efficacy of SOD1 Inhibition by Pyrimethamine in Familial ALS			
	\$200,000.00	4/1/2009	3/31/2010	Year 1
	\$200,000.00	4/1/2010	3/31/2011	Year 2
	\$100,000.00	4/1/2011	3/30/2012	Year 3

*Summary* ALS is a relentlessly progressive neurodegenerative disease that inevitably causes death from respiratory muscle paralysis within 3-5 years from onset. The disease is sometimes caused by a mutation in a gene that produces an enzyme known as superoxide dismutase (SOD1). Interfering with production of this enzyme in mice with ALS causes significant slowing of progression. We have shown that some patients with familial ALS show a reduction in the level of SOD1 when taking the drug pyrimethamine. However, some patients have had problems with tolerating higher doses of the drug, which we believe is related to the rate and amount of increase in dose. We also found that the degree that SOD1 is lowered by pyrimethamine may vary with mutation. We would like to continue our studies with a different rate of increase in pyrimethamine dose and to expand our study sites so as to include as many different mutations as possible. This will enable us to see if there is indeed a differential effect which would give us insight into the mechanism by which this mutation produces disease and information about possible effect of therapy.

## New York - New York University School of Medicine

### James Salzer M.D., Ph.D.

RG	Characterization of Signaling Pathways in Charcot-Marie-Tooth Disease			
	\$107,839.00	1/1/2009	12/31/2009	Year 1
	\$112,496.00	1/1/2010	12/31/2010	Year 2
	\$115,964.00	1/1/2011	12/31/2011	Year 3

*Summary* Inherited neuropathies (CMT) are a major source of disability and pain that result in part from loss of myelin (dysmyelination) around nerve fibers. While there have been significant advances in determining the genetic basis of inherited neuropathies, progress in understanding how these genetic mutations cause neuropathy and how to treat them, has remained limited. Our laboratory is characterizing signals that control whether cells make and maintain myelin around nerves. Some of these signals appear to be abnormally activated in these neuropathies and may therefore be candidates for therapeutic intervention. We have identified neuregulin/erbB signaling and a downstream target, mTOR (the mammalian target of rapamycin), as being aberrantly activated in nerve injury and in a neuropathy model. mTOR signaling enables over growth of a variety of cells and is therefore being targeted in cancer clinical trials. Our preliminary studies suggest that inhibiting mTOR activity effectively blocks Schwann cell proliferation and demyelination that is triggered by aberrant growth factors. We propose to build on these initial studies by: i) further characterizing these signaling pathways in rodent models of CMT ii) developing tissue culture models of CMT that will allow us to study these signaling pathways in more detail, and iii) determining whether we can prevent dysmyelination in CMT models by blocking mTOR and other aberrant signals with pharmacological inhibitors.

## New York - Sloan-Kettering Institute for Cancer Research

### Scott J. Nowak Ph.D.

DG	Molecular regulation of actin cytoskeleton during myoblast fusion			
	\$45,000.00	7/1/2008	6/30/2009	Year 3

*Summary* The researchers will use knockdown strategies coupled to novel imaging techniques and pharmacological inhibitors to characterize the role of the actin cytoskeleton during mouse myoblast fusion.

## New York - The Trustees of Columbia University in the City of New York

### Michio Hirano M.D.

RG	Biochemical therapy for mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)			
	\$99,924.00	7/1/2008	6/30/2009	Year 3

*Summary* This research will test enzyme replacement therapy in cultured cells and in a small number of patients, who will undergo allogeneic stem cell transplants (formerly known as bone marrow transplants).

### Peter Hook Ph.D.

DG	Regulation of cytoplasmic dynein force production for retrograde axonal transport			
	\$45,000.00	7/1/2008	6/30/2009	Year 3

*Summary* The proposed research aims at determining how cytoplasmic dynein produces movement, and how its activity is regulated using molecular biological, biophysical, and structural approaches.

### Hiroshi Mitsumoto D.Sc.

RG	Ambispective study of oxidative stress in the etiology and progression of ALS			
	\$120,000.00	7/1/2008	6/30/2009	Year 2
	\$100,000.00	7/1/2009	6/30/2010	Year 3

*Summary* ALS patients will be tested for oxidative injury and will determine if continued exposure to oxidative stressors is detrimental in ALS.

**Catarina M. Quinzii M.D.**

DG	Identifying the molecular genetic bases of human coenzyme Q10 deficiency
\$45,000.00	1/1/2009 12/31/2009 Year 3

*Summary* Researchers will study CoQ10 deficiency caused by various mutations. This should allow molecular tests for accurate genetic counselling, diagnosis and initiation of therapy.

**Howard J. Worman**

RG	MAP kinase inhibition to treat Emery-Dreifuss muscular dystrophy
\$109,413.00	1/1/2009 12/31/2009 Year 3

*Summary* Researchers will test effects of drugs to inhibit MAP kinases in a mouse model of EDMD which may be foundation of new therapies.

**New York - Columbia University****Patricia Richard Ph.D.**

DG	Function of the putative helicase senataxin in ALS4.
\$60,000.00	1/1/2009 12/31/2009 Year 1
\$60,000.00	1/1/2010 12/31/2010 Year 2
\$60,000.00	1/1/2011 12/31/2011 Year 3

*Summary* Neurological diseases are disorders of the brain, spinal cord and nerves that control the body. Of over 600 neurological disorders known, amyotrophic lateral sclerosis (ALS) is a serious and progressive nervous system disease for which there is currently no significant treatment to alter a usual fatal outcome. In ALS, nerve cells that control muscle movement die, resulting in people with ALS losing their ability to move. Several possible causes exist for ALS leading to several forms of the disease. One form of ALS, juvenile amyotrophic lateral sclerosis or ALS4 is a neurological disorder caused by mutations in the Senataxin (SETX) gene. I am interested in understanding how mutations in this yet uncharacterized gene can lead to this disease. By using biochemical and molecular biology approaches, I will investigate the function of SETX in normal cells and in cells expressing mutants of SETX. An understanding of the cellular function(s) of SETX will lead to a better understanding of ALS and ultimately to novel therapeutic approaches to prevent and treat them.

**Rochester - University of Rochester****Robert Griggs M.D.**

RG	Recruitment for HYP HOP Phase III Trial in the Periodic Paralysis
\$55,802.00	7/1/2008 6/30/2009 Year 1
\$56,321.00	7/1/2009 6/30/2010 Year 2
\$56,856.00	7/1/2010 6/30/2011 Year 3

*Summary* A clinical trial called HYP HOP is being conducted to see whether either of two drugs, acetazolamide, or dichlorphenamide, helps to decrease attacks of weakness in hyper-periodic paralysis and hypo-periodic paralysis and whether either one helps to prevent the permanent weakness that develops in these diseases. This can provide physicians with a standard treatment for the diseases. NIH has funded the study but additional funds are requested to help to complete the study.

**Robert Griggs M.D.**

SG	Experimental Therapeutics of Neuromuscular Disease			
	\$15,000.00	7/1/2008	6/30/2009	Year 1

*Summary* The conference will assemble translational and clinical scientists to discuss current and novel therapies with international clinical trial experts. 90 attendees are expected. The informal, isolated environment is designed to expand the expertise and mentor the career of beginning investigators. It brings trainees together with senior investigators, NIH program staff, and foundation representatives. The proposal was developed by the Muscle Study Group and European TREAT-NMD leadership. The aims are to: provide state-of-the-art presentations with a translational focus by investigators whose work is in/may be brought to clinical trial (Kate Bushby, Hanns Lochmuller, Jerry Mendell, John Day, Thurman Wheeler, Michael Hanna, Stephen Cannon); discuss/debate the most appropriate, efficient ways to demonstrate clinical efficacy of novel treatment strategies; provide a setting away from competing activities for interaction/development of collaboration between established and junior investigators; give new investigators a sense of "history" and longitudinal development of experimental therapeutics of neuromuscular disease by interaction with senior "icons" of the field (Stanley Appel, Michael Brooke, Andrew Engel, George Karpati, Lord John Walton of Denchant, Lewis P. Rowland); provide a collaborative environment for new project development. The conference offers opportunities to develop plans for translational research to further the goal of treating diseases of interest to the MDA.

**Chad R Heatwole M.D.**

TR-IG	The Development and Use of Disease-Specific Instruments for Muscular Dystrophies			
	\$74,539.00	4/1/2008	3/31/2009	Year 1
	\$67,810.00	4/1/2009	3/29/2010	Year 2
	\$76,336.00	4/1/2010	3/29/2011	Year 3

*Summary* This study is in response to a national call for clinically meaningful outcome measures in muscular dystrophy research. This project will develop, test, and validate a myotonic dystrophy disease-specific instrument of quality-of-life for use in clinical trials. The infrastructure used to create this instrument will be utilized to develop additional disease-specific instruments for both facioscapulohumeral muscular dystrophy and myotonic dystrophy type-2. The project will produce three viable research instruments, create the necessary infrastructure for further quality-of-life instrument development, and promote meaningful outcome measures in muscular dystrophy research.

**NORTH CAROLINA****Chapel Hill - The University of North Carolina at Chapel Hill****Zheng Fan M.D.**

CRTG	Clinical Research Training Grant			
	\$87,528.00	7/1/2008	6/30/2009	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.

**Joe Kornegay D.V.M., Ph.D.**

TR-IG	Natural History and Immunological Parameters in the GSHPM Dog			
	\$284,854.00	1/1/2009	12/31/2009	Year 1
	\$330,432.00	1/1/2010	12/31/2010	Year 2
	\$269,578.00	1/1/2011	12/31/2011	Year 3

*Summary* Before initiating gene therapy in Duchenne muscular dystrophy, the nature of the immune response to dystrophin protein or viral vector capsid antigens must be determined. Dogs with golden retriever muscular dystrophy (GRMD) express some dystrophin and should, therefore, be partially tolerized. In contrast, German shorthaired pointers with muscular dystrophy (GSHPM) have a large deletion that encompasses the entire dystrophin gene. The complete absence of dystrophin provides a "clean" background in which to dissect the relative contributions that dystrophin and viral antigens make to the immune response. In this study, we will first systematically study the natural history of both GRMD and GSHPM dogs from 3 months to 1 year of age using functional tests, pathology, and MRI. We will then conduct a series of experiments in both GRMD and GSHPM dogs to determine the nature of their immune response to viral-mediated dystrophin gene therapy.

**Da-Zhi Wang Ph.D.**

RG	MicroRNAs in muscle biology and muscle diseases			
	\$120,000.00	1/1/2009	12/31/2009	Year 3

*Summary* The role of muscle-specific microRNAs (miRNAs) during muscle development, regeneration and repair will be studied in order to develop therapies for muscle dysfunction in disease.

**Durham - Duke University****G. Vann Bennett M.D., Ph.D.**

RG	Role of ankyrin-B in congenital myopathy and cellular targeting of dystroglycan			
	\$114,382.00	7/1/2008	6/30/2009	Year 3

*Summary* This research may uncover the mechanism for forms of muscular dystrophy that are currently not understood. Moreover, it may be possible in the future to develop strategies to promote assembly, which could be therapeutic in some forms of muscular dystrophy.

**Paul Rosenberg M.D.**

RG	TRPC channels and muscle myopathies			
	\$107,285.00	7/1/2008	6/30/2009	Year 3

*Summary* This research will determine whether calcium entry into muscle cells that is independent of contractile calcium influences downstream proteins that influence gene transcription specific to muscle.

**Baodong Sun Ph.D.**

DG	Muscle-targeted gene therapy in acid maltase deficiency (AMD)			
	\$45,000.00	1/1/2009	12/31/2009	Year 3

*Summary* Researchers will investigate muscle-targeted gene therapy with AAV vectors for treating acid maltase deficiency (AMD = Pompe's). This study will provide basis for clinical trial in AMD.

**Raleigh - North Carolina State University****Christian Melander Ph.D.**

RG	Sequence specific targeting of poly-CUG motifs			
	\$43,926.00	7/1/2008	6/30/2009	Year 2

*Summary* Researchers will design bioavailable therapeutics to disrupt the aberrant RNA/protein interaction seen in DM.

## Winston-Salem - Wake Forest University Health Sciences

### Oswaldo Delbono M.D., Ph.D.

RG	Calcium Signaling in Muscular Dystrophy			
	\$100,000.00	7/1/2008	6/30/2009	Year 1
	\$100,000.00	7/1/2009	6/30/2010	Year 2
	\$100,000.00	7/1/2010	6/30/2011	Year 3

*Summary* The long term goal of this project is to elucidate the underlying mechanisms and design a successful therapy for Duchenne Muscular Dystrophy (DMD). In this project, we will test the hypothesis that decreased intracellular calcium availability in response to cell stimulation results in skeletal muscle weakness beyond the period of active tissue damage. We will also test the premise that improving cell excitability-Ca<sup>2+</sup> availability coupling will lead to increased muscle strength.

## OHIO

### Cincinnati - University of Cincinnati

#### Tom Thompson Ph.D.

RG	Structure/function studies of myostatin blockade through propeptide interactions			
	\$97,989.00	7/1/2008	6/30/2009	Year 3

*Summary* Myostatin is a naturally occurring protein that inhibits muscle growth. Strong evidence supports the therapeutic potential of myostatin inhibitors for muscular dystrophy. This research will focus on the structural and functional characterization of myostatin inhibitors. This work will facilitate design of novel anti-myostatin antibodies and small molecule inhibitors.

#### Tom Thompson Ph.D.

RG	Towards the development of alternative anti-myostatin therapeutics			
	\$99,000.00	7/1/2008	6/30/2009	Year 1
	\$99,000.00	7/1/2009	6/30/2010	Year 2
	\$99,000.00	7/1/2010	6/30/2011	Year 3

*Summary* Myostatin is a naturally occurring protein that inhibits muscle growth. Strong evidence supports the therapeutic potential of myostatin inhibitors for muscular dystrophy. On the other hand, several naturally occurring proteins exist that bind and neutralize myostatin. These includes the antagonist follistatin (FS), which forms a nearly unbreakable complex with myostatin. Our research will focus on characterizing the structure of myostatin with the antagonist FS, and will develop novel strategies to inactivate myostatin with FS. These efforts will facilitate design of novel anti-myostatin molecules with potential to improve muscle growth.

## Cleveland - Cleveland Clinic Foundation

### Andrea N. Ladd Ph.D.

RG	Alternative splicing programs in normal muscle and myotonic dystrophy			
	\$110,000.00	7/1/2008	6/30/2009	Year 1
	\$110,000.00	7/1/2009	6/30/2010	Year 2
	\$110,000.00	7/1/2010	6/30/2011	Year 3

*Summary* Myotonic dystrophy (DM) is an inherited disease that affects 1 in 8500 individuals worldwide. Symptoms of the disease include myotonia (i.e., the inability to relax voluntarily contracted muscles), muscle wasting, cardiac conduction defects, insulin resistance, cataracts, testicular atrophy, and cognitive dysfunction. In families afflicted with this disease, children may also be born with a severe congenital form of DM characterized by deficiencies in muscle development and mental retardation. An important connection has been made between the development of disease in DM patients and a molecular process called alternative splicing. Alternative splicing allows the production of multiple proteins with different functions from a single gene. Alternative splicing can determine the fate of cells: what kind of cells form, how they function, and even whether they live or die. We previously identified a family of related proteins that regulate alternative splicing in muscle and are disrupted in DM. Inappropriate alternative splicing of genes regulated by these proteins has been shown to contribute to symptoms of the disease, including myotonia, the hallmark of DM. The goals of my research are to investigate the role of these proteins in normal muscle development, and to test whether repressing the function of these proteins may be used to reverse the molecular defects in alternative splicing that contribute to DM, thus alleviating the disease.

### Lan Zhou M.D., Ph.D.

RG	Therapeutic Effects of Imatinib on Duchenne Muscular Dystrophy			
	\$91,608.00	7/1/2008	6/30/2009	Year 1
	\$92,994.00	7/1/2009	6/30/2010	Year 2
	\$87,780.00	7/1/2010	6/30/2011	Year 3

*Summary* Imatinib is an FDA-approved drug with promising anti-inflammatory and anti-fibrotic therapeutic applications. Researchers will test whether imatinib can reduce muscle inflammation and fibrosis in DMD to improve muscle function and survival using the DMD mouse models, mdx and mdx/utrn+/-.

## Cleveland - The MetroHealth System

### David Birnkrant MD

SG	Publication of Proceedings on Pulmonary Management from the 30th C-K Symposium			
	\$7,500.00	8/1/2008	7/30/2009	Year 1

*Summary* This request is to assist with funding of the publication of the "Program on Pulmonary Management of the Pediatric Neuromuscular Patient," a one day meeting that preceded the Thirtieth annual Carrell-Krusen Neuromuscular Symposium. The meeting took place at The Texas Scottish Rite Hospital for Children, Dallas, Texas on February 20, 2008. We have received approval from the journal Pediatrics to submit these proceedings for consideration for publication as a sponsored supplement to the journal, which will appear in print and on-line. We have initial funding commitment from two corporate sponsors: Respiroics and Hill-Rom. We are requesting partial funding from MDA to help us with the cost of publication. Respiroics, Hill-Rom and MDA were all sponsors of the Carrell-Krusen meeting itself.

## Columbus - Ohio State University

### Patrice Hamel Ph.D.

RG	Unraveling the mitochondrial redox pathway in cytochrome c maturation			
	\$113,249.00	1/1/2009	12/31/2009	Year 3

*Summary* Two c-type cytochrome assembly factors will be studied to determine how cytochrome c is assembled and other factors that may be involved in the process of energy production and cellular death.

**Velimir Matkovic M.D., Ph.D.**

RG	Skeletal development in boys with Duchenne muscular dystrophy (DMD)
\$127,610.00	1/1/2009 12/31/2009 Year 3

*Summary* Studies of bone mass in DMD patients will determine from where the loss of bone mass may occur. In addition the use of steroids will be evaluated relative to bone mass.

**Columbus - Research Institute at Nationwide Children's Hospital****Scott Q. Harper Ph.D.**

DG	RNAi therapy for facioscapulohumeral muscular dystrophy
\$45,000.00	7/1/2008 6/30/2009 Year 2
\$45,000.00	7/1/2009 6/30/2010 Year 3

*Summary* Researchers will test if RNAi against FRG1 will improve symptoms in a mouse model of FSHD.

**Brian K. Kaspar Ph.D.**

RG	Regional vascular delivery of AAV-IGF-1 to skeletal muscle for ALS therapy
\$82,500.00	7/1/2008 6/30/2009 Year 3

*Summary* This research will develop a clinical trial using a potent neuroprotective gene (insulin-like Growth Factor-1) with significant potential for modifying the disease and developing human clinical trials for ALS patients.

**Jerry Mendell M.D.**

RRG	Dysferlin Gene Therapy
\$34,500.00	9/1/2008 8/31/2009 Year 1

*Summary* Dysferlin deficiency is one of the major causes of limb girdle muscular dystrophy. Patients with this condition are designated LGMD2B or Miyoshi Myopathy. There are no treatments available for dysferlin deficiency. Our goal is to replace the defective dysferlin gene in the muscle fiber. In this way the replacement gene can potentially restore normal function to the muscle fiber. There is a mouse model for this disease that has features simulating the human disease. Our studies will be targeted toward replacing the gene in the mouse model. If we are successful this can lead to a clinical trial.

**Jerry Mendell M.D.**

CRNG	Request to be a designated MDA DMD Clinical Research Center
\$100,000.00	8/1/2008 7/31/2009 Year 1
\$100,000.00	8/1/2009 7/31/2010 Year 2
\$100,000.00	8/1/2010 7/31/2011 Year 3

*Summary* The overall premise and comprehensive theme for the MDA DMD Clinical Research Center (CRC) at Nationwide Children's Hospital (NCH) is that the heart of Duchenne muscular dystrophy patient is a critical, yet understudied, component of this devastating disease. While we are all encouraged by the progress of potential treatments evolving for skeletal muscle, we have a limited repertoire of treatments for cardiac muscle. In order to rescue the cardiac dystrophinopathy we must: 1) know more about the natural history of the dilated cardiomyopathy and associated cardiac arrhythmias; 2) establish the benefit of current treatments; and 3) determine if additional approaches are necessary to sustain efficacy.

## OKLAHOMA

### Oklahoma City - University of Oklahoma Health Sciences Center

#### Sanjay Bidichandani MD, PhD

RG	Somatic instability as a phenotypic determinant in Friedreich's ataxia		
\$114,589.00	7/1/2008	6/30/2009	Year 2

*Summary* Researchers will study expansion of repeats in DRG cells which may be specific to FA versus other tissues.

## OREGON

### Eugene - University of Oregon

#### Andrew Berglund Ph.D.

RG	A small molecule approach to myotonic dystrophy		
\$122,632.00	7/1/2008	6/30/2009	Year 1
\$128,213.00	7/1/2009	6/30/2010	Year 2

*Summary* Myotonic dystrophy is caused by an expansion of CTG repeats at the genomic level. These CTG repeats are made into RNA (CUG repeats) and become toxic molecules within the cell. The CUG repeat RNA molecules are toxic because they sequester a protein factor, disrupting its function as well as increasing the cellular levels of other protein factors involved in myotonic dystrophy. The goal of this project is to determine the ability of a small molecule (and related molecules) that binds the toxic CUG repeats to reverse the molecular defects associated with myotonic dystrophy. This small molecule or a derivative of it could lead to a therapy for patients with myotonic dystrophy.

### Portland - Oregon Health & Science University

#### Jamie Fitzgerald Ph.D.

RG	The pathophysiology of two new collagen VI genes, COL6A5 and COL6A6, in CMD		
\$107,256.00	7/1/2008	6/30/2009	Year 1

*Summary* The goal of this research is to understand whether mutations in two new collagen VI genes play a role in congenital muscular dystrophies (CMDs). Mutations in the known collagen VI genes, COL6A1, COL6A2 and COL6A3 result in two forms of CMD; Bethlem myopathy and Ullrich congenital muscular dystrophy. We have recently discovered two additional collagen VI genes in humans, COL6A5 and COL6A6. These new genes are present in a wide range of tissues, including in skeletal muscle. Therefore, we hypothesize that mutations in COL6A5 and COL6A6 are involved in congenital muscular dystrophy. In support of this hypothesis is our discovery in a pilot mutation screen of nucleotide changes in two families with Ullrich congenital muscular dystrophy. These DNA changes alter the amino acid sequence and are not present in more than 150 control chromosomes. The goal of this project is to identify and then characterize mutations in more than 40 individuals with congenital muscular dystrophy.

**David B Morton PhD**

RG	Characterization of the Drosophila orthologue of a gene linked to sporadic ALS
	\$64,063.00                      1/1/2009                      12/31/2009                      Year 1

*Summary* Sporadic amyotrophic lateral sclerosis (ALS) affects 90% of ALS patients and results in the degeneration of specific neurons in the brain and spinal cord. It is thought to be triggered by a complex interaction between environmental and genetic cues. Little is known about the identities or functions of the genes that confer susceptibility for sporadic ALS. A recent whole genome analysis of ALS patients and healthy control subjects has identified a candidate human gene, named FLJ10986 that has a strong association with sporadic ALS. Nothing is known, however, about the function of this gene. I recently searched the genome databases for the fruit fly for orthologues of this gene and found that there is a strong candidate that is 48% identical and 70% similar to the human gene. There is a long history of using invertebrate model organisms such as Drosophila to understand the function of genes/proteins that are important in human health and disease. The short life cycle and wealth of genetic tools that are available in Drosophila makes it a wonderful model system that can be used to understand the role of a particular gene much faster than equivalent studies can be achieved in mammalian model systems. This proposal describes experiments that will determine whether the Drosophila gene plays a role in neurodegeneration.

**PENNSYLVANIA****Philadelphia - Drexel University****Gordon Lutz Ph.D**

RG	Dystrophin induction in growth stimulated DMD muscles
	\$100,000.00                      7/1/2008                      6/30/2009                      Year 3

*Summary* This project will utilize bloodstream delivery of the polymer-oligonucleotide compounds in growth-stimulated mdx mice to obtain body-wide induction of dystrophin expression. The goal is to show significant and prolonged improvements in skeletal muscle strength, and decreased susceptibility to cellular injury in mdx mice.

**Philadelphia - The Children's Hospital of Philadelphia****Carsten Bonnemann M.D.**

RG/TCL	Allele-specific RNAi mediated knockdown of dominant negative Col6 mutations
	\$125,000.00                      7/1/2008                      6/30/2009                      Year 1
	\$125,000.00                      7/1/2009                      6/30/2010                      Year 2
	\$125,000.00                      7/1/2010                      6/30/2011                      Year 3

*Summary* Mutations in the three genes coding for collagen type VI cause the severe congenital muscular dystrophy type Ullrich, as well as the milder type Bethlem. Mutations in Bethlem are always dominant, whereas mutations in the more severe Ullrich type were thought to be recessive, but more recent data suggests that dominant mutations underlie at least 50% of cases of Ullrich, making dominant mutations the predominant mutation mechanism in collagen VI. The potential severity of these mutations results from their ability to act in a dominant negative fashion, i.e., the mutant gene product is able to negatively interfere with any normal collagen VI formed. This study is concerned with developing strategies to selectively knock down the mutant gene transcript using RNA interference technology. We will be developing oligo- as well as viral-based systems to deliver RNA interference to cells and to experimental animals with the goal of improving collagen VI production by interfering with the mutant gene product, ultimately ameliorating the disease.

**David Lynch MD, PhD**

TR-IG	Clinical Research Network for Friedreich's Ataxia
	\$200,914.00                      3/1/2008                      2/28/2009                      Year 2
	\$140,877.00                      3/1/2009                      2/28/2010                      Year 3

*Summary* Using recent support from the MDA and FARA, a group of investigators collaborated on development of clinical measures that can quantitatively assess FA. While a large amount of measure refinement remains to be performed, the data from their collaboration provide a framework for further investigation and for creating a network for performing further clinical translational research including clinical trials.

**Michele Yang M.D.**

<b>CRTG</b>	Targeted therapies for Duchenne Muscular Dystrophy			
	\$89,800.00	7/1/2008	6/30/2009	Year 1
	\$89,550.00	7/1/2009	6/30/2010	Year 2

*Summary***Jinbin Zhai Ph.D.**

<b>DG</b>	Regulation of CMT mutant NFL aggregation and neurotoxicity			
	\$45,000.00	1/1/2008	12/31/2009	Year 3

*Summary* Researchers will study how p190RhoGEF regulates aggregation and neurotoxicity in Charcot-Marie-Tooth mutant light neurofilament gene to identify targets for therapeutic intervention.**Philadelphia - University of Pennsylvania****Stephen Baylor M.D.**

<b>RG</b>	Comparison of calcium signaling in muscle fibers of normal and mdx mice			
	\$112,412.00	1/1/2009	12/31/2009	Year 2
	\$115,079.00	1/1/2010	12/31/2010	Year 3

*Summary* This project will compare intracellular calcium levels in mdx mice (an animal model of DMD) and normal mice to quantify the ways in which intracellular calcium signaling may be altered in DMD. The knowledge gained should lead to an increased understanding of the patho-physiological changes that occur in DMD and, possibly, to identification of new therapeutic targets for treatment of this disease.**Clara Franzini-Armstrong Laurea**

<b>RG</b>	IP3 receptors in myonuclei of normal and diseased muscle models			
	\$74,901.00	7/1/2008	6/30/2009	Year 1
	\$76,868.00	7/1/2009	6/30/2010	Year 2
	\$79,202.00	7/1/2010	6/30/2011	Year 3

*Summary* Calcium is a ubiquitous intracellular messenger, responsible for initiating events, most notably contraction in muscle and the activation of transcription in nuclei. Calcium for these events may come from outside the cell, or from intracellular compartments. Ryanodine receptors, or RyRs, are channels that rapidly release calcium from the stores. However, calcium delivered by this system activates contraction but does not affect events in the nucleus. Instead, calcium released from the stores by a different channel, the InsP3 receptor, activates transcription of DNA to RNA within the nucleus. A fundamental aspect of InsP3-mediated signaling is that calcium is released in a graded and slow manner in response to incremental levels of stimuli. In addition, InsP3 receptors are located in the nuclear envelope. The combination of these two factors is presumably responsible for the fact that nuclei seem to sense calcium liberated from the InsP3 receptor but not that released by RyRs. We have developed a unique way of detecting InsP3 in the nuclear envelope and plan to use this to elucidate changes in levels and types of these receptors that occur in dystrophic muscle.**Brett Anthony Kaufman Ph.D.**

<b>DG</b>	Identification and characterization of genes affecting mitochondrial myopathies			
	\$45,000.00	1/1/2009	12/31/2009	Year 2
	\$45,000.00	1/1/2010	12/31/2010	Year 3

*Summary* I am striving to identify genes involved in the normal and biased transmission of the mitochondrial genome. I have identified the mitochondrial protein TFAM, a known transcription factor, as having a direct role in the coordination and compaction of multiple mtDNAs together. Because compaction is essential to the transmission of mtDNA, our studies will garner insights into the causes of mtDNA-related diseases, which may in turn lead to therapeutic interventions for affected patients.

**Eran Perlson Ph.D**

DG	Axonal transport alterations disrupt NMJ structure and function in ALS			
	\$45,000.00	1/1/2009	12/31/2009	Year 2
	\$45,000.00	1/1/2010	12/31/2010	Year 3

*Summary* Recent studies in animal models have shown that defects in axonal transport result in progressive neurodegenerative disease. The studies proposed here will characterize the role of those signaling factors in NMJ structure and maintenance as well as on nerve degeneration. We expect that the characterization of those signals will provide novel insights into mechanisms of NMJ destabilization and neurodegeneration as well as provide a molecular basis for therapies and drug delivery.

**Philadelphia - Thomas Jefferson University****Michael P. King Ph.D.**

RG	Mitochondrial translation in MELAS			
	\$94,976.00	1/1/2009	12/31/2009	Year 2

*Summary* We seek to characterize the protein synthesis deficiencies associated with mutations in one tRNA gene that results in the mitochondrial disease MELAS (mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Stroke-like episodes). We have also found a way to correct the deficiencies resulting from these tRNA gene mutations in human cells and will seek to identify the changes that take place to permit normal mitochondrial protein synthesis. These studies will serve as a model for the eventual treatment of some human neuromuscular diseases caused by mutations in mitochondrial DNA.

**Michael Lisanti PhD**

RG	Proteasome inhibitor treatment of Becker and Duchenne muscular dystrophies			
	\$158,355.00	7/1/2008	6/30/2009	Year 3

*Summary* The researchers will try to understand the role of proteasomal degradation in the pathogenesis of Duchenne Muscular Dystrophy.

**Philadelphia - University of Pennsylvania Medical Center****Maria Pennuto Ph.D.**

DG	Targeting androgen receptor for development of SBMA therapeutics			
	\$59,953.00	7/1/2008	6/30/2009	Year 1
	\$59,691.00	7/1/2009	6/30/2010	Year 2
	\$59,976.00	7/1/2010	6/30/2011	Year 3

*Summary* Spinobulbar muscular atrophy (SBMA) is caused by expansion of a CAG sequence, encoding glutamine, to over 38 residues in the androgen receptor (AR) gene. In SBMA only males are fully symptomatic because mutant AR becomes toxic only in the presence of ligand, testosterone. However, little is known about how the ligand converts the protein into a toxic species. Based on preliminary findings, we hypothesize that phosphorylation, one of the ligand-induced modifications, alters toxicity of mutant androgen receptor. We have previously shown that phosphorylation by Akt reduces toxicity of mutant AR. We have now obtained evidence that another kinase, PKA, reduces mutant AR toxicity in the cell. We will survey the effect of activation of PKA signaling pathway on SBMA cells. We have preliminary evidence that IGF-1, which initiates the Akt signaling, ameliorates the phenotype of SBMA mice. We intend to confirm the effect of IGF-1 in mice with histopathological and behavioral analyses, and to develop methods to safely and efficiently deliver IGF-1 as therapy for SBMA.

## TENNESSEE

### Memphis - St. Jude Children's Research Hospital

#### Udai B. Pandey Ph.D.

DG The role of histone deacetylase 6 in spinal and bulbar muscular dystrophy (SBMA)  
\$45,000.00 1/1/2009 12/31/2009 Year 3

*Summary* Researchers developed a fly model for SBMA showing many pathological features of human form. studies will determine how histone deacetylase 6 almost completely blocks degeneration in this model.

#### J. Paul Taylor MD, PhD

RG The molecular pathogenesis of spinobulbar muscular atrophy  
\$100,000.00 1/1/2009 12/31/2009 Year 2  
\$100,000.00 1/1/2010 12/31/2010 Year 3

*Summary* With prior MDA funding we developed a Drosophila model SBMA. We used this model to 1) characterize the roles of protein degradation pathways in disease and 2) discover a gene that rescues neurodegeneration when over-expressed. In this study we will 1) test our hypothesis that aberrant interaction of the disease protein with other transcription factors contributes to disease, 2) evaluate the therapeutic potential of a new class of drugs called SARMs for SBMA, and 3) perform a genetic screen to identify heretofore unrecognized genes involved in the disease.

### Nashville - Vanderbilt University Medical Center

#### Allison Limpert Ph.D.

DG Regulation of NFkB activity during Schwann cell myelination  
\$60,000.00 1/1/2009 12/31/2009 Year 1  
\$60,000.00 1/1/2010 12/31/2010 Year 2  
\$60,000.00 1/1/2011 12/31/2011 Year 3

*Summary* Defects in Schwann cell proliferation and myelination characterize several forms of Charcot Marie Tooth (CMT) disease. Ligands of the Neuregulin (NRG) family are well characterized axonal signals known to regulate Schwann cell proliferation and differentiation by binding to ErbB receptors on Schwann cells. While axons can express multiple NRG isoforms, these different ligands activate the same ErbB receptor complex on Schwann cells; however, the stimulation of these same receptors can result in varying biological outcomes. Correspondingly, we report that activation of ErbB receptors by a membrane bound, but not a soluble NRG isoform allows for the activation of NFkB, a transcription factor required for Schwann cell myelination. We hypothesize that the activation of this transcription factor by membrane bound NRG, is a crucial event which promotes Schwann cell differentiation over proliferation. We propose to investigate the mechanisms by which NRG isoforms regulate NFkB during Schwann cell development and evaluate NRG signaling in mouse models of CMT. This will allow us to determine whether this signaling pathway can be used as a potential therapeutic target for demyelinating disorders.

## TEXAS

### Dallas - UT Southwestern Medical Center

#### Steve Cannon MD, PhD

RG A mouse model of hypokalemic periodic paralysis type 2  
\$101,788.00 7/1/2008 6/30/2009 Year 2  
\$100,000.00 7/1/2009 6/30/2010 Year 3

*Summary* Researchers will develop a mouse model of periodic paralysis to understand the ion channel functions in these disorders.

**Jeffrey Leigh Elliott M.D.**

RRG Differential effect of CCS on mutant SOD1 related Disease  
\$430,167.00 4/1/2008 3/31/2009 Year 1

*Summary* Mutations in the superoxide dismutase (SOD1) gene cause one form of familial ALS in humans as well as in transgenic mice. We previously found that the disease can be markedly accelerated in G93A SOD1 mutant mice by the over-expression of another protein called copper chaperone for SOD1 (CCS). Disease onset is 7 days rather than 6 months, and this acceleration is accompanied by marked changes in the mitochondria, the "powerhouse" of the cell. In this study we will determine whether the effect of CCS on disease is dependent on the specific SOD1 mutation, and if so, what accounts for that difference.

**Woodring Wright M.D., Ph.D.**

RG Immortal Cells for Myoblast Transfer Therapy  
\$100,000.00 1/1/2009 12/31/2009 Year 2  
\$100,000.00 1/1/2010 12/31/2010 Year 3

*Summary* We have successfully immortalized adult skeletal myoblasts by introducing telomerase, an enzyme that prevents the telomere shortening that is normally used to count cell divisions. Our long-term goal is to create a universal donor that expresses molecules that prevent the cells from dying during the immediate post-transplantation period, maintains them transiently in a proliferative and migratory state, and which express dystrophin and factors that stimulate muscle hypertrophy.

**Galveston - The University of Texas Medical Branch at Galveston**

**Premkumar Christadoss M.B.B.S**

RG Innate Immunity in Autoimmune Myasthenia Gravis Pathogenesis  
\$125,000.00 1/1/2009 12/31/2009 Year 1  
\$125,000.00 1/1/2010 12/31/2010 Year 2  
\$125,000.00 1/1/2011 12/31/2011 Year 3

*Summary* Myasthenia Gravis (MG) is an autoimmune neuromuscular disease. Patients with MG have muscle weakness or paralysis due to failure of nerve muscle electrical transmission. Antibodies destroy the nerve muscle signaling protein (acetylcholine receptor) and cause muscle weakness in MG. MG is often preceded by infection. We hypothesize that chemicals and/or proteins expressed in infectious agents act as adjuvants in triggering autoimmune (self reactive) response, culminating in MG. We have developed a new mouse model of MG by immunizing mice with a chemical derived from E.coli called lipopolysaccharide (LPS) with acetylcholine receptor protein. In this model antibodies to acetylcholine receptors are produced without CD4 cell help. We will study the immunological mechanisms by which LPS triggers autoimmune MG. These studies would lead to specific therapy of MG by inhibiting the pathway of pathogenic antibody production in myasthenia gravis.

## Houston - Baylor College of Medicine

### Hasan Orhan Akman PhD

DG	Generation and Characterization of a Mouse Model of Polyglucosan Body Disease			
	\$58,979.00	7/1/2008	6/30/2009	Year 1
	\$58,039.00	7/1/2009	6/30/2010	Year 2
	\$59,246.00	7/1/2010	6/30/2011	Year 3

*Summary* The synthesis of glycogen is catalyzed by the sequential actions of two enzymes: (i) glycogen synthetase, which "strings" glucose to form linear chains to a length of approximately 10 glucose "beads"; and (ii) the branching enzyme, which attaches a short branch of approximately 4 glucose units to a linear chain in an alpha-1,6-glycosidic bond. Glycogen storage disease (GSD) type IV (OMIM 232500) is an autosomal recessive disorder caused by deficiency of the glycogen branching enzyme (GBE), and leads to the accumulation of an abnormal amylopectin-like polysaccharide in multiple tissues, including liver, heart, skeletal muscles, and central nervous system (CNS). A late-onset clinical variant, known as adult polyglucosan body disease (APBD), causes a neurodegenerative disorder simulating amyotrophic lateral sclerosis (ALS, Lou Gehrig disease), but often associated with bladder dysfunction and dementia. The mutated gene, GBE1, has been mapped to chromosome 3p14. The two naturally occurring animal models of this disorder, American quarter horses and Norwegian forest cats, are not practical laboratory animals. Therefore, we propose to develop a mouse model of GSD IV, which would be invaluable to better understand the pathogenesis of the disease and to test therapeutic strategies aimed at increasing the residual activity of branching enzyme in tissues.

### Thomas A. Cooper M.D.

RG	An inducible mouse model for CNS manifestations of myotonic dystrophy			
	\$116,415.00	1/1/2009	12/31/2009	Year 3

*Summary* Researchers will turn on the toxic RNA found in myotonic dystrophy in different regions of the brain to reproduce symptoms of DM and attempt to identify molecular changes causing the symptoms.

### Susan Hamilton Ph.D.

RG	The role of FKBP in Skeletal Muscle Function and Disease			
	\$121,000.00	7/1/2008	6/30/2009	Year 1
	\$121,612.00	7/1/2009	6/30/2010	Year 2
	\$121,758.00	7/1/2010	6/30/2011	Year 3

*Summary* FKBP is an immunophilin that regulates skeletal muscle excitation-contraction coupling. We have strong evidence that one immunophilin, FKBP12.6, can slow muscle fatigue and enhance recovery from injury. We now want to define the molecular mechanisms for these effects and use this knowledge to develop interventions that will slow fatigue and enhance recovery from muscle injury.

### Muge N. Kuyumcu-Martinez Ph.D.

DG	The mechanism of Protein Kinase C induced pathogenesis in Myotonic Dystrophy 1			
	\$60,000.00	7/1/2008	6/30/2009	Year 1
	\$60,000.00	7/1/2009	6/30/2010	Year 2
	\$60,000.00	7/1/2010	6/30/2011	Year 3

*Summary* Regulation of signaling pathways is tightly controlled in response to stimuli, and inappropriate activation can lead to disease. Our studies have recently shown that prolonged activation of Protein Kinase C (PKC) signaling is important in Myotonic Dystrophy 1 (DM1). This activation leads to a change in the protein, CUG binding protein 1 (CUGBP1), such that the protein becomes phosphorylated, leading to its increased levels in heart tissue from individuals with the disease. Higher levels of CUGBP1 have been implicated in the cause of DM1 and these results explain the basis for this increase. Inhibition of PKC signaling by specific inhibitors in a DM1 heart-specific mouse model prevents mortality of the mice and reduces phosphorylation and steady state of CUGBP1 protein levels. The goal of my research is to understand what role PKC plays in the disease and to explore PKC inhibitors as a therapy option for DM1 patients. The findings from heart model may provide insights for alleviating the severe skeletal muscle phenotype seen in DM1 patients.

**Xander H.T. Wehrens M.D., Ph.D.**

RG	Role of abnormal calcium homeostasis in cardiac disease in Muscular Dystrophy			
	\$103,186.00	1/1/2009	12/31/2009	Year 2
	\$103,802.00	1/1/2010	12/31/2010	Year 3

*Summary* Dystrophin deficiency in the heart causes abnormalities in calcium signaling, which in turn cause heart failure and fatal arrhythmias. Using biopsies from patients with MD and a mouse model of dystrophin deficiency, the role of abnormal calcium release in heart muscle cells will be investigated.

**Houston - Methodist Neurological Institute****Stanley Appel MD**

RG	Immune mechanisms in amyotrophic lateral sclerosis			
	\$100,000.00	7/1/2008	6/30/2009	Year 2
	\$100,000.00	7/1/2009	6/30/2010	Year 3

*Summary* Studies will define protective or toxic properties of immune cells in disease, particularly ALS.

**Stanley Appel MD**

CRNG	Clinical Research Network Grant			
	\$100,000.00	8/1/2008	7/31/2009	Year 1
	\$100,000.00	8/1/2009	7/31/2010	Year 2
	\$100,000.00	8/1/2010	7/31/2011	Year 3

*Summary* We hypothesize that ALS patients with hyperlipidemia progress slower and have longer survival than those with normal or low lipid levels. Furthermore, these patients have more stable nutrition and metabolism throughout the disease, but also a greater prevalence of cardiovascular disease risk factors and associated indices of inflammation. We propose a three year, multicenter, prospective study of blood lipid profiles in ALS and its relation with disease progression and survival, in addition to other co-variables disease.

**Houston - The University of Texas Health Science Center at Houston****Rebecca Berdeaux Ph.D.**

DG	The role of CREB in skeletal muscle regeneration and hypertrophy			
	\$45,000.00	1/1/2009	12/31/2009	Year 2
	\$45,000.00	1/1/2010	12/31/2010	Year 3

*Summary* The proposed studies are designed to explore the cellular and physiological consequences of over-activation of CREB in cultured muscle cells and in the muscle of mice. We will test whether over-activation of CREB can also improve muscle of mice with muscular dystrophy. Through these studies, we hope to determine how this DNA binding protein may control the balance between muscle growth and muscular dystrophy.

**Houston - University of Texas M.D. Anderson Cancer Center****William H. Klein PhD**

RG	Myogenic in embryonic and adult muscle stem cells			
	\$108,424.00	1/1/2009	12/31/2009	Year 3

*Summary* Propose to develop a new mouse model by removing myogenin to determine effect on muscle repair and aging. Will also learn how myogenin is selective in turning on specific genes.

**Ralf Krahe Ph.D.**

RG	A transgenic mouse model for myotonic dystrophy type 2 (DM2)			
	\$130,000.00	7/1/2008	6/30/2009	Year 2
	\$130,000.00	7/1/2009	6/30/2010	Year 3

*Summary* Investigators will study a mouse model to determine effect of DM2 expansion on development as well as other stages.

**San Antonio - Univ of Texas Health Science Center at San Antonio**

**Huiyun Liang Ph.D.**

DG Protective Effect of PGC-1 alpha on the Development of ALS Disease  
\$44,991.00 1/1/2009 12/31/2009 Year 2

*Summary* Recent studies suggest an important role of mitochondria dysfunction and oxidative stress in the development of ALS. PGC-1a is a transcription coactivator that is involved in multiple biological responses. We hypothesize that PGC-1a attenuates ALS-related muscle atrophy leading to extended lifespan by stimulating mitochondrial biogenesis in spinal cord and muscle. To test this hypothesis, we will cross a widely used ALS mouse model (G93AGur(dI) transgenic mouse) either with the PGC-1a transgenic mouse (Tg(PGC-1a(+/-))) or PGC-1a deficient mouse (Pgc-1a (+/-)).

**Holly Van Remmen PhD**

RG PLA2 Related Inflammatory Pathways in the Pathogenesis of ALS  
\$125,000.00 7/1/2008 6/30/2009 Year 1  
\$125,000.00 7/1/2009 6/30/2010 Year 2  
\$125,000.00 7/1/2010 6/30/2011 Year 3

*Summary* In this study, we will examine the role of inflammation in neuronal and muscular degeneration in ALS. We will determine the role of the enzyme phospholipase A2 (PLA2) and inflammatory mediators in inducing loss of innervation in muscle and effects on mitochondrial dysfunction and muscle atrophy using mouse models of ALS bred to knockout mice lacking PLA2. We will also determine the ability of anti-inflammatory agents to alter neuromuscular degeneration to better understand role of inflammatory pathways in ALS, hopefully to lead to new interventions.

**UTAH**

**Salt Lake City - University of Utah**

**Russell J. Butterfield MD, PhD**

CRTG Natural history and genetic epidemiology of collagen VI related myopathies  
\$86,000.00 7/1/2010 6/30/2011 Year 2

*Summary* Congenital muscular dystrophies are a group of disorders resulting in muscle weakness. Patients with Ullrich congenital muscular dystrophy (UCMD) have early onset of severe weakness, contractures, and hyper-elasticity of joints. Bethlem myopathy (BM) is a milder syndrome with slowly progressive weakness and contractures in the joints of the hands with onset in the childhood or adolescence. Both BM and UCMD are caused by mutations in the genes that produce collagen VI. Once thought to be rare clinical entities, collagen VI related myopathies are now considered among the most common causes of congenital muscle weakness. Multiple mutations in the genes producing collagen VI have been reported including 75 unique variants. The Genome Center at the University of Utah has developed a method for rapid and complete sequencing of the collagen VI genes and has evaluated approximately 135 patients. Despite the growing pool of patients with genetic testing, clinical information is lacking. Our proposal is to develop a database housing both clinical and genetic information on patients with collagen VI related myopathies. Having both clinical and genetic data on these patients, we will be able to study relationship between the particular genetic mutation, and the manifestation of disease. We expect that the database will be a resource to investigators studying collagen VI related disorders and provide a pool of patients available for clinical trials and other studies.

**Michael Therron Howard Ph.D.**

RG Antisense Mediated Suppression of DMD Frameshift Mutations  
\$130,000.00 1/1/2009 12/31/2009 Year 2  
\$130,000.00 1/1/2010 12/31/2010 Year 3

*Summary* The goal of this study is to develop a novel antisense oligonucleotide based approach for treating Duchenne Muscular Dystrophy patients with frameshift mutations in the DMD gene. We will test the ability of antisense oligonucleotides to alter protein synthesis in a controlled way to suppress the effects of frameshift mutations. As this approach is generally applicable to frameshift mutations in any gene, the therapeutic strategy developed here may be adapted for the treatment of many different genetic diseases of the muscle and nervous systems.

**Kathryn J. Swoboda M.D.**

RG	Phase I/II Study of NaPB in Pre-symptomatic Infants with SMA: STOP SMA STUDY			
	\$111,144.00	1/1/2009	12/31/2009	Year 1
	\$124,378.00	1/1/2010	12/31/2010	Year 2
	\$108,769.00	1/1/2011	12/31/2011	Year 3

*Summary* Most babies with SMA are normal or nearly normal as newborns. However, babies who are at risk to develop SMA type I or type II typically develop significant weakness in the first few weeks or months of life. STOP SMA is a clinical trial designed to assess safety and effectiveness of sodium phenylbutyrate (NAPB) in infants confirmed to have SMA by genetic testing. Eligible infants are those likely to develop either type I or type II SMA because they have an affected older sibling and have tested positive for SMA via genetic testing. Babies predicted to develop SMA type I must be enrolled by 3 months of age, and babies predicted to develop SMA type II must be enrolled by 6 months of age. All babies will receive study drug, and we will assess safety and possible effectiveness by comparing them to children in our natural history database.

**VIRGINIA****Charlottesville - University of Virginia****Mani S. Mahadevan M.D.**

RG/TCL	Insights into RNA toxicity in DM1			
	\$110,000.00	7/1/2008	6/30/2009	Year 2
	\$110,000.00	7/1/2009	6/30/2010	Year 3

*Summary* Investigators will utilize a new mouse model of RNA toxicity for DM1 to study modulation of Nkx2.5 seen to be important in cardiac effects in DM1.

**Mani S. Mahadevan M.D.**

RG	Modifiers of RNA Toxicity in DM1			
	\$158,605.00	1/1/2009	12/31/2009	Year 1
	\$159,093.00	1/1/2010	12/31/2010	Year 2
	\$165,320.00	1/1/2011	12/31/2011	Year 3

*Summary* Myotonic muscular dystrophy type 1 (DM1) is the most common muscular dystrophy in adults. DM1 is caused by an expanded (CTG) tract in the 3' untranslated region of the DM protein kinase (DMPK) gene. DM1 is the prototype for a mutation that results in the production of a toxic RNA. The toxic RNA is thought to mediate its effects through RNA-binding proteins, primarily Muscleblind (MBNL1) and CUG-binding protein (CUGBP1), both of which are proteins involved in a process called RNA splicing (in which RNAs are "cut and pasted" together). MBNL1 is believed to be sequestered from its normal function by the mutant DMPK RNA and CUGBP1 levels are elevated. The result is aberrant splicing of target RNAs. It has been shown that increasing MBNL1 levels alleviates myotonia, a key feature of DM1. But reducing CUGBP1 levels has not been studied. We propose to use our novel, inducible mouse model of RNA toxicity in DM1 to study the effects of reducing CUGBP1. This will be done using three strategies: 1) breeding our mice with mice having reduced amounts of CUGBP1, 2) breeding our mice with mice deficient in enzymes that are thought to be responsible for increasing CUGBP1 levels, and 3) treating our mice with drugs known to inhibit those enzymes. The mice will be analyzed to see if this reduces the RNA toxicity. Our goal is to characterize the contribution of elevated CUGBP1 to DM1 pathogenesis and identify possible therapeutic modalities to reducing CUGBP1 in DM1.

**Ramesh S Yadava Ph.D.**

DG	Development of RNA-based Therapy for Myotonic Dystrophy (DM1)			
	\$60,000.00	7/1/2008	6/30/2009	Year 1
	\$60,000.00	7/1/2009	6/30/2010	Year 2
	\$60,000.00	7/1/2010	6/30/2011	Year 3

*Summary* Myotonic dystrophy (DM1) is the most common form of inherited muscular dystrophy in adults, with a prevalence of 1 in 8,000. It is a multi-system disorder that affects skeletal muscles, smooth muscles the heart, eyes, and endocrine and central nervous systems. At present, there is no therapy for myotonic dystrophy. The overall aim of this proposal is to develop RNA-based therapeutics to selectively destroy the toxic mutant DMPK mRNA that causes DM1. We plan to screen a large number of RNA molecules (antisense RNAs, shRNAs and ribozymes) for silencing the mutant DMPK mRNA using cell culture system, and test their efficacy in an inducible mouse model of RNA toxicity that was developed in our lab. The ultimate goal is to generate novel therapeutic agents capable of selectively eliminating the toxic RNA in DM1 patients.

**Richmond - Insmad Incorporated****Geoffrey Allan Ph.D.**

TR-CG	Phase II Clinical Study of rhIGF-I/rhIGFBP-3 in Myotonic Dystrophy Type 1			
	\$1,043,662.00	12/1/2008	11/30/2009	Year 2

*Summary* Myotonic dystrophy type 1 (DM1) is characterized by muscle weakness, wasting and disruption of many body systems, including cardiac disease, decreased cognitive functioning, gastrointestinal disturbances and insulin resistance. Insmad is developing a drug, IPLEX, which has shown promise in treating disorders associated with insulin resistance and/or abnormal anabolism. To learn whether IPLEX may be beneficial to patients with DM1, we are conducting a clinical study in 60 patients with DM1. Patients will receive IPLEX or placebo for 6 months and undergo assessments to determine the effect of IPLEX on muscle strength, mass, endurance, cognitive functioning, gastrointestinal symptoms, and general health status. The results of this study will be used to plan future studies. If IPLEX is safe, well tolerated and positively affects muscle mass and strength, it offers hope of becoming the first effective treatment for muscle wasting and weakness in patients with DM1.

**WASHINGTON****Seattle - Fred Hutchinson Cancer Research Center****Galina Filippova Ph.D.**

RG	Role of chromatin structure in FSHD			
	\$140,437.00	1/1/2009	12/31/2009	Year 2
	\$144,615.00	1/1/2010	12/31/2010	Year 3

*Summary* This study will identify chromatin changes specific to FSHD associated D4Z4 repeats and test the hypothesis that these changes alter the binding of a chromatin insulator factor, CTCF, as the interaction of this region with other regions in the genome. We anticipate that this study will contribute to our understanding of the epigenetic mechanisms underlying FSHD. Moreover, the identified epigenetic mechanisms involving higher order chromatin organization will provide new insights in the complex etiology of other genetic disorders.

**Maura H. Parker Ph.D.**

DG	Myogenic cell transplant in an immune-tolerant canine model of DMD			
	\$45,000.00	7/1/2008	6/30/2009	Year 2
	\$45,000.00	7/1/2009	6/30/2010	Year 3

*Summary* Researchers have induced immune tolerance in GRMD dog model for DMD and will access methods to affect myogenic stem cell repair in this model.

**Zejing Wang M.D., Ph.D**

DG	The immunological barrier to AAV-mediated gene therapy in a canine model of DMD			
	\$60,000.00	1/1/2009	12/31/2009	Year 1
	\$60,000.00	1/1/2010	12/31/2010	Year 2
	\$60,000.00	1/1/2011	12/31/2011	Year 3

*Summary* Duchenne Muscular Dystrophy (DMD) in both humans and dogs is a lethal, X chromosome linked muscle disease caused by lack of an anchor protein, dystrophin the result of mutations in the dystrophin gene. Adeno-associated virus (AAV)-mediated micro-dystrophin delivery to skeletal muscle has been successful in restoring muscle function in mice. However, recent human studies indicated that the efficacy of AAV-mediated therapies is limited by immune responses to viral capsid proteins. Also, we demonstrated robust cellular immune responses to AAV capsid proteins after direct intramuscular injection of AAV vectors in wild type and DMD dogs, establishing the dogs as model system for studying the role of immunity in AAV-mediated gene therapy. We further demonstrated that immune responses to AAV vectors could be averted by a brief course of immunosuppression. In this proposal, I will develop and validate assays to better characterize immune responses to AAV vectors and transgene in dogs, and develop efficient and non-toxic strategies to induce immunological tolerance to these immunogens using newly developed blockers of T-lymphocyte activation and T-cell regulatory molecules. In our hands, the dog has an unexcelled track record of > 40 years of translating laboratory work in hematopoietic cell transplantation to the treatment of human patients with various blood diseases. We, therefore, anticipate that results of our work in dogs can be directly translated to DMD clinical trials.

**Seattle - University of Washington****Jeffrey S Chamberlain Ph.D.**

RRG	Systemic delivery of AAV vectors to muscle			
	\$415,431.00	10/1/2008	9/30/2009	Year 1

*Summary* Duchenne muscular dystrophy (DMD) is a devastating x-linked recessive genetic disease. Affected children present with progressive muscle wasting, typically use wheelchairs by age 12, and are on respirators and heart support often by the late teens. There is no cure, and current therapies are only able to slow disease progression and provide postural and breathing support. Gene therapy would be an ideal solution for this genetic disease. The ability to replace the broken gene in human muscles is a critical goal. Finding a way to deliver the gene to each and every muscle cell in the body, having the gene work, getting the therapy to last long term, and finding a way to reverse damage which has already occurred are all major components to curing this disease. Our group was the first to show that new genes can be delivered to all the muscles of an adult animal. Our previous studies show we can essentially cure DMD in mice by whole body delivery of a new dystrophin gene carried in a delivery shuttle vector known as AAV. This application is to follow-up preliminary data showing that the method might be scaled-up, and to determine the feasibility of bringing this treatment method into the clinic.

**Albert La Spada M.D., Ph.D.**

RG	Modeling motor neuron degeneration in SBMA			
	\$100,000.00	7/1/2008	6/30/2009	Year 2
	\$100,000.00	7/1/2009	6/30/2010	Year 3

*Summary* AAV vector with one isoform of VEGF will test for therapeutic value in SBMA motor neurons.

**Daniel G. Miller M.D., Ph.D.**

RG	DUX4 gene expression differences in facioscapulohumeral muscular dystrophy			
	\$110,000.00	7/1/2008	6/30/2009	Year 2

*Summary* Hypothesis is DUX4 gene is altered in FSHD. How does this alteration affect muscle strength will be studied.

**Maria-Ceu Moreira MSc., Ph.D.**

DG	Functional biology of senataxin, the protein mutated in AOA2 and in ALS4			
	\$45,000.00	1/1/2009	12/31/2009	Year 3

*Summary* Different alterations of senataxin causes two disorders, ALS and AOA2. How these alterations result in these disorders will be studied.

**Guy Leary Odom Ph.D.**

DG	Vectors to avoid a cellular immune response against dystrophin in DMD patients			
	\$60,000.00	1/1/2009	12/31/2009	Year 1
	\$60,000.00	1/1/2010	12/31/2010	Year 2
	\$60,000.00	1/1/2011	12/31/2011	Year 3

*Summary* Duchenne muscular dystrophy (DMD), the most prevalent fatal genetic muscle disorder of children, is caused by mutations in the gene for the protein dystrophin. Dystrophin provides a structural link within muscle cells that protects them against damage during strain. One caveat for dystrophin replacement therapy in these patients is the possibility of the immune system seeing the newly introduced protein as foreign. In fact, it has been publicly stated at the 2008 American Society of Gene Therapy conference that in human gene therapy trials use of adeno-associated virus (AAV) mediated delivery of microdystrophin was accompanied by a robust cytotoxic T-cell response generated against dystrophin. Utrophin, a protein very similar to dystrophin in structure and function is normally expressed in nearly all cells of the human body. Targeted striated muscle gene delivery of utrophin may provide the benefit of avoiding destructive cellular immune responses, thus improving the efficiency of gene transfer to DMD patients. We have recently designed and delivered a murine microutrophin cassette which shows a tremendous reduction in muscle abnormalities in muscular dystrophy mice that lack both dystrophin and utrophin (mdx/utrn<sup>-/-</sup>). We propose to characterize the functionality of human microutrophin in mdx/utrn<sup>-/-</sup> mice. We further propose to test AAV-mediated delivery of human microutrophin in non-human primates as part of preclinical studies aimed at developing gene therapy for DMD.

**Justin Percival Ph.D.**

DG	Reevaluation of nNOS Isozyme Function in mdx Skeletal Muscle			
	\$44,992.00	1/1/2009	12/31/2009	Year 2
	\$44,992.00	1/1/2010	12/31/2010	Year 3

*Summary* We have identified a novel nNOS signaling pathway based on nNOSbeta, which appears to regulate muscle mass and strength. We propose to further characterize the function of the nNOSbeta signaling pathway in normal and mdx muscle and determine if increased nNOSbeta activity can improve the dystrophic phenotype of mdx skeletal muscle.

**WISCONSIN****Madison - University of Wisconsin-Madison****Jeff Hardin Ph.D.**

RG	The role of tropomodulin in regulating myofibrillogenesis			
	\$100,000.00	1/1/2009	12/31/2009	Year 3

*Summary* Studies in *C. elegans* will help determine parts of tropomodulin (Tmods) and tropomyosin (TM) important in muscle attachments that may cause muscle diseases.

**F. Michael Hoffmann PhD**

RG	New TGF-beta Signaling Inhibitors for Activating Muscle Regeneration			
	\$125,000.00	1/1/2009	12/31/2009	Year 2
	\$125,000.00	1/1/2010	12/31/2010	Year 3

*Summary* We intend to discover chemical agents that can inhibit the problems caused by excess TGF-beta on muscle regeneration but that do not interfere with the positive roles of TGF-beta. Initial screens have identified candidate chemical inhibitors that are being optimized for potency and selectivity. We will do additional screens of small molecule chemical libraries to identify chemicals that are selective for TGF-beta's affect on muscle regeneration. These compounds could provide initial leads for developing drugs that would activate muscle regeneration by inhibiting TGF-beta signaling.

**John Svaren Ph.D.**

RG	Peripheral neuropathy protein interaction network			
	\$78,813.00	1/1/2008	6/30/2009	Year 2

*Summary* A protein interaction library for PMP22, MPZ and other genes when mutated that cause demyelinating disorders will be created to assist researchers in this field of study.

## AUSTRALIA

### Clayton - Monash University

#### Peter Currie PhD

RG	Elucidation of cellular pathology in muscular dystrophy, using zebrafish models			
	\$121,800.00	1/1/2009	12/31/2009	Year 2
	\$121,800.00	1/1/2010	12/31/2010	Year 3

*Summary* We propose to use fluorescent transgenic technology to follow individual detached fibres to determine what happens to cell when they detach and use different treatments to prevent the death of muscle cells in these models. Furthermore, we are now able to test the extent to which muscle degeneration in both models is a direct result of perturbation of the dystrophin-glycoprotein complex (DGC), alterations of which cause the vast majority of muscular dystrophy in humans.

#### Christina Anne Mitchell Ph.D.

RG	Role of FHL1 in regulating skeletal muscle mass and myopathy			
	\$101,212.00	7/1/2008	6/30/2009	Year 1
	\$109,811.00	7/1/2009	6/30/2010	Year 2
	\$116,627.00	7/1/2010	6/30/2011	Year 3

*Summary* Factors that promote muscle growth (hypertrophy) are potential new treatments to reduce muscle wasting (atrophy). We have investigated a protein called FHL1, and predict FHL1 controls muscle hypertrophy and wasting. We have engineered mice to produce excess FHL1. These mice exhibit increased muscle size, greater muscle strength and are protected from age-induced weakness. We have shown FHL1 stimulates hypertrophy by regulating two known factors that control muscle mass, NFATc1 and Foxo. Very recently, multiple errors, called mutations, have been identified in the FHL1 gene in three human myopathies. The effect of mutant FHL1 on muscle growth versus wasting will be determined by engineering mutant FHL1 expression in muscle cells, and measuring NFATc1 and Foxo activity, characterizing the molecular basis of these interactions. Duchenne Muscular Dystrophy (DMD) is caused by loss of the protein dystrophin. The protein utrophin can substitute for dystrophin and is a potential treatment for DMD. Utrophin expression is stimulated by NFATc1. Given that FHL1 increases NFATc1 activity, we will investigate if FHL1 can also stimulate production of utrophin in muscle cell lines and in a mouse model of DMD. We will also examine if FHL1 can reduce muscle wasting in a mouse model of this disease.

### CONCORD - Anzac Health & Medical Research Foundation

#### Garth A Nicholson M.D., PhD

RG	Finding the gene causing x-linked Charcot-Marie-Tooth (CMTX3) neuropathy			
	\$72,285.00	7/1/2008	6/30/2009	Year 2

*Summary* The locus linked to X-linked CMTX3 will be studied to determine the causative gene.

### Crawley - The University of Western Australia

#### Steve D Wilton Ph.D

RG	Refined AO design for enhanced dystrophin exon skipping			
	\$116,160.00	7/1/2008	6/30/2009	Year 2
	\$116,160.00	7/1/2009	6/30/2010	Year 3

*Summary* Investigators will refine AOs for exon skipping therapy development for DMD.

## Melbourne - Baker IDI Heart and Diabetes Institute

### Paul Gregorevic Ph.D.

RG	Gene-transfer based follistatin expression for treatment of muscular dystrophy			
	\$110,000.00	1/1/2009	12/31/2009	Year 2
	\$110,000.00	1/1/2010	12/31/2010	Year 3

*Summary* Restoring dystrophin expression in patients' muscles early in life may halt further strength loss, but patients often already display considerable muscle weakness when diagnosed. Co-delivering genes that stimulate growth of muscle fibers may help to compensate for the loss of muscle strength seen in severe muscular dystrophies. I have observed that follistatin genes delivered in particles made with viral proteins can dramatically increase the strength of muscles in healthy mice, and when delivered with a dystrophin gene can improve the strength of a single muscle in dystrophic mice more than treatment with the dystrophin gene alone. I will assess if delivery of a follistatin gene to muscles body-wide can preserve or restore strength and reduce disease symptoms in dystrophic mice. Secondly, I will study the changes in cell signaling that occur in the muscles of healthy and dystrophic mice following follistatin expression to determine if the signals that control muscle fiber growth are impaired in dystrophic muscles. Thirdly, I will investigate whether short-term administration of recombinant follistatin protein to dystrophic mice can enhance muscle strength without using viral vectors.

## Melbourne, Victoria - Murdoch Childrens Research Institute

### Joseph Sarsero Ph.D.

RG	Pharmacological therapies for Friedreich ataxia using cellular and mouse models			
	\$125,000.00	1/1/2009	12/31/2009	Year 2
	\$125,000.00	1/1/2010	12/31/2010	Year 3

*Summary* Our aim is to identify and develop new pharmacological approaches for the restoration of FRDA gene expression and the therapy of FRDA.

### David Ross Thorburn Ph.D.

RG	Mechanisms of cellular damage in mitochondrial oxidative phosphorylation disease			
	\$125,456.00	1/1/2009	12/31/2009	Year 1
	\$125,000.00	1/1/2010	12/31/2010	Year 2
	\$125,000.00	1/1/2011	12/31/2011	Year 3

*Summary* Our cells convert food into energy in tiny power plants called mitochondria. This process can go wrong, affecting any organ. Brain and muscle are particularly affected due to their high energy requirement. Inherited mitochondrial energy generation disorders are the most common genetic metabolic diseases, affecting at least 1/5,000 of the population. Current treatments are ineffective because we do not understand the disease mechanisms that cause damage to cells, particularly in the brain. Study of these is limited by the difficulty in accessing brain tissue and the relative lack of suitable animal models. The overall aim of this application is to gain a greater understanding of the molecular mechanisms by studying cultured cells from patients with the most common energy generation disorder, complex I deficiency. We will also use other newly available model systems of complex I deficiency, including cultured brain cells from complex I deficient mice, and human adult stem cells and mouse embryonic stem cells with potential to be differentiated into cell types that reflect brain function more closely. We will determine whether problems in calcium handling and oxidative stress offer new approaches to treatment of mitochondrial disease. Outcomes will be relevant not only for patients with such diseases, but also for our understanding and potential treatment of mitochondrial dysfunction in related conditions such as Friedreich ataxia and Parkinson disease.

## Parkville - The University of Melbourne

### Gordon Stuart Lynch Ph.D.

RG Growth factor therapy for improving muscle function in muscular dystrophy  
\$99,912.00 7/1/2008 6/30/2009 Year 3

*Summary* This project investigates the potential for growth factor (IGF-1 and IL-15) administration to ameliorate the muscle wasting and the progressive loss of function common to the muscular dystrophies.

## Sydney, NSW - The University of Sydney

### William D. Phillips Ph.D.

RG Anti-MuSK antibodies and the mechanisms of seronegative myasthenia gravis  
\$33,236.00 7/1/2008 6/30/2009 Year 3

*Summary* This research will test whether patients' antibodies against MuSK really causes MD, by injecting their antibodies into mice.

### Des Richardson Ph.D., D.Sc.

RG The Role of Iron in Friedreich's Ataxia and the Use of Iron Chelation Therapy  
\$135,598.00 1/1/2009 12/31/2009 Year 2  
\$135,598.00 1/1/2010 12/31/2010 Year 3

*Summary* My group has developed novel iron binding drugs that can remove toxic iron in FA mouse model (MCK) preventing heart problems seen in Friedreich's ataxia patients. We now want to assess if these new iron binding drugs can prevent the neural damage that is observed in another mouse model of Friedreich's ataxia which is known as NSE. Our aim in these studies is to develop a new drug for treatment of FA. This exciting work is currently supported by MDA and we hope that we can continue our studies in the present proposal.

## BELGIUM

### Ghent - Flanders Interuniversity Institute for Biotechnology (VIB)

#### Peter Carmeliet PhD. , M.D.

RG Designing new therapies with VEGF and a novel homologue VEGF-B in rodent models of ALS  
\$128,700.00 7/1/2008 6/30/2009 Year 3

*Summary* This study will generate insights with important implications to further optimize VEGF-based treatment strategies for ALS.

## CANADA

### MANITOBA

#### Winnipeg - University of Manitoba

#### Jiming Kong PhD

RG Rescue of motor neuron death in ALS by targeting the BNIP3 death gene family  
\$106,930.00 1/1/2009 12/31/2009 Year 2  
\$107,682.00 1/1/2010 12/31/2010 Year 3

*Summary* The present proposal is built on our previous studies to further define the BNIP3-induced cell death pathway and to test new neuroprotective strategies by targeting members of the BNIP3 death gene family. With greater understanding of mechanisms causing motor neuron cell death new and effective therapeutic strategies to protect against neuronal cell death in ALS may be identified.

## ONTARIO

### Ottawa - Ottawa Health Research Institute

#### Rashmi Kothary Ph.D.

RG	The role of the actin remodeling pathway in SMA pathogenesis			
	\$117,447.00	7/1/2008	6/30/2009	Year 3

*Summary* This research will address the biological consequences of SMN dosage. These efforts will improve the understanding of Smn in motor neurons in the context of the SMA disease.

#### Michael A. Rudnicki PhD

RG	Molecular regulation of satellite cell function			
	\$100,000.00	7/1/2008	6/30/2009	Year 1
	\$100,000.00	7/1/2009	6/30/2010	Year 2
	\$100,000.00	7/1/2010	6/30/2011	Year 3

*Summary* Wnts are members of a large family of secreted proteins involved in regulating the formation and repair of tissues. We have found that overexpression of Wnt7a during skeletal muscle regeneration results in the marked enhancement of repair by stimulating the growth of muscle stem cells. In addition, we have noted that in the muscle of a mouse model of Duchenne Muscular Dystrophy, the muscle stem cell pool is apparently depleted. However, overexpression of Wnt7a is nevertheless capable of stimulating muscle repair in mdx muscle, suggesting that Wnt7a has additional activities. These experiments will determine the activities of the different Wnts expressed during regeneration, and establish at which level they function. This work will generate important new information concerning the underlying basis for the dysfunction of dystrophin-deficient muscle stem cells and explore the utility of Wnt delivery into dystrophic muscle as a potential strategy for the treatment of DMD.

#### Luc A Sabourin Ph.D.

RG	Role of the Ste20 kinase SLK in myoblast migration and differentiation			
	\$115,000.00	7/1/2008	6/30/2009	Year 1
	\$115,000.00	7/1/2009	6/30/2010	Year 2
	\$110,000.00	7/1/2010	6/30/2011	Year 3

*Summary* Migration of myogenic cells occurs extensively during skeletal muscle regeneration and is important in myoblast transfer therapy. Up to now, the treatment of muscular dystrophy using myoblast transfer into muscle tissue has had limited success due in part to the low dispersion of grafted cells outside the primary site of injection. Our laboratory has recently isolated a novel protein kinase, termed SLK, involved in the control of cell death and cellular reorganization. Our experiments will focus on understanding the molecular mechanisms that regulate cellular rearrangements and myoblast migration using in vitro and in vivo approaches. Dissection of the regulatory mechanisms that govern cellular reorganization and cell migration will contribute significantly to the design of more efficient repair therapies.

### Ottawa - The University of Ottawa

#### Alexandre Blais Ph.D.

RG	Characterization of the role of the Six1 transcription factor during myogenesis.			
	\$115,631.00	1/1/2009	12/31/2009	Year 2
	\$115,631.00	1/1/2010	12/31/2010	Year 3

*Summary* Our lab is interested in defining the transcriptional regulatory events that oversee skeletal muscle development. Elucidation of the network of molecular interactions that occur during myogenesis will reveal the identity of the key players and uncover their function in this complex process. This will allow us to reach our ultimate goal, which is to genetically reprogram cells, enhance and exploit their myogenic potential, and use them to restore muscle function in cell-based therapies of muscular illnesses.

**Bernard Jasmin PhD**

RG	Promoting the slow oxidative myofiber program to stimulate utrophin A expression
	\$140,800.00                      1/1/2009                      12/31/2009                      Year 3

*Summary* Studies to understand mechanisms regulating utrophin expression will be conducted with intent to compensate for the lack of dystrophin in DMD/BMD

**Ilona Skerjanc Ph.D.**

RG	Enhanced muscle repair with human embryonic stem cells
	\$120,000.00                      1/1/2009                      12/1/2009                      Year 1
	\$120,000.00                      1/1/2010                      12/1/2010                      Year 2
	\$120,000.00                      1/1/2011                      12/1/2011                      Year 3

*Summary* Cell therapies to reverse muscle atrophy and to strengthen skeletal muscle would greatly enhance and extend the lives of patients with dystrophic diseases, including muscular dystrophy. Several cell sources for therapy are currently under study by others, including satellite, adult stem, and mesenchymal stem cells. However, difficulties have been encountered with these approaches, including the requirement for invasive procedures, the availability of suitable donors, and the limited long-term proliferation potential. In contrast, human embryonic stem (hES) cells could provide an unlimited number of cells, with an enhanced proliferation ability. A recent study has reported the isolation of skeletal myoblasts from differentiating hES cells and their transplantation into mice, indicating the potential of this approach for future therapeutic applications. However, the ability of hES-derived myoblasts to contribute to the satellite cell niche and to enhance skeletal muscle function was not assessed. To this end, we propose to use a novel method to isolate a skeletal myoblast/progenitor population from hES cells and examine their ability to engraft into skeletal muscle in mdx mice, assessed by their contribution to the satellite cell niche, and enhancement of muscle function. The overall goal is to provide a method of hES cell differentiation and enrichment that will generate human myoblasts/progenitors for long-term engraftment and future therapeutic applications.

**Toronto - University of Toronto****Janice Robertson Ph.D.**

RG	Alternative splicing of the neurofilament-light subunit in amyotrophic lateral sclerosis (ALS)
	\$79,876.00                      1/1/2009                      12/31/2009                      Year 3

*Summary* Determination of how neurofilament accumulations occur will help reveal shared pathways of familial and sporadic ALS to target therapeutic approaches.

**QUÉBEC****Montreal - CRCHUM - Hopital Notre-Dame****Bernard BRAIS M.D.**

RG	Studying the role of mutated integrins in two new forms of muscular dystrophies
	\$90,000.00                      1/1/2009                      12/31/2009                      Year 1
	\$90,000.00                      1/1/2010                      12/31/2010                      Year 2

*Summary* Advances in genetics lead to the identification of a growing number of distinct recessive muscular dystrophies (MD) and their causal genes. These new discoveries allow better diagnosis and genetic counseling and open the way to a specific understanding of the underlining pathology essential for the development of new treatments. We have recruited two distinct cohorts of French-Canadian families affected by two new forms of MD. A first grant from the MDA allowed the original identification of mutations in an integrin in a cohort of 16 individuals from 13 families affected by a novel congenital muscular dystrophy with hyperlaxity (CMDH). In parallel, we have identified a probable mutation in another integrin in families of Acadian ancestry affected by a new childhood onset limb girdle muscular dystrophy (LGMD). These MD are only the second and third to be found to be caused by mutations in an integrin since the discovery in 1998 of mutation in ITGA7 in a very rare form of congenital MD. Integrins form a large family of transmembrane proteins involved in numerous functions. Their function in muscle is still not fully understood. We propose to investigate how mutations in these two integrins cause these new forms of MD and explore in more general the roles of integrins in normal muscle development and function.

## Montreal - McGill University

### Salvatore Carbonetto Ph.D.

RG	Dystroglycan signaling in nerve muscle synapse formation			
	\$115,731.00	7/1/2008	6/30/2009	Year 3

*Summary* Dystroglycan is necessary for skeletal muscle integrity and in the proper development and synapse formation. There is little known of how it functions in these disparate processes. Researchers will study the formation of relatively simple and accessible nerve-muscle synapses to elucidate these mechanisms. This information will contribute to strategies to mitigate the severe muscular dystrophy and mental retardation that accompanies dystroglycan.

### Heather D. Durham Ph.D.

RG	Common Pathogenic Factors in Motor Neuron Diseases as Targets for Intervention			
	\$117,827.00	7/1/2008	7/1/2009	Year 1
	\$107,679.00	7/1/2009	7/1/2010	Year 2
	\$109,214.00	7/1/2010	7/1/2011	Year 3

*Summary* Mutations that cause certain inherited forms of ALS and other neurological diseases that affect motor neurons, such as Kennedy's disease and Charcot-Marie-Tooth disease (CMT) have been identified. By expressing those mutant genes in cultured cells and animals, scientists have created experiment models to explore how the mutant proteins cause dysfunction and even death of motor neurons. To improve our ability to identify, test and predict the usefulness of a potential therapy, we can identify the critical ways that these various mutant proteins disrupt the function of neurons, and focus on those that occur early and in multiple diseases. We can determine how candidate drugs prevent these early difficulties as well as more disastrous consequences, including motor neuron death and loss of locomotion. We can improve our screening methods to more quickly identify the best therapies to move forward for further testing. This research project will address those goals by improving upon our primary culture models of ALS, CMT and Kennedy's disease to measure and understand early, subtle changes in mitochondria (energy producing factories in cells) movement of intracellular traffic, and control of intracellular calcium, and by determining how therapeutic candidates intervene with these more subtle aspects of motor neuron function.

### Scot C. Leary Ph.D.

DG	Mitochondrial regulation of cellular copper homeostasis in mitochondrial myopathy			
	\$45,000.00	7/1/2008	6/30/2009	Year 3

*Summary* The objective is to define the biochemical pathway(s) that not only handles copper within mitochondria but also impinges upon intracellular copper homeostasis.

## Montreal - Universite de Montreal

### Emmanuelle Querido Ph.D.

DG	Live cell study of CUG triplet repeat RNA foci involved in myotonic dystrophy (DM)			
	\$44,990.00	1/1/2009	12/31/2009	Year 3

*Summary* Researchers will study how mutant CUG repeats in myotonic dystrophy 1 (DM1) are retained in the nucleus of mouse muscle cells in culture, the proposed mechanism of the disorder..

## Montréal - Institut de recherches cliniques de Montréal

### Artur Kania Ph. D

RG	Motor neuron survival factors in development			
	\$126,775.00	7/1/2008	6/30/2009	Year 1
	\$119,075.00	7/1/2009	6/30/2010	Year 2
	\$119,075.00	7/1/2010	6/30/2011	Year 3

*Summary* Many motor neuron disorders are characterized by motor neuron loss leading to paralysis and eventual patient death. Thus, blocking motor neuron death through administration of neuronal survival factors is a key strategy for therapeutic approaches. Many neuronal survival factors have been identified by studying normal neuronal death that occurs in the developing nervous system, but how such factors work to prevent neuronal death is still unclear. My laboratory is studying the development of spinal cord motor neurons that innervate and control limb muscles. The objective of this study is a detailed characterization of signals secreted by muscles that prevent the death of motor neurons during embryonic development. We anticipate that this research will (1) tell us whether different classes of motor neurons require specific combinations of survival factors to stay alive, and (2) possibly lead to new therapies aimed at improving motor neuron survival in neurodegenerative diseases such as Spinal Muscular Atrophy or Amyotrophic Lateral Sclerosis.

## Quebec - Laval University

### Francois Berthod Ph.D.

RG	Development of a tissue-engineered model of spinal cord to study amyotrophic lateral sclerosis			
	\$75,445.00	7/1/2008	6/30/2009	Year 2
	\$75,445.00	7/1/2009	6/30/2010	Year 3

*Summary* Researchers will construct a 3-D cellular model to test various factors influencing survival of these cells in FALS.

### Jack Puymirat M.D., Ph.D.

RG	Preclinical in vivo evaluation of a gene therapy for myotonic dystrophy type 1			
	\$89,039.00	7/1/2008	6/30/2009	Year 3

*Summary* This proposal outlines an ordered series of experiments aimed at testing RNA-based strategy in transgenic mice having the DM1 phenotype. Investigators anticipate that this preclinical in vivo evaluation could lead to a Phase I clinical trial based on the intramuscular injection of a rAAV1(6)/antisense/or ribozyme gene vector in adult DM1 patients.

## CHILE

### Santiago - Institute of Biomedical Sciences, Faculty of medicine, University of Chile

### Claudio Hetz Ph.D

RG	Targeting Autophagy for the removal of mutant SOD1 in ALS			
	\$65,190.00	7/1/2008	6/30/2009	Year 1
	\$60,500.00	7/1/2009	6/30/2010	Year 2

*Summary* The primary mechanism responsible for the progressive motoneuron loss in ALS remains unknown. Clues have been obtained from families who have a genetic form of ALS that is accompanied by a mutation in superoxide dismutase (SOD1). It has been suggested that perturbation in the function of the endoplasmic reticulum (ER) and lysosomes may determine the neurotoxicity of ALS-linked mutant SOD1. We have obtained preliminary data supporting an involvement of this stress response in the elimination of disease related mutant SOD1 protein through a cellular pathway termed autophagy. In this project we aim to characterize in detail the contribution of this pathway to motoneuron dysfunction in ALS and assess the possible therapeutic benefits of targeting autophagy with well characterized and safe prototypic drugs. In addition, we plan to complement our studies with the analysis of samples of sporadic and familial ALS patients to corroborate the role of autophagy in the disease.

## Santiago - Pontificia Universidad Catolica de Chile

### Enrique Brandan Ph.D.

RG	CTGF the factor involved in fibrosis development in DMD				
	\$89,879.00	7/1/2008	6/30/2009		Year 1
	\$68,075.00	7/1/2009	6/30/2010		Year 2
	\$70,336.00	7/1/2010	6/30/2011		Year 3

*Summary* Reports suggest an increase in connective tissue growth factor (CTGF) mRNA in dystrophic dogs, and microarray analysis, indicate an enhanced level of CTGF in mdx mice. Although the participation of CTGF in fibrosis has gained attention in the last years, little information regarding the function of CTGF in skeletal muscle fibrosis is available. The main goal of this project is to elucidate the biological role of CTGF, decorin and LRP on skeletal muscle fibrosis. Experiments are designed to: genetically determine whether CTGF is responsible for fibrosis development in dystrophic muscles; determine the possible complex formation between LRP-decorin-CTGF and its role in muscle fibrosis; evaluate the inhibitory interaction between some proteoglycans and CTGF; identify activators and/or inhibitors of CTGF obtained using CTGF affinity chromatography followed by proteomic analyses; study the CTGF gene promoter region and several putative response elements, particularly those related with skeletal muscle formation, atrophy and inflammation. This project will provide important basic information on the mechanisms underlying fibrosis development in skeletal muscle and will allow us to identify possible target molecules that interfere with fibrosis.

## FRANCE

### Lyon - INSERM

#### Severine Boillee Ph.D.

DG	Analyzing the motor neuron neighborhood effect of microglial-derived toxicity in amyotrophic lateral				
	\$45,000.00	1/1/2009	12/31/2009		Year 3

*Summary* Researchers will attempt to determine how damaged immune cells contribute to motor neuron death using purified microglia and motor neurons to identify the toxic molecules produced by microglia.

## Paris - Institut National de la Santé et de la Recherche Médical ADR Paris 6

#### Edgar R. Gomes Ph.D.

DG	Role of nuclear position in myofiber formation				
	\$45,000.00	7/1/2008	6/30/2009		Year 3

*Summary* By elucidating the molecular pathways that contribute to nuclear movements and positioning in muscle cells and how these may be specifically affected in dystrophic cells, the researchers hope to contribute to a better understanding of the basic etiology of muscular dystrophies and to identify novel rationales and targets for therapeutic diagnosis and intervention.

## GERMANY

### Hannover - Medizinische Hochschule Hannover (MHH)

#### Christoph M. Fahlke M.D.

RG	Chloride channel dysfunction in myotonia congenita			
	\$116,634.00	1/1/2009	12/31/2009	Year 1
	\$121,299.00	1/1/2010	12/31/2010	Year 2
	\$126,150.00	1/1/2011	12/31/2011	Year 3

*Summary* Myotonia congenita is a genetic human muscle disease characterized by muscle stiffness upon sudden forceful movement. The life-long muscle stiffness can be quite disabling, and the current treatment is largely ineffective and poorly tolerated by many patients. The molecular cause of this disease is well understood and known for many years. Both autosomal dominant and recessive myotonia congenita are caused by mutations in the gene encoding the principal human skeletal muscle Cl<sup>-</sup> channel, hCIC-1 (CLCN1 gene). However, information linking genetic information to clinical symptoms is still missing. We propose to study the effects of a large number of CLCN1 mutations found in myotonia congenita on various aspects of muscle chloride channel function. We will evaluate how mutant channels conduct anion and open and close upon changes of the membrane potential. Disease-causing mutations might also affect the number of channels in the muscle fiber or its subcellular distribution. Lastly, mutations might impair the ability of CIC-1 proteins to form dimeric chloride channels. We will study these different functions and correlate them to clinical symptoms of the respective patients. We expect from these studies insights into the molecular determinants of the various symptoms of myotonia congenita. This information will be important for identifying novel pharmacological treatments for myotonia congenita.

## ISRAEL

### Jerusalem - Hebrew University of Jerusalem

#### Yosef Gruenbaum Ph.D.

RG	Mechanism of emerin and LEM-2 regulation and function			
	\$63,250.00	7/1/2008	6/30/2009	Year 2
	\$63,250.00	7/1/2009	6/30/2010	Year 3

*Summary* Investigators will study overlap of emerin and other LEM-domain proteins to determine factors in X-linked EDMD

#### Orna Halevy Ph.D.

RG	Inhibition of fibrosis and mode of action of halofuginone in muscle dystrophies			
	\$117,700.00	1/1/2009	12/31/2009	Year 2
	\$117,700.00	1/1/2010	1/31/2010	Year 3

*Summary* We discovered the clinical potential of halofuginone (halo) as a novel anti-fibrotic therapy. By inhibiting fibrosis halo protects against muscle damage and lessens the need for excessive muscle regeneration. In this proposal we will evaluate the effect of halo on muscle fibrosis in a CMD mouse model (dy2J/dy2J). Success in the study would demonstrate that halo treatment would be beneficial for other MDs

## Raanana - Open University of Israel

### Miriam Souroujon Ph.D.

RG	Suppression of myasthenia gravis by regulatory T cells: studies in EAMG			
	\$103,518.00	1/1/2009	12/31/2009	Year 1
	\$109,741.00	1/1/2010	12/31/2010	Year 2
	\$108,630.00	1/1/2011	12/31/2011	Year 3

*Summary* We aim to develop improved immunotherapies for the autoimmune neuromuscular disease myasthenia gravis (MG) that would not have the adverse side effects of the treatments used today. Our studies are conducted mainly in experimental autoimmune MG (EAMG) in rats as a model. The proposed project focuses on regulatory T cells (Treg) that are known as key players in maintaining immune tolerance and were reported to display impaired function in MG, suggesting their involvement in the immunopathology of the disease and their potential in its therapy. Our recent data point to differences between Treg from EAMG rats and healthy controls and demonstrate that Treg from healthy donors can suppress EAMG. This proposal is aimed at extending these studies along the following lines: further analyze qualitative and quantitative differences between Treg in EAMG and healthy controls, assess the contribution of the equilibrium between the suppressive Treg and the pathogenic Th17 cells to the susceptibility and course of myasthenia and understand the importance of antigen specificity for the suppressive activity of Treg. These analyses will lead to in vivo studies in which we will use Treg from sick syngeneic or healthy allogeneic donors to treat EAMG. Finally, the humanized SCID/NOD mouse model will be used to test the therapeutic potential of autologous and allogeneic Treg in a system closer to human MG. Hopefully, these studies will lead to Treg-based clinical trials in MG.

## ITALY

### Milan - National Neurological Institute Carlo Besta

#### Elena I. Rugarli M.D.

RG	Defective processing of specific paraplegin substrates at the basis of hereditary spastic paraplegia			
	\$62,425.00	7/1/2008	6/30/2009	Year 3

*Summary* Paraplegin is an enzyme that cuts other molecules and allow their maturation to functional forms. This study seeks to understand how defective maturation of this protein leads to hereditary spastic paraplegia.

### Milano - Fondazione Centro San Raffaele del Monte Tabor

#### Davide Gabellini Ph.D.

RG	Characterization of the molecular mechanisms altered in FSHD.			
	\$121,000.00	1/1/2009	12/31/2009	Year 1
	\$111,100.00	1/1/2010	12/31/2010	Year 2
	\$103,400.00	1/1/2011	12/31/2011	Year 3

*Summary* The goal of this research project is to understand the molecular mechanism of facioscapulohumeral muscular dystrophy (FSHD). FSHD is the third most common muscular dystrophy. Presently, there is no treatment or cure for FSHD. FSHD is associated with reduction in the number of copies of DNA on chromosome 4, called D4Z4, that is repeated many times toward the end of the long arm of chromosome 4. We hypothesized that D4Z4 may control the activity of nearby FSHD genes. We found that in FSHD patients there is an increased production of the proteins encoded by the genes close to D4Z4. Interestingly, we found that these proteins are over-produced specifically in the muscles of FSHD patients explaining the fact that FSHD is primarily a disease of skeletal muscle. More recently, with the idea of modeling in an animal the same conditions observed in FSHD patients, we generated mice over-producing the same proteins that are over-produced in the muscles of FSHD patients. We found that mice over-producing a protein called FRG1 display several features of FSHD patients. Based on these results, we propose that loss of D4Z4 causes over-production of FRG1, which leads to FSHD. We plan to: - understand the molecular mechanism responsible for increased production of 4q35 proteins in FSHD - understand the specific processes that go awry in muscles of patients suffering from FSHD. Results of our research will contribute to develop effective therapeutic approaches for FSHD.

## Roma - Provincia Italiana CFIC-Istituto Dermopatico dell' Immacolata

### Carlo Gaetano M.D.

RG	HDAC inhibitors as experimental therapeutics in Duchenne cardiomyopathy			
	\$28,000.00	7/1/2008	6/30/2009	Year 1
	\$28,000.00	7/1/2009	6/30/2010	Year 2
	\$27,000.00	7/1/2010	6/30/2011	Year 3

*Summary* The lack of functional dystrophin predisposes DMD patients to contraction-induced muscle cell disruption. In skeletal muscle, satellite cells participate in muscle regeneration, producing newly formed myotubes. This process counterbalances degeneration in the first phase of the disease. However, the excessive myogenic cell division results in accelerated senescence, which is a leading cause of the progressive skeletal muscle failure. Currently it is unknown whether similar pathogenetic mechanisms play a role in DMD cardiomyopathy (CM). Recently we reported that histone deacetylase inhibitors (HDACi) are beneficial, improving skeletal muscle regeneration in MDX mice, acting at least in part on satellite cell proliferation and differentiation. Little is known, however, about their effect on cardiac muscle. Our preliminary evidence indicates that prolonged treatment with suberoylanilide hydroxamic acid (SAHA), a pan-HDACi suitable for human use, reduced the number of ventricular arrhythmias in MDX mice exposed to different social challenges. The aim of this project is to establish in vivo and at cellular and molecular levels whether and how HDACi treatment may improve the cardiac muscle performance in the MDX mouse model of Duchenne muscular dystrophy.

## JAPAN

### Sendai - Tohoku University, Graduate School of Medicine

#### Mari Dezawa M.D., Ph.D.

RG	Auto-cell transplantation therapy for muscle dystrophy using bone marrow stromal cells			
	\$128,440.00	1/1/2009	12/31/2009	Year 3

*Summary* Researchers will clarify the molecular mechanism of bone marrow stromal cells induction to skeletal muscle lineage and confirm efficiency and safety of our system in dog muscular dystrophy model. This will help establish auto-cell transplantation as a therapy in dystrophic disorders.

## NETHERLANDS

### Baarn - European Neuro Muscular Centre

#### Kate Bushby MB, ChB, MSc, MD, FRCP

SG	ENMC workshops			
	\$20,000.00	6/1/2007	1/31/2009	Year 1

*Summary* Funding to support the attendance of US participants to the workshops from the European Neuro Muscular Centre (ENMC). The ENMC is an international research support organization for neuromuscular disorders and strives to facilitate communication amongst scientists and clinicians working in the area of neuromuscular disease. The workshops are based on well focussed topics within the neuromuscular field.

### Leiden - Leiden University Medical Center

#### Silvere Maria van der Maarel Ph.D.

RG	The developmental role of D4Z4 in FSHD pathogenesis			
	\$85,441.00	7/1/2008	6/30/2009	Year 2
	\$85,441.00	7/1/2009	6/30/2010	Year 3

*Summary* Using transgenic mice, studies will address issues of chromatin structure and DNA stability in FSHD.

**Silvere Maria van der Maarel Ph.D.**

RG	NIH-RFA: Intrabody-mediated aggregation studies in models of OPMD
	\$100,000.00                      8/1/2008                      7/31/2009                      Year 2

*Summary* Oculopharyngeal muscular dystrophy (OPMD) belongs to the group of protein aggregation disorders: a mutation in the PABPN1 gene causes the PABPN1 protein to aggregate in the nucleus of the muscle cells. The exact disease mechanism of OPMD is largely unknown but several observations in cells and mice suggest an important role of the aggregation process in OPMD. Our studies focused on identification of novel pathogenic pathways in OPMD and to identify novel therapeutic strategies to interfere with the aggregation process. In our cell model we identified an unexpected involvement of the extracellular matrix which we will study in detail. In addition, we developed a new and unique OPMD-specific therapeutic approach with the selection of Camelid-derived antibody fragments specifically preventing PABPN1 aggregation. To investigate the beneficial effects of this antibody fragment we will study the therapeutic possibility of the antibody in a mouse model for OPMD.

**SINGAPORE****Singapore - National University of Singapore****Reshma Taneja Ph.D.**

RG	Regulation of skeletal muscle regeneration by Stra13
	\$105,237.00                      7/1/2008                      6/30/2009                      Year 1
	\$108,042.00                      7/1/2009                      6/30/2010                      Year 2
	\$110,847.00                      7/1/2010                      6/30/2011                      Year 3

*Summary* Myofibers in DMD patients undergo continuous cycles of degeneration and regeneration leading to necrosis, fibrosis and inflammation. The identification of genes involved in muscle regeneration is critical to design therapeutic approaches for muscular dystrophies. We have identified deregulated signaling of two critical pathways in Stra13 mutant mice that may contribute to defective regeneration of muscle. We will examine the relative contribution of each pathway in defective regenerative capacity of Stra13<sup>-/-</sup> mice. We expect that these studies will lead to novel therapeutic targets and impact on our understanding of the molecular basis of muscular dystrophies.

**SPAIN****Barcelona - Universitat Pompeu Fabra****Pura Munoz Canoves Ph.D.**

RG	Therapeutic fibrinolysis for Duchenne muscular dystrophy in mdx mice
	\$100,000.00                      7/1/2008                      6/30/2009                      Year 2
	\$100,000.00                      7/1/2009                      6/30/2010                      Year 3

*Summary* Investigators will test anicrod therapy to reduce fibrin in DMD models to determine if progression may be slowed.

**Valencia - University of Valencia****Ruben Artero Ph.D.**

RG	Discovery of anti-myotonic dystrophy drugs using a Drosophila model
	\$90,000.00                      7/1/2008                      6/30/2009                      Year 3

*Summary* The researchers propose to perform drug discovery in a myotonic dystrophy fly model. They will employ three libraries of chemical compounds to this end.

**SWEDEN****Lund - Experimental Medical Science, Lund University****Madeleine Durbeej-Hjalt Ph.D.**

RG	Laminins and congenital muscular dystrophy
	\$137,443.00                      1/1/2009                      12/31/2009                      Year 2

\$137,443.00 1/1/2010 12/31/2010 Year 3

*Summary* The aim of this project is to develop therapies for MDC1A lacking laminin alpha2. We will test whether similar laminins can function equally well as laminin alpha2 chain in muscle to avoid immune reactions. We will study a potential signaling molecule. These studies will provide new insights into laminin alpha2 chain signaling and open potential avenues for therapy of MDC1A.

## SWITZERLAND

### Basel - Biozentrum, University of Basel

#### Christoph Handschin Ph.D.

RG Amelioration of muscle atrophy and Duchenne muscular dystrophy by PGC-1alpha  
\$110,900.00 1/1/2009 12/31/2009 Year 2  
\$110,900.00 1/1/2010 12/31/2010 Year 3

*Summary* The peroxisome proliferator-activated receptor gamma co-activator 1alpha (PGC-1alpha) has been shown to be a key regulator of the adaptations of skeletal muscle to endurance exercise. We observed that mice with elevated PGC-1alpha are resistant to disuse-induced muscle atrophy and have markedly improved muscle function when crossed to a mouse model of Duchenne muscular dystrophy. We therefore aim at expanding our knowledge about PGC-1alpha in skeletal muscle in order to identify more attractive drug targets that are linked with the PGC-1alpha-mediated improvement of muscle atrophy and dystrophies.

## UNITED KINGDOM

### London - Imperial College of Science, Technology and Medicine

#### Susan Brown PhD

RG FKRP knock-in mice as a model for the pathogenesis of the dystroglycanopathies  
\$125,000.00 1/1/2009 12/31/2009 Year 2  
\$125,000.00 1/1/2010 12/31/2010 Year 3

*Summary* We have now generated mice which carry a mutation in FKRP. When this mutation is found in human patients it is associated with muscular dystrophy (dystroglycanopathy). This unique animal model will provide us with the means to understand the pathogenesis of the most common dystroglycanopathy and also allow us to assess therapeutic intervention to improve the clinical features which characterise FKRP mutant patients and mice.

### London - Institute of Child Health

#### Francesco Muntoni M.D.

RG The molecular basis of core myopathies  
\$125,000.00 1/1/2009 12/31/2009 Year 2

*Summary* Our preliminary studies suggest a protein defect which regulates the assembly and stability of the DHPR and RyR1 complex. Further studies could lead to the identification of a novel gene involved in core myopathies.

### London - Institute of Neurology, UCL

#### Henry Houlden M.D., Ph.D., MRCP

DG Genetic Modifiers of the CMT1A phenotype  
\$60,000.00 1/1/2009 12/31/2009 Year 1  
\$60,000.00 1/1/2010 12/31/2010 Year 2  
\$60,000.00 1/1/2011 12/31/2011 Year 3

*Summary* CMT1A is caused by having an extra copy of a region on chromosome 17 and patients have a wide range of severities and age of onset. This suggests there are other genetic and environmental factors that affect CMT1A. These factors are very important, as they will effect all types of CMT and neuropathy in general. The gene(s) that effect CMT1A will be important therapeutic targets. We plan to select 250 British, 350 American, 200 Italian and 200 Brazilian CMT1A patients with characterized

clinical and electrical features. We will look to analyze patients over the full spectrum of disease severity and age of onset. In these cases we will carry out a whole genome polymorphism and expression study on DNA in each patient and on mRNA extracted from Sural nerve biopsies from patients to identify which genetic regions are associated with the more severe or milder types of CMT1A.

#### **Nottingham - University of Nottingham**

##### **Jane Elizabeth Hewitt PhD**

RG	Determination of full D4Z4 array sequences in FSH muscular dystrophy		
\$100,000.00	1/1/2009	12/31/2009	Year 2

*Summary* This means that the protein coding function of D4Z4 and its unusual organization has been conserved for over 100 million years of evolution. In this application we plan to sequence complete D4Z4 arrays in both controls and FSHD patients, using a polymerase chain reaction technique, to identify D4Z4 sequence variants. This work will both improve molecular diagnostic analyses and provide a better understanding of the role of D4Z4 in FSHD.

#### **Oswestry - Robert Jones & Agnes Hunt Hospital**

##### **G.E. Morris D. Phil.**

TR-IG	The MDA monoclonal antibody resource		
\$114,034.00	10/1/2008	9/30/2009	Year 2
\$117,176.00	10/1/2009	9/30/2010	Year 3

*Summary* Professor Morris's Biochemistry Group has, over the past 20 years, built up a library of monoclonal antibodies for neuromuscular disease research, diagnosis and clinical trials. A collection of over 150 exon-specific antibodies against dystrophin is, and will continue to be, especially useful internationally in trials of potential therapies for Duchenne muscular dystrophy. Very popular antibodies have also been produced for research, diagnosis and drug evaluation in spinal muscular atrophy, Emery-Dreifuss muscular dystrophy, laminopathies and myotonic dystrophy. This project will ensure that these antibodies will continue to be available to researchers for the foreseeable future and will also add to and refine the library.

#### **Oxford - University of Oxford**

##### **Kay Davies PhD, MD, FRS**

RG	DMD therapy through utrophin up-regulation		
\$113,597.00	1/1/2009	12/31/2009	Year 3

*Summary* Researchers will study candidate molecules found to increase utrophin expression discovered by a small molecule screen in the hopes of compensating for the loss of dystrophin.

#### **Sheffield - University of Sheffield**

##### **Mimoun Azzouz Ph.D.**

RG	Treatment of familial ALS using lentiviral mediated silencing of mutant SOD1		
\$120,000.00	1/1/2009	12/31/2009	Year 3

*Summary* Studies are to use RNAi to reduce abnormal SOD1 in ALS patients to become a new therapeutic approach to this disease.