2003 ACTIVE GRANTS

FUNDING PROGRAM LEGEND

(EMG)	Earmarked Gift
(NIDA)	New Investigator Development Award
(TRAC)	Translational Research Advisory Committee
(RF)	Research Fellowship
(RG)	Research Grant
(SG)	Special Grant
(DG)	Development Grant

ALABAMA

Birmingham - University of Alabama

J. Edwin Blalock, Ph.D.

(RG) A therapeutic vaccine for myasthenia gravis (MG)

$ 75,000 7/1/02 - 6/30/03 Year 3

Summary MG is caused by an individual making antibodies (Abs) to their own acetylcholine receptors (AChR) so that muscle cells do not receive information from nerves and weakness results. Researchers have designed peptide vaccines that may cure the disease.

David Curiel, M.D., Ph.D.

(RG) Exploiting transcytosis to facilitate adenovirus-mediated muscle cell transduction

$ 90,000 7/1/03 - 6/30/04 Year 1
$ 90,000 7/1/04 - 6/30/05 Year 2
$ 90,000 7/1/05 - 6/30/06 Year 3

Summary This proposal seeks to improve systemic delivery of Ad vectors into muscle by targeting the vectors to the albumin transcytosis pathway, a cellular process employed by albumin to cross the endothelial barrier along the vessel walls.

Joanne T. Douglas, Ph.D.

(RG) A new mouse model in which to evaluate Duchenne muscular dystrophy (DMD) gene therapy

$ 100,000 7/1/02 - 6/30/03 Year 2
$ 100,000 7/1/03 - 6/30/04 Year 3

Summary Researchers propose to elucidate the barriers to efficient infection of mature skeletal muscle by the adenoviral vector, one of the most promising vehicles for DMD gene therapy. This would permit rationally designed strategies to overcome these obstacles.

Birmingham - University of Alabama (Cont'd)

Lin Mei, M.D., Ph.D.

(RG) Erbin regulation of AChR expression

$	90,000	7/1/03 - 6/30/04	Year 1
$	90,000	7/1/04 - 6/30/05	Year 2
$	90,000	7/1/05 - 6/30/06	Year 3

Summary Muscle contraction occurs when the neurotransmitter acetylcholine binds to its receptor (AChR). Investigators propose to study mechanism how the level of AChR expression is controlled in muscle cells. Results will provide a better understanding of neuromuscular disorders and contribute to development of therapeutic intervention.

Selvarangan Ponnazhagan, Ph.D.

(RG) Targeted adeno-associated virus vectors for muscular dystrophy

$	81,000	1/1/03 - 12/31/03	Year 2
$	81,000	1/1/04 - 12/31/04	Year 3

Summary Despite the potential benefits of AAV-mediated gene therapy, transduction of the vector is limited only to the site of administration. Thus, development of novel systemically injectable targeted-AAV that investigators plan to undertake will provide a key to achieve both high-efficiency gene transfer and restricted-expression of therapeutic genes in multiple muscled tissue.

ARIZONA

Tempe - Arizona State University

Ronald Nieman, Ph.D.

(RG) Characterization of SMN protein binding interactions involved in spinal muscular atrophy (SMA)

$	56,700	1/1/02 - 6/30/03	Year 1

Summary Nuclear magnetic resonance spectroscopy will be used to determine the molecular basis for changes in cellular function in mutant forms of the protein involved in SMA.

J. Alan Rawls, Ph.D.

(RG) Paraxis regulates the specification of the myogenic lineage

$	64,205	1/1/03 - 12/31/03	Year 2
$	66,431	1/1/04 - 12/31/04	Year 3

Summary Researchers propose to use a cell tracing approach developed in the laboratory for assessing cell migration in the somites of mouse tails. They anticipate that this approach can be used to both identify the origins of cells fated to form skeletal muscle and examine the potential role of known regulatory genes in this process.

Tucson - University of Arizona

Ronald E. Allen, Ph.D.

(RG) Myostatin regulation of satellite cell activity

$	73,665	7/1/02 - 6/30/03	Year 2
$	76,540	7/1/03 - 6/30/04	Year 3

Summary Treatment of Duchenne dystrophy will depend on repair and growth of muscle fibers, events normally mediated by muscle satellite cells. The role of myostatin in regulating satellite cell activity will be studied.

Tucson - University of Arizona (Cont'd)

Diana Benenati, Ph.D.
(RF) S Mouchly Small MDA Research Fellowship Award
$ 32,000 7/1/02 - 6/30/04 Year 6

Valerie Cwik, M.D.
(EMG) Restricted for research
$ 6,330 4/1/02 - 3/31/03 Year 2
$ 200 4/1/03 - 3/31/04 Year 3

Robert P. Erickson, M.D.
(RG) Mapping and cloning Athabaskan brainstem dysgenesis
$ 53,275 4/1/02 - 3/31/03 Year 3
Summary Researchers plan to map and clone the gene which, when abnormal, causes a rare genetic neuromuscular disorder among Navajo and Apache children.

Darrel Goll, Ph.D.
(RG) Role of the calpain system in muscle degeneration
$ 72,684 1/1/03 - 12/31/03 Year 1
$ 75,548 1/1/04 - 12/31/04 Year 2
Summary The loss of muscle mass in the muscular dystrophies is due to a greatly increased rate of muscle protein degradation by two proteolytic enzymes belonging to the calpain system found in muscle. This project describes studies attempting to learn how properties of the calpain system are changed in dystrophic muscle and how these changes lead to increased and/or unregulated muscle protein degradation.

CALIFORNIA

Berkeley - University of California

Richard M. Harland, Ph.D.
(RG) The roles of BMP antagonists in limb and muscle development
$ 75,000 1/1/03 - 12/31/03 Year 2
$ 75,000 1/1/04 - 12/31/04 Year 3
Summary Researchers will study the role of the gremlin gene in the development of muscle and bone in the embryo.

Davis - University of California

Ricardo Maselli, M.D.
(RG) Pathogenesis of congenital myasthenic syndromes
$ 72,643 1/1/03 - 12/31/03 Year 3
Summary The long-term objective of this project is to develop effective treatment for children affected with congenitally impaired transmission of electrical impulses from nerve to muscle.

Guolin Tan, Ph.D.
(EMG) Restricted funds for Friedreich's ataxia research
$ 17,795 4/1/03 - 3/31/04 Year 1

Duarte - Beckman Research Institute

Nan Sook Lee, Ph.D.

(DG) RNA trafficking in myotonic dystrophy (DM)

$	45,000	1/1/03 - 12/31/03	Year 2
$	45,000	1/1/04 - 12/31/04	Year 3

Summary Investigators will study human muscle cells and observe alteration in the localization of DMPK transcripts. These changes will be correlated with a dM disease phenotype. This work will ultimately result in identification of new therapeutic targets that can be used to treat the disease. Based on this, investigators will develop a potential approach to treat the disease.

Emeryville - University of California

Hongkyun Kim, Ph.D.

(DG) A genetic study of muscular dystrophy in c. elegans

$	45,000	7/1/02 - 6/30/03	Year 1
$	45,000	7/1/03 - 6/30/04	Year 2
$	45,000	7/1/04 - 6/30/05	Year 3

Summary Researchers have identified a mutant that appears to have a mutation in a novel MD gene in C. elegans. The human form of this gene has not yet been identified. Researchers propose to characterize this gene further, which should allow identification of the human form of the gene. This work should contribute to our understanding of MD and may also result in the identification of a new therapeutic target for MD.

Irvine - University of California

Sara Winokur, Ph.D.

(RG) Therapeutic approaches to aberrant myoblast differentiation in facioscapulohumeral dystrophy (FSHD)

$	107,699	7/1/02 - 6/30/03	Year 1
$	82,345	7/1/03 - 6/30/04	Year 2
$	85,634	7/1/04 - 6/30/05	Year 3

Summary Previous work has indicated that FSHD muscle is subject to a disease specific defect in the process of differentiation (muscle cell development). The current proposal will examine this process of altered differentiation in depth through proliferation and fusion studies of SHD myoblasts, correlated with gene and protein expression analysis throughout a time-course of differentiation. Therapeutic agents will then be tested in our system for their effectiveness in correcting the differentiation defect with the aim of moving these compounds into clinical trials for therapeutic treatment of FSHD.

La Jolla - Burnham Institute

Eva Engvall, Ph.D.

(RG) Using ADAM12 to promote muscle regeneration in muscular dystrophy

$	72,565	7/1/02 - 6/30/03	Year 1
$	75,278	7/1/03 - 6/30/04	Year 2

Summary ADAM12 is a protein that helps normal muscle recover from acute injury. Researchers will use genetic methods in mice to test whether this protein helps muscle recover from the chronic injury in muscular dystrophy.

La Jolla - Burnham Institute (Cont'd)

Dongxian Zhang, Ph.D.

(RG) Property of NMDA receptors in a mice model for amyotrophic lateral sclerosis (ALS)

$ 60,000 1/1/03 - 12/31/03 Year 2

Summary Researchers have recently cloned a new member of the glutamate receptor family, tentatively designated NR3B, which is expressed almost exclusively in motor neurons. More importantly, expression of NR3B dramatically alters the ion permeability of the glutamate reeptor and may thus protect motor neurons from glutamate toxicity. Researchers propose that disruptions in the expression, localization, or processing of the NR3B could contribute to degeneration of motor neurons, such as that observed in ALS and/or other motor neuron diseases. These hypotheses will be tested in a mouse model for ALS.

La Jolla - Salk Institute for Biological Studies

Samuel Pfaff, Ph.D.

(RG) Function of hereditary sacral agenesis gene HB9 in motor neurons

$ 59,935 7/1/02 - 6/30/03 Year 3

Summary This proposal is designed to examine the function and mechanism-of-action of the HB9 transcription factor in spinal motor neurons.

Pier Puri, Ph.D.

(DG) Control of muscle cell growth and differentiation by MyoD acetylation: Perspectives for muscle regeneration

$ 35,000 1/1/03 - 12/31/03 Year 3

Summary This research will address the role of MyoD acetylation in regulating satellite muscle cells activation during muscle regeneration.

La Jolla - Scripps Research Institute

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

(DG) The innate immune pathways in the pathogenesis of myasthenia gravis (MG)

$ 45,000 1/1/03 - 12/31/03 Year 2

$ 45,000 1/1/04 - 12/31/04 Year 3

Summary Investigators want to determine Toll like receptors and interleukin-15, the newly identified essential immune molecules are critical for the development of myasthenia gravis, thus help to design new therapies.

La Jolla - University of California

Ju Chen, Ph.D.

(RG) Roles of cypher in skeletal muscle

$ 90,292 7/1/02 - 6/30/03 Year 3

Summary The goal of this proposal is to define the molecular role of a novel striated muscle restricted cytoskeletal protein, Cypher, in skeletal muscle structure and function and to understand how lack of Cypher results in the skeletal muscle defects seen in Cypher null mutant mice.

Theodore Friedmann, M.D.

(SG) A celebration of 50 years of DNA in medicine

$ 10,000 11/1/03 - 11/30/03 Year 1

La Jolla - University of California (Cont'd)

Paul Martin, Ph.D.

(RG) Overexpression of synaptic molecules in mdx mice

$ 64,800 7/1/02 - 6/30/03 Year 3

Summary This proposal will investigate whether the expression of certain proteins in the muscles of mice with muscular dystrophy will inhibit muscular dystrophy from occurring in these animals.

(RG) CT carbohydrate therapy in mdx mice

$ 75,000 1/1/03 - 12/31/03 Year 1

$ 75,000 1/1/04 - 12/31/04 Year 2

Summary The goal of this grant is to identify ways to treat Duchenne muscular dystrophy (DMD) by increasing levels of a carbohydrate found in skeletal muscle. Experiments on this carbohydrate in mice suggest that it can inhibit the formation of muscular dystrophy in an animal model of DMD.

Immo Scheffler, Ph.D.

(RG) A mouse model for mitochondrial diseases

$ 75,600 1/1/03 - 12/31/03 Year 3

Summary Mitochondria have been called the "power house" of the cell. Partially defective mitochondria cause mitochondrial diseases. The relationship between the severity of the biochemical defect and symptoms is still poorly understood. Animal models promise to contribute to an understanding of these diseases and hopefully, amelioration and a cure.

G. Diane Shelton, DVM, Ph.D.

(RG) Canine inflammatory myopathy: An animal model for human inflammatory myopathy

$ 63,472 7/1/02 - 6/30/03 Year 1

$ 65,066 7/1/03 - 6/30/04 Year 2

$ 66,713 7/1/04 - 6/30/05 Year 3

Summary The dog has proven to be a valuable spontaneous animal model for neuromuscular diseases such as X-linked muscular dystrophy and autoimmune myasthenia gravis. Inflammatory myopathies also occur spontaneously in the dog, and researchers propose that this species may be an excellent animal model for the differential diagnosis and treatment of human inflammatory myopathies. Full characterization of the canine inflammatory myopathies will be performed to establish canine inflammatory myopathies as an animal model for human inflammatory myopathies.

Gregory Taylor, Ph.D.

(DG) MTM1 and MTMR2: Lipid phosphatases linked to neuromuscular disease

$ 45,000 1/1/03 - 12/31/03 Year 2

$ 45,000 1/1/04 - 12/31/04 Year 3

Summary Researchers propose to study the function and regulation of myotubularin and MTMR2, inositol lipid phosphatases that are mutated in myotubular myopathy and type 4B Charcot-Marie-Tooth disease.

Los Angeles - University of California

Michael Graves, M.D.

(EMG) Restricted funds for support of the MDA/ALS Nursing Research Endowment at UCLA

$ 3,045 4/1/02 - 3/31/03 Year 3

Los Angeles - University of California (Cont'd)

Michael Graves, M.D.

(EMG) Restricted funds for support of the MDA/ALS Clinic and Research Center

$	7,600	4/1/02 - 3/31/03	Year 1
$	300	4/1/03 - 3/31/04	Year 2

Patrice Hamel, Ph.D.

(DG) Functional dissection of a cytochrome c assembly machinery in mitochondria

$	45,000	7/1/03 - 6/30/04	Year 1
$	45,000	7/1/04 - 6/30/05	Year 2
$	45,000	7/1/05 - 6/30/06	Year 3

Summary The goal of this project is to decipher how c-type cytochomes, which are crucial protein molecules in the production of energy and cell death processes, are made in the mitochondria.

Peter Hynds, Ph.D.

(DG) Mouse models of mitochondrial myopathies

$	45,000	7/1/02 - 6/30/03	Year 1
$	45,000	7/1/03 - 6/30/04	Year 2
$	45,000	7/1/04 - 6/30/05	Year 3

Summary The mitochondrial dysfunction of a mouse model for mitochondrial myopathy will be characterized.

Carla Koehler, Ph.D.

(RG) Characterization of a mouse model for mitochondrial myopathy

$	80,244	1/1/03 - 12/31/03	Year 1
$	81,648	1/1/04 - 12/31/04	Year 2
$	83,052	1/1/05 - 12/31/05	Year 3

Summary The objective is to determine how proteins assemble in the mitochondrion, the energy-producing unit of the cell, with the goal of understanding the basis of mitochondrial myopathies and developing treatments.

York Marahrens, Ph.D.

(RG) Designer proteins to identify FSHD genes and control mechanism

$	9,900	7/1/03 - 6/30/04	Year 1
$	42,900	7/1/04 - 6/30/05	Year 2
$	22,550	7/1/05 - 6/30/06	Year 3

Summary FSHD is a neuromuscular disorder that arises when patients are missing a number of tandemly repeated DNA sequences, located near the end of chromosome 4. It is thought that an unidentified disease gene, located somewhere far away from the repeats, malfunctions when the repeats are missing. Based on what we know about how repeats work, researchers hypothesize that looping interactions bring the repeats in physical contact with the FSHD gene, allowing the repeats to influence the gene. They propose to identify the FSHD gene by attaching a chemical to the repeats in live cells that modifies chromosomal sites that it contacts. The FSHD gene is then identified by virtue of its modification that occurs when it touches the repeats/chemical.

Los Angeles - University of California (Cont'd)

Kent Small, M.D.

(RG) Hereditary motor and sensory neuropathy type VI, gene mapping and Charcot-Marie-Tooth disease

$	68,410	7/1/03 - 6/30/04	Year 1
$	71,104	7/1/04 - 6/30/05	Year 2

Summary CMT type 6 is a disease that causes weakness, paralysis and blindness. Investigators are studying a large family with this in order to find the gene abnormality causing this disease.

Melissa Spencer, Ph.D.

(RG) Analysis of the LGMD2A protein calpain 3 and its binding to titin

$	128,482	7/1/02 - 6/30/03	Year 2
$	128,482	7/1/03 - 6/30/04	Year 3

Summary The goal of this investigation is to understand the relationship between calpain3, the protein mutated in LGMD2A and its binding partner, titin.

(RG) Double-blind, placebo-controlled study of albuterol in Duchenne muscular dystrophy (DMD)

$	58,423	1/1/03 - 12/31/03	Year 2
$	50,987	1/1/04 - 12/31/04	Year 3

Summary The goal of this investigation is to determine if albuterol is effective in increasing strength in DMD patients.

Julio Vergara, Ph.D.

(RG) Excitation-contraction coupling in dystrophic skeletal muscle

$	88,230	1/1/03 - 12/31/03	Year 1
$	91,507	1/1/04 - 12/31/04	Year 2
$	95,140	1/1/05 - 12/31/05	Year 3

Summary Using novel techniques, researchers will investigate the role of dystrophin in the preservation of the mechanisms that control the release of calcium in muscle fibers isolated from mice with an without this protein. Specifically, they will focus on the effects that the lack of dystrophin (in the presence or absence of utrophin) has on the electrical properties of the transverse tubular system and on the localized release of calcium from the terminal cisternae of the sarcoplasmic reticulum.

Los Angeles - University of Southern California

Valerie Askanas, M.D., Ph.D.

(RG) Mechanisms upstream to BAPP overexpression in inclusion body myositis (IBM)

$	83,255	1/1/03 - 12/31/03	Year 3

Summary Sporadic and hereditary IBM are severe and highly debilitating progressive muscle diseases. Researchers will utilize their established experimental human muscle tissue-culture models, including cultured hereditary IBM muscle fibers and ABPP-gene transferred into normal human muscle fibers to investigate steps of the pathologic cascade leading to muscle degeneration. The models provide unique opportunities to develop treatment strategies.

W. King Engel, M.D.

(EMG) Restricted funds for ALS research

$	40,250	4/1/02 - 3/31/03	Year 2
$	15,000	4/1/03 - 3/31/04	Year 3

Los Angeles - University of Southern California (Cont'd)

W. King Engel, M.D.

(EMG) Restricted funds for research
$ 28,200 4/1/02 - 3/31/03 Year 1

(EMG) Restricted funds for neuromuscular disease research
$ 250 4/1/03 - 3/31/04 Year 1

Chien-Ping Ko, Ph.D.

(RG) The role of perisynaptic Schwann cells at the neuromuscular junction
$ 62,225 7/1/02 - 6/30/03 Year 3

Summary This proposal examines the role of a supporting cell, called the perisynaptic Schwann cell, in the function, formation, sprouting, and maintenance of the nerve-muscle contact.

Sita Reddy, Ph.D.

(RG) Role of SIX5 loss in myotonic dystrophy (DM) skeletal myopathy
$ 100,000 1/1/03 - 12/31/03 Year 3

Summary DM is an adult onset muscular dystrophy for which there is currently no treatment or cure. Elucidating the mechanisms that are responsible for the development of the DM is an essential first step in the development of a cure. Experiments described in this proposal are aimed at the characterization of animal models that recapitulate defects observed in severely affected DM patients. Thus, these experiments will allow important insights into the molecular mechanisms that result in DM and should allow the development of novel therapies for this serious neuromuscular disorder.

(RG) Role of the muscleblind proteins in myotonic dystrophy (DM)
$ 110,000 1/1/03 - 12/31/03 Year 1
$ 110,000 1/1/04 - 12/31/04 Year 2
$ 110,000 1/1/05 - 12/31/05 Year 3

Summary Myotonic dystrophy 1 (DM1) is the most common adult onset muscular dystrophy in humans. There is currently no treatment or cure for DM1. Understanding the mechanism that causes the disease is an esential first step in the development of a cure. Experiments described in this proposal are aimed at the characterization of the role of the muscleblind family of proteins in DM1. These experiments will allow important insights into the molecular mechanism of DM1 concurrent with the development of therapeutic strategies for this serious neuromuscular disease.

Novato - Buck Institute for Research in Aging

Lisa Ellerby, Ph.D.

(RG) Characterization of cell-death proteases in spinal muscular atrophy (SMA)
$ 100,000 1/1/03 - 12/31/03 Year 3

Summary These studies are directed at understanding the mechanism by which Kennedy's disease is initiated. Understanding the mechanism should help in design of new therapy.

San Diego - San Diego State University

Sanford Bernstein, Ph.D.

(RG) Probing muscle function by genetic suppression of myopathies

$	75,000	1/1/03 - 12/31/03	Year 2

Summary Researchers are analyzing how modified genes can prevent muscle degeneration caused by genetic mutation.

San Francisco - California Pacific Medical Center

Robert Miller, M.D.

(EMG) Restricted funds for support of the Forbes Norris MDA/ALS Center

$	75,000	4/1/03 - 3/31/04	Year 6

(EMG) Restricted funds for support of the MDA Clinic - Zimmerman Fund

$	31,437	4/1/02 - 3/31/03	Year 4
$	9,900	4/1/03 - 3/31/04	Year 5

(RG) Minocycline in amyotrophic lateral sclerosis (ALS)

$	103,968	7/1/02 - 6/30/03	Year 1
$	105,793	7/1/03 - 6/30/04	Year 2
$	54,457	7/1/04 - 6/30/05	Year 3

Summary This clinical trial will determine the effect of minocycline in slowing progression of ALS.

San Francisco - University of California

Marc Diamond, M.D.

(RG) Molecular and genetic modifiers of AR protein toxicity in spinal bulbar muscular atrophy (SBMA)

$	100,000	7/1/02 - 6/30/03	Year 1
$	100,000	7/1/03 - 6/30/04	Year 2
$	100,000	7/1/04 - 6/30/05	Year 3

Summary This project seeks to understand why a specific inherited mutation in the androgen receptor causes a neurodegenerative disease, spinobulbar muscular atrophy.

Charles Ordahl, Ph.D.

(RG) Myogenic progenitor cells: A new muscle stem cell class

$	75,438	7/1/03 - 6/30/04	Year 1
$	80,068	7/1/04 - 6/30/05	Year 2
$	81,793	7/1/05 - 6/30/06	Year 3

Summary Successful myoblast transfer therapy depends upon the ability of implanted myogenic cells to build and organize new muscle tissue from scratch. A newly discovered type of embryonic stem cell, named Myogenic Progenitor Cells, possess this essential characteristic. Researchers have successfully isolated thse cells and analyzed their activities in vivo, both in situ and after transplantation. The research proposed here is directed at growing (expanding) MPCs in vitro and identifying the cellular and molecular properties that confer their tissue building capacities. These properties are expected to yield new information about how therapeutic myoblast transfer might be improved to the point of being practical.

San Francisco - University of California (Cont'd)

Mhairi Towler, Ph.D.

(DG) A role for the second isoform of clathrin heavy chain in skeletal muscle

$	45,000	7/1/03 - 6/30/04	Year 1
$	45,000	7/1/04 - 6/30/05	Year 2
$	45,000	7/1/05 - 6/30/06	Year 3

Summary Investigators will define the role of muscle protein CHC22, in muscle development and function and determine its relationship to muscle disease, thus identifying potential targets for therapeutic intervention.

Sara Venters, Ph.D.

(DG) Muscle progenitor cells: Controlling growth and morphogenesis

$	45,000	1/1/03 - 12/31/03	Year 2
$	45,000	1/1/04 - 12/31/04	Year 3

Summary To utilize an existing in vivo system to develop an in vitro system for culturing muscle progenitor cells, producing cells for transplant that are competent for muscle growth and morphogenesis.

Kai Zhang, Ph.D.

(DG) Mouse model for periodic paralysis in Andersen's syndrome (AS)

$	45,000	7/1/03 - 6/30/04	Year 1
$	45,000	7/1/04 - 6/30/05	Year 2
$	45,000	7/1/05 - 6/30/06	Year 3

Summary AS is a familial disease of periodic paralysis associated with cardiac arrhythmias. The defects of a potassium channel (Kir2.1) have been identified to cause this disease. But, the underlying pathogenesis of periodic paralysis found in the patients of AS is still unknown. This porposal is designed to generate a mouse model for the periodic paralysis of AS, which will enable a detailed in vivo study about the pathogenic mechanism of periodic paralysis at the molecular, cellular and organismic levels. The findings from this proposal should benefit the development of new treatment strategies for periodic paralysis patients.

Santa Cruz - University of California

Brian Ackley, Ph.D.

(DG) A genetic analysis of the role of the ECM in synaptogenesis in C. elegans

$	45,000	7/1/03 - 6/30/04	Year 1

Summary The goal of this proposal is to identify molecules that provide neurons information about their environment. With regard to muscular dystrophies, investigators are asking how neurons tell the difference between environmental signals they need to find the appropriate muscles and then form neuromusuclar junctions. The results of this research are likely to identify novel targets for therapeutics and/or significantly enhance replacement therapies such as gene transfer or cell transplantation.

Stanford - Stanford University

Thomas Rando, M.D., Ph.D.

(EMG) Restricted funds for DMD research

$	11,125	4/1/02 - 3/31/03	Year 2

Stanford - Stanford University (Cont'd)

Thomas Rando, M.D., Ph.D.

(RG) Chimeraplast mediated gene therapy for muscular dystrophies

$ 130,709 1/1/03 - 12/31/03 Year 3

Summary Researchers are studying a novel approach to gene therapy for muscular dystrophies involving "chimeraplasts," molecules which have the potential to repair certain kinds of gene defects.

Eric M. Shooter, Ph.D.

(RG) Neurotrophin therapy for Charcot-Marie-Tooth disease (CMT)

$ 93,443 7/1/02 - 6/30/03 Year 1

$ 88,776 7/1/03 - 6/30/04 Year 2

Summary Evaluate the therapeutic potential of neurotrophins, potent nerve cell growth factors, in treating Charcot-Marie-Tooth disease.

(RG) Peripheral myelin protein 22 (PMP22) in Charcot-Marie-Tooth disease type 1 (CMT1)

$ 75,167 7/1/02 - 6/30/03 Year 1

$ 77,387 7/1/03 - 6/30/04 Year 2

Summary To understand how an alteration of one gene causes the loss of myelin in CMT1A disease and whether one neurotrophin is a candidate to promote remyelination.

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

(RG) A pilot therapeutic trial of hydroxyurea on type 1 spinal muscular atrophy (SMA)

$ 100,000 7/1/03 - 6/30/04 Year 1

$ 100,000 7/1/04 - 6/30/05 Year 2

$ 100,000 7/1/05 - 6/30/06 Year 3

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.

Yanmin Yang, M.D., Ph.D.

(RG) Functional characterization of gigaxonin

$ 101,712 1/1/03 - 12/31/03 Year 1

$ 100,500 1/1/04 - 12/31/04 Year 2

$ 103,668 1/1/05 - 12/31/05 Year 3

Summary A general disorder of cytoskeleton exists in the giant axonal neuropathy (GAN). Recently, a new study reported the gene cloning underlying GAN, called gigaxonin. The goal of this proposed research is to characterize functions of gigaxonin, and to determine how this protein contributes to the structure and function of muscle cells and neurons and also to examine its mutated forms for their abnormal activity or loss of functions.

COLORADO

Aurora - University of Colorado

Luisa Mestroni, M.D.

(RG) Cytoskeletal gene mutations in dilated cardiomyopathy with variable skeletal muscle involvement

$ 74,327 1/1/03 - 12/31/03 Year 3

Summary The type, frequency and phenotypic features of cytoskeletal gene mutations are analyzed in patients with dilated cardiomyopathy and variable skeletal muscle dystrophy.

Boulder - University of Colorado

Dawn Cornelison, Ph.D.

(DG) Signaling in satellite cells of mdx and other dystrophic muscle

$	45,000	7/1/02 - 6/30/03	Year 1
$	45,000	7/1/03 - 6/30/04	Year 2
$	45,000	7/1/04 - 6/30/05	Year 3

Summary Signaling pathways essential for myogenic stem cell (satellite cell) function will be identified and examined both on cultured myofibers and in live-animal regeneration studies for potential means of manipulating satellite cell activity in compromised muscle.

Kevin R. Jones, Ph.D.

(RG) Neurotrophic factor requirements in peripheral nerve

$	78,822	1/1/03 - 12/31/03	Year 2
$	82,344	1/1/04 - 12/31/04	Year 3

Summary Researchers propose to use mouse genetics to determine the functions of two growth factor genes, individually and together, in the maintenance and regeneration of nerves.

Leslie Leinwand, Ph.D.

(RG) Sequence determinants of muscle myosin assembly

$	67,525	7/1/02 - 6/30/03	Year 3

Summary Researchers plan to identify mutations in myosin that prevent its incorporation into muscle and thereby understand part of the process by which muscle is made and repaired in humans with disease.

Bradley Olwin, Ph.D.

(RG) Satellite cell activation and proliferation

$	86,188	1/1/03 - 12/31/03	Year 3

Summary Regeneration of skeletal muscle tissue is dependent on satellite cells. These cells are not active until the surrounding muscle is damaged. Researchers plan to identify factors that are critical to promoting the involvement of satellite cells in muscle regeneration. Researchers then plan to enhance the activity of their factors by using viral gene transfer.

(RG) A molecular switch for satellite cells

$	77,938	7/1/02 - 6/30/03	Year 1
$	76,690	7/1/03 - 6/30/04	Year 2
$	80,091	7/1/04 - 6/30/05	Year 3

Summary Researchers have recently identified a protein kinase that when inhibited maintains satellite cells for long periods of time in a quiescent and undifferentiated state, even in the presence of pro-activation and proliferation signals. Researchers hope that reserving satellite cells would delay loss of muscle function in dystrophic patients. In addition, manipulation of this kinase may allow enhancement of myoblast transfer therapies that have been plagued by losses of the majority of satellite cells following transplantation.

Denver - University of Colorado

William Betz, Ph.D.

(RG) Synaptic vesicle recycling in motor nerve terminals
$ 54,000 7/1/02 - 6/30/03 Year 3

Summary All voluntary movement depends on faithful transmission across the neuromuscular synapse, which requires steady delivery of synaptic vesicles to the presynaptic membrane. The proposed projects will provide new information about the physiological processes that regulate this vesicle traffic.

(RG) Synaptic vesicle recycling in motor nerve terminals
$ 66,000 7/1/03 - 6/30/04 Year 1
$ 66,000 7/1/04 - 6/30/05 Year 2
$ 66,000 7/1/05 - 6/30/06 Year 3

Summary A resting skeletal muscle fiber is like a sleeping giant. To arouse it to contract, a motor nerve terminal - which is about 10,000 times smaller than the muscle fiber it innervates - must secrete large amounts of acetylcholine, faithfully and repeatedly to keep the muscle fiber contracting. A collection of acetylcholine storage vesicles inside the nerve terminals is repeatedly empties and refilled to accomplish this. Investigators study this synaptic vesicle recycling in the belief that a better understanding of fundamental processes will be beneficial in treating neuromuscular diseases.

Nicholas Seeds, Ph.D.

(RG) Growth factor (HGF/SF) action during muscle & motoneuron loss
$ 68,345 1/1/03 - 12/31/03 Year 3

Summary Studies will characterize the growth factor HGF/SF as a potential therapy to retard muscle and motoneuron loss in neuromuscular disease.

Fort Collins - Colorado State University

Katarina Stroffekova-Polakova, Ph.D.

(DG) Possible regulatory role of calmodulin (CaM) in skeletal muscle excitation-contraction coupling
$ 35,000 7/1/02 - 6/30/03 Year 3

Summary The DHPR and RyR1 are two key proteins involved in EC coupling. Mutations in these proteins have been shown to cause the inherited human muscular diseases of hypokalemic periodic paralysis, malignant hyperthermia and central core disease. The proposed experiments will provide new understanding on how those two proteins are regulated and how they interact with each other. This information should be useful for development of new treatment strategies for these diseases.

CONNECTICUT

Farmington - University of Connecticut

William Mohler, Ph.D.

(RG) Molecular and cellular mechanism of cell fusion
$ 65,000 7/1/02 - 6/30/03 Year 3

Summary All damaged or diseased human muscle is repaired by cell fusion. The model organism C. elegans will be used to find genes controlling the cell fusion process.

Storrs - University of Connecticut

David J. Goldhamer, Ph.D.

(RG) Satellite cell development, commitment and renewal

$	80,000	1/1/03 - 12/31/03	Year 2
$	80,000	1/1/04 - 12/31/04	Year 3

Summary The proposed studies investigate the developmental origin, differentiation capacity and self-renewal properties of muscle stem (satellite) cells.

DISTRICT OF COLUMBIA

Washington - Children's National Medical Center

Marina Bakay, Ph.D.

(DG) Downstream consequences of biochemical defects in muscular dystrophies

$	45,000	1/1/03 - 12/31/03	Year 1
$	45,000	1/1/04 - 12/31/04	Year 2
$	45,000	1/1/05 - 12/31/05	Year 3

Summary The aim of this proposal is to understand the etiology of muscle dystrophy in general, to define both molecular signatures of each known type of dystrophy and biochemical pathways specific for each type, and possibly to develop microarray-based molecular diagnosis of problematic dystrophies, such as calpainopathy.

Diana Escolar, M.D.

(RG) High-dose prednisone in Duchenne muscular dystrophy (DMD)

$	115,220	1/1/03 - 12/31/03	Year 1
$	115,220	1/1/04 - 12/31/04	Year 2
$	115,220	1/1/05 - 12/31/05	Year 3

Summary This study seeks to determine whether a high-dose wekly course of prednisone therapy is at least as effective as daily dose therapy for people with DMD, with fewer side effects.

Eric Hoffman, Ph.D.

(EMG) Restricted funds for support of Duchenne muscular dystrophy research

$	129,100	4/1/02 - 3/31/03	Year 5
$	120,000	4/1/03 - 3/31/04	Year 6

(EMG) Restricted funds for limb-girdle research

$	117,500	4/1/02	3/31/03	Year 1
$	140,566	4/1/03 - 3/31/04	Year 2	

(RG) Delineation of temporal gene clusters in muscle regeneration

$	79,131	7/1/02 - 6/30/03	Year 2
$	82,425	7/1/03 - 6/30/04	Year 3

Summary The proposed research uses new "GeneChips" containing many 10's of thousands of genes to define the molecular events during muscle degeneration and regeneration.

Washington - George Washington University

Margaret Sutherland, Ph.D.
(RG) Neuroprotection through increased glutamate transport in amyotrophic lateral sclerosis (ALS)
$ 77,918 7/1/02 - 6/30/03 Year 3
Summary This project will test the hypothesis that increased glutamate uptake can slow the progression and severity of ALS using genetically engineered mouse models of ALS and glutamate transporter overexpression.

Washington - Georgetown University

Lee-Jun Wong, Ph.D.
(RG) Improved diagnosis of mitochondrial disorders
$ 56,349 1/1/03 - 12/31/03 Year 3
Summary A novel rating system will be designed to evaluate the probability of having identifiable mtDNA mutations in patients suspected of mitochondrial disorders. The application of this discriminating model will improve the diagnosis of mitochondrial disease.

FLORIDA

Gainesville - University of Florida

Barry Byrne, M.D., Ph.D.
(PPG) Preclinical study of gene replacement in muscular dystrophy
$ 810,382 1/1/03 - 12/31/03 Year 2
$ 282,105 1/1/04 - 12/31/04 Year 3
Summary Recombinant adeno-associated virus vectors will be produced and tested for purity and efficacy. These vectors will then be used to treat dystrophic animals as a prelude to clinical trials.

Lucia Notterpek, Ph.D.
(RG) Targets for therapy in the cellular pathogenesis of Charcot-Marie-Tooth (CMT) neuropathies
$ 59,820 7/1/02 - 12/31/03 Year 3
Summary Experiments will be performed to understand the cellular changes underlying the progressive pathogenesis of peripheral neuropathies and to identify potential targets for therapy.

Carolyn Spencer, M.D.
TRA Pompe's trial - AGLU01702 and AGLU01602
$ 50,000 1/1/03 - 12/31/03 Year 1
Summary Investigational enzyme replacement therapy administered to patients with infantile-onset Pompe disease.

Maurice Swanson, Ph.D.
(RG) Mouse models for myotonic dystrophy (DM)
$ 82,216 1/1/03 - 12/31/03 Year 3
Summary Although DM1 is he most common form of adult-onset muscular dystrophy, the cellular mechanisms responsible for this disease have not yet been elucidated. Researchers recently proposed a model in which the DM1 mutation inhibits the function of proteins crucial for the development of muscular and eye tissue. The proposed research is designed to test this hypothesis.

Gainesville - University of Florida (Cont'd)

Maurice Swanson, Ph.D.

(RG) Gene therapy for myotonic dystrophy (DM)

$ 84,849 1/1/03 - 12/31/03 Year 2
$ 87,361 1/1/04 - 12/31/04 Year 3

Summary The research objective is to determine whether a novel gene therapy strategy will restore normal muscle function in a transgenic model for DM.

Jacksonville - Mayo Clinic Jacksonville

Terrone Rosenberry, Ph.D.

(RG) Interactions in the active site of acetylcholinesterase

$ 54,000 1/1/03 - 12/31/03 Year 3

Summary These studies of the essential enzyme acetylcholinesterase will focus on its catalytic mechanism and on ways in which drug binding to its peripheral site alters catalytic activity.

Miami - University of Miami

Ellen Barrett, Ph.D.

(RG) Motor terminal function in a mouse model of familial amyotrophic lateral sclerosis (FALS)

$ 66,173 7/1/03 - 6/30/04 Year 1
$ 67,680 7/1/04 - 6/30/05 Year 2
$ 69,232 7/1/05 - 6/30/06 Year 3

Summary Investigators will study the function of motor nerve terminals in transgenic mice bred to express a mutant form of human superoxide dismutase (SOD1G93A), which causes some cases of FALS. They will stimulate these terminals and measure transmitter release and the increase in calcium concentration within the terminals and their mitochondria. Motor terminals and mitochondria show early damage in these mice and our functional studies will uncover mechanisms underlying these early changes. Motor neurons in SOD1G93A mice are especially susceptible to a death mechanism involving nitric oxide, and we will also investigate mechanisms underlying the detrimental effects of nitric oxide on motor terminals.

Antonio Barrientos, Ph.D.

(RG) Cytochrome c oxidase assembly in health and disease

$ 63,720 4/1/03 - 3/31/04 Year 1

Summary This project will investigate the biogenesis and regulation controlling cytochrome c oxidase assembly and how these processes bear on human neuromuscular disorders.

Miami - University of Miami (Cont'd)

Lisa L. Baumbach, Ph.D.

(RG) Final steps in discovery of the X-linked SMA gene

$ 100,465 7/1/03 - 6/30/04 Year 1
$ 101,742 7/1/04 - 6/30/05 Year 2

Summary The combined results of these studies will allow for the first understanding and eventual treatment of this devastating illness, as well as potentially provide insights and therapeutic rationales for other forms of human lower motor neuron disease. It is the ultimate goal of the investigative team to eentually apply the knowledge gained from these studies to the prenatal and antenatal detection of such cases, for the purposes of disease prevention and early intervention not only for XL-SMA families but also for the thousands of children who are born annually with congenital hypotonia of unknown etiology.

Sandy Black, Executive Director

(SG) Miami Nature Biotechnology Winter Symposium - 50 years on: From the double helix to molecular medicine

$ 8,000 2/1/03 - 2/28/03 Year 1

Francisca Diaz, Ph.D.

(DG) A mouse model of cytochrome oxidase deficiency

$ 45,000 7/1/02 - 6/30/03 Year 1
$ 45,000 7/1/03 - 6/30/04 Year 2
$ 45,000 7/1/04 - 6/30/05 Year 3

Summary Specific mitochondrial defects have been associated with different neuromuscular diseases (e.g. Leigh syndrome). In this study, researchers propose to create a mouse model for cytochrome oxidase deficiency in muscle to provide answers regarding the association of different pathologies with specific respiratory chain defects. In addition, this animal will facilitate the study of potentially beneficial drugs or the development of new therapies for mitochondrial disorders.

Aldrin Gomes, Ph.D.

(DG) Troponin T truncation and nemaline myopathy

$ 35,000 7/1/02 - 6/30/03 Year 1
$ 35,000 7/1/03 - 6/30/04 Year 2

Summary A mutation in slow skeletal troponin T causes a severe form of nemaline myopathy in Amish people. How this mutant protein or any of the other mutations found in the other sarcomeric proteins causes nemaline myopathy is unclear. The purpose of this investigation is to establish a mouse model system to facilitate identification of physiological factors that promotes nemaline myopathy caused by theTroponin T truncation.

Miami - University of Miami (Cont'd)

Alison Grossman, Ph.D.

(DG) Impact of psychosocial factors on ALS onset and disease progression

$	45,000	7/1/03 - 6/30/04	Year 1
$	45,000	7/1/04 - 6/30/05	Year 2
$	45,000	7/1/05 - 6/30/06	Year 3

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

Karl Magleby, Ph.D.

(RG) Modulation of BK channels by beta subunits

$	67,716	7/1/03 - 6/30/04	Year 1
$	71,053	7/1/04 - 6/30/05	Year 2
$	77,337	7/1/05 - 6/30/06	Year 3

Summary The mechanism by which ion channels (small proteins) are modulated to control the activity of nerve and muscle cells will be examined.

Akila Mayeda, Ph.D.

(RG) Mechanisms of dystrophin pre-mRNA splicing

$	75,000	7/1/02 - 6/30/03	Year 2
$	75,000	7/1/03 - 6/30/04	Year 3

Summary The novel mechanism, recursive splicing, in the human dystrophin gene will be demonstrated. Some cases of Duchenne muscular dystrophy may be caused by deficiency of the recursive splicing.

Carlos Moraes, Ph.D.

(RG) Protecting CNS mitochondria in amyotrophic lateral sclerosis (ALS)

$	74,697	7/1/02 - 6/30/03	Year 3

Summary Mitochondria, the powerhouse of the cells has shown to have structural abnormalities in an animal model of ALS. Researchers plan to study mitochondrial function in these animals and create a new model that will facilitate the analysis of potentially beneficial drugs.

(RG) Mitochondrial dysfunction in amyotrophic lateral sclerosis (ALS)

$	85,686	7/1/03 - 6/30/04	Year 1
$	97,824	7/1/04 - 6/30/05	Year 2
$	98,906	7/1/05 - 6/30/06	Year 3

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

Miami - University of Miami (Cont'd)

Richard Rotundo, Ph.D.

(RG) Assembly of acetylcholinesterase and the synaptic basal lamina

$	52,789	1/1/03 - 12/31/03	Year 1
$	54,340	1/1/04 - 12/31/04	Year 2
$	55,939	1/1/05 - 12/31/05	Year 3

Summary Understanding the molecular mechanisms of acetylcholinesterase (AChE) attachment to the neuromuscular junction will help us design artificial ways of replacing defective molecules when they have become inactivated, or inserting new ones into vacant spaces at sites of nerve-muscle contact, as in cases of patients with congenital myasthenia with endplate AChE deficiency (EPAD).

Tallahassee - Florida State University

Peter Fajer, Ph.D.

(RG) Structural mechanism of muscle activation

$	75,300	1/1/03 - 12/31/03	Year 3

Summary To determine the structure of the troponin complex of the thin filament using site-specific labeling and to test the current models for muscle activation and thereby provide an insight into many muscle diseases.

ILLINOIS

Chicago - Northwestern University

Robert Goldman, Ph.D.

(RG) Functional aspects of nuclear lamins in muscular dystrophy

$	100,264	7/1/03 - 6/30/04	Year 1
$	113,744	7/1/04 - 6/30/05	Year 2
$	116,557	7/1/05 - 6/30/06	Year 3

Summary This research is aimed at determining the functional alterations in lamins that are related to EDMD and LGMD mutations. The biochemical and structural information obtained from these studies will provide important insights into the molecular basis of these diseases. The results will be useful in the development of therapies for these forms of muscular dystrophy.

Teepu Siddique, M.D.

(RG) High throughput screening

$	55,000	7/1/03 - 6/30/04	Year 1
$	54,865	7/1/04 - 6/30/05	Year 2

Summary Screening of FDA approved compounds for therapeutic application to those familial cases of ALS linked to SOD1 mutations will be performed. Those indicating positive effects will be tested in the mouse models preparatory to human trials.

Chicago - Northwestern University (Cont'd)

Jianhua Yan, M.D.

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

$	45,000	7/1/03 - 6/30/04	Year 1
$	45,000	7/1/04 - 6/30/05	Year 2
$	45,000	7/1/05 - 6/30/06	Year 3

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

Chicago - University of Chicago

James R. Brorson, M.D.

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

$	79,355	7/1/03 - 6/30/04	Year 1
$	81,736	7/1/04 - 6/30/05	Year 2
$	84,187	7/1/05 - 6/30/06	Year 3

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

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

(RG) Myoferlin in muscular dystrophy

$	69,779	7/1/02 - 6/30/03	Year 3

Summary Dysferlin causes limb girdle muscular dystrophy and Miyoshi Myopathy. Researchers discovered a new protein, myoferlin, that is like dysferlin. Researchers will study if myoferlin can substitute for dysferlin.

(RG) Stem cell transplantation in limb-girdle muscular dystrophy

$	64,793	7/1/03 - 6/30/04	Year 1
$	86,372	7/1/04 - 6/30/05	Year 2
$	88,007	7/1/05 - 6/30/06	Year 3

Summary Investigators will test whether bone marrow stem cells can grow into muscle cells by performing bone marrow transplant experiments in mouse models of limb-girdle muscular dystrophy.

Evanston - Oligotrail

Peter C. Dau, M.D.

(EMG) Restricted funds for research

$	614.45	4/1/02 - 3/31/03	Year 1

Urbana - University of Illinois

James Campanelli, Ph.D.
(RG) Molecular mechanisms of muscle induced nerve differentiation
$ 65,777 1/1/03 - 12/31/03 Year 3
Summary The neuromuscular junction is highly specialized to perform efficient synaptic transmission. A technique will be used to identify molecules which induce the formation of these synaptic specializations and allow us to identify the proteins involved in neuromuscular junction formation and stability.

Stephen Kaufman, Ph.D.
(RG) Integrin alleviation of muscular dystrophy: DMD, LGMD and SPMD
$ 125,000 1/1/03 - 12/31/03 Year 3
Summary Increasing expression of the a7b1 integrin protects against the development of DMD in mice. Researchers propose to optimize conditions that give the best protection against the development of muscle disease and determine how human a7 integrin levels may be regulated. Researchers will also determine whether the production of more integrin can protect against the development of limb-girdle muscular dystrophy in mice.

Derek Milner, Ph.D.
(DG) Alpha-7 beta-1 integrin mediated alleviation of muscular dystrophy
$ 45,000 7/1/03 - 6/30/04 Year 1
$ 45,000 7/1/04 - 6/30/05 Year 2
$ 45,000 7/1/05 - 6/30/06 Year 3
Summary Investigators propose to determine if enhanced expression of the alpha-7 beta-1 integrin can ameliorate the development of pathology seen in mouse mutant models for several forms of muscular dystrophy.

INDIANA

Indianapolis - Indiana University

William J. Groh, M.D.
(RG) Predictors of sudden cardiac death in myotonic dystrophy
$ 45,306 7/1/03 - 6/30/04 Year 1
$ 46,285 7/1/04 - 6/30/05 Year 2
Summary Heath rhythm abnormalities are common in myotonic dystrophy. The goal of this study is to determine who is at highest risk thus opening the door for treatment.

Muncie - Ball State University

Derron Bishop, Ph.D.
(RG) Axon loss in a mouse model of amytrophic lateral sclerosis (ALS)
$ 97,367 7/1/03 - 6/30/04 Year 1
$ 82,289 7/1/04 - 6/30/05 Year 2
$ 83,867 7/1/05 - 6/30/06 Year 3
Summary This project will resolve the cellular defects within degenerating motoneurons in a mouse model of ALS using three-dimensional confocal and electron microscopy.

IOWA

Ames - Iowa State University

Richard Robson, Ph.D.
(RG) Define/characterize specific site interactions between synemin and dystrophin
$ 64,491 1/1/03 - 12/31/03 Year 1
$ 58,752 1/1/04 - 12/31/04 Year 2
Summary Researchers will determine how the unique protein synemin, which together with the protein desmin forms long intermediate filaments, helps link the contractile elements in muscle cells to the dystrophin and utrophin proteins present at the cell membrane. This knowledge will be useful information for those scientists designing gene therapy approaches for the Duchenne and Becker muscular dystrophies.

Iowa City - University of Iowa

Kevin P. Campbell, Ph.D.
(RG) Development of therapeutic strategies for dysferlin-deficient muscular dystrophy
$ 93,218 9/1/02 - 11/30/03 Year 3
Summary This project is a pre-clinical investigation aimed at seeking treatment for autosomal recessive muscular dystrophies. Dysferlin was recently discovered and has been shown to be defective in individuals with proximal LGMD. The proposed project is aimed at the development of therapeutic strategies for dysferlin-related muscular dystrophies.

Chien-Chang Chen, Ph.D.
(DG) Role of T-type calcium channels in the development of skeletal muscle and muscle regeneration
$ 35,000 1/1/03 - 12/31/03 Year 3
Summary The goal of this project is to understand the role alpha1H T-type calcium channels in the normal muscle development and myogenic stem cell repair of dystrophy muscle.

Shawn Flanagan, Ph.D.
(DG) Cytoprotective role of copper chaperone in mutant-SOD1 model of amyotrophic lateral sclerosis (ALS)
$ 44,976 1/1/03 - 12/31/03 Year 1
Summary Using a human cell culture model, this proposal seeks to determine the mechansisms of how an ALS-associated mutation in the antioxidant enzyme CuZnSOD kills neuronal cells. Utilizing this model, researchers have found that increasing the concentration of the protein CCS, the protein involved in delivering the required copper to the enzyme CuZnSOD, protects cells against mutant CuZnSOD toxicity. The objective of this research proposal is to provide an enhanced understanding of the role of copper in ALS, and to examine whether alterations in copper chemistry play a role of the killing of neuronal cells in ALS.

Alice B. Fulton, Ph.D.
(RG) Muscle phenotypes induced by RNA and potential tissue rescue
$ 67,215 1/1/03 - 12/31/03 Year 2
Summary An RNA turns skin into muscle. Researchers will see how good and which muscle it is, and if it fuses with normal muscle. It may provide ample muscle cells for patients.

Iowa City - University of Iowa (Cont'd)

Hamime Kusano, Ph.D.

(DG) Functional analysis of dystroglycan through targeted truncation in mice

$	45,000	7/1/03 - 6/30/04	Year 1
$	45,000	7/1/04 - 6/30/05	Year 2
$	45,000	7/1/05 - 6/30/06	Year 3

Summary The goal of this project is to understand how dystrophin attaches to the muscle cell membrane and how beta-dystroglycan functions in muscle cell signaling pathways. Elucidation of beta-dystroglycan signaling pathways related to pathogenetic processes will lead to a therapeutic approach to the treatment of muscular dystrophies via pharmacological modulation of these pathways. Furthermore, information obtained during this project will help in the design of dystrophin gene therapy and understanding the pathogenesis of Duchenne muscular dystrophy and dystroglycan related congenital muscular dystrophies.

Steven Moore, M.D., Ph.D.

(RG) Astrocyte dystroglycan complexes in congenital muscular dystrophy (CMD)

$	76,853	1/1/03 - 12/31/03	Year 3

Summary Through genetic engineering techniques in mice, researchers will study a model of brain abnormalities that accompany CMD's such as Fukuyama muscular dystrophy.

Lori Wallrath, Ph.D.

(RG) Drosophila as a model for Emery-Dreifuss muscular dystrophy

$	76,428	7/1/03 - 6/30/04	Year 1
$	79,398	7/1/04 - 6/30/05	Year 2
$	82,484	7/1/05 - 6/30/06	Year 3

Summary Emery-Dreifuss muscular dystrophy is a rare muscular dystrophy characterized by muscle wasting and heart problems. Mutation of lamins, proteins that provide structural support in the nucleus of a cell, is one known cause of EDMD. It is hypothesized that cells undergoing mechanical stress, such as muscle cells, are sensitive to mutations in lamins. This proposal describes experiments to develop the fruit fly as a model system to test this "mechanical stress hypothesis." The fruit fly is well characterized model system in which genetics and locomotion assays can easily be performed. This research will she dlight on the intracellular defects associated with EDMD and lead to new strategies for therapy.

Robert Weiss, M.D.

(RG) Stress-induced cardiac dysfunction in dystrophinopathy

$	80,000	1/1/03 - 12/31/03	Year 1
$	80,000	1/1/04 - 12/31/04	Year 2
$	80,000	1/1/05 - 12/31/05	Year 3

Summary The goals of this project are to discover mechanisms by which muscular dystrophy carriers develop heart disease, and to improve diagnosis and treatment thereof.

KENTUCKY

Lexington - University of Kentucky

Stephen Testa, Ph.D.

(RG) The development and assessment of a therapeutic strategy for myotonic dystrophy (DM)

$	64,102	7/1/02 - 6/30/03	Year 1
$	59,746	7/1/03 - 6/30/04	Year 2
$	62,192	7/1/04 - 6/30/05	Year 3

Summary The development and assessment of a novel therapeutic strategy for eliminating the genetic mutation that leads to DM.

Louisville - University of Louisville

Rugao Liu, Ph.D.

(RG) Protein transduction therapy of mutant SOD1-mediated motor neuron degeneration

$	56,959	1/1/03 - 12/31/03	Year 2
$	58,298	1/1/04 - 12/31/04	Year 3

Summary The goal of the research project is to develop a protein transduction therapy to prevent motor neuron death in ALS disease.

LOUISIANA

New Orleans - Louisiana State University

Edward Grabczyk, Ph.D.

(EMG) Restricted funds for FA research

$	27,500	4/1/02 - 3/31/03	Year 1

Judith M. Venuti, Ph.D.

(RG) TCF in myogenic determination and differentiation

$	60,368	1/1/03 - 12/31/03	Year 2
$	62,740	1/1/04 - 12/31/04	Year 3

Summary Researchers will study how muscle precursors respond to signals from other tissues known to influence their potential to become muscle. This will enable the design of therapies that convert stem cells into muscle.

New Orleans - Tulane University

Fan Yang, M.D., M.S.

(DG) DNA methylation and chromatin analysis to study the mechanism of facioscapulohumeral dystrophy (FSHD)

$	45,000	7/1/03 - 6/30/04	Year 1
$	45,000	7/1/04 - 6/30/05	Year 2

Summary Investigators will test a prediction of the most popular hypothesis for how genes become abnormally expressed in FSHD. Insights from this study may lead to effective therapy which is not available now.

MAINE

Bar Harbor - Jackson Laboratory

Leonard Shultz, Ph.D.

(RG) SCID mouse models for stem cell therapy of muscular dystrophy

$	60,000	1/1/03 - 12/31/03	Year 1
$	60,000	1/1/04 - 12/31/04	Year 2
$	60,000	1/1/05 - 12/31/05	Year 3

Summary It is critical that small animal models of muscular dystrophy be developed to test the ability of hematopoietic stem cells (HSC) to generate normal muscle cells. These models serve as a bridge between animal experimentation and clinical trials of stem cell therapy. Researchers will develop mouse models with Duchenne or severe tibial muscular dystrophy and assess the therapeutic effectiveness of human and mouse HSC.

MARYLAND

Baltimore - Johns Hopkins University

Daniel B. Drachman, M.D.

(EMG) Restricted funds for specific immunotherapy

$	11,616.58	4/1/02 - 3/31/03	Year 4
$	5,437.50	4/1/03 - 3/31/04	Year 5

(RG) Specific therapy of myasthenia gravis (MG) by gene transfer

$	72,000	7/1/02 - 6/30/03	Year 3

Summary This proposal describes a new gene transfer strategy to treat MG by "targeting" and killing only those cells specifically involved in the disease-producing autoimmune process. The genes will induce cells to act as "guided missiles" to target and destroy key autoimmune cells.

(PPG) Clinical trial of Celebrex in amyotrophic lateral sclerosis (ALS)

$	190,000	7/1/02 - 6/30/03	Year 2
$	52,118	7/1/03 - 6/30/04	Year 3

Summary The specific aims of the proposed study are to determine: (1) whether treatment with Celebrex slows the progression of weakness in patients with ALS; and (2) whether treatment with a dose of 800 mg/day is safe and well tolerated in patients with ALS.

(RG) Specific immunotherapy of myasthenia gravis by gene transfer

$	126,277	7/1/03 - 6/30/04	Year 1
$	130,032	7/1/04 - 6/30/05	Year 2
$	133,900	7/1/05 - 6/30/06	Year 3

Summary This proposal is to continue work on a powerful gene transfer strategy to treat MG. Researchers have made extensive progress indicating that their method will lead to practical beneficial therapy for MG, and are now improving its efficiency in a mouse model of MG. This strategy will yield information that is scientifically important and will be applicable to other autoimmune neuromusuclar diseases in addition to MG.

Baltimore - Johns Hopkins University (Cont'd)

J. Marie Hardwick, Ph.D.

(RG) Role of SMN in neuron survival

$	50,000	7/1/02 - 6/30/03	Year 2
$	50,000	7/1/03 - 6/30/04	Year 3

Summary Spinal muscular atrophy (SMA) is caused by mutations in the SMN1 gene leading to the loss of spinal cord motor neurons. However, the molecular mechanisms by which mutations in the SMN protein lead to dysfunction and premature death of this neuron subset are not known. Researchers have shown that SMN regulates programmed cell death of neurons and have a unique model in which to study these newly assigned functions of SMN. Researchers will now explore the molecular mechanisms by which SMN modulates the neuronal death pathway.

Vassilis Koliatsos, M.D.

(RG) Neural stem cells as experimental therapies for motor neuron disease

$	155,634	1/1/03 - 12/31/03	Year 1
$	162,456	1/1/04 - 12/31/04	Year 2
$	167,071	1/1/05 - 12/31/05	Year 3

Summary Researchers will establish the preclinical requirements for the consideration of neural stem cells as experimental therapies to replace dead motor neurons in motor neuron disease.

Nicholas Maragakis, Ph.D.

(RG) Stem cell transplantation in models of amyotrophic lateral sclerosis (ALS)

$	75,000	1/1/03 - 12/31/03	Year 3

Summary Stem cells give rise to mature cells, including the brain and spinal cord. To study the potential for use of these cells in ALS, researchers have developed a spinal cord model that survives in a culture dish. In addition, using a mouse model of ALS, researchers propose to transplant neural stem cells into the spinal cord. The combination of these studies will serve as preliminary studies to human trials in ALS.

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

(EMG) Restricted funds for ALS research

$	998,606	4/1/02 - 3/31/03	Year 4

(RG) Clinical trial of creatine in amyotrophic lateral sclerosis (ALS)

$	19,893	9/1/2000 - 2/28/03	Year 2

Summary A multicenter clinical trial of the nutritional supplement creatine to determine benefit in ALS will be conducted.

(RG) Excitatory amino acid transporters: Development of a therapy

$	45,000	7/1/02 - 6/30/03	Year 1
$	45,000	7/1/03 - 6/30/04	Year 2
$	45,000	7/1/04 - 6/30/05	Year 3

Summary Excess glutamate is one pathway for motor neuron death in amyotrophic lateral sclerosis (ALS). In this grant, researchers will explore a new potential therapy for ALS – increasing the brain synthesis of a protein that could potentially protect against glutamate toxicity - glutamate transporters.

Baltimore - Johns Hopkins University (Cont'd)

Shanthini Sockanathan, Ph.D.

(RG) The specification of spinal motor neurons

$	80,000	7/1/02 - 6/30/03	Year 1
$	80,000	7/1/03 - 6/30/04	Year 2
$	80,000	7/1/04 - 6/30/05	Year 3

Summary Researchers aim to define when and how a signaling molecule, retinoic acid, acts to generate different types of spinal motor neurons. This may help to understand the basis of motor neuron diseases.

Kathryn Wagner, M.D., Ph.D.

(DG) Effect of myostatin on satellite cells and muscle regeneration

$	45,000	7/1/02 - 6/30/03	Year 1
$	45,000	7/1/03 - 6/30/04	Year 2
$	45,000	7/1/04 - 6/30/05	Year 3

Summary Researchers hypothesize that blocking myostatin signaling will disinhibit satellite cells and enhance regeneration. Increased regenerative capacity and muscle bulk will not cure underlying genetic or immune-mediated deficits, but may improve clinical outcomes in the muscular dystrophies and myopathies.

Katherine Wilson, Ph.D.

(RG) Emery-Dreifuss muscular dystrophy (EDMD): Test gene expression hypothesis using lamin A null mice

$	70,000	7/1/02 - 6/30/03	Year 3

Summary Researchers will use lamin A/C knockout mice to test the hypothesis that EDMD is caused by changes in gene expression in muscle cells.

Baltimore - University of Maryland

Robert Bloch, Ph.D.

(RG) Intermediate filaments organizing the sarcolemma

$	62,658	1/1/03 - 12/31/03	Year 3

Summary In healthy muscle, the cell membrane is stabilized by a network containing dystrophin and by filaments linking the dystrophin network to nearby contractile structures. In dystrophic muscle, the network and the filaments are disrupted, and the membrane becomes more fragile. Researchers will learn how these filaments stabilize the membrane of healthy muscle, and how they are altered in muscular dystrophy.

Aikaterini Kontrogianni-Konstantopoulos, Ph.D.

(DG) Proteins organizing the sarcomere and the SR of skeletal muscle

$	45,000	7/1/03 - 6/30/04	Year 1
$	45,000	7/1/04 - 6/30/05	Year 2
$	45,000	7/1/05 - 6/30/06	Year 3

Summary This proposal aims towards the functional characterization of the factors that govern the coordinated assembly of the SR with nearby sarcomeres and specify the diameter of the myofibrils.

Martin Schneider, Ph.D.

(SG) Gordon Research Conference on Muscle 03: Excitation-contraction coupling

$	8,000	5/1/03 - 9/1/03	Year 1

Boston - Beth Israel Deaconess Medical Center

Changiz Geula, Ph.D.

(RG) Calcium binding proteins and motor neuron disease

$ 99,918 4/1/03 - 3/31/04 Year 1

Summary The pathology of amyotrophic lateral sclerosis (ALS) has been shown to increase intracellular calcium. High levels of intracellular calcium are lethal to neurons. Cells cope with high levels of calcium with the help of calcium binding proteins (CBP), which regulate intracellular calcium levels. Investigators will test the hypothesis that CBP-positive motor neurons are preserved in ALS, that deletion of CBPs exacerbates motor neuron loss and that overexpression of CBP is protective to motor neurons.

Richard P. Junghans, M.D., Ph.D.

(RG) Influence of DM disease locus on a distant gene in myotonic dystrophy: cis or trans?

$ 93,682 7/1/02 - 6/30/03 Year 2

$ 84,754 7/1/03 - 6/30/04 Year 3

Summary Myotonic dystrophy (DM) is a complex disease with complex, diverse features that is not fully understood. The site on the chromosome of the DM abnormality is far from another gene (FCGRT) on the same chromosome that is suppressed in DM patients. This research aims to learn how the DM genetic abnormality causes changes in other genes at a great distance. This may help to understand the cause of the disease's different features and may lead to new treatments to prevent its effects.

Boston - Brigham & Women's Hospital

Steven Greenberg, M.D.

(RG) Gene expression in inflammatory myopathies

$ 53,120 4/1/03 - 3/31/04 Year 1

Summary Researchers plan to approach current uncertainties in the classification and causes of the inflammatory myopatheis throught the study of large-scale patterns of gene expression in muscle tissue from affected individuals. This GeneChip technology has the potential to serve as a fundamentally new approach, analogous to the microscope, to see a comprehensive, dynamic molecular picture of the living cell and provides the opportunity to define characteristic disease "signatures" and potential therapeutic targets rapidly and comprehensively.

Yaming Wang, M.D.

(RG) HSV/AAV vectors for autologous myoblast gene therapy of Duchenne muscular dystrophy (DMD)

$ 81,000 1/1/03 - 12/31/03 Year 1

$ 81,000 1/1/04 - 12/31/04 Year 2

Summary Researchers will investigate the possibility to improve MT by converting myoblasts into stem cell-like cells with overexpression of msx1 and the feasibility of AMT using HSV/AAV hybrid vector to transducing dystrophic myoblasts with full-length dystrophin and excisable msx1 genes.

Boston - Children's Hospital

Alan H. Beggs, Ph.D.

(RG) Molecular genetics of congenital myopathies

$	94,194	7/1/02 - 6/30/03	Year 1
$	96,982	7/1/03 - 6/30/04	Year 2
$	99,852	7/1/04 - 6/30/05	Year 3

Summary Researchers propose to continue their work to identify the genetic basis, and understand the pathophysiology of nemaline myopathy. They are building a resource of clinical data, DNA and skeletal muscle specimens from patients with nemaline myopathy and other congenital myopathies. They are using this to identify genes responsible for these disorders and to understand how these mutations lead to weakness by studying large-scale patterns of gene expression.

Emanuela Gussoni, Ph.D.

(RG) Myogenic potential and systemic delivery of human muscle SP cells

$	93,637	7/1/03 - 6/30/04	Year 1
$	100,450	7/1/04 - 6/30/05	Year 2
$	101,928	7/1/05 - 6/30/06	Year 3

Summary The major goal of this proposal is to identify a fraction of stem cells within human muscle able to efficiently target dystrophic skeletal muscle upon systemic injection into the circulation. Identification of such cells will be a first important step in the optimization of muscle stem cell-mediated therapy for Duchenne muscular dystrophy.

(NIDA) Isolation and characterization of human muscle stem cells

$	94,286	7/1/02 - 6/30/03	Year 3

Summary Researchers will identify and characterize immature (stem) cells from human skeletal muscle. They will evaluate the potential of these stem cells as a therapy for muscular dystrophy.

Jeffrey Guyon, Ph.D.

(DG) Isolation of zebrafish with mutations causing muscular dystrophy

$	45,000	7/1/03 - 6/30/04	Year 1
$	45,000	7/1/04 - 6/30/05	Year 2
$	45,000	7/1/05 - 6/30/06	Year 3

Summary Zebrafish are small vertebrates with similar muscle structure and protein composition as mammals suggesting that these animals may be good organisms for modeling human muscle disease. In addition, the molecular similarities between zebrafish and mammals suggest that findings made using zebrafish will likely be applicable to humans. We now propose to use the zebrafish to genetically isolate mutations in genes causing muscular dystrophy. As this proposal provides for the first large scale genetic analysis selecting for muscular dystrophy in vertebrates, this approach is likely to isolate mutations in novel genes which will broaden our understanding of the disease.

Louis Kunkel, Ph.D.

(EMG) Restricted for research at the Children's Hospital of Boston

$	50,358	4/1/02 - 3/31/03	Year 2

Orah Platt, M.D.

(SG) WAVE-based mutation analysis for MD

$	200,000	3/1/02 - 2/28/03	Year 1

Boston - Children's Hospital (Cont'd)

William Tse, M.D., Ph.D.

(RG) Myogenic stem cell transplantation in muscular dystrophy

$ 83,160 4/1/03 - 3/31/04 Year 1

Summary Recent research suggests that muscle and marrow stem cell transplantation may benefit patients with muscular dystrophy, but the level of donor cell contribution in muscle is currently very low. Researchers hypothesize that this level can be improved with the use of stem cells that have been recruited into the circulation and that are competent in finding their way to muscles. They propose to analyze in a mouse model the ability of these stem cells to form healthy muscle after transplantation and to identify growth signals present in regenerating muscles that stimulate their development.

Giles Watts, Ph.D.

(DG) Molecular basis of h-IBM, Paget disease of bone and dementia

$ 45,000 1/1/03 - 12/31/03 Year 1

$ 45,000 1/1/04 - 12/31/04 Year 2

$ 45,000 1/1/05 - 12/31/05 Year 3

Summary This is a newly described and clinically distinct lethal disorder, where affected individuals die from progressive muscle weakness and respiratory and cardiac failure in their forties to sixties. Its association with Paget disease and frontotemporal dementia, makes it particularly interesting as it suggests that there is a common gene involved in these seemingly unrelated disorders. Having located its chromosomal location, they want to identify this gene and characterize its structure and function. This will also facilitate the study of the pathways within which the gene is involved, leading to the complex physical manifestation of this disorder.

Yumin Zhang, M.D., Ph.D.

(DG) Nitric oxide neurotoxicity modulated by FALS mutant SOD1 genes

$ 35,000 7/1/02 - 6/30/03 Year 3

Summary Point mutations in Cu, Zn- superoxide dismutase (SOD1) confer a striking neuropathology in one form of familiar amyotrophic lateral sclerosis (FALS). Researchers have observed increased vulnerability to nitric oxide induced injury with expression of mutant SOD1 genes. The possible mechanisms of nitric oxide toxicity enhanced by mutant SOD1 expression will be studied.

Boston - Harvard Medical School

Alfred Goldberg, Ph.D.

(RG) Protein breakdown in muscle in normal and disease states

$ 81,302 1/1/03 - 12/31/03 Year 3

Summary Muscle atrophy seen in many disease states or with disuse results mainly from increased breakdown of muscle proteins. The goal of this research is to understand the biochemical basis for this excessive protein breakdown.

Boston - Harvard University

Andrew B. Lassar, Ph.D.

(RG) Cell cycle control of skeletal muscle differentiation

$	80,000	7/1/02 - 6/30/03	Year 1
$	80,000	7/1/03 - 6/30/04	Year 2
$	80,000	7/1/04 - 6/30/05	Year 3

Summary Signals that promote cell proliferation block skeletal muscle differentiation. In this proposal, researchers outline a series of experiments to determine how one factor that prmotes cell proliferation, cyclin D/cdk4, blocks skeletal muscle differentiation.

Boston - Massachusetts General Hospital

Merit Cudkowicz, M.D., MSc

(RG) Caspase inhibition by baculoviral protein p35 in a mouse model of amyotrophic lateral sclerosis (ALS)

$	60,281	1/1/03 - 12/31/03	Year 1
$	61,799	1/1/04 - 12/31/04	Year 2

Summary ALS is a progressive disease of the motor neurons. One step in the motor neuron cell death process appears to be activation of the cells' own self-destruct mechanism, a process called apoptosis. To test the importance of apoptosis in ALS, researchers will breed ALS mice that express a viral protein that shuts off apoptosis. If apoptosis is central to the progression of ALS, the presence of the viral protein should extend the life of the ALS mice. This information may lead to new treatments for ALS.

(RG) Clinical trial of coenzyme Q10 in patients with amyotrophic lateral sclerosis (ALS)

$	102,763	5/1/03 - 4/30/04	Year 1
$	93,577	5/1/04 - 4/30/05	Year 2

Summary ALS is a progressive disease for which there is no known cure. Strategies that improve mitochondrial function, such as Coenzyme Q10 (CoQ10), may delay clinical progression in ALS. Investigators will test the safety and tolerability of high dose CoQ10 (3000 mg/day) in 30 people with ALS. The study results will help plan a large study to determine if high dose CoQ10 slows the progression of ALS.

Cambridge - Brigham and Women's Hospital

Michael Chin, M.D., Ph.D.

(RG) Role of CHF2 in muscle regeneration

$	70,000	1/1/03 - 12/31/03	Year 1

Summary Muscle tissue is limited in its capacity to regenerate after injury. A method to increase the proliferative capacity of muscle cells would be a major breakthrough in therapy for myopathic diseases. Researchers have recently cloned the transcription factor, CHF2, that is expressed in proliferating, undifferentiated muscle cells, but turned off in nonproliferating, differentiated muscle cells. They propose that CHF2 will improve the capacity of muscle cells to regenerate, and that overexpression of CHF2 in muscular dystrophy will ameliorate the muscle wasting in this disease.

Charlestown - Massachusetts General Hospital

Khemissa Bejaoui, Ph.D.

(DG) Cloning and characterization of the HSN-1 gene

$ 35,000 7/1/02 - 6/30/03 Year 3

Summary This is a proposal to find the gene defect that causes a type of mutilating, debilitating neuropathy known as hereditary sensory neuropathy type 1, or HSN-1. The long term goals are to use knowledge of this defect to understand how the disease develops in humans and to make a mouse model of HSN-1 to help in the search for treatments for this disease.

Jonathan Francis, Ph.D.

(RG) Tetanus toxin fragment C for delivery of GDNF to the CNS

$ 45,659 7/1/03 - 6/30/04 Year 1

$ 71,972 7/1/04 - 6/30/05 Year 2

Summary Recent clinical trials of growth factors for the treatment of ALS have been hampered by the poor ability of the growth factors to reach diseased motor neurons in the brain and spinal cord. This research project will examine whether a non-toxic fragment of tetanus toxin can serve as a vehicle or carrier to increase the delivery of the growth factor, GDNF, to motor neurons.

Kimi Kong, Ph.D.

(DG) Investigation of stem cell therapy in Miyoshi myopathy and LGMD-2B

$ 45,000 7/1/03 - 6/30/04 Year 1

$ 45,000 7/1/04 - 6/30/05 Year 2

$ 45,000 7/1/05 - 6/30/06 Year 3

Summary This is a proposal to investigate whether transplantation of human umbilical cord blood stem cells can rescue the dystrophic phenotype in sjl mice, which is a nature model for MM and LGMD-2B.

Piera Pasinelli, Ph.D.

(DG) Proteomic analysis of apoptosis in GFP-labeled motor neurons of amyotrophic lateral sclerosis (ALS) mice

$ 45,000 1/1/03 - 12/31/03 Year 1

$ 45,000 1/1/04 - 12/31/04 Year 2

$ 45,000 1/1/05 - 12/31/05 Year 3

Summary The main objective of this project is to elucidate the mechanisms of mutant SOD1-mediated apoptosis.

Davide Trotti, Ph.D.

(RG) Mechanisms of excitotoxicity in amyotrophic lateral sclerosis (ALS)

$ 58,307 7/1/02 - 6/30/03 Year 3

Summary ALS is a lethal neurodegenerative disease which affects motor neurons in the spinal cord and motor cortex. The goal of this study is to elucidate the role of the human glutamate transporter hGLT1 (EAAT2) in the progression of the disease.

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

(RG) Hsp27 and motor neuron survival

$ 84,954 7/1/03 - 6/30/04 Year 1

$ 87,977 7/1/04 - 6/30/05 Year 2

$ 91,109 7/1/05 - 6/30/06 Year 3

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

Ruxton - Mitochondria Research Society

Keshav Singh, Ph.D.
(SG) Mitochondria 03
$ 8,000 6/1/03 - 6/30/03 Year 1

Waltham - Brandeis University

Carolyn Cohen, Ph.D.
(RG) Atomic structures of the muscle motor
$ 63,854 7/1/02 - 6/30/03 Year 1
$ 66,234 7/1/03 - 6/30/04 Year 2
$ 68,712 7/1/04 - 6/30/05 Year 3

Summary Myosin is the fundamental protein involved in muscle contraction. Researchers seek to visualize, in atomic detail, how this motor works by obtaining "snap-shots" of the molecule in different stages of contraction. This motor is switched "on" and "off" by calcium ions which bind to regulatory proteins such as troponin/tropomyosin and - in certain cases – to myosin itself. Atomic structures of these switches will also be sought to understand how the motor activity is controlled. Many critical muscle diseases are due to defects in the motor itself or in the control machinery. These studies aim to establish this information for structure-based drug design.

Watertown - Boston Biomedical Research Institute

Jeffrey B. Miller, Ph.D.
(RG) Dysferlinopathy model studies
$ 35,000 7/1/02 - 6/30/03 Year 1
$ 35,000 7/1/03 - 6/30/04 Year 2
$ 35,000 7/1/04 - 6/30/05 Year 3

Summary The human disease limb-girdle muscular dystrophy type 2B (LGMD2B) is caused by mutations in the gene that encodes the protein dysferlin. An inbred mouse strain, SJL/J, appears to have a muscle disease due to a similar dysferlin mutation. Because SJL/J mice have disadvantages as a model for the human disease, researchers propose methods to improve the mouse model and increase our understanding of the human disease. An improved animal model will be important for further studies designed to produce therapies for the disease.

Worcester - University of Massachusetts

Davide Gabellini, Ph.D.
(DG) Definition of the molecular basis of facioscapulohumeral muscular dystrophy (FSHD)
$ 45,000 1/1/03 - 12/31/03 Year 1
$ 45,000 1/1/04 - 12/31/04 Year 2
$ 45,000 1/1/05 - 12/31/05 Year 3

Summary This proposal focuses on the identification of candidate genes for FSHD, the generations of animal models and the characterization of the D4Z4-associated transcriptional repressing complex.

Worcester - University of Massachusetts (Cont'd)

Lawrence Hayward, M.D., Ph.D.

(RG) Autophagic stress and neuroprotection in SOD1-mediated amyotrophic lateral sclerosis (ALS)

$	60,287	7/1/02 - 6/30/03	Year 1
$	66,954	7/1/03 - 6/30/04	Year 2
$	70,141	7/1/04 - 6/30/05	Year 3

Summary The proposed study will investigate the consequences of an ALS-associated mutant enzyme upon cellular physiology and will apply the results to the development of novel assays to screen for neuroprotective compounds in ALS.

Jeanne Lawrence, Ph.D.

(RG) The role of nuclear structure in myotonic dystrophy (DM) and facioscapulohumeral dystrophy (FSHD)

$	70,567	7/1/02 - 6/30/03	Year 1
$	73,066	7/1/03 - 6/30/04	Year 2
$	72,177	7/1/04 - 6/30/05	Year 3

Summary Researchers will examine the organization of genes and gene messages involved in normal muscle formation, and in DM1 and FSHD, in the nucleus of the cell and how their arrangement affects both diseases.

Elizabeth Luna, Ph.D.

(RG) Membrane skeletons in normal and dystrophic muscle

$	75,709	7/1/02 - 6/30/03	Year 2
$	73,521	7/1/03 - 6/30/04	Year 3

Summary The goal of this study is to identify proteins that are part of "backup" systems that stabilize muscle plasma membranes in the absence of dystrophin and to establish protocols for testing whether increases, or decreases, in the expression levels of these proteins modulate the dystrophic phenotype. The ultimate goal is to identify therapeutic strategies that may complement dystrophin replacement for treatment of Duchenne and Becker muscular dystrophies.

Rossella Tupler, M.D., Ph.D.

(RG) Dissection of the molecular mechanism causing facioscapulohumeral dystrophy (FSHD)

$	75,000	1/1/03 - 12/31/03	Year 2
$	75,000	1/1/04 - 12/31/04	Year 3

Summary In summary, this search of novel genes in the FSHD chromosomal region and studies on mechanisms controlling gene expression will provide relevant information to understand the molecular basis of FSHD and to develop effective therapeutic strategies.

Zuoshang Xu, M.D., Ph.D.

(RG) Understanding the therapeutic potential of RNAi for amytrophic lateral sclerosis (ALS)

$	112,472	7/1/03 - 6/30/04	Year 1
$	113,033	7/1/04 - 6/30/05	Year 2

Summary ALS involves motoneuron degeneration, paralysis and death. Toxicity generated by mutant enzyme SOD1 kills motoneurons and causes ALS. Investigators propose to use RNAi to reduce the mutant enzyme expression and to lower its toxicity.

Worcester - University of Massachusetts (Cont'd)

Jianhua Zhou, Ph.D.

(RG) Drosophila models for spinal muscular atrophy (SMA) and Drosophila SMN interacting proteins

$ 59,130 7/1/02 - 6/30/03 Year 2

Summary Drosophila provides a useful model for genetic analysis of gene functions. Researchers will generate fruit-fly SMA models that can be used to identify mutant SMN modifiers (enhancers or suppressors) by genetic screens. SMN modifiers in flies could also be identified by the yeast two hybrid screens.

MICHIGAN

Ann Arbor - University of Michigan

Denise Figlewicz, Ph.D.

(RG) Pathogenesis of facioscapulohumeral muscular dystrophy (FSHD)

$ 80,516 1/1/02 - 6/30/03 Year 2

Summary Previous studies have identified genes and cellula rprocesses which differ in muscle cells from FSHD patients. Researchers aim to characterize intracellular pathways related to those changes.

(RG) AMPA receptor subunit synthesis and editing in models of amyotrophic lateral sclerosis (ALS)

$ 75,629 7/1/02 - 6/30/03 Year 1

$ 68,706 7/1/03 - 6/30/04 Year 2

Summary Researchers will examine the synthesis and editing of AMPA-type glutamate receptor subunits in motor neurons which are experimentally stressed, and in individual motor neurons isolated from the spinal cords of the trangenic mouse model of ALS at preclinical and disease stages. Because AMPA receptors are the main source of excitatory input for motor neurons and represent a likely target of pharmaceutic agents, researchers believe these studies will provide direction for future therapeutic strategies.

Andrew Lieberman, M.D., Ph.D.

(RG) Altered androgen receptor function in Kennedy's disease

$ 73,408 7/1/02 - 6/30/03 Year 1

$ 71,481 7/1/03 - 6/30/04 Year 2

$ 74,297 7/1/04 - 6/30/05 Year 3

Summary Researchers will study the affects of a mutation in the androgen receptor known to cause a degenerative disease of motor nerve cells, so as to identify therapeutic targets for treating this disease.

Detroit - Children's Hospital of Michigan

Thomas L'Ecuyer, M.D.

(RG) UTR binding protein: expression and influence on differentiation

$ 75,872 1/1/03 - 12/31/03 Year 2

Summary This project seeks to define how a small RNA sequence causes conversion of nonmuscle cells into muscle. Results from this study may guide future treatments for degenerative diseases of muscle.

Detroit - Wayne State University

Gyula Acsadi, M.D., Ph.D.

(RG) Gene therapy for spinal muscular atrophy (SMA)

$ 85,730 1/1/03 - 12/31/03 Year 2
$ 84,062 1/1/04 - 12/31/04 Year 3

Summary SMA is the most prevalent genetic motor neuron disease of humans. There is no effective therapy available. The primary defect in SMA is related to the loss of spinal motor neurons due to a genetic defect in the survival motor neuron gene. Researchers propose a gene therapy approach to deliver trophic molecules to spinal cord motor neurons as well as to carry out SMN1 gene replacement in recently developed trasngenic mouse models of SMA.

(RG) Gene therapy for amyotrophic lateral sclerosis (ALS) by AAV mediated gene transfer

$ 88,568 1/1/03 - 12/31/03 Year 1
$ 91,095 1/1/04 - 12/31/04 Year 2
$ 93,696 1/1/05 - 12/31/05 Year 3

Summary Currently, there is no effective therapy for ALS. Neurotrophic factors have the potential to promote motor neuron survival. However, systemic administration of trophic factors has been unsuccessful in ALS. The experimental strategy in this grant is focused on a gene therapy approach to find a safe and efficient method to delier therapeutic factors at the site of injury, the lower motor neurons. This grant aims at the optimization of AAV mediated gene therapy in the SOD1 mouse and rat model for ALS.

Michael Shy, M.D.

(RG) Adeno associate virus gene therapy for Charcot-Marie-Tooth (CMT)

$ 97,983 7/1/02 - 12/31/03 Year 2

Summary CMT1 is one of the most common inherited neuromuscular diseases. Currently there is no treatment for CMT1. Researchers propose to use a portion of a benign virus to introduce genes for a growth factor, GDNF, into nerves of a mouse model of CMT1 to both prevent nerve degeneration and promote nerve regeneration.

East Lansing - Michigan State University

William Atchison, Ph.D.

(RG) Unmasking of L type CA channels in ACh release in Lambert-Eaton syndrome (LEMS)

$ 76,920 1/1/03 - 12/31/03 Year 1
$ 79,224 1/1/04 - 12/31/04 Year 2

Summary In LEMS, release of chemical messenger acetylcholine between nerve and muscle is disrupted. A critical protein controlling entry of calcium into the nerve is thought to be the target in LEMS. The goal of this tudy is to identify the protein targets in LEMS by treating mice, in which the gene expressing the component parts of this protein is mutated, with antiodies of patients with LEMS, and examining their neuormuscular function.

MINNESOTA

Minneapolis - University of Minnesota

Charlotte Brown, Ph.D.

(RG) Role of altered forms of laminin A/C in the pathogenesis of Emery-Dreifuss (EDMD) muscular dystrophy

$ 50,303 7/1/02 - 6/30/03 Year 3

Summary Researchers will identify patients with EDMD due to mutations in lamins A and C and investigate how the presence of the altered proteins in muscle cause disease.

Laura Ranum, Ph.D.

(RG) Murine model of myotonic dystrophy type 2 (DM2)

$ 110,000 1/1/03 - 12/31/03 Year 2

$ 110,000 1/1/04 - 12/31/04 Year 3

Summary Researchers propose to create a mouse model of DM2 to use as a tool to better understand pathogenic mechanisms of the disease process.

Morayma Reyes, Ph.D.

(DG) Use of multipotent adult progenitor cells (MAPC) as therapy for muscular dystrophy

$ 45,000 1/1/03 - 12/31/03 Year 1

$ 45,000 1/1/04 - 12/31/04 Year 2

$ 45,000 1/1/05 - 12/31/05 Year 3

Summary Investigators propose to conduct studies of genetically reconstructed (utrophin+) mdx-MAPC and mdx-utrn-/- MAPC transplants into mdx and mdx-utrn mice. For that, MAPC will be generated from mdx and mdx-utrn-/- mice. They will design retroviral and lentiviral constructs containing the truncated utrophin gene driven by a constitutive or a muscle specific promoter. Then, they will transduce the mdx-MAPC and mdx-utrn-/- MAPC with these vectors. Utrophin expression as well as its effects during ex vivo expansion and differentiation will be studied. Then, they will perform serial syngeneic transplants of genetically reconstructed MAPC into mdx mice and mdx-utrn mice.

David Thomas, Ph.D.

(RG) Engineering new molecular probes of muscle

$ 79,570 1/1/03 - 12/31/03 Year 3

Summary Researchers are engineering new probes to understand the molecular movements that produce force in muscle, and to understand how these molecular movements change during the process of muscle degeneration.

Wei Wang, M.D.

(DG) AChR epitopes restricted by DR and DQ molecules relevant to myasthenia gravis (MG)

$ 45,000 7/1/03 - 6/30/04 Year 1

$ 45,000 7/1/04 - 6/30/05 Year 2

$ 45,000 7/1/05 - 6/30/06 Year 3

Summary Investigators want to determine the epitope repertoire of anti-AChR CD4+ T helper cells recognized in association with the DR2, DR3, DR4, DQ6 or DQ8 molecules, to identify characteristics that correlate with susceptibility or resistance to MG.

Rochester - Mayo Clinic

Andrew Engel, M.D.

(RG) Congenital myasthenic syndromes

$	93,389	1/1/03 - 12/31/03	Year 3

Summary Congenital myasthenias will be studied by a multifaceted approach to gain better insights into pathologic mechanisms, diagnosis, treatment and prevention.

(EMG) Restricted funds for support of congenital myasthenia gravis research

$	1,120	4/1/02 - 3/31/03	Year 2

Grazia Isaya, M.D., Ph.D.

(RG) Function and regulation of human frataxin

$	86,400	1/1/03 - 12/31/03	Year 1
$	86,400	1/1/04 - 12/31/04	Year 2
$	86,400	1/1/05 - 12/31/05	Year 3

Summary Friedreich's ataxia is a relentless degenerative disease in which young individuals become progressively disabled and most frequently die prematurely from heart failure. The disease is caused by a deficiency of frataxin, a mitochondrial protein required to handle iron safely. This research aims at obtaining basic information on the mechanism of action and regulation of frataxin, that may help in understanding the natural history of the disease and developng therapies.

Ann M. Reed, M.D.

(RG) HLA genetics and chimerism in juvenile dermatomyositis

$	75,922	7/1/02 - 6/30/03	Year 1
$	77,406	7/1/03 - 6/30/04	Year 2
$	78,933	7/1/04 - 6/30/05	Year 3

Summary Children with juvenile dermatomyositis have persistence of maternal cells. These cells are related to immune response genes and appear to be active in the immune response.

St. Paul - University of Minnesota

Monica Milani, Ph.D.

(DG) Pathogenic and innocuous autoantibodies in myasthenia gravis (MG)

$	45,000	1/1/03 - 12/31/03	Year 2
$	45,000	1/1/04 - 12/31/04	Year 3

Summary MG is caused by antibodies to the muscle acetylcholine receptor, but not all antibodies are dangerous. The investigator will identify characteristics that explain why some antibodies are dangerous while others are not.

MISSISSIPPI

Jackson - University of Mississippi

Michael Hebert, Ph.D.

(RG) Regulation of coilin and SMN interaction by coilin associated proteins

$	80,000	7/1/03 - 6/30/04	Year 1
$	80,000	7/1/04 - 6/30/05	Year 2
$	80,000	7/1/05 - 6/30/06	Year 3

Summary Altered SMN protein activity causes SMA. Investigators have found an interaction between SMN and the protein coilin. This research will explore other factors that may regulate the SMN/coilin interaction.

MISSOURI

Columbia - University of Missouri

Martin Childers, D.O.

(DG) Muscle fiber survival and function in a canine model of Duchenne muscular dystrophy (DMD)

$ 35,000 1/1/03 - 12/31/03 Year 3

Summary This proposal investigates mechanisms that protect DMD muscles from injury and paradoxically enlarge while other muscles incur severe injury and deteriorate.

Dongsheng Duan, Ph.D.

(RG) Heterodimer rAAV vectors for gene therapy of Duchenne's muscular dystrophy (DMD)

$ 137,743 4/1/02 - 3/31/03 Year 2

$ 141,843 4/1/03 - 3/31/04 Year 3

Summary This proposal will test the feasibility of utilizing dual vector approaches for gene therapy of DMD.

Joe Kornegay, DVM, Ph.D.

(RG) Cellular effects of prednisone treatment in canine dystrophy

$ 78,034 1/1/03 - 12/31/03 Year 3

Summary Prednisone treatment provides limited benefit in Duchenne muscular dystrophy. The cellular basis of this benefit will be investigated in dystrophic dogs.

Catherine Krull, Ph.D.

(RG) Ephs and ephrins in muscle precursor cell development

$ 78,209 1/1/03 - 12/31/03 Year 2

$ 80,105 1/1/04 - 12/31/04 Year 3

Summary Researchers are interested in the mechanisms that govern the formation of limb muscle from somites. Specifically, they are focusing on the role of the Eph receptors and their partners, the ephrins, in this process.

Sinead O'Connell, Ph.D.

(DG) Motor axon pathway selection to muscle targets

$ 45,000 7/1/03 - 6/30/04 Year 1

$ 45,000 7/1/04 - 6/30/05 Year 2

$ 45,000 7/1/05 - 6/30/06 Year 3

Summary The primary objective is to understand the molecular signals that control the pathways taken by motor axons as they grow towards their target muscles. Members of the Eph family, a collection of signaling receptors and ligands, are expressed by motor neurons, their axon pathways and target muscles. Here, the aim is to understand how these molecules function in specific cellular interactions to direct motor axons on their appropriate pathways.

Kansas City - Stowers Institute for Medical Research

Olivier Pourquie, Ph.D.

(RG) Role of atrophins in patterning/differentiating early muscle precursers

$	106,746	7/1/03 - 6/30/04	Year 1
$	111,378	7/1/04 - 6/30/05	Year 2
$	115,900	7/1/05 - 6/30/06	Year 3

Summary Among the most promising treatments for muscular dystrophies are the cellular therapies involving the transfer of stem cells able to reconstitute the affected muscles. The Notch signaling pathway has been involved in the maintenance of the stem cell state of muscle precursors and thus the ability to control its regulation could be of great importance for such therapies. This project proposes to further the understanding of the regulation of the Notch pathway during early steps of myogenesis.

St. Louis - Saint Louis University

Medha Gautam, Ph.D.

(RG) Molecular mechanism of acetylcholine receptor clustering

$	68,872	1/1/03 - 12/31/03	Year 3

Summary The goal of this project is to understand the regulation and function of rapsyn in response to signals from the nerve is essential for understanding the mechanism of AchRs clustering at the neuromuscular synapse and could lead to new strategies in the diagnosis and treatment of myasthenic syndromes and other neuromuscular disorders.

St. Louis - Washington University

Anne Connolly, M.D.

(RG) Complement's role in animal models of muscular dystrophy

$	63,475	7/1/02 - 6/30/03	Year 3

Summary In biopsies of patients with muscular dystrophy, damaged muscle fibers are removed through a process that involves proteins called complement components. Activation of complement proteins has been known to be a part of the biopsy changes in muscular dystrophy for many years. These proteins may have other effects. This work will study the effects of eliminating complement completely from three well-stablished animal models of congenital and Duchenne muscular dystrophy.

(RG) Role of complement 3 and B-cells in muscular dystrophy

$	90,000	7/1/03 - 6/30/04	Year 1
$	89,605	7/1/04 - 6/30/05	Year 2
$	92,261	7/1/05 - 6/30/06	Year 3

Summary In biopsies of patients with muscular dystrophy, damaged muscle fibers are removed through a process which involves proteins called complement components. Investigators have shown that this complement system may lead to more damage in one dystrophic mouse model. This work will study both the effect of complement and B-cells in models of Duchenne and congenital muscular dystrophy.

St. Louis - Washington University (Cont'd)

Didier Hodzic, Ph.D.

(DG) Sun2-lamin B1: The end of [another] affair for muscular dystrophy?

$	45,000	1/1/03 - 12/31/03	Year 1
$	45,000	1/1/04 - 12/31/04	Year 2
$	45,000	1/1/05 - 12/31/05	Year 3

Summary Emery-Dreifuss muscular dystrophy (EDMD) is attributed to defective interactions between lamin A/C (a lamina component) and emerin (an inner nuclear membrane protein). Researchers have shown that Sun2 (a new inner nuclear membrane protein) interacts with laminB1 (another lamina component). In cell culture, inhibition of Sun2 interaction with laminB1 results in nuclear structure alterations that are comparable to the nuclear defects observed in EDMD patient biopsies. Therefore, they propose to uncover Sun2's biological functions and address the question of its potential implication in muscular diseases.

Jeff Lichtman, M.D., Ph.D.

(RG) Acetylcholine receptor dynamics: Normal and dystrophic muscle

$	66,763	1/1/03 - 12/31/03	Year 3

Summary There are a variety of neuromuscular diseases that alter the number or density of acetylcholine receptors at the neuromuscular junction, the site of signaling between spinal cord neurons and muscle fibers. This proposal focuses on attaining a better understanding of the factors that regulate the stability and migratory behavior or receptors so that researchers may develop strategies to increase the density of receptors in diseases where neuromuscular weaknesses is a major clinical feature.

Jane Wu, M.D., Ph.D.

(NIDA) Molecular mechanisms regulating alternative splicing of survival motor neuron gene

$	100,000	7/1/02 - 6/30/03	Year 2
$	100,000	7/1/03 - 6/30/04	Year 3

Summary A number of human neuromuscular disorders such as SMA and other muscular dystrophy are caused by defects in processing of genes, in particular, at the step of messenger RNA precursor splicing (pre-mRNA splicing) and alternative splicing regulation. Investigating molecular mechanisms of pre-mRNA splicing regulation is important for not only understanding the pathogenesis of these diseases but also designing therapy based on correcting splicing defects. The proposed study aims at identifying factors critical for splicing of survival of motor neuron (SMN) genes and exploring the potential of treating SMA by modulating SMN gene splicing.

MONTANA

Great Falls - McLaughlin Research Institute

John Bermingham, Ph.D.

(RG) Positional cloning of the mouse hypomyelination mutation claw paw

$	58,471	1/1/03 - 12/31/03	Year 1
$	74,347	1/1/04 - 12/31/04	Year 2
$	65,107	1/1/05 - 12/31/05	Year 3

Summary The mouse mutation claw paw delays peipheral myelination. Researchers propose to identify the underlying genetic lesion to elucidate the genetic mechanisms that control myelin formation.

NEVADA

Reno - University of Nevada

Dean Burkin, Ph.D.

(DG) Integrin alleviation of muscular dystrophy

$ 35,000 7/1/02 - 6/30/03 Year 3

Summary Researchers propose to study the role that the a7b1 integrin plays in alleviating the pathology of transgenic mice that would normally develop severe muscular dystrophy.

NEW JERSEY

Newark - University of Medicine and Dentistry of NewJersey

Natalia Shirokova, Ph.D.

(RG) Metabolic control of calcium signaling in skeletal muscle

$ 78,473 7/1/02 - 6/30/03 Year 1

$ 82,384 7/1/03 - 6/30/04 Year 2

$ 84,784 7/1/04 - 6/30/05 Year 3

Summary Many muscle functions are controlled by the cytosolic Ca2+. Changes in intracellular Ca2+ concentration are tightly controlled by various components of Ca2+ handling apparatus. Abnormalities in one of the components often lead to muscular diseases. The molecular mechanisms of Ca2+ homeostasis in muscle are still poorly understood. The present proposal seeks to clarify the role of major Ca2+ handling organelle - mitochondrion - in regulation of local Ca2+ signaling in healthy and diseased muscle.

NEW MEXICO

Albuquerque - University of New Mexico

David G. Bear, Ph.D.

(RG) Structure and function of PABP2 in oculopharyngeal muscular dystrophy (OPMD)

$ 75,000 1/1/03 - 12/31/03 Year 2

$ 75,000 1/1/04 - 12/31/04 Year 3

Summary OPMD is a neuromuscular disease caused by a mutation in the PABP2 gene. The goal of this project is to understand normal PABP2 function, and how the PABP2 mutation causes OPMD.

Mark W. Becher, M.D.

(RG) Characterization of intranuclear inclusions in oculopharyngeal muscular dystrophy (OPMD)

$ 46,211 7/1/02 - 6/30/03 Year 2

Summary Researchers will study the pathology of OPMD through special tissue staining techniques and electron microscopy in order to characterize protein aggregates that form in the nuclei of muscle cells in patients with OPMD.

Albuquerque - University of New Mexico (Cont'd)

Richard Cripps, D.Phil.

(RG) Transcriptional control of muscle remodeling in Drosophila

$	81,413	7/1/03 - 6/30/04	Year 1
$	78,377	7/1/04 - 6/30/05	Year 2
$	77,897	7/1/05 - 6/30/06	Year 3

Summary The aim of this research is to understand how genes work to control muscle formation and remodeling in the fruit fly. Investigators anticipate that the genes which function in this animal to make muscles are similar to those which function in higher animals including humans, and will help us identify how muscle formation sometimes does not occur properly.

NEW YORK

Albany - State University of New York

Gang Li, Ph.D.

(DG) Inhibition of GluR2 AMPA receptors: A microsecond time resolution study

$	45,000	7/1/02 - 6/30/03	Year 1
$	45,000	7/1/03 - 6/30/04	Year 2
$	45,000	7/1/04 - 6/30/05	Year 3

Summary When glutamate receptor proteins on the motor neurons become hyperactive, the neurons may be destroyed, which causes ALS. This research is to study how chemical inhibitors work on these receptor proteins, because knowing more will allow us to design better inhibitors to control receptor hyperactivity.

Li Niu, Ph.D.

(RG) Discovery of aptamers to prevent excitotoxicity in amyotrophic lateral sclerosis (ALS)

$	94,400	7/1/02 - 6/30/03	Year 1
$	73,616	7/1/03 - 6/30/04	Year 2
$	77,064	7/1/04 - 6/30/05	Year 3

Summary Researchers will attempt to discover new and powerful inhibitors as drugs to control the hyperactivity of glutamate receptors, which cause ALS.

Bronx - Albert Einstein College of Medicine

Zaven Kaprielian, Ph.D.

(RG) Motor axon development in the mammalian spinal cord

$	72,350	1/1/03 - 12/31/03	Year 3

Summary This study will investigate the growth and molecular composition of a distinct subclass of motor neurons/axons in the developing mammalian spinal cord.

Michael Lisanti, M.D., Ph.D.

(RG) The CAV-3 gene, muscle development, and muscular dystrophy

$	75,000	1/1/03 - 12/31/03	Year 3

Summary Limb-girdle muscular dystrophy (LGMD-1C) is an inherited form of muscular dystrophy that is due to mutations within the CAV-3 gene. Here, researchers propose to create an animal model of this disease in mice by deleting the CAV-3 gene.

Bronx - Albert Einstein College of Medicine (Cont'd)

Hanh Nguyen, Ph.D.

(RG) Analysis of skeletrophin, a novel essential component of muscle differentiation

$	77,440	7/1/03 - 6/30/04	Year 1
$	77,440	7/1/04 - 6/30/05	Year 2
$	77,440	7/1/05 - 6/30/06	Year 3

Summary The goals of this project are to characterize the role of skeletrophin, a novel gene in the developmental pathway of skeletal myoblasts, and to uncover the mechanisms by which skeletrophin mediates its function in generating functional muscles. These studies will provide a better understanding of the normal development of founder myoblasts and critica cell fusion events occuring between these myoblasts and their cognate partners, the fusion-competent myoblasts. The results from these studies will provide important insights into a new essential gene which may have similar functions during vertebrate muscle development.

Honglai Zhang, M.D., Ph.D.

(DG) Role of survival motor neuron protein in mRNA localization to growth cones

$	35,000	1/1/03 - 12/31/03	Year 3

Summary Spinal muscular atrophy (SMA) is caused by mutations in a gene which encodes survival motor neuron protein (SMN). Researchers will test the hypothesis that one important function for SMN is to participate in the mechanism of b-actin mRNA localization within neurons, which may be essential for neurite outgrowth and structure.

Buffalo - State University of New York

Luc Gosselin, Ph.D.

(RG) Muscular Dystrophy: Inflammation, dysfunction and fibrosis

$	68,329	7/1/02 - 6/30/03	Year 2
$	71,421	7/1/03 - 6/30/04	Year 3

Summary The purpose of this proposal is to study potential mechanisms leading to muscle fibrosis in muscular dystrophy and to test potential drugs aimed at preventing muscle fibrosis.

Michael Hudecki, Ph.D., D.Sc.

(RF) S. Mouchly Small MDA Research Fellowship

$	32,000	7/1/02 - 6/30/03	Year5
$	32,000	7/1/03 - 6/30/04	Year6

Georgirene D. Vladutiu, Ph.D.

(RG) Improved diagnosis of metabolic diseases among the statin myopathies

$	84,190	7/1/03 - 6/30/04	Year 1
$	87,723	7/1/04 - 6/30/05	Year 2
$	90,735	7/1/05 - 6/30/06	Year 3

Summary Investigators will determine the prevalence of underlying muscle disease in people who become symptomatic while taking cholesterol-lowering medications and develop cost-effective screening tests for the detection of high-risk individuals in order to take measures to prevent serious side effects.

New York - Columbia Presbyterian Medical Center

Hiroshi Mitsumoto, M.D.
(EMG) Restricted funds for the Eleanor and Lou Gehrig MDA/ALS Center
$ 989,397.60 4/1/02 - 3/31/03 Year 2

New York - Columbia University

Salvatore DiMauro, M.D.
(RG) Studies of human mitochondrial myopathies
$ 108,854 7/1/02 - 6/30/03 Year 3
Summary Mitochondria are the organelles that provide the cell with energy and they contain their own DNA. Researchers propose to study myopathies due to defects in nuclear DNA as well as those due to mutations in mitochondrial DNA.

(RG) Pathogenesis of the human glycogenoses
$ 95,000 1/1/03 - 12/31/03 Year 1
$ 95,000 1/1/04 - 12/31/04 Year 2
$ 95,000 1/1/05 - 12/31/05 Year 3
Summary Glycogenoses are hereditary diseases in which sugar utilization in muscle is impaired, causing pain, cramps, and acute breakdown of the muscle fibers. In other conditions, there is accumulation in muscle and brain of an abnormal glycogen, causing weakness and seizures. Researchers are defining the genetic defects in these disorders to facilitate prenatal and family counseling.

(RG) Studies of human mitochondrial myopathies
$ 100,000 7/1/03 - 6/30/04 Year 1
$ 100,000 7/1/04 - 6/30/05 Year 2
$ 100,000 7/1/05 - 6/30/06 Year 3
Summary Mitochondria are the organelles that provide most of the energy needed by our cells. They have their own DNA (mtDNA), but are also dependent on the DNA of the nucleus (nDAN). Investigators propose to study myopathies due to mutations in mtDNA, myopathies due to mutations in nDNA, and those due to problems of communication between the two genomes.

Arthur P. Hays, M.D.
(RG) Expression of peripherin in amyotrophic lateral sclerosis (ALS)
$ 55,000 1/1/03 - 12/31/03 Year 2
Summary This project analyzes peripherin in spinal cord to determine whether mutations of the gene or non-genetic abnormalities of the protein are linked to ALS.

Veronica Hinton, Ph.D.
(RG) Cognitive phenotype associated with Duchenne muscular dystrophy (DMD)
$ 40,724 1/1/03 - 12/31/03 Year 1
$ 42,257 1/1/04 - 12/31/04 Year 2
$ 42,949 1/1/05 - 12/31/05 Year 3
Summary Children with DMD have poor verbal working memory. An easy-to-administer test will be developed to identify children at risk for learning problems. Genetic analysis will also be done.

Michio Hirano, M.D.

(RG) Molecular pathogenesis and treatment of MNGIE

$	63,138	1/1/03 - 12/31/03	Year 1
$	59,051	1/1/04 - 12/31/04	Year 2
$	60,407	1/1/05 - 12/31/05	Year 3

Summary MNGIE is a devastating neuromuscular disorder affecting the gastrointestinal tract, eye muscles, and limbs. Researchers propose to study the disease and to test therapies using cells from patients and a mouse model.

Oliver Hobert, Ph.D.

(RG) Genetic analysis of motor axon sprouting

$	73,293	1/1/03 - 12/31/03	Year 3

Summary Researchers propose to utilize a simple model organism, C.elegans, to investigate the genetic basis of a pathological nerve defect often found to be associated with neuromuscular disorders.

Edward Laufer, Ph.D.

(RG) Control of limb motor axon dorsal-ventral projection

$	84,656	7/1/03 - 6/30/04	Year 1
$	68,222	7/1/04 - 6/30/05	Year 2
$	67,519	7/1/05 - 6/30/06	Year 3

Summary Limb muscles are innervated by groups of motor axons that project from the spinal cord; the precise control of this process during development is necessary for coordinated muscular control after birth. This project takes advantage of chick and mouse mutants to define how motor axons entering the limb choose to appropriatelyproject towards either dorsal or ventral limb muscles. Identifying the signals controlling the precise targeting of these axons can aid in designing regenerative therapies for neuromuscular diseases such as amyotrophic lateral sclerosis and spinal muscular atrophy.

Ronald Liem, Ph.D.

(RG) Characterization of MACF: A hybrid of dystonin and dystrophin

$	70,000	7/1/02 - 6/30/03	Year 3

Summary Researchers have identified a novel protein, MACF that is likely to be associated with some forms of muscular dystrophy. MACF appears to be crucial for the normal functions of muscle and nerves, because fruit flies without MACF exhibit severe muscular and neuronal deficits. Researchers propose to study the functions of MACF and its relationship to muscular dystrophy.

Chung-Ming Lin, Ph.D.

(DG) Studies of muscular dystrophy in dystonia musculorum mice

$	45,000	7/1/03 - 6/30/04	Year 1
$	45,000	7/1/04 - 6/30/05	Year 2
$	45,000	7/1/05 - 6/30/06	Year 3

Summary Mutations of BPAG1 gene cause neuromuscular deficits in mouse mutant dystonia musculorum (dt). As dt mice can be used as a model of studying neuromuscular diseases, defining the function of BPAG1 in muscle is of tremendous value. Hence, investigators propose to study the muscle form of BPAG1 by various techniques in order to determine how its loss leads to muscle fragility.

New York - Columbia University (Cont'd)

Hiroshi Mitsumoto, M.D.
(SG) ALS Clinical Trials - The challenge of the next century
$ 50,000 6/1/03 - 6/30/03 Year 1

Makiko Nagai, M.D., Ph.D.
(FRS) Stem cell research for ALS
$ 45,000 7/1/02 - 6/30/03 Year 1
$ 45,000 7/1/03 - 6/30/04 Year 2
$ 45,000 7/1/04 - 6/30/05 Year 3

Eric Schon, Ph.D.
(RG) Mitochondrial diseases: Cellular models and gene therapy
$ 62,277 1/1/03 - 12/31/03 Year 3
Summary Researchers are working on a novel gene therapy approach to treat neuromuscular diseases associated with mutations in mitochondrial DNA.

Howard Worman, M.D.
(RG) Nuclear lamins and Emery-Dreifuss muscular dystrophy (EDMD)
$ 86,777 1/1/03 - 12/31/03 Year 3
Summary One form of EDMD is caused by mutations in nuclear lamin proteins. Researchers will study mutant lamins to lay the foundation for the development of novel therapies.

New York - Cornell University

Mahmoud Kiaei, Ph.D.
(DG) Effects of combined treatment with creatine and cyclooxygenase-2 inhibitors in amyotrophic lateral sclerosis (ALS)
$ 45,000 7/1/02 - 6/30/03 Year 1
$ 45,000 7/1/03 - 6/30/04 Year 2
Summary Researchers will investigate whether a combination of creatine and anti-inflammatory drugs could further improve survival in ALS trangenic mice to understand the role of energy and inflammation in motor neuron death.

Giovanni Manfredi, M.D., Ph.D.
(RG) Compartmentalization of ATP in mitochondrial disorders
$ 74,544 1/1/03 - 12/31/03 Year 3
Summary Energy metabolism defects cause mitochondrial encephalopathies. Understanding the distribution of energy storage in affected cells might indicate appropriate therapeutic targets.

New York - Mount Sinai School of Medicine

Giulio Pasinetti, M.D., Ph.D.
(RG) The role of cyclooxygenase-2 inhibitors in a model of ALS neurodegeneration
$ 87,698 7/1/03 - 6/30/04 Year 1
$ 87,698 7/1/04 - 6/30/05 Year 2
$ 87,698 7/1/05 - 6/30/06 Year 3
Summary Researcher's will generate a profile of protein biomarkers that represent the therapeutic benefit of cyclooxygenase in ALS and study these proteins as a function of the clinical and pathological progression of this disease.

New York - Mount Sinai School of Medicine (Cont'd)

Serafin Pinol-Roma, Ph.D.

(RG) RNA-protein complexes in mitochondrial gene expression

$	70,000	1/1/03 - 12/31/03	Year 1
$	70,000	1/1/04 - 12/31/04	Year 2
$	70,000	1/1/05 - 12/31/05	Year 3

Summary Mitochondria are responsible for generating much of the energy in our cells. Mitochondrial function is controlled by genes located in mitochondria themselves, as well as by genes located in the cell nucleus. Mutations in both classes of enes are the cause of several muscular dystrophies. This research will study proteins encoded in the nucleus that are required for expression of mitochondrial genes, to provide a better framework for developing therapies to treat mitochondrial myopathies.

New York - New York University

Frank Martiniuk, Ph.D.

(RG) Enzyme replacement therapy for acid maltase deficiency

$	127,980	1/1/03 - 12/31/03	Year 1

Summary Investigators plan to study the safety and efficacy of enzyme replacement therapy for a means of treatment of acid maltase deficiency in animal models and in human.

Rochester - University of Rochester

Emma Ciafaloni, M.D.

(RG) The pathophysiology of hypersomnolence in myotonic dystrophy

$	47,934	7/1/03 - 6/30/04	Year 1
$	48,886	7/1/04 - 6/30/05	Year 2

Summary The purpose of this study is to better understand the cause of the pathologic and frequently disabling hypersomnolence experienced by many myotonic dystrophy patients.

Robert T. Dirksen, Ph.D.

(RG) Altered excitation-contraction coupling in myotonic dystrophy (DM)

$	83,396	1/1/03 - 12/31/03	Year 2
$	85,866	1/1/04 - 12/31/04	Year 3

Summary DM is caused by a CTG-repeat expansion in the 3'-untransplated region of the myotonic dystrophy protein kinase (DMPK) that results in both reduced DMPK levels and the expression of mRNA molecules containing expanded CUG triplet repeats. However, it is unknown how this genetic defect leads to muscle weakness. This project will dissect the roles of these two cellular mechanisms (DMPK deficiency and mRNA CUG repeat expansion) in altering normal calcium homeostasis and excitation-contraction coupling in DM1. The conclusions will lead to a more comprehensive understanding of the underlying causes of DM1 and will hopefully lead to the development of more rational and effective therapeutic strategies.

Rochester - University of Rochester (Cont'd)

Robert Griggs, M.D.

(RG) Pathomechanisms and treatment of channelopathies

$ 95,775 1/1/03 - 12/31/03 Year 3

Summary Researchers are beginning 16-center treatment trials of attacks of weakness and of interattack weakness in the periodic paralyses. Over 200 patients will have their specific mutation of calcium or sodium channel defined. Researchers expect to discover why specific mutations cause specific symptoms, which should help explain the cause(s) of weakness in the periodic paralyses and lead to better treatments for channelopathies.

M. Kerry O'Banion, M.D., Ph.D.

(RG) Inflammatory processes in motor neuron degeneration

$ 77,779 1/1/03 - 12/31/03 Year 3

Summary Inflammation in the spinal cord may contribute to ALS. Researchers will correlate inflammation and disease in a model of ALS and determine whether inflammatory factors can kill spinal cord neurons.

Rabi Tawil, M.D.

(RG) Pathophysiology of facioscapulohumeral muscular dystrophy (FSHD)

$ 81,616 7/1/02 - 6/30/03 Year 3

Summary The purpose of this project is to try to find the cause of facioscapulohumeral muscular dystrophy (FSHD) by looking for abnormal gene expression in muscle biopsy samples from affected individuals.

Charles Thornton, M.D.

(RG) Pathophysiology of myotonic dystrophy (DM)

$ 79,937 1/1/03 - 12/31/03 Year 3

Summary DM is the most common form of muscular dystrophy in adults. The goal of this project is to understand the causes of muscle weakness and muscle stiffness in DM so that more effective treatments can be developed.

(RG) Pathogenesis of oculopharyngeal dystrophy (OPMD)

$ 67,321 7/1/02 - 6/30/03 Year 2

$ 69,270 7/1/03 - 6/30/04 Year 3

Summary The goal of this project is to understand how mutations in the polyadenylate binding protein 2 gene cause muscle degeneration and weakness in OPMD.

Stony Brook - State University of New York

Gary Zieve, Ph.D.

(RG) Is spinal muscular atrophy (SMA) a defect in snRNP particle assembly?

$ 59,933 7/1/02 9/30/03 Year 3

Summary Researchers hypothesize the SMN complex is a template for the assembly of the snRNP core particles and that arginine methylation of the snRNP proteins releases the mature particles from the template.

NORTH CAROLINA

Chapel Hill - University of North Carolina

Robert Sealock, Ph.D.

(RG) Molecular physiology of utrophin-syntrophin interactions

$	93,998	1/1/03 - 12/31/03	Year 1
$	91,511	1/1/04 - 12/31/04	Year 2

Summary A promising avenue for Duchenne muscular dystrophy (DMD) therapy is to encourage expression in entire muscle cells of utrophin, which is normally found only at the neuromuscular junction. In mice which do not express alpha-syntrophin (a dystrophin-and utrophin-associated protein), utrophin is absent. Encouraging sufficient incorporation of utrophin into the place of dystrophin may require that we understand fully this phenomenon. The proposed project aims to use the alpha-syntrophin-minus mice to do that.

Da-Zhi Wang, Ph.D.

(RG) Control of skeletal muscle differentiation and function by SRF and myocardin family of transcription factors

$	80,000	7/1/03 - 6/30/04	Year 1
$	80,000	7/1/04 - 6/30/05	Year 2
$	80,000	7/1/05 - 6/30/06	Year 3

Summary This project is designed to study the molecular mechanisms of SRF and myocardin family of transcription factors that regulate skeletalmuscle determination and differentiation as well as the in vivo functions of these factors during skeletal muscle development. These studies are the important prerequisite to developing therapeutic strategies that correct or circumvent skeletal muscle dysfunction accompanying neuromusuclar disease. SRF and the myocardin family of transcription factors could become specific targets for therapeutic application. Furthermore, the transgenic gene targeted mice established from this study could serve as valuable animal models of human muscular disease.

Durham - Duke University

Andrea Amalfitano, D.O., Ph.D.

(RG) Therapeutic potential of replication competent/incompetent adenovirus vectors encoding human acid-alpha-glucosidase in animal models of acid-maltase deficiency

$	107,659	9/1/02 - 8/31/03	Year 2
$	110,838	9/1/03 - 8/31/04	Year 3

Summary Researchers will investigate the ability of a virus to deliver a beneficial gene into the muscles of acid-maltase deficient mice, in the hopes of developing a therapy for patients affected by acid-maltase deficiency.

Duke University

(EMG) MDA/CITGO Corporation restricted funds for use at Duke Children's Hospital

$	207,965.75	4/1/02 - 3/31/03	Year 1
$	207,965.75	4/1/03 - 3/31/04	Year 2

Durham - Duke University (Cont'd)

Michael D. Ehlers, M.D., Ph.D.

(RG) Regulation of motor neuron sensitivity in glutamate

$ 75,000 1/1/03 - 12/31/03 Year 2

$ 75,000 1/1/04 - 12/31/04 Year 3

Summary The goal of this research is to determine why motor neurons are hypersensitive to the neurotransmitter glutamate and thus selectively degenerate in ALS.

Dwight D. Koeberl, M.D., Ph.D.

(RG) AAV vectors for muscle-targeted gene therapy in acid maltase deficiency (AMD)

$ 83,285 1/1/03 - 12/31/03 Year 2

Summary The goal of this project is the development of adeno-associated virus (AAV) vectors for gene therapy in acid-maltase deficiency (AMD). Gene therapy for AMD could provide treatment after one injection, as opposed to enzyme treatment that must be given weekly.

Winston-Salem - Wake Forest University

Osvaldo Delbono, M.D., Ph.D.

(RG) IGF-1, anomalous calcium channel and amyotrophic lateral sclerosis (ALS)

$ 69,120 1/1/03 - 12/31/03 Year 2

$ 73,440 1/1/04 - 12/31/04 Year 3

Summary The main goal of this proposal is to determine the mechanisms and therapeutics for sporadic amyotrophic lateral sclerosis. The hypothesis is that age-dependent decreases in trophic factors (i.e. IGF-1) results in changes in the expression of specific proteins involved in calcium fluxes with subsequent alterations in cellular calcium ahndling and motoneuron death and that the overexpression of IGF-1 exclusively in skeletal muscle can prevent these alterations.

OHIO

Cincinnati - Children's Hospital Medical Center

Nancy Leslie, M.D.

(TRAC) Pompe's trial - AGLU01702 and AGLU01602

$ 50,000 1/1/03 - 12/31/03 Year 1

Summary Investigational enzyme replacement therapy administered to patients with infantile-onset Pompe disease.

James Lessard, Ph.D.

(RG) Mouse models of actin-based nemaline myopathy

$ 45,000 1/1/03 - 12/31/03 Year 2

$ 45,000 1/1/04 - 12/31/04 Year 3

Summary Investigators propose to make mutations in the skeletal actin gene of mice to provide models that will help us understand how and why muscle is affected by mutations. Since mouse skeletal actin is identical to the human form, these models will be used to follow the progression of the disease and determine the way in which skeletal muscle responds to this devastating disorder. These studies may provide novel insights and that will lead to new approaches for treating muscle diseases in humans.

Cincinnati - Children's Hospital Medical Center (Cont'd)

Jeffery Molkentin, Ph.D.

(RG) Role of calcineurin/NFAT signaling in muscle regeneration

$	84,240	1/1/03 - 12/31/03	Year 3

Summary Muscular dystrophy is a disease that involves muscle degeneration. The ability of one's muscle to undergo regeneration slowly diminishes with age which partially explains why affected children progressively deteriorate. Researchers have uncovered a novel regulatory pathway that is believed to aid in this regenerative pathway. Such an understanding will allow us to directly target this pathway to stimulate greater regeneration in muscle.

Cincinnati - University of Cincinnati

John Quinlan, M.D.

(RG) Prevention and treatment of cardiomyopathy in mdx mice

$	100,000	1/1/03 - 12/31/03	Year 1
$	100,000	1/1/04 - 12/31/04	Year 2
$	100,000	1/1/05 - 12/31/05	Year 3

Summary Researchers will test four FDA-approved drugs in muscular dystrophy (mdx) mice in order to determine which drugs are likely to prevent heart failure from developing in boys with Duchenne and Becker dystrophy.

Cleveland - Case Western Reserve University

Francisco Andrade, Ph.D.

(RG) Mechanisms of muscle sparing in muscular dystrophy

$	59,634	1/1/03 - 12/31/03	Year 3

Summary This project will evaluate potential mechanisms that explain why the extraocular muscles are uniquely spared in Duchenne muscular dystrophy.

J. P. Jin, M.D., Ph.D.

(SG) Muscle Symposium at 03 Experimental Biology Meeting

$	2,000	4/1/03 - 4/30/03	Year 1

A. Gregory Matera, Ph.D.

(RG) Spinal muscular atrophy (SMA) and snRNA biogenesis

$	75,588	1/1/03 - 12/31/03	Year 2
$	82,015	1/1/04 - 12/31/04	Year 3

Summary SMA is primarily caused by mutations in the SMN1 gene, whose product is involved in metabolism of small RNAs. In order to better understand this process, researchers plan to create genetic "knockouts" of other genes known to interact with SMN.

M. Edward Medof, M.D., Ph.D.

(RG) An active model of myasthenia gravis (MG) with targeted treatment

$	98,685	1/1/03 - 12/31/03	Year 1
$	103,123	1/1/04 - 12/31/04	Year 2
$	108,313	1/1/05 - 12/31/05	Year 3

Summary The respective roles that proteins termed complement and their regulators play in MG are incompletely understood. Researchers will clarify which complement proteins and which regulators are most critical and test new therapies that may be valuable in patients.

Cleveland - Case Western Reserve University (Cont'd)

John Porter, Ph.D.
(RG) Integrins and extraocular muscle protection in muscular dystrophy
$ 70,823 7/1/02 - 6/30/03 Year 3
Summary Proposed studies will evaluate the means by which a novel muscle group, the extraocular muscles, is selectively spared in several types of muscular dystrophy.

Cleveland - University Hospital of Cleveland

John D. Porter, Ph.D.
(RG) Pathogenic mechanisms in dystrophic mice by DNA microarray
$ 110,640 1/1/03 - 12/31/03 Year 2
Summary State of the art DNA microchip technology will provide for simultaneous testing of several hypotheses as to the mechanism of muscle damage in an animal model of Duchenne muscular dystrophy.

Columbus - Ohio State University

Gail Herman, M.D., Ph.D.
(RG) Molecular studies of x-linked myotubular myopathy (MTM)
$ 67,955 1/1/03 - 12/31/03 Year 3
Summary This research will examine the role of the myotubularin protein in normal muscle development and why mutations in its gene cause the human muscle disorder X-linked MTM.

John Kissel, M.D.
(PPG) Clinical trial of albuterol and oxandrolone in facioscapulohumeral dystrophy (FSHD)
$ 118,512 1/1/03 - 12/31/03 Year 2
$ 110,220 1/1/04 - 12/31/04 Year 3
Summary In this study, two drugs with anabolic (or muscle building) qualities will be given alone or in combination to patients with FSHD. The drugs are oxandrolone and albuterol. Patients will be treated for one year, with their strength and muscle mass checked frequently to see if the drugs are having a positive effect. The study should determine whether this approach to treatment is effective in FSHD.

Jerry Mendell, M.D.
(RG) Gentamicin treatment of Duchenne and limb-girdle muscular dystrophy
$ 88,344 7/1/02 - 6/30/03 Year 2
$ 90,345 7/1/03 - 6/30/04 Year 3
Summary The antibiotic gentamicin will be studies to find out if it is a useful treatment for DMD and other forms of muscular dystrophy. Preliminary studies suggest that it might be beneficial.

Columbus - Ohio State University (Cont'd)

Umrao Monani, Ph.D.

(DG) Does expression of SMN in the motor neurons/muscle rescue the SMA phenotype?

$ 35,000 1/1/03 - 12/31/03 Year 3

Summary Although the gene that is defective in SMA was cloned five years ago, it is still not absolutely clear whether the disease primarily targets the motor neurons, muscle or both. In this proposal, researchers will try answering this question by separately expressing the SMN protein in each of these tissues of an SMA mouse model. Rescue of the disease phenotype in one or both cases will identify the specific tissue to be targeted in procedures designed to treat SMA.

Thomas Prior, Ph.D.

(PPG) WAVE-based mutation analysis for MD

$ 200,000 3/1/02 - 2/28/03 Year 1

$ 77,760 3/1/03 - 9/30/04 Year 2

Jill Rafael, Ph.D.

(RG) Mechanisms of fiber-type abnormalities in muscular dystrophy models

$ 65,080 1/1/03 - 12/31/03 Year 3

Summary This proposal aims to identify the mechanisms leading to the fiber-type abnormalities present in DMD and a wide variety of congenital myopathies. The results of this study will enable novel approaches for treatment of these disorders.

OKLAHOMA

Oklahoma City - University of Oklahoma

Sanjay Bidichandani, MBBS, Ph.D.

(RG) Properties and determinants of GAA triplet-repeat instability

$ 80,000 1/1/03 - 12/31/03 Year 1

$ 80,000 1/1/04 - 12/31/04 Year 2

$ 80,000 1/1/05 - 12/31/05 Year 3

Summary This research is focused on the unique gene defect that causes Friedreich's ataxia. It is hoped that these studies will help to prevent or reverse the gene defect as a possible future therapy.

OREGON

Eugene - University of Oregon

J. Andrew Berglund, Ph.D.

(RG) Understanding the RNA structure responsible for myotonic dystrophy

$	97,951	7/1/03 - 6/30/04	Year 1
$	97,951	7/1/04 - 6/30/05	Year 2
$	97,951	7/1/05 - 6/30/06	Year 3

Summary The development of an in vitro assay to study protein binding to the CUG triplet repeat RNA will lead to a method for screening small molecules that inhibit this interaction, potentially providing lead molecules for the design of therapeutic agents for DM. Also a structure of the CUG triplet repeat RNA could lead to the development of drugs through rational drug design based on docking of small molecules to unique features of the CUG triplet repeat RNA structure. The molecules discovered through rational drug design could then be put back into the in vitro assay to determine how well these designed molecules inhibit.

Portland - Oregon Health Sciences University

Peter Rotwein, M.D.

(RG) Growth factor - Co-activator interactions in myoblast survival

$	102,920	7/1/02 - 6/30/03	Year 2
$	106,470	7/1/03 - 6/30/04	Year 3

Summary This project will investigate how growth factors regulate myoblast viability with a long-term goal of identifying targets for therapeutic intervention in neuromuscular diseases.

PENNSYLVANIA

Bryn Mawr - Bryn Mawr College

Ralph Kuncl, M.D., Ph.D.

(RG) Bringing PEDF towards clinical trials in amyotrophic lateral sclerosis (ALS)

$	75,000	7/1/02 - 6/30/03	Year 2

Summary PEDF is a novel neurotrophic factor for motor nerve cells. Other factors like GDNF and IGF-I are more established, but they too need further understanding to reach clinical utility. This study will provide the pre-clinical rationales for these neurotrophic factor drugs (and combinations) in ALS and other motor neuron disorders to bring them to clinical availability sooner.

Hershey - Pennsylvania State University

James R. Connor, Ph.D.

(RG) Genotyping analysis for Hfe mutations in amyotrophic lateral sclerosis

$	102,020	7/1/03 - 6/30/04	Year 1
$	80,032	7/1/04 - 6/30/05	Year 2
$	83,190	7/1/05 - 6/30/06	Year 3

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

Philadelphia - Children's Hospital of Philadelphia

Alan Flake, M.D.

(RG) Prenatal strategies for treatment of muscular dystrophy

$	125,364	7/1/02 - 6/30/03	Year 2
$	127,248	7/1/03 - 6/30/04	Year 3

Summary The aim of this proposal is to develop cellular and gene therapy strategies for the prenatal treatment of fetuses diagnosed with muscular dystrophy.

David Lynch, M.D., Ph.D.

(EMG) Restricted funds for Friedreich's ataxia research

$	9,000	4/1/02 - 3/31/03	Year 1
$	13,907.50	4/1/03 - 3/31/04	Year 2

(PPG) Clinical measures in Friedreich's ataxia (FA)

$	175,861	7/1/03 - 6/30/04	Year 1
$	160,658	7/1/04 - 6/30/05	Year 2
$	164,263	7/1/05 - 6/30/06	Year 3

Summary FA is a neurodegenerative disease leading to progressive loss of balance and coordination, and speech difficulty. Possible therapies based on antioxidants are being considered for clinical trials but at present no clinical measure exists for following patients with FRDA. Such clinical measures need to be validated in this patient population so that they can be utilized in brief trials of medications. Investigators will compare the ability of an FA scale based on quantitation of neurologicl exam components with simple performance measures of walking ability, coordination and visual function to design a scale for clinical evaluation of patients with FA.

David Pleasure, M.D.

(RG) FGF-5: Schwann cell-derived motor neuron survival factor

$	88,870	1/1/03 - 12/31/03	Year 3

Summary Researchers now propose to test the specific hypothesis that FGF-5 is a Schwann cell-derived motor neuron survival factor. These studies will determine whether FGF-5 is a promising candidate for therapy of human motor neuron diseases.

(RG) Neuropilin-2 facilitates axonal regeneration in PNS

$	95,064	7/1/03 - 6/30/04	Year 1
$	95,064	7/1/04 - 6/30/05	Year 2
$	95,064	7/1/05 - 6/30/06	Year 3

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

Weidong Xiao, Ph.D.

(RG) Optimization of AAV vector for gene therapy of neuromuscular diseases

$	99,144	1/1/03 - 12/31/03	Year 1
$	100,596	1/1/04 - 12/31/04	Year 2
$	102,090	1/1/05 - 12/31/05	Year 3

Summary Researchers propose a novel way to establish a cell line that allows large scale production of AAV vectors economically. In addition, they will generate AAV hybrid vectors that can be purified to very high purity and retain high transduction efficacy for muscle. Moreover, they will screen AAV with tropism for myoblast cells which are very important in repairing damaged muscle. Finally, they will improve the delivery of AAV vectors using isolated limb perfusion technique.

Philadelphia - Hahnemann University

Terry Heiman-Patterson, M.D.

(EMG) Restricted funds for support of the MDA/ALS Center of Hope

$	40,000	4/1/02 - 3/31/03	Year 2
$	40,000	4/1/03 - 3/31/04	Year 3

(RG) Genetic analysis of amyotrophic lateral sclerosis (ALS) in inbred transgenic mice

$	88,247	7/1/02 - 6/30/03	Year 2
$	40,000	7/1/02 - 6/30/03	Year 2
$	90,714	7/1/03 - 6/30/04	Year 3

Summary This study will utilize a mouse model of ALS. These mice have been genetically modified to carry the mutant human gene for the enzyme Cu-Zn superoxide dismutase (SOD1), that is known to cause ALS. In these mice, researchers will construct different strains and examine genetic factors that can influence the course of the disease in order to help identify genes that modify ALS.

Philadelphia - Thomas Jefferson University

Michael King, Ph.D.

(RG) Import of tRNA's into human mitochondria

$	62,947	7/1/02 - 6/30/03	Year 2
$	66,041	7/1/03 - 6/30/04	Year 3

Summary Mitochondria contain their own genetic material. Researchers are studying potential genetic therapies to treat human neuromuscular diseases resulting from mutations of this genetic material.

Diane E. Merry, Ph.D.

(RG) Pathogenesis and treatment of a mouse model of spinal and bulbar muscular atrophy (SBMA)

$	75,000	7/1/02 - 6/30/03	Year 1
$	75,000	7/1/03 - 6/30/04	Year 2
$	75,000	7/1/04 - 6/30/05	Year 3

Summary Using transgenic mouse models of SBMA, researchers plan to study the mechanisms of motor neuron dysfunction, and to develop novel therapeutic strategies for SBMA.

Philadelphia - University of Pennsylvania

Elisabeth Barton, Ph.D.

(DG) Role of dystrophin complex in mechanical signal transduction

$	35,000	1/1/03 - 12/31/03	Year 3

Summary Dystrophic muscle displays a high susceptibility to damage. The dystrophin complex, in addition to serving a structural role, might also sense the load imposed on the muscle membrane when the muscle generates force, and convey that information to the inside of the muscle cell. This may also be critical to maintaining healthy muscle.

Michael Granato, Ph.D.

(RG) Genetic screens for genes in neuromuscular development and disease

$	70,000	1/1/03 - 12/31/03	Year 3

Summary The goal of this proposal is to isolate and study the key genes controlling the development and function of the neuromuscular system.

Philadelphia - University of Pennsylvania (Cont'd)

Tejvir Khurana, M.D., Ph.D.

(RG) Myostatin blockade for rescuing the dystrophic phenotype

$ 50,000 1/1/03 - 12/31/03 Year 1

Summary Researchers intend to test whether the strategy of myostatin blockade can rescue the dystrophic muscle in animal models of muscular dystrophy. This strategy has great potential in the treatment of Duchenne's muscular dystrophy.

Arnold Levinson, M.D.

(RG) Intrathymic pathogenesis of myasthenia gravis (MG)

$ 100,000 1/1/03 - 12/31/03 Year 3

Summary In the pathogenesis of MG, the expression of the autoantigen, acetylcholine receptor (AChR), in the thymus has raised the hypothesis that immunity to this self-protein may be initiated or perhaps perpetuated in this organ. The overall objective of this project is to understand this mechanism.

Christiane Massicotte, DVM, MS, Ph.D.

(RG) Trafficking of Cx32 mutant protein that cause inherited neuropathy

$ 66,588 1/1/03 - 12/31/03 Year 1

$ 64,347 1/1/04 - 12/31/04 Year 2

Summary Mutations in the human connexin-32 gene (Cx32-GJB1) cause the X-linked form of Charcot-Marie-Tooth disease, which affects about 1/2000 people. Researchers have devised a simple and novel method of transfecting yelinating Schwann cells in vivo, which will enable them to evaluate the trafficking and interactions of many different Cx32 mutants, bypassing the time and expense reuired for making transgenic animals that would otherwise have to be generated to perform the analyses proposed.

Joseph W. Sanger, Ph.D.

(RG) Talin in myofibril assembly: Insights into diseases

$ 62,885 1/1/03 - 12/31/03 Year 2

$ 64,731 1/1/04 - 12/31/04 Year 3

Summary The focus of this proposal is on determining the role of talin in the formation of muscle in developing skeletal myotubes.

Hansell Stedman, M.D.

(PPG) Systemic gene therapy for inherited muscle disease

$ 100,000 7/1/02 - 6/30/03 Year 2

$ 100,000 7/1/03 - 6/30/04 Year 3

Summary Researchers will further investigate gene transfer from bloodstream to muscle throughout the body.

H. Lee Sweeney, Ph.D.

(RG) Viral modulation of muscular dystrophy

$ 150,000 1/1/03 - 12/31/03 Year 3

Summary The goal of this research program is to develop gene therapy approaches to treating Duchenne and Becker muscular dystrophies. Researchers are trying to identify molecules that will fit into AAV and that will slow the progression of these and other muscular dystrophies.

Philadelphia - University of Pennsylvania (Cont'd)

H. Lee Sweeney, Ph.D.
(EMG) Restricted funds for research
$ 36,280 4/1/02 - 3/31/03 Year 1

Pittsburgh - Children's Hospital of Pittsburgh

Johnny Huard, Ph.D.
(RG) Improving skeletal and cardiac muscle function via stem cell transplantation
$ 100,000 7/1/02 - 6/30/03 Year 1
$ 100,000 7/1/03 - 6/30/04 Year 2
$ 100,000 7/1/04 - 6/30/05 Year 3
Summary The goals of the proposed project are to 1) investigate the capability of muscle stem cells to deliver dystrophin and restore muscle function via intravenous injection, and 2) improve cardiac function of dystrophic mice via intravenous and intracardiac injection of muscle stem cells.

Pittsburgh - University of Pittsburgh

Paula R. Clemens, M.D.
(RG) Adenoviral vector targeting for muscle gene transfer
$ 85,000 7/1/02 - 6/30/03 Year 1
$ 85,000 7/1/03 - 6/30/04 Year 2
$ 85,000 7/1/04 - 6/30/05 Year 3
Summary Duchenne muscular dystrophy (DMD) is caused by the absence of dystrophin, a protein that is necessary for the proper functioning of muscle. To facilitate delivery of a gene transfer vector to widespread muscle through the bloodstream, reseachers propose to target the delivery vehicle to muscle.

Johnny Huard, Ph.D.
(SG) Federation of American Societies for Experimental Biology (FASEB) Skeletal Muscle Satellite and Stem Cells
$ 10,000 7/1/03 - 7/31/03 Year 1

Chau-Ching Liu, Ph.D.
(RG) Molecular pathogenesis of polymyositis (PM): The role of muscle cell apoptosis
$ 64,296 7/1/02 - 12/31/03 Year 3
Summary PM is an inflammatory disease affecting muscle tissues and many other organs. Researchers intend to elucidate how muscle cells are becoming the target of so-called "cytotoxic lymphocytes" - a special type of immune cells. The information is anticipated to lead to more effective treatment.

Stephen D. Meriney, Ph.D.
(RG) High resolution imaging of Ca2+ influx in motor nerve terminals
$ 68,951 1/1/03 - 12/31/03 Year 2
$ 70,647 1/1/04 - 12/31/04 Year 3
Summary The proposed experiments will provide a deeper understanding of the magnitude and spatial distribution of the calcium entry at motor nerve terminals that triggers chemical transmitter release. The effects on this calcium entry of common treatment approaches for Lambert-Eaton myasthenic syndrome will be evaluated with the goal of refining the therapeutic approach.

Marcia Ontell, Ph.D.

(RG) Muscle regeneration and myogenic regulatory factors

$ 65,000	1/1/02	6/30/03	Year 3

Summary Muscular dystrophy is characterized by regeneration that fails to keep pace with degeneration. Proposed studies focus on the role of Myf-5 and MyoD, myogenic regulatory factors, in muscle maturation and regeneration.

Chunping Qiao, M.D., Ph.D.

(DG) Congenital muscular dystrophy (CMD) gene therapy with novel AAV-mini-agrin vectors

$ 45,000	1/1/03 - 12/31/03	Year 1
$ 45,000	1/1/04 - 12/31/04	Year 2
$ 45,000	1/1/05 - 12/31/05	Year 3

Summary CMD is a severe and lethal early childhood muscle-wasting disease. Researchers will systemically and stably deliver a therapeutic gene product, mini-agrin, by a harmless viral vector to treat CMD.

Alexandre Stewart, Ph.D.

(RG) Molecular mechanisms of myogenesis

$ 99,630	1/1/03 - 12/31/03	Year 1
$ 102,618	1/1/04 - 12/31/04	Year 2

Summary In patients with congenital diseases of skeletal muscle like muscular dystrophy, stem cells that normally restore muscle following injury fail to do so, possibly because these cells are blocked from proceeding beyond the early phase of muscle differentiation. Researchers have identified a new protein that promotes muscle differentiation. They propose to determine how this protein is regulated during muscle differentiation with the long-term objective of developing a treatment to promote muscle restoration.

Zuo-Zhong Wang, Ph.D.

(RG) Antigenic structure of acetylcholine receptor in myasthenia gravis (MG)

$ 70,000	7/1/02 - 6/30/03	Year 2
$ 70,000	7/1/03 - 6/30/04	Year 3

Summary This research is aimed at defining the molecular structure of antigenic determinants on the acetylcholine receptor responsible for stimulating the production of and binding to autoimmune antibodies from patients with MG.

(RG) Role of agrin in muscle development and regeneration

$ 100,000	7/1/03 - 6/30/04	Year 1
$ 100,000	7/1/04 - 6/30/05	Year 2

Summary This project will investigate the role of muscle agrin in ameliorating apoptotic cell death and promoting muscle fiber regeneration in an animal model of Duchenne muscular dystrophy.

Chuanyue Wu, Ph.D.

(RG) Role of muscle integrin binding protein in myogenic differentiation

$ 70,200	7/1/02 - 6/30/03	Year 3

Summary This project focuses on the role of a muscle protein (MIBP) in myoblast proliferation and differentiation, and may lead to new therapeutic approaches to control muscular dystrophies.

Pittsburgh - University of Pittsburgh (Cont'd)

Xiao Xiao, Ph.D.

(RG) AAV vectors for stem cell-mediated Duchenne muscular dystrophy gene therapy

$ 100,000 7/1/02 - 6/30/03 Year 1
$ 100,000 7/1/03 - 6/30/04 Year 2
$ 100,000 7/1/04 - 6/30/05 Year 3

Summary Researchers will use different serotypes of adeno-associated virus (AAV) to carry the therapeutic genes into the muscle-derived stem cells (MDSC) or directly into muscle tissues to treat DMD.

University Park - Pennsylvania State University

Fumiko Kawasaki, Ph.D.

(DG) Transgenic analysis of NSF function at neuromuscular synapses

$ 35,000 7/1/02 - 6/30/03 Year 3

Summary Molecular analysis of neuromuscular transmission: A role for untranslated mRNA sequences in NSF protein function.

TENNESSEE

Memphis - University of Tennessee

Harry Jarrett, Ph.D.

(RG) Muscular dystrophy relevant adapter proteins

$ 60,322 7/1/02 - 6/30/03 Year 3

Summary Protein adapters assemble complicated structures within cells that control whether a cell lives or dies. These structures may not form properly in muscular dystrophy, causing muscle wasting. By understanding these processes, drugs can be developed to help.

Nashville - Vanderbilt University

Charles Sanders, Ph.D.

(RG) Structure, folding and misfolding of PMP22

$ 60,000 7/1/03 - 6/30/04 Year 1

Summary Some forms of Charcot-Marie-Tooth disease (CMT) are caused by genetically-encoded mutations in peripheral myelin protein 22 (PMP22) which results in dysfunction of this protein and resulting disease. This project involves comparing the 3-D structure, stability, and folding behaviour of normal (healthy) PMP22 with disease-associated mutant forms of the protein. This may lead directly to the design of drugs for CMT: if we understand exactly what how disease mutations perturb the PMP22 protein then we know what it is we are trying to fix and can formulate novel drugs which are tailored to correct the problem.

TEXAS

College Station - Texas A&M University

John Lawler, Ph.D.
(RG) Oxidative stress and inflammatory and signaling in the diaphragm and limb muscles of mdx mice
$ 75,000 4/1/03 - 3/31/04 Year 1
Summary The most severe type of muscular dystrophy is Duchenne muscular dystrophy (DMD), and results in progressive skeletal muscle wasting and weakness. DMD results in inflammation of skeletal muscle. Investigators propose link between inflammation and muscle weakness is through "oxidative stress," where the production of oxidants overwhelms the antioxidant system. Their research will identify the cause of oxidative stress and muscle weakness with DMD including respiratory muscles. Their researchwill also identify specific targets for the design of antioxidant drugs that will relieve the symptoms of DMD.

Dallas - Texas Scottish Rite Hospital for Children

Susan T. Iannaccone, M.D.
(EMG) Restricted funds for SMA research
$ 50,000 4/1/02 - 3/31/03 Year 2

(EMG) Restricted funds for Duchenne muscular dystrophy research
$ 82,000 4/1/02 - 3/31/03 Year 4
$ 82,000 4/1/03 - 3/31/04 Year 5

Dallas - University of Texas Southwestern Medical Center

Stephen Cannon, M.D., Ph.D.
(RG) Cloning and characterization of two-pore potassium channels in skeletal muscle
$ 68,909 7/1/02 - 6/30/03 Year 2
$ 65,709 7/1/03 - 6/30/04 Year 3
Summary The nondystrophic myotonias and periodic paralyses are inherited disorders of skeletal muscle in which the primary defect is an alteration in the electrical excitability of the muscle fiber. Flaccid weakness and electrical inexcitability occur during attacks of periodic paralysis because of a failure to maintain the resting membrane potential (-90mV). The proposed studies will characterize a novel class of potassium channels that likely play a major role in setting the resting potential of skeletal muscle.

George DeMartino, Ph.D.
(RG) Regulation of muscle protein degradation by the proteasome
$ 80,604 7/1/02 - 6/30/03 Year 2
$ 83,786 7/1/03 - 6/30/04 Year 3
Summary This project will study the mechanisms that cause muscles to destroy proteins and atrophy.

Jeffrey Elliott, M.D.
(EMG) Restricted funds for ALS research
$ 83,636.98 4/1/02 - 3/31/03 Year 3

Ronald Haller, M.D.
(RG) Evaluation and treatment of metabolic myopathies
$ 80,304 1/1/03 - 12/31/03 Year 3
Summary Researchers will evaluate whether and by what means regular exercise or nutritional supplements improve exercise capacity in patients with mitochondrial or with glycolytic myopathies.

Mark Henkemeyer, Ph.D.
(RG) Wiring of the spinal cord: Roles for ephrin-B3 in the midline guidance of axons
$ 82,364 7/1/02 - 6/30/03 Year 2
$ 83,689 7/1/03 - 6/30/04 Year 3
Summary Experiments are proposed that will help in the understanding of how neurons form their connections with muscles to control locomotion and other motor activities.

Annette Meeson, Ph.D.
(DG) Molecular mechanisms of muscle regeneration and stem cell biology
$ 35,000 7/1/02 - 6/30/03 Year 3
Summary Researchers propose to use novel genetic mouse models and a "state of the art microarray analysis to increase our understanding of the regulation of muscle regeneration. It is the goal to use this information to propose novel approaches for treatment of muscular dystrophies such as Duchenne muscular dystrophy.

Osamu Nakagawa, M.D., Ph.D.
(RG) Roles of MEF2-regulated kinase Stk23 in muscular dystrophy
$ 65,000 7/1/03 - 6/30/04 Year 1
$ 65,000 7/1/04 - 6/30/05 Year 2
$ 65,000 7/1/05 - 6/30/06 Year 3
Summary Stk23 is a muscle-specific enzyme that modifies proteins relevant to muscular dystrophy. The mouse model expressing an excessive amount of Stk23 displays musce abnormalities reminiscent of muscular dystrophy. This proposal seeks to elucidate the signficance of Stk23 in muscle diseases, using molecular biology and various mouse models. This research will provide insights into muscle biology and the etiology of muscular dystrophy.

Eric Olson, Ph.D.
(RG) Regulation of skeletal muscle regeneration and development by the bHLH transcription factor
$ 60,000 1/1/03 - 12/31/03 Year 3
Summary This project will investigate the basic molecular mechanisms that control muscle regeneration in response to disease and the perturbation of this process in muscular dystrophy.

Jose Rizo-Rey, Ph.D.
(RG) Structure and function of MUNC13 and RIM
$ 80,568 4/1/03 - 3/31/04 Year 1
Summary The structural and biochemical properties of two presynaptic proteins, munc13 and RIM, will be studied to understand their function in neurotransmitter release.

Dallas - University of Texas Southwestern Medical Center (Cont'd)

James Stull, Ph.D.

(RG) Vascular derangements in limb-girdle muscular dystrophy type 2E (LGMD2E)

$ 63,382 1/1/03 - 12/31/03 Year 3

Summary Loss of b-sarcoglycan leads to LGMD2E. Loss of b-sarcoglycan in smooth muscle of blood vessels may result in vascular irregularities that aggravates skeletal and heart pathology. Researchers plan to determine if the loss of b-sarcoglycan from smooth muscle in blood vessels results in a hyper-contractile, vasospasm and thus contribute to the pathology.

Tanja Taivassalo, Ph.D.

(DG) Exercise training as therapy for mitochondrial myopathies

$ 45,000 1/1/03 - 12/31/03 Year 1

$ 45,000 1/1/04 - 12/31/04 Year 2

$ 45,000 1/1/05 - 12/31/05 Year 3

Summary The goal of this project is to determine the safety and efficacy of endurance and resistance exercise training in the treatment of patients with mitochondrial myopathies associated with mutations of mitochondrial DNA, who endure disabling fatigue and weakness. Endurance and resistance training are designed to induce normal adaptive proliferation of mitochondria from muscle and satellite (muscle precursor) cells respectively. The aim of both approaches is to increase levels of normal muscle itochondrial DNA and the capacity for mitochondrial energy production, thereby reducing symptoms of exercise intolerance.

Galveston - University of Texas

Raj Kumar, Ph.D.

(DG) Prevention of the protein aggregation caused by polyglutamine chain elongation in the androgen receptor

$ 45,000 1/1/03 - 12/31/03 Year 2

$ 45,000 1/1/04 - 12/31/04 Year 3

Summary In this proposal, the investigator will test the ability of an osmolyte, and a fragment of the glucocorticoid receptor to help prevent the protein aggregation due to polyglutamine stretch elongation. The results are expected to be of significance in developing osmolyte and/or gene therapy for SBMA and other related diseases.

Huan Yang, M.D., Ph.D.

(DG) Therapy of experimental myasthenia gravis (MG) with AChR peptide and anti-interleukin 6 (anti-IL6) antibody (Ab)

$ 35,000 1/1/03 - 12/31/03 Year 3

Summary Researchers will treat EAMG in HLA-DQ8 transgenic mice by human AChR T cell epitope tolerance and IL-6 neutralization to eliminate AChR-specific T cells and B cells and ameliorate clinical EAMG.

Houston - Baylor College of Medicine

Keltoum Anflous, Ph.D.

(DG) Control of mitochondrial respiration by the mitochondrial outer membrane
$ 45,000 1/1/03 - 12/31/03 Year 2
$ 45,000 1/1/04 - 12/31/04 Year 3

Summary Humans with mitochondrial respiration deficiency usually exhibit exercise intolerance. VDACs are the main pathways for small metabolites across the mitochondrial outer membrane. Previous results on VDAC1 deficient mice have reported alterations in mitochondrial function and structure in heart and skeletal muscles. Investigators are seeking funding to extend these studies to VDAC3 and VDAC1/VDAC3 deficient mice. The investigator will also measure the respiratory enzyme activities and evaluate the exercise tolerance in control and VDACs deficient mice.

Stanley H. Appel, M.D.

(EMG) Restricted funds for the support of the Ronny and Linda Finger MDA/ALS Center
$ 12,815 4/1/02 - 3/31/03 Year 5

(PPG) Allogeneic adoptive immunotherapy for amyotrophic lateral sclerosis
$ 200,000 1/1/03 - 12/31/03 Year 2

Summary Investigators will use a modified bone marrow transplant strategy to block a potential autoimmune response in ALS. Patients will be followed for five years post-transplant to evaluate rates of respirator dependence and mortality.

(RG) Immune mechanisms in amyotrophic lateral sclerosis (ALS)
$ 92,664 7/1/02 - 6/30/03 Year 2
$ 96,371 7/1/03 - 6/30/04 Year 3

Summary These studies will investigate whether increased intracellular calcium in motorneurons is a common early change in genetic and immune-mediated models of ALS and whether the calcium-binding protein parvalbumin can protect against such injury.

(EMG) Restricted funds for ALS research
$ 1,002,575 4/1/02 - 3/31/03 Year 1

Michael Barry, Ph.D.

(RG) Development of biotinylated gene therapy vectors
$ 100,000 1/1/03 - 12/31/03 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.

(RG) Development of muscle-targeting gene therapy vectors
$ 110,157 7/1/02 - 6/30/03 Year 2
$ 114,303 7/1/03 - 6/30/04 Year 3

Summary This project will identify proteins to seek out and target therapeutic drugs, genes, or cells to he diseased muscle. This project will determine the usefulness of these proteins by testing whether they can delivery genes specifically to muscle cells in the body for the treatment of Duchenne and other muscular dystrophies.

Houston - Baylor College of Medicine (Cont'd)

Henry F. Epstein, M.D.

(RG) A molecular chaperone in muscle development and atrophy

$	70,000	1/1/03 - 12/31/03	Year 2
$	70,000	1/1/04 - 12/31/04	Year 3

Summary UNC-45 protein is suggested to be a key regulator of whether myosin assembles into thick filaments and remains a stable protein in muscle, or whether it is shunted to the major proteolytic degradation systems. Any effective therapy of neuromuscular diseases must lead to the increased production and stabilization of myosin and its assembly into functioning thick filaments. Researchers wish to investigate the role of UNC-45 in these processes using the genetics of the laboratory mouse.

(RG) Regulation of myotonic dystrophy protein kinase (DMPK) in brain

$	76,237	7/1/02 - 6/30/03	Year 1
$	79,244	7/1/03 - 6/30/04	Year 2
$	82,371	7/1/04 - 6/30/05	Year 3

Summary Myotonic dystrophy affects many organs of the human body. Severe mental retardation is associated with neonatal myotonic dystrophy, and significant cognitive deficits are associated with disease of later onset. The proposed research seeks to understand the molecular mechanisms in brain underlying these significant problems.

Margaret Goodell, Ph.D.

(RG) Stem cell transplantation for therapy of neuromuscular disease

$	95,000	7/1/02 - 6/30/03	Year 1
$	95,000	7/1/03 - 6/30/04	Year 2
$	95,000	7/1/04 - 6/30/05	Year 3

Summary Recent studies have suggested that cells from bone marrow may be able to be used to repair skeletal and cardiac muscle. The goal is to determine the exact cell types involved and study the mechanisms of repair. Researchers hope that better understanding of the cells and mechanisms will allow us to determine how to improve the efficiency for future clinical use. The stem cell repair strategies that they envision will be potentially applicable to all types of neuromuscular disease.

Yasuo Hamamori, M.D., Ph.D.

(RG) Regulation of muscle differentiation by notch effectors

$	93,954	7/1/03 - 6/30/04	Year 1
$	95,294	7/1/04 - 6/30/05	Year 2
$	96,661	7/1/05 - 6/30/06	Year 3

Summary Muscular dystrophy has the loss of muscle mass due to muscle degradation, and the treatment will depend on growth of muscle fibers. One potential therapeutic approach is to promote growth of satellite cells that become myofibers. Notch signaling stimulates satellite cell growth. Therefore, growth of satellite cells could be greatly enhanced by activating Notch with drugs and gene therapy. Notch actions are mediated by effector proteins. However, Notch effectors in muscle are unknown. Researchers previously isolated such effector candidate genes, HERP. This study is designed to analyze HERP functions in muscle cells. Thus, knowledge from the study might ultimately contribute to development of new therapeutics for muscular dystrophy, based on satellite cell growth promotion.

Houston - Baylor College of Medicine (Cont'd)

Susan Hamilton, Ph.D.

(RG) Alterations in the calcium release channel in central core disease, malignant hyperthermia, and nemaline myopathy

$ 58,633 7/1/02 - 6/30/03 Year 2
$ 60,833 7/1/03 - 6/30/04 Year 3

Summary The research described in this application is designed to elucidate the molecular mechanisms by which mutations in the skeletal muscle calcium release channel produce central core disease (CCD) and malignant hyperthermia (MH). The strategy is to analyze the structure and function of the two parts of the protein where the mutations occur.

Jenny Henkel, Ph.D.

(DG) The role of dendritic cells in ALS pathogenesis

$ 45,000 7/1/02 - 6/30/03 Year 1
$ 45,000 7/1/03 - 6/30/04 Year 2
$ 45,000 7/1/04 - 6/30/05 Year 3

Summary Increasing evidence implicates inflammatory reactions in the pathogenesis of ALS. The preliminary studies document that specialized immune cells-dendritic cells-are present in ALS spinal cord and correlate with rapid disease progression. Reseachers have also detected an increase in ALS tissue of the chemokine signal (MCP-1) that can recruit dendritic cells into the spinal cord. They will confirm these results with other markers of immune cells in ALS spinal cord and in mouse and rat models of ALS; and will determine whether preventing dendritic cell infiltration can prevent disease in the ALS animal model.

Ken Inoue, M.D., Ph.D.

(DG) SOX10 and EGR2 transcription pathways may regulate genes involved in Charcot-Marie-Tooth (CMT)

$ 35,000 1/1/03 - 12/31/03 Year 3

Summary Researchers seek to identify genes and molecular mechanisms responsible for common inherited neuropathies.

Kathyjo Jackson, Ph.D.

(DG) Improvement of bone marrow incorporation into skeletal muscle

$ 45,000 1/1/03 - 12/31/03 Year 1
$ 45,000 1/1/04 - 12/31/04 Year 2
$ 45,000 1/1/05 - 12/31/05 Year 3

Summary Bone marrow-derived cells have been shown to participate in muscle regeneration following injury, but the levels of engraftment were to low to be of use in a clinical setting. The experiments outlined in this proposal attempt to unravel the factors that inhibit bone marrow incorporation into regenerating skeletal muscle fibers. The factors being tested include recruitment of bone marrow-derived cells to regenerating tissue, and bone marrow incorporation when muscle stem cells are inhibited or absent. Once the mechanisms of inhibition are known, clinical treatments can be developed for fighting neuromuscular diseases.

James Lupski, M.D., Ph.D.

(RG) Molecular genetics of Charcot-Marie-Tooth (CMT)

$ 90,000 7/1/02 - 6/30/03 Year 3

Summary Researchers work seeks to determine the complete structure of a genomic region important to common inherited peripheral neuropathies.

Houston - Baylor College of Medicine (Cont'd)

Minako Oshima, Ph.D.

(RG) Suppression of myasthenia gravis (MG) by targeting MHC

$	75,000	1/1/03 - 12/31/03	Year 2
$	75,000	1/1/04 - 12/31/04	Year 3

Summary This project will investigate the efficacy of new immunological treatments for MG, by targeting gene products related to this disease.

Pragna Patel, Ph.D.

(RG) Regulation of PMP22, the gene underlying CMT1A and HNPP

$	89,726	7/1/02 - 6/30/03	Year 2
$	89,902	7/1/03 - 6/30/04	Year 3

Summary Researchers will confirm the ability of a short DNA sequence associated with the PMP22 gene (which underlies Charcot-Marie-Tooth disease type 1A) to amplify levels of PMP22 mRNA. Researchers will identify and characterize the protein(s) that are responsible for this activity. They will develop an assay to allow identification of pharmaceutical agents to modulate levels of PMP22 as a therapeutic strategy.

Michael Reid, Ph.D.

(RG) Redox mechanisms in dystrophic muscle

$	72,388	7/1/02 - 6/30/03	Year 2
$	72,388	7/1/03 - 6/30/04	Year 3

Summary Researchers will test a hypothesis using muscles from mice that develop muscular dystrophy. They will determine the type(s) of free radicals produced in dystrophic muscle and the effects of these molecules on protein breakdown. The resulting data will advance our understanding of muscular dystrophy and may identify new targets for therapeutic intervention.

Carolyn Sue Richards, Ph.D.

(RG) Dystrophin sequence variations, biological and clinical consequences

$	74,290	1/1/03 - 12/31/03	Year 2

Summary An important aspect of future therapeutic applications for DMD/BMD is the ability to detect virtually all of the molecular defects in the dystrophin gene, which is the focus of this proposal.

Irina Serysheva, Ph.D.

(RG) Structure-function correlations within skeletal muscle L-type Ca2+ channel

$	76,572	1/1/03 - 12/31/03	Year 1
$	77,047	1/1/04 - 12/31/04	Year 2
$	78,366	1/1/05 - 12/31/05	Year 3

Summary In skeletal muscle, the excitation-contraction (EC) coupling is thought to result from direct coupling between the voltage-gated L-type calcium channel and the sarcoplasmic reticulum calcium release channel. The primary focus of this research is to define structural domains critical for EC coupling, in the three-dimensional architecture of the L-type channel by using electron cryomicroscopy and single-particle processing.

George Snipes, M.D., Ph.D.

(RG) Cellular biology of Charcot-Marie-Tooth (CMT) related disorders

$	84,507	7/1/02 - 6/30/03	Year 2
$	84,507	7/1/03 - 6/30/04	Year 3

Summary Researchers will investigate the effects of mutations in myelin proteins that cause CMT disease to better understand myelin biology and develop effective therapies.

Houston - Baylor College of Medicine (Cont'd)

Lubov Timchenko, Ph.D.

(RG) CUGBP1 transgenic mice as a model for congenital myotonic dystrophy (DM)

$	75,000	1/1/03 - 12/31/03	Year 2
$	75,000	1/1/04 - 12/31/04	Year 3

Summary This project is focused on the identification of molecular pathways by which the elevation of CUGBP1 in DM tissues disturbs skeletal muscle function. The performance of this project will help establish a therapy to prevent and treat the DM disease.

Jeffrey Towbin, M.D.

(RG) The cytoskeleton in cardiomyopathies and muscular dystrophy

$	94,554	7/1/02 - 6/30/03	Year 2
$	97,393	7/1/03 - 6/30/04	Year 3

Summary Researchers will identify basic mechanisms responsible for the development of dilated cardiomyopathy, a primary form of heart muscle dysfunction.

John Wilson, Ph.D.

(RG) Molecular basis of dynamic mutation in Friedreich's ataxia (FA)

$	73,008	7/1/02 - 6/30/03	Year 2
$	74,520	7/1/03 - 6/30/04	Year 3

Summary Researchers propose a comprehensive set of experiments, using selectable genes in mammalian cells, to define the basis for the GAA/TTC repeat instability that underlies the most common form of FA.

Houston - Texas A & M University

Robert D. Wells, Ph.D.

(EMG) Restricted funds for Friedreich's ataxia research

$	19,191	4/1/03 - 3/30/04	Year 1

Houston - University of Texas

Roger Janz, Ph.D.

(RG) Role of SV2C at the neuromuscular junction

$	68,025	7/1/02 - 6/30/03	Year 2
$	73,120	7/1/03 - 6/30/04	Year 3

Summary Researchers want to study the role of a newly discovered protein at the neuromuscular junction. This protein named SV2C will be studied by generating mice with a null mutation in the SV2C gene by genetic engineering. The phenotype of the mutant mice will be investigated. Researchers predict that these studies will lead to a better understanding of the molecular components that are important for the neuromuscular synapse.

Houston - University of Texas M.D. Anderson CancerCenter

William Klein, Ph.D.

(RG) Myogenin's role as an essential transcription factor in skeletal muscle formation

$	71,984	1/1/03 - 12/31/03	Year 3

Summary The fundamental question of how an undifferentiated pre-muscle cell differentiates into a muscle cell is largely unanswered. Myogenin is a regulatory protein whose role is to activate genes that define the skeletal muscle cell. Researchers will address how myogenin performs this essential function in pre- and postnatal life.

Houston - University of Texas M.D. Anderson CancerCenter (Cont'd)

Robert Schulz, Ph.D.
(RG) Intercellular signaling in muscle cell specification
$ 75,247 1/1/03 - 12/31/03 Year 3
Summary This research will investigate mechanisms of communication between neural and myoblast cells needed for the formation of muscle precursor cells.

San Antonio - University of Texas

Eileen Lafer, Ph.D.
(RG) Basic mechanisms underlying neurotransmission
$ 85,532 1/1/03 - 12/31/03 Year 1
$ 88,909 1/1/04 - 12/31/04 Year 2
$ 92,422 1/1/05 - 12/31/05 Year 3
Summary This research focuses on understanding basic mechanisms which underlie nerve-muscle communication. Defects in this process have been associated with Eaton-Lambert's syndrome, congenital myasthenic syndromes, distal muscular dystrophy, oculopharyngeal muscular dystrophy and congenital muscular dystrophy. This work may lead to the rationale design of therapeutic strategies for the treatment of neuromuscular disease.

UTAH

Logan - Utah State University

Peter Ruben, Ph.D.
(RG) Sodium channel deactivation in non-dystrophic myotonia
$ 75,000 7/1/02 - 6/30/03 Year 2
$ 75,000 7/1/03 - 6/30/04 Year 3
Summary Certain paralytic diseases are caused by changes in protein structure. This study will measure how protein properties is altered by those changes in protein structure, and how therapeutic pharmaceutical agents act on those properties.

Salt Lake City - University of Utah

John Atkins, Ph.D.
(RG) Aminoglycoside suppression of dystrophin mutations
$ 80,497 1/1/03 - 12/31/03 Year 3
Summary Researchers propose to determine the sequence specific factors which influence aminoglycoside suppression of stop codon mutations and suppress frameshift mutations. This information may be used to predict patient response to aminoglycoside treatment and may allow treatment regimes to be tailored to individual patients.

Mark B. Bromberg, M.D., Ph.D.
(EMG) Restricted funds for ALS research
$ 46,650 4/1/02 - 3/31/03 Year 2

Salt Lake City - University of Utah (Cont'd)

Kevin Flanigan, M.D.

(RG) Molecular and phenotypic characterization of facioscapulohumeral dystrophy (FSHD) in Utah

$ 54,756 7/1/02 - 6/30/03 Year 2

Summary By studying the genetic and clinical characteristics of large families affected by FSHD, researchers propose to clarify the fundamental molecular mechanisms of the disease.

Louis Ptacek, M.D.

(RG) Characterizing potassium channels causing periodic paralysis

$ 95,920 1/1/03 - 12/31/03 Year 3

Summary This proposal is aimed at studying mutations in two new periodic paralysis genes, to look for additional periodic paralysis genes and to identify a gene for Andersen's syndrome, a type of periodic paralysis with heart arrhythmias.

Kathryn J. Swoboda, M.D.

(RG) Refinement of outcome parameters for clinical trials in SMA

$ 44,963 7/1/03 - 6/30/04 Year 1

$ 44,963 7/1/04 - 6/30/05 Year 2

$ 44,963 7/1/05 - 6/30/06 Year 3

Summary MUNE is a technique which allows us to make an estimate fo the number of motor neurons in the spinal cord supplying a particular muscle. It is noninvasive, causes minimal discomfort and requires no voluntary participation, so that even infants and young children with SMA can be tested. Investigators propose to evalute MUNE in conjunction with other measures including SMN2 copy number, SMN protein and RNA levels, lean muscle mass as measured by DEXA scanning, and functional status. Such information will ensure the development of appropriate clinical trial design for assessing promising new therapies in SMA patients.

VIRGINIA

Blacksburg - Virginia Polytechnic Institute

Robert Grange, Ph.D.

(RG) Mechanisms of force loss in Duchenne s muscular dystrophy (DMD)

$ 49,064 7/1/03 - 6/30/04 Year 1

Summary Researchers will determine if the loss of muscle force in Duchenne's muscular dystrophy is due to muscle membrane damage or due to changes in the proteins that produce force in the muscle. They believe the initial force loss in DMD muscle is independent of membrane damage. These studies will help us understand the early stages of DMD pathogenesis.

Charlottesville - University of Virginia

Mani S. Mahadevan, M.D.

(RG) Identifying targets for effects of DMPK mRNA on muscle differentiation

$	70,000	1/1/03 - 12/31/03	Year 2
$	70,000	1/1/04 - 12/31/04	Year 3

Summary Investigators will study how the mutant myotonic dystrophy protein kinase (DMPK) mRNA acts as a toxic molecule to impair muscle development and muscle regeneration using a muscle cell culture model. The model is also an excellent system that will be used for identifying target moleculares and pathways for screening potential therapeutic strategies.

Sonia Pearson-White, Ph.D.

(EMG) Restricted funds for research

$	200	4/1/02 - 3/31/03	Year 2

(RG) TGF- b signaling pathways and muscle regeneration

$	78,792	7/1/02 - 6/30/03	Year 3

Summary Researchers are examining the mechanism by which TGF-B and the Sno proto-oncogene regulate skeletal muscle regeneration after traumatic or neuromuscular disease injury.

Norfolk - Eastern Virginia Medical School

Earl Godfrey, Ph.D.

(RG) Role of nitric oxide synthase pathway in neuromuscular development

$	89,800	7/1/03 - 6/30/04	Year 1
$	90,450	7/1/04 - 6/30/05	Year 2
$	93,120	7/1/05 - 6/30/06	Year 3

Summary Investigators will study how nitric oxide synthese acts in forming nerve-muscle connections, and how it may increase utrophin, which could limit degeneration in muscular dystrophies.

WASHINGTON

Seattle - Fred Hutchinson Cancer Research Center

F. Jeffrey Dilworth, Ph.D.

(DG) Delineating the molecular mechanism of muscle development

$	35,000	7/1/02 - 6/30/03	Year 2
$	35,000	7/1/03 - 6/30/04	Year 3

Summary An in vitro transcription system will be used to examine how myogenic basic helix-loop-helix proteins mediate differential gene expression to regulate skeletal muscle development.

Marie-Terese Little, Ph.D.

(RG) Allogeneic stem cell transplantation in the canine DMD (cxmd) model

$	133,140	7/1/02 - 6/30/03	Year 2
$	137,102	7/1/03 - 6/30/04	Year 3

Summary Researchers propose to examine if allogeneic stem cell transplantation can 1) restore dystrophin expression in dogs affected with canine X-linked muscular dystrophy (cxmd) and 2) promote a state of tolerance to insure long-term maintenance of the transplanted cells and continued dystrophin expression.

Seattle - University of Washington

Marvin Adams, Ph.D.

(DG) Syntrophin regulation of utrophin and acetylcholine receptor levels

$ 35,000 1/1/03 - 12/31/03 Year 3

Summary This project will investigate how the dystrophin associated protein, a-syntrophin, regulates expression of the neuromuscular junction proteins utrophin and acetylcholine receptor.

William Catterall, Ph.D.

(RG) Regulation of Ca2+ channel by protein phosphorylation

$ 83,325 7/1/02 - 6/30/03 Year 1
$ 85,734 7/1/03 - 6/30/04 Year 2
$ 88,238 7/1/04 - 6/30/05 Year 3

Summary Forceful contractions of human muscles are caused by high frequency discharges of the motor nerves which innervate them. This project will examine the molecular mechanism of this process by analyzing the regulation of the calcium channels of normal and dystrophic skeletal muscle by rapid electrical stimulation and by activation of hormonal regulatory pathways.

Jeffrey Chamberlain, Ph.D.

(EMG) Restricted funds for research

$ 292,938 4/1/02 - 3/31/03 Year 3

(RG) Viral vectors for gene therapy of muscular dystrophy

$ 130,000 7/1/02 - 6/30/03 Year 2
$ 130,000 7/1/03 - 6/30/04 Year 3

Summary This project will develop new, safer viral vectors for delivery of therapeutic genes to muscle. If successful, such vectors could be tested in clinical trials for gene therapy of muscular dystrophy.

Phillip F. Chance, M.D.

(RG) Gene isolation in families with Charcot-Marie-Tooth type 1C (CMT1C)

$ 60,225 7/1/02 - 12/31/03 Year 3

Summary Researchers are pursuing the genetic element causing an inherited peripheral neuropathy called CMT1C in two large multi-generational families referred to as K1550 and K1551.

(RG) Genetic analysis in juvenile amyotrophic lateral sclerosis (ALS)

$ 90,307 7/1/02 - 12/31/03 Year 3

Summary Researchers seek to identify a gene for an adolescent-onset form of Lou Gehrig's disease so that insights into how an abnormality in this gene leads to this disorder.

Ying-Zhang Chen, M.D., Ph.D.

(DG) Genetic analysis in amyotrophic lateral sclerosis 4 (ALS4)

$ 45,000 7/1/02 - 6/30/03 Year 1
$ 45,000 7/1/03 - 6/30/04 Year 2
$ 45,000 7/1/04 - 6/30/05 Year 3

Summary The goal of this project is to identify and characterize the gene mapping to chromosome 9 that carries mutations within six multigenerational families affected by a form of adolescent Lou Gehrig's disease or classical ALS. This gene identification may provide valuable clues into the molecular disease mechanism of devastating classical Lou Gehrig's disease.

Seattle - University of Washington (Cont'd)

Stanley C. Froehner, Ph.D.

(RG) Dystrobrevins and syntrophins in human muscular dystrophies

$	92,172	7/1/02 - 6/30/03	Year 2
$	95,815	7/1/03 - 6/30/04	Year 3

Summary Researchers will determine if muscular dystrophies in humans are caused by mutations in the seven genes that produce syntrophins and dystrobrevins, two interesting protein families in the dystrophin complex. It is known that disruption fo the alpha-dystrobrevin gene causes muscular dystrophy in mice. Their work will attempt to extend this observation to humans. A full understanding of the potential for abnormalities in the dystrophin complex to cause human muscular dystrophies is important in designing rationale.

(EMG) Restricted funds for research

$	130,248	4/1/02 - 3/31/03	Year 2

Stephen D. Hauschka, Ph.D.

(RG) Regulatory cassettes for expressing therapeutic proteins in diseased muscle

$	104,972	7/1/02 - 6/30/03	Year 1
$	107,083	7/1/03 - 6/30/04	Year 2
$	112,500	7/1/04 - 6/30/05	Year 3

Summary Muscle gene therapy requires high expression of the therapeutic gene in muscle and low expression in nonmuscle cells. Regulatory cassettes designed in these studies seek to achieve this goal with many vector types presently used for gene transfer. Special versions of these cassettes may also permit physicians to optimize the levels of therapeutic products produced in each patient by administering non-toxic drugs that control product expression levels.

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

(RG) Modeling motor neuron degeneration in spinal bulbar muscular atrophy (SBMA)

$	79,816	1/1/03 - 12/31/03	Year 3

Summary SBMA is an adult onset form of spinal muscular atrophy affecting only men. This research is aimed at the production of an accurate mouse model of SBMA. With an SBMA mouse available, researchers will be able to determine why motor neurons are dying and to test potential use available, researchers will be able to determine why motor neurons are dying and to test potential therapies.

Sheng Li, M.D., Ph.D.

(DG) Developing bone marrow stem cell based ex vivo gene therapy for Duchenne muscular dystrophy (DMD)

$	45,000	1/1/03 - 12/31/03	Year 1
$	45,000	1/1/04 - 12/31/04	Year 2
$	45,000	1/1/05 - 12/31/05	Year 3

Summary Researchers will explore the use of bone marrow stem cells to systemically deliver therapeutic dystrophins into widely distributed muscles of mdx mice, a DMD animal model.

Seattle - University of Washington (Cont'd)

Valerie Street, Ph.D.

(DG) Gene isolation in families with Charcot-Marie-Tooth neuropathy type 1C (CMT1C)

$ 10,000 1/1/03 - 12/31/03 Year 3
$ 35,000 1/1/03 - 12/31/03 Year 3

Summary Researchers are pursuing the genetic element causing an inherited peripheral neuropathy called CMT disease in two large multi-generational families referred to as K1550 and K1551.

Inez Vincent, Ph.D.

(RG) Cdk5 inhibitors to treat amyotrophic lateral sclerosis (ALS)

$ 82,499 7/1/03 - 6/30/04 Year 1

Summary Goaded by their success using cdk5 inhibitors to block progressive Niemann-Pick type C neurodegeneration in mice, researchers will determine if a similar strategy abolishes neurodegeneration in ALS mice.

WISCONSIN

Madison - University of Wisconsin

Benjamin R. Brooks, M.D.

(RG) Retrovirus expression in human motor neuron diseases

$ 31,728 7/1/02 - 6/30/03 Year 2

Summary Recent reports indicate (i) retroviral activity in the serum of a majority of ALS patients, (ii) antibodies to retroviral proteins in ALS patient serum, and (iii) that anti-retroviral therapy improved the ALS of a patient who also has AIDS. Researchers will examine serum and cells from ALS patients for retroviral activity, particles, and transmissibility to cultured cells. They will also look for retroviral genes in ALS using methods that identified retroviruses associated with multiple sclerosis and schizophrenia.

(RG) Protein kinase C inhibitor therapy in amyotrophic lateral sclerosis (ALS)

$ 38,165 1/1/03 - 12/31/03 Year 3

Summary A preliminary phase 2 dose-escalation clinical trial will determine if there is a clinical benefit on computerized muscle strength in ALS patients.

James M. Ervasti, Ph.D.

(RG) Role of costameric actin in dystrophinopathies

$ 96,498 7/1/02 - 6/30/03 Year 1
$ 91,079 7/1/03 - 6/30/04 Year 2
$ 94,593 7/1/04 - 6/30/05 Year 3

Summary It is necessary to understand the physiologic function of dystrophin in order to most effectively focus efforts to design effective therapies for individuals suffering from dystrophinopathies like Duchenne and Becker muscular dystrophies. The objective of this project is to elucidate how defects in gamma-actin contribute to the pathogenesis of dystrophin-deficient muscular dystrophies.

John Svaren, Ph.D.

(RG) The role of EGR2 dysfunction in peripheral neuropathies

$ 57,592 7/1/02 - 6/30/03 Year 3

Summary The proposed project examines how mutations of the EGR2 gene cause peripheral nerve disease by interfering with formation of the myelin sheath of peripheral nerves.

Madison - University of Wisconsin (Cont'd)

Jon Wolff, M.D.

(RG) Intravascular injection of naked plasmid DNA into the mouse model for Duchenne muscular dystrophy (DMD)

$ 103,551 7/1/02 - 6/30/03 Year 2
$ 109,469 7/1/03 - 6/30/04 Year 3

Summary Researchers have spectacular preliminary results that show that a gene within a plasmid can be delivered via blood vessel into more than 10% of the muscle cells throughout the limbs of rats and monkeys. This approaches the critical minimum percentage necessary to be curative in children with DMD. Their studies also indicate that this approach should lead to stable expression of the gene. Given the huge success in these animals, clinical trials in humans could begin in the future based upon these animal studies in the mouse model.

Milwaukee - University of Wisconsin

R. David Heathcote, Ph.D.

(RG) Dystroglycan and synaptic differentiation on muscle

$ 60,652 1/1/03 - 12/31/03 Year 2
$ 63,576 1/1/04 - 12/31/04 Year 3

Summary Dystroglycan, a critical membrane link, is reduced in Duchenne and Becker muscular dystrophy. This proposal examines dystroglycan regulation and function by increasing its production. It also studies the role of the muscle in stimulating maturation of the nerve terminal. Nerve muscle communication is disrupted in myasthenia gravis.

ARGENTINA

Buenos Aires - University of Buenos Aires

Osvaldo Uchitel, M.D., Ph.D.

(RG) Calcium and potassium channels function in neuromuscular transmitter release

$ 27,000 7/1/02 - 6/30/03 Year 2
$ 27,000 7/1/03 - 6/30/04 Year 3

Summary Researchers plan to study the expression, localization and physiological role of L-type calcium channels, and fast transient potassium channels. An understanding of their role is essential to gain insights into the defaults in synaptic transmission and for the search and design of drugs acapable of modulating short and long term synaptic functions in particular at the neuromuscular junction. Therefore, patients with myasthenia gravis, Lambert-Eaton syndrome and ALS will have a direct benefit.

AUSTRALIA

Concord - University of Sydney

Garth Nicholson, Ph.D.

(RG) Construction and characterisation of hereditary sensory neuropathy type I transgenic mouse

$	44,401	7/1/02 - 6/30/03	Year 1
$	44,107	7/1/03 - 6/30/04	Year 2
$	47,065	7/1/04 - 6/30/05	Year 3

Summary Hereditary sensory neuropathy type I is the most common hereditary cause of severe sensory loss in the feet and hands in man. Researchers recently found the damaged gene (gene mutation) in an enzyme of known function. In order to understand how this mutation causes disease this study aims to create a model of the disease in mouse with the long term hope of developing effective treatment.

Fitzroy - University of Melbourne

Andrew Kornberg, M.D.

(RG) SFHR dystrophin gene repair in the mouse, dog and human Duchenne muscular dystrophy (DMD)

$	59,769	1/1/03 - 12/31/03	Year 3

Summary Researchers seek to improve gene repair efficiency in mdx mouse muscle and stem cells. They will use the repaired cells from the animal models for remodelling dystrophic muscle and repair the frame-shift deletion in cell lines from boys with DMD and the splice mutation in GRMD dog myoblasts.

Melbourne - Murdoch Children's Research Institute

Panayiotis Ioannou, Ph.D.

(EMG) Restricted for Friedreich's ataxia research

$	50,000	4/1/02 - 3/31/03	Year 2

Melbourne - Royal Children's Hospital

Hans-Henrik Dahl, Ph.D.

(RG) Molecular and genetic investigations of autosomal dominant progressive external ophthalmoplegia (ADPEO)

$	60,413	7/1/02 - 6/30/03	Year 2

Summary Researchers will identify and characterize causative genes for adPEO, thereby improving diagnosis and counseling. They will also generate animal models crucial for the development of therapies.

Panayiotis Ioannou, Ph.D.

(RG) Novel approaches to the therapy of Friedreich's ataxia (FA)

$	50,000	7/1/02 - 6/30/03	Year 3

Summary A sensitive assay will be developed for agents that may overcome the effects of the most common mutation in FA, as a potential form of drug therapy for such patients.

Melbourne - Royal Children's Hospital (Cont'd)

David Thorburn, Ph.D.

(RG) Molecular genetics of mitochondrial complex I deficiency
$ 58,431 7/1/02 - 6/30/03 Year 3

Summary Researchers aim to identify the genes causing mitochondrial respiratory chain complex I deficiency in order to improve diagnosis, counseling, treatment and prevention.

Melbourne - University of Melbourne

Gordon Lynch, Ph.D.

(RG) Functional roles of utrophin and dystrophin in animal models of Duchenne muscular dystrophy
$ 64,256 4/1/03 - 3/31/04 Year 1

Summary Muscle wasting is one of the major symptoms of many neuromuscular disorders, including Duchenne muscular dystrophy, the most severe of the muscle diseases. This project will investigate the role of exogenous IGF-I administration for ameliorating muscle wasting and preserving muscle function in muscular dystrophy.

(RG) Growth factor therapy for improving muscle function in muscular dystrophy
$ 81,682 7/1/03 - 6/30/04 Year 1
$ 83,264 7/1/04 - 6/30/05 Year 2
$ 84,843 7/1/05 - 6/30/06 Year 3

Summary Muscle wasting and weakness are symptoms of neuromuscular disorders, including Duchenne muscular dystrophy. This project investigates the potential for growth factor (IGF-I and/or IL-15) administration to ameliorat emuscle wasting and improve function in muscular dystrophy. The aim is to develop a treatment that will provide an immediate improvement in the quality of life for muscular dystrophy patients.

(RG) IGF-I treatment for improving muscle function in muscular dystrophy
$ 51,855 7/1/02 - 6/30/03 Year 3

Summary Muscle wasting is one of the major symptoms of many neuromuscular disorders, including Duchenne muscular dystrophy, the most severe of the muscle diseases. This project will investigate the role of exogenous IGF-I administration for ameliorating muscle wasting and preserving muscle function in muscular dystrophy.

Murdoch - Murdoch University

John M. Howell, DVSc, FRCPath

(RG) Gene therapy for an ovine model of McArdle's disease
$ 25,000 1/1/03 - 12/31/03 Year 3

Summary Gene therapy treatment trials are being undertaken in sheep with McArdle's disease to induce the production in muscles of the enzyme the absence of which leads to disease in humans.

Murdoch - Murdoch University (Cont'd)

John M. Howell, DVSc, FRCPath

(RG) Gene transfer to mature muscle in myophosphorylase deficiency

$	64,800	7/1/02 - 6/30/03	Year 1
$	56,160	7/1/03 - 6/30/04	Year 2
$	82,080	7/1/04 - 6/30/05	Year 3

Summary The phosphorylase-deficient sheep provide an excellent model for McArdle's disease in which to evaluate enzyme production by the approach of gene transfer. Once this is achieved effectively, progression to human gene trials can be envisaged.

Nedlands - University of Western Australia

Luba Kalaydjieva, M.D., Ph.D.

(RG) Cloning the gene for a severe autosomal recessive form of Charcot-Marie-Tooth (CMT) disease

$	49,334	1/1/03 - 12/31/03	Year 2

Summary Molecular studies of CMT disease are likely to provide an insight into the development, differentiation and maintenance of the PNS, and demyelinating neuropathies. With MDA support, researchers have mapped HMSNR to a small interval on 10q23 in close proximity to EGR2. Through the analysis of additional families and the Human Genome Project, cloning of the HMSNR gene will allow functional studies.

Nigel Laing, Ph.D.

(RG) Investigation of childhood onset distal myopathy myosin variants

$	58,103	1/1/03 - 12/31/03	Year 1
$	58,414	1/1/04 - 12/31/04	Year 2

Summary This project aims to determine how the myosin mutations identified in childhood onset distal myopathy cause the disease.

Leanne Sammels, Ph.D.

(RG) Modulation of the acute inflammatory response to enhance transplant therapies for Duchenne muscular dystrophy (DMD)

$	75,000	7/1/02 - 6/30/03	Year 1
$	75,000	7/1/03 - 6/30/04	Year 2

Summary This proposal is focused on improving the success of MTT specifically to reduce the early death of donor myoblasts by modifying the hosts rapid and nonspecific inflammatory response. In addition, a new multiple immunosuppressive drug therapy to control the host specific immune response to MTT will be investigated. The goal of this research is to understand the mechanisms that result in the rapid and massive death of donor myoblasdts after transplntation and, in doing so, develop new intervention strategies to greatly improve MTT as a treatment of DMD in humans.

Stephen Wilton, Ph.D.

(RG) Antisense oligonucleotide genetic therapy for Duchenne muscular dystrophy (DMD)

$	50,264	1/1/03 - 12/31/03	Year 3

Summary Nucleic acid drugs may allow DMD patients to by-pass/skip their dystrophin gene mutation. A DMD gene would be processed into a milder Becker-like gene transcript with a reduction in disease severity.

Parkville - University of Melbourne

Robert Kapsa, Ph.D.

(RG) Improved delivery of wt dystrophin locus in the mdx mouse

$	75,531	7/1/02 - 6/30/03	Year 1
$	65,195	7/1/03 - 6/30/04	Year 2
$	66,545	7/1/04 - 6/30/05	Year 3

Summary Boys affected by Duchenne muscular dystrophy (DMD) undergo a progressive loss of the cells responsible for the regeneration of muscle after the muscle breakdown associated with DMD. Using a mouse model, the mutation causing DMD has been corrected in up to 20% of cells in cultured muscle cells. If this can be done in stem cells from non-muscle tissues such as liver, fat and skin which are relatively renewable tissues, then these cells can be returned after genetic correction as autologous transplants to supplement the depleted muscle cells of boys with DMD. This project aims to characterize the best cell types for this purpose and optimize the delivery of these cells to dystrophic muscle in the mdx mouse.

Perth - University of Western Australia

Miranda Grounds, Ph.D.

(RG) IGF-1 based stem cell therapy and rescue of Duchenne muscular dystrophy (DMD)

$	150,000	4/1/02 - 3/31/03	Year 2
$	150,000	4/1/03 - 3/31/04	Year 3

Summary Novel stem cell therapy and conventional myoblast transfer therapy are strategies to replace the missing protein dystrophin in Duchenne muscular dystrophy. Insulin-like growth factor-I increases the recruitment of stem cells into myoblasts, increases myoblast proliferation and promotes myofiber. This research will use IFG-I and other factors to improve stem cell and myoblast therapy for DMD. IGF-I will also be used to increase the strength and prevent the breakdown of dystrophic muscle, using animal models of DMD.

Sydney - Children's Hospital at Westmead

Sandra Cooper, Ph.D.

(DG) The role of dysferlin in the pathogenesis of limb girdle muscular dystrophy

$	44,272	7/1/03 - 6/30/04	Year 1
$	44,832	7/1/04 - 6/30/05	Year 2
$	44,952	7/1/05 - 6/30/06	Year 3

Summary Dysferlin deficiency causes muscular dystrophy. Investigators will study dysferlin in skeletal muscle, to better understand why muscle damage occurs and to identify possible approaches to therapy.

Sydney - University of New South Wales

Des Richardson, BSc., MSc., Ph.D.

(RG) The role of iron in Friedreich's ataxia (FA) and the use of chelation therapy

$	68,720	1/1/03 - 12/31/03	Year 2
$	69,660	1/1/04 - 12/31/04	Year 3

Summary Friedreich's ataxia is a severe neurological disease that results in dangerous iron build-up in important tissues such as the nervous system and heart. The preliminary research has developed a new series of effective drugs to remove the iron called chelators. Studies with chelators may lead to therapies in FA.

Sydney - Victor Chang Cardiac Research Institute

Peter Currie, Ph.D.

(RG) Characterisation of zebrafish dystrophin mutants

$	70,000	7/1/03 - 6/30/04	Year 1
$	70,000	7/1/04 - 6/30/05	Year 2
$	70,000	7/1/05 - 6/30/06	Year 3

Summary To understand how mutation in the dystrophin gene leads to muscle weakness, investigators will study zebrafish that lack dystrophin protein, and identify genes that modulate the dystrophic phenotype.

Toowoomba - University of Southern Queensland

Andrew Hoey, Ph.D.

(RG) Cardiac dysfunction in Duchenne muscular dystrophy (DMD)

$	67,457	7/1/03 - 6/30/04	Year 1
$	69,152	7/1/04 - 6/30/05	Year 2
$	70,475	7/1/05 - 6/30/06	Year 3

Summary This project will examine two major mechanisms through which cardiac function can be enhanced so as to reduce the progression or development of heart failure. The first approach is to regulate the neural and hormonal influences on the heart while the second approach will aim to bypass the genetic lesion and restore synthesis of the missing dystrophin protein in cardiac muscle. The benefits on cardiac and skeletal muscle function and integrity will be examined to further ascertain the role that degeneration of cardiac performance plays in muscle deterioration.

AUSTRIA

Graz - University of Graz

Klaus Wagner, Ph.D.

(RG) Cloning and characterization of the distal hereditary motor neuronopathy V gene

$	60,000	1/1/03 - 12/31/03	Year 1

Summary After identification of a second locus for dHMN V on chromosome 11, researchers aim to narrow down the critical region by investigating new DNA markers and further new families. As soon as the region is small enough, they will start to analyze functional and positional candidate genes to identify the disease causing gene. This study will contribute to an improved diagnosis and to the development of treatments for dHMN V patients.

BELGIUM

Brussels - Universite Libre de Bruxelles

Massimo Pandolfo, M.D.

(EMG) Restricted funds for the support of Friedreich's ataxia research

$	70,000	4/1/02 - 3/31/03	Year 5

Leuven - VIB

Peter Carmeliet, M.D., Ph.D.

(RG) Vascular and neuroprotective effects of VEGF in amyotrophic lateral sclerosis (ALS)

$ 100,000 1/1/03 - 12/31/03 Year 2

Summary This project will study the pathogenetic role and therapeutic potential of VEGF in stimulating perfusion and providing survival protection of motor neurons in ALS.

Mons - University Mons-Hainaut

Alexandra Belayew, Ph.D.

(RG) Evaluation of the DUX4 gene as a candidate for facioscapulohumeral dystrophy (FSHD)

$ 75,000 7/1/02 - 6/30/03 Year 2

Summary FSHD is linked to partial deletions in an array of 3.3 kb repeated elements close to one end of chromosome 4. Researchers have identified a gene (DUX4) within each 3.3 kb element, and hypothesize that its expression is triggered by the deletion, and causes the disease. Researchers will evaluate this hypothesis.

Frederique Coppee, Ph.D.

(DG) Characterization of DUX4c and its role in facioscapulohumeral dystrophy (FSHD)

$ 44,712 1/1/03 - 12/31/03 Year 1

$ 44,712 1/1/04 - 12/31/04 Year 2

$ 44,712 1/1/05 - 12/31/05 Year 3

Summary Researchers will study a gene (DUX4c) located in the 4q35 region linked to FSHD, its product, its expression in patient myoblasts and its interplay with DUX4, a homologue present in the D4Z4 repeats.

CANADA

Hamilton - McMaster University

Mark Tarnopolsky, M.D., Ph.D.

(RG) Novel nutritional interventions in mdx mice

$ 33,982 1/1/03 - 12/31/03 Year 1

Summary Investigators will evaluate whether four nutritional compounds will, in isolation or in combination, reduce muscle damage and weakness in the mdx mouse treated with and without corticosteroids.

Montreal - McGill University

Jeffrey N. Agar, Ph.D.

(DG) Mechanisms and consequences of altered protein solubility in amyotrophic lateral sclerosis (ALS)

$ 44,804 7/1/02 - 6/30/03 Year 1

$ 44,820 7/1/03 - 6/30/04 Year 2

$ 44,820 7/1/04 - 6/30/05 Year 3

Summary Mutations in the Cu/Zn-Superoxide dismutase (SOD-1) gene are responsible for a familial form of amyotrophic lateral sclerosis. Rather than a loss of the normal function of the protein, a gain of some toxic property seems to be responsible for the disease. Researchers have isolated a potentially toxic fraction of the mutant SOD-1 from cell and will characterize chemically the modifications to this protein in order to identify mechanisms responsible for toxicity.

Montreal - McGill Universitym (Cont'd)

Salvatore Carbonetto, Ph.D.

(RG) Dystroglycan associated proteins in synaptic vesicle recycling

$	90,000	1/1/03 - 12/31/03	Year 1
$	90,000	1/1/04 - 12/31/04	Year 2
$	90,000	1/1/05 - 12/31/05	Year 3

Summary Several muscular dystrophies are accompanied by cognitive deficiencies and more severe brain defects. Alpha and beta dystroglycan are essential for normal brain development, synaptic formation and function. The studies proposed here will identify novel complexes of proteins associated with dystroglycan in the brain and assess their functions. Ultimately, such information may lead to strategies to treat these and related cognitive disorders that accompany muscular dystrophies.

Heather Durham, Ph.D.

(RG) Mechanisms of motor neuron vulnerability in amyotrophic lateral sclerosis (ALS)

$	74,439	1/1/03 - 12/31/03	Year 3

Summary This research investigates how even normal levels of glutamate might contribute to the death of motor neurons in ALS. Therapies that target these mechanisms, coupled with drugs that reduce glutamate levels, could provide defense against the disease process.

George Karpati, M.D.

(RG) Molecular therapies for dystrophin deficiency

$	78,596	1/1/03 - 12/31/03	Year 1
$	80,135	1/1/04 - 12/31/04	Year 2

Summary Researchers are planning to perform a novel adenovirus and plasmid-mediated dystrophin and utrophin gene transfer to mdx mouse and GRD dog models of Duchenne muscular dystrophy (DMD). They will also pursue a new angle of utrophin upregulation in mdx muscle. Both strategies will potentially be useful in designing molecular therapy for DMD.

Basil J. Petrof, M.D.

(RG) Plasmid-mediated delivery of therapeutic genes in muscular dystrophy

$	70,000	7/1/02 - 6/30/03	Year 1
$	70,000	7/1/03 - 6/30/04	Year 2

Summary These studies are aimed at making gene therapy with plasmid DNA safe and effective for patients with Duchenne and limb girdle dystrophies. Studies in a large animal model (average weight approximately that of a 10 year old child) are relevant to the scale-up and other feasibility issues that will be faced in patients. In addition, researchers will also explore the role of oxidative stress in muscular dystrophy.

Eric Shoubridge, Ph.D.

(RG) Assembly of cytochrome c oxidase in mitochondrial myopathy

$	80,233	7/1/02 - 6/30/03	Year 1
$	81,313	7/1/03 - 6/30/04	Year 2
$	82,393	7/1/04 - 6/30/05	Year 3

Summary Researchers are investigating the function of proteins that are critical for the assembly of an enzyme complex in the oxidative energy producing system of muscles and nerves.

Montreal - Montreal General Hospital

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

(RG) Investigation of the pathogenesis of oculopharyngeal muscular dystrophy (OPMD)

$	100,000	7/1/02 - 6/30/03	Year 1
$	100,000	7/1/03 - 6/30/04	Year 2
$	100,000	7/1/04 - 6/30/05	Year 3

Summary Researchers aim to better understand the basic disease mechanisms in order to develop new therapies and improve the quality of life of OPMD patients.

(RG) Identification of a new gene for autosomal dominant familial amyotrophic lateral sclerosis (ALS)

$	110,000	1/1/03 - 12/31/03	Year 2
$	110,000	1/1/04 - 12/31/04	Year 3

Summary Mutations in one gene (superoxide dismutase 1: SOD1) have been identified and account for about 10-20% of familial cases of ALS. This research aims to identify another gene which is altered in familial ALS patients.

Montreal - Montreal Neurological Institute

Paul C. Holland, Ph.D.

(RG) Modification of the muscle cell surface to increase gene transfer

$	82,553	1/1/03 - 12/31/03	Year 2
$	83,765	1/1/04 - 12/31/04	Year 3

Summary Researchers will investigate the factors limiting the efficiency of gene transfer to mature muscle. They will determine if gene therapy of neuromuscular diseases can be made more efficient, by causing muscle to make more of a protein (receptor) that the adenovirus gene therapy vector uses to enter mammalian cells. They will also determine if temporary removal of part of the coating surrounding muscle fibers facilitates gene transfer to muscle using adenovirus or specially developed adenovirus vectors modified to direct them to new targets.

Montreal - University of Montreal

Bernard Brais, M.D., M.Phil., Ph.D.

(RG) Polyalanine toxicity in oculopharyngeal muscular dystrophy (OPMD) and inclusion body myositis (IBM)

$	60,000	1/1/03 - 12/31/03	Year 2

Summary Researchers will study the shared pathological features and screen 408 candidate genes in OPMD and IBM. They will design a high throughput screen assay to identify therapeutic agents.

Ottawa - Ottawa General Hospital

Atsushi Asakura, Ph.D.

(DG) Specification and potential of muscle-derived stem cell: Application to therapeutic stem cell transplantation for muscular dystrophies

$	35,000	7/1/02 - 6/30/03	Year 3

Summary Researchers plan to elucidate the relationship between satellite cells, as well as identify molecular events involved in pluripotentiality of the satellite cell and MSCs.

Ottawa - Ottawa Health Research Institute

Christine DiDonato, Ph.D.

(RG) Gene therapy for animal models of spinal muscular atrophy (SMA)

$	113,514	7/1/03 - 6/30/04	Year 1
$	92,360	7/1/04 - 6/30/05	Year 2
$	94,668	7/1/05 - 6/30/06	Year 3

Summary Investigators will use mouse models of the human disease SMA, to investigate the potential of re-introducing the corrective gene, survival motor neuron (SMN) to ameliorate the pathological effects of the disease.

Rashmi Kothary, Ph.D.

(RG) The role of sodium channel 8a in skeletal and cardiac muscle function

$	100,000	7/1/03 - 6/30/04	Year 1
$	100,000	7/1/04 - 6/30/05	Year 2
$	100,000	7/1/05 - 6/30/06	Year 3

Summary Neuromuscular disorders are a heterogeneous group of diseases that lead to progressive muscle atrophy, weakness, degeneration, loss of movement, and often to early death in affected patients. Identification of protein networks whose expression or activities are altered as a common theme in the many neuromuscular disorders is an important step prior to designing therapies that might be applicable for the treatment of muscle atrophy in general. With that in mind, the latter half o this proposal dealing with molecular profiling of partially (the dmu mouse) or completely (experimentally) denervated skeletal muscle will allow us to identify potential targets for therapeutic intervention in the many disease states that lead to muscle atrophy.

(RG) Molecular and genetic analysis of a novel mouse muscle degeneration mutant, dm

$	84,240	7/1/02 - 6/30/03	Year 2

Summary Characterizing dm, a novel mouse mutant suffering from muscle degeneration, is important to gain a better insight into disease etiology in this mouse and gene identity. The information they garner will also be applicable to the study of human muscle degenerative diseases in general.

Lynn Megeney, Ph.D.

(RG) Defining the proatrophic JNK1 signal cascade in dystrophic muscle

$	100,000	1/1/03 - 12/31/03	Year 2
$	100,000	1/1/04 - 12/31/04	Year 3

Summary Dystrophic muscle signaling pathways will be characterized and tested as potential therapeutic targets for treatment of Duchenne muscular dystrophy (DMD).

Michael Rudnicki, Ph.D.

(RG) Molecular regulation of satellite cell function

$	122,143	1/1/03 - 12/31/03	Year 2
$	122,143	1/1/04 - 12/31/04	Year 3

Summary In this application, researchers propose to investigate the molecular mechanisms that regulate muscle regeneration. Insights from this work may lead to novel modes of therapy in the treatment of muscular dystrophy.

(SG) Molecular biology of muscle development and regeneration

$	15,000	5/1/03 - 6/30/03	Year 1

Ottawa - University of Ottawa

Bernard Jasmin, Ph.D.

(RG) Regulation of utrophin expression in muscle cells

$ 85,450 1/1/03 - 12/31/03 Year 3

Summary An approach to counteract the effects of DMD consists in utilizing a protein normally expressed in diseased muscle which could compensate for the lack of dystrophin. A good candidate for this role is utrophin. In this context, it thus becomes essential to understand how expression of utrophin is regulated.

Melissa Jones, Ph.D.

(DG) Molecular mechanisms involved in nitric oxide regulation of utrophin in dystrophic muscle

$ 44,815 1/1/03 - 12/31/03 Year 1

$ 44,772 1/1/04 - 12/31/04 Year 2

$ 44,820 1/1/05 - 12/31/05 Year 3

Summary One potential cure for Duchenne muscular dystrophy (DMD) consists of utilizing a protein, utrophin, normally expressed in dystrophic muscle, which once expressed at the plasma membrane, could functionally compensate for the lack of dystrophin. In contrast to dystrophin, which is expressed along the length of healthy muscle fibers, utrophin accumulates selectively at the neuromuscular junction of muscle fibers. Therefore, it becomes important to decipher the mechanisms involved in maintaining utrophin expression at the neuromuscular junction in attempts to induce via pharmacological interventions, expression of utrophin into extrasynaptic regions of dystrophic muscle fibers.

Robert Korneluk, Ph.D.

(RG) Investigating pathogenic mechanisms in myotonic dystrophy (DM)

$ 80,000 1/1/03 - 12/31/03 Year 3

Summary A major challenge has been to determine how the DM mutation causes the diverse detrimental effects. Researchers will study the inappropriate activation of a cellular "suicide" mechanism in the tissues of patients affected by DM.

Luc Sabourin, Ph.D.

(RG) The role of SLK (Ste20-like kinase) in myoblast migration

$ 65,000 1/1/03 - 12/31/03 Year 3

Summary This laboratory has recently isolated a novel protein kinase, termed SLK, involved in the control of cell death and cellular reorganization. Study of the regulatory mechanisms that govern cellular reorganization and cell migration will contribute significantly to the design of more efficient myoblast transfer therapies.

Ste-Foy - Laval University

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

(RG) Stratagems in vitro for a gene therapy for myotonic dystrophy

$ 78,400 7/1/03 - 6/30/04 Year 1

$ 80,720 7/1/04 - 6/30/05 Year 2

$ 86,450 7/1/05 - 6/30/06 Year 3

Summary This proposal outlines an ordered series of experiments aimed at testing a myotonic dystrophy gene therapy based on the specific targeting of the mutant DMPK transcripts.

Toronto - Centre for Addiction and Mental Health

Paul S. Fitzmaurice,
(EMG) Restricted funds for Friedreich's ataxia research
$ 18,184 4/1/02 - 3/31/03

Toronto - Hospital For Sick Children

Christopher Pearson, Ph.D.
(RG) DNA replication, DNA repair and drug-induced CTG repeat instability in DM1 patient cells
$ 75,000 7/1/02 - 6/30/03 Year 1
$ 75,000 7/1/03 - 6/30/04 Year 2
$ 75,000 7/1/04 - 6/30/05 Year 3
Summary Long-term goal of this project is to prevent or treat DM1 at the DNA level - essentially by inhibiting or reversing CTG expansion. This work is aimed at genetically or pharmacologically modulating the DM1 mutation, which may offer disease treatment for affected families.

Toronto - Mount Sinai Hospital

Hao Ding, M.D., Ph.D.
(DG) Functional role(s) of DUX4 gene in facioscapulohumeral muscular dystrophy (FSHD) development: Transgenic approaches
$ 35,000 7/1/02 - 6/30/03 Year 2
$ 35,000 7/1/03 - 6/30/04 Year 3
Summary Researchers propose to develop a mouse model for FSHD based on their hypothesis that expression of the DUX4 gene present in the FSHD locus causes the disease.

Winnipeg - University of Manitoba

Judy Anderson, Ph.D.
(RG) Nitric oxide and mdx mouse muscular dystrophy
$ 65,000 7/1/02 - 6/30/03 Year 2
$ 65,000 7/1/03 - 6/30/04 Year 3
Summary The impact of nitric oxide manipulations on X-linked muscular dystrophy in mice will be examined by studies of structural and functional outcomes of treatment with steroids. The hypothesis is that changes in NO levels will change the severity of dystrophy and ultimately improve function.

CYPRUS

Nicosia - Cyprus Institute of Neurology and Genetics

Kyproula Christodoulou, Ph.D.
(RG) Identification of a novel Charcot-Marie-Tooth Type 2 (CMT2) gene
$ 94,600 1/1/03 - 12/31/03 Year 2
Summary This research project focuses on the identification of a novel CMT2 gene, that researcher's have recently mapped to chromosome 9q33-q34 through an MDA funded research project.

Nicosia - Cyprus Institute of Neurology and Genetics (Cont'd)

Kyproula Christodoulou, Ph.D.

(RG) Neuromuscular diseases in Eastern Mediterranean countries

$	62,640	7/1/02 - 6/30/03	Year 1
$	63,610	7/1/03 - 6/30/04	Year 2
$	65,930	7/1/04 - 6/30/05	Year 3

Summary Clinical and molecular genetic studies of CMT, SMA/HMN, LGMD with cardiomyopathy and other neuromuscular diseases that are prevalent in the region.

FRANCE

Gif sur Yvette Cedex - Centre National de la Recherche Scientifique

Sabine De La Porte, Ph.D.

(RG) Finding the best NO-related compound for treating Duchenne and Becker dystrophies

$	42,000	7/1/03 - 6/30/04	Year 1
$	28,350	7/1/04 - 6/30/05	Year 2

Summary Investigators have focused their attention on the NO way in an attempt to reactivate the expression of utrophin, the alternative approach proposed to treat Duchenne and Becker dystrophies. As their results open the way to a potential treatment, they propose to develop a therapeutic molecule and to explore the molecular mechanisms implicated in the observed effects.

(DG) The NO way to increase utrophin expression: A potential treatment for Duchenne dystrophy?

$	35,000	7/1/02 - 6/30/03	Year 2

Summary Researchers propose to develop a therapeutic molecule and to explore the molecular mechanisms.

Illkirch - Institut de Genetique et de Biologie

Michel Koenig, M.D., Ph.D.

(RG) Pharmacological therapeutic trials on Friedreich's ataxia (FA) cellular and mouse models

$	53,000	7/1/02 - 6/30/03	Year 2
$	71,500	7/1/03 - 6/30/04	Year 3

Summary The objective is to identify and validate efficient therapeutic compounds for the treatment of FA by constructing and testing mouse models of the disease in preclinical trials with anti-oxidants.

ISRAEL

Rehovot - Weizmann Institute of Science

Sara Fuchs, Ph.D.

(RG) Immunotherapy of experimental myasthenia gravis (MG)

$	78,408	7/1/02 - 6/30/03	Year 2
$	81,000	7/1/03 - 6/30/04	Year 3

Summary Antigen specific and some other therapies for rat experimental MG are being developed and investigated. Hopefully, such therapies could be employed to treat human MG.

Rehovot - Weizmann Institute of Science (Cont'd)

Eldad Tzahor, Ph.D.

(DG) Signals controlling myogenesis in the head

$	35,000	7/1/02 - 6/30/03	Year 2

Summary The proposed research attempts to understand at a fundamental level the molecular events that lead to the development of head skeletal muscles. It may provide insight into the basis for neuromuscular diseases in which normal processes of muscle development are disrupt.

David Yaffe, Ph.D.

(RG) Comparative analysis of the functions of the DMD gene products in human and drosophila

$	81,324	1/1/03 - 12/31/03	Year 2
$	83,484	1/1/04 - 12/31/04	Year 3

Summary The complex DMD gene specifies the synthesis of several proteins. Researchers showed that this complex structure and expression has been highly conserved during evolution, indicating important different functions of the encoded proteins. Reseachers intend to investigate the function of the DMD gene homologue in the fruit fly drosophila. Studies in drosophila have led to the understanding of the function and evolution of many genes involved in human development and genetic diseases.

ITALY

Napoli - TIGEM

Elena I. Rugarli, M.D.

(RG) Towards a therapy for hereditary spastic paraplegia due to paraplegin deficiency

$	71,500	7/1/03 - 6/30/04	Year 1
$	65,560	7/1/04 - 6/30/05	Year 2
$	65,560	7/1/05 - 6/30/06	Year 3

Summary Hereditary spastic paraplegia is characterized by weakness and rigidity of the lower limbs and has no effective cure. Researchers propose to use a mouse model to investigate its cause and develop new therapies.

Trieste - Scuola Internazionale Superiore di Studi Avanzati

Annalisa Pastore, Ph.D.

(EMG) Restricted funds for Friedreich's ataxia research

$	24,000	4/1/02 - 3/31/03	Year 1
$	24,000	4/1/03 - 3/31/04	Year 2

THE NETHERLANDS

Leiden - Leiden University

Silvere van der Maarel, Ph.D.

(RG) Epigenetic studies of facioscapulohumeral muscular dystrophy (FSHD)

$	112,541	1/1/03 - 12/31/03	Year 1
$	116,176	1/1/04 - 12/31/04	Year 2
$	119,590	1/1/05 - 12/31/05	Year 3

Summary In this project, the packaging of the DNA in the region on chromosome 4q that is rearranged in FSHD will be investigated. Researchers have preliminary data that this region has a more open structure in FSHD patients. Such open structure could disturb proper gene regulation. Detailed knowledge of these changes in DNA packaging may lead to new possibilities of therapeutic intervention.

Judith C. T. van Deutekom, Ph.D.

(RG) Antisense therapy in different Duchenne muscular dystrophy (DMD) mouse models

$	100,000	7/1/03 - 6/30/04	Year 1
$	100,000	7/1/04 - 6/30/05	Year 2
$	100,000	7/1/05 - 6/30/06	Year 3

Summary DMD is caused by mutations in the DMD gene that disrupt its genetic code such that the synthesis of the dystrophin protein is aborted prematurely. Due to the consequent dystrophin deficiency patients suffer from a progressive and lethal muscle weakness. Researchers have recently demonstrated the therapeutic potential of small synthetic "antisense" molecules to restore the disrupted genetic code and induce dystrophin synthesis in cultured muscle cells from DMD patients. In this project, they aim at further optimizing this antisense strategy towards clinical applications. They will focus on developing the safest and most efficient delivery of the antisense molecules to muscle tissue in vivo, using different mouse models.

Nijmegen - University of Nijmegen

Berend Wieringa, Ph.D.

(RG) Treatment of somatic (CTG) n repeat instability in myotonic dystrophy (DM)

$	94,704	1/1/03 - 12/31/03	Year 1
$	99,630	1/1/04 - 12/31/04	Year 2
$	103,475	1/1/05 - 12/31/05	Year 3

Summary Expansions in the DNA of chromosomes 19 or 3 cause toxic gain-of-function-effects that underlie the multi-systemic features common to two forms of DM (DM1 and DM2). After years of studying functions of genes in and around the region of expansion-mutation in DM1, researchers now propose directing their efforts to specific DNA features and cellular mechanisms that play a role in the ongoing (CTG)-repeat mutation during growth and ageing of tissues of affected members of DM1 families.

SPAIN

Burjasot - University of Valencia

Manuel Perez-Alonso, Ph.D.
(RG) A Drosophila model for myotonic dystrophy (DM)
$ 61,925 1/1/03 - 12/31/03 Year 2
$ 62,551 1/1/04 - 12/31/04 Year 3

Summary Researchers propose to create a DM1 model in Drosophila using the human expanded CTG repeats and to use this model to elucidate the molecular mechanisms triggering DM1 pathogenesis by conducting genetic screens to identify genes that modify the DM1-like defects in Drosophila, which will be functionally relevant to DM1.

SWITZERLAND

Basel - University of Basel

Markus A. Ruegg, Ph.D.
(RG) Treatment of congenital muscular dystrophy (CMD) by an agrin minigene
$ 97,514 7/1/02 - 6/30/03 Year 1
$ 93,437 7/1/03 - 6/30/04 Year 2
$ 92,716 7/1/04 - 6/30/05 Year 3

Summary Merosin-deficient congenital muscular dystrophy although rare, is one of the most severe muscle-wasting diseases. This research in devoted to test whether a replacement strategy, using the extracellular matrix molecule agrin, which is not related to the disease-causing LAMA2 gene, can be used for the treatment of merosin-deficient congenital muscular dystrophy.

TUNISIA

Tunis - Institut National De Neurologie

Faycal Hentati, MD
(RG) Phenotype genotype relation study in limb girdle muscular dystrophies (LGMD) in Tunisia
$ 47,300 7/1/02 - 6/30/03 Year 3

Summary Careful phenotype analysis of patients with genetically defined autosomal recessive LGMD in order to analyze genetic factors related to the expression of the course in these disorders. The identification of such factors will be important in the understanding of how to potentially treat patients with severe form of the disease.

UNITED KINGDOM

Cambridge - Medical Research Council

Michael Murphy, Ph.D.
(EMG) Restricted funds for FA research
$ 33,265 4/1/02 - 3/31/03 Year 1

Harrow - Imperial College London

Mark Pook, Ph.D.
(EMG) Restricted funds for Friedreich's ataxia research
$ 11,850 4/1/03 - 3/30/04 Year 1

London - Imperial College School of Medicine

Charles Coutelle, Prof. Dr. Sci. Med.

(RG) An in utero approach to gene therapy for Duchenne/Becker muscular dystrophies

$ 80,000 4/1/03 - 3/31/04 Year 1

Summary Delivery of gene therapy in utero is a novel gene therapy approach, which may provide life-long cure. Investigators propose investigations in utro gene therapy in fetal mdx mice, a model for the severe human genetic muscle wasting disease Duchenne muscular dystrophy (DMD) by applying a novel gene delivery system. This approach is directed only to the individually treated fetus and does not intend to treat future generations.

Terence Partridge, Ph.D.

(RG) Stem cell identification and characterization

$ 85,000 7/1/02 - 6/30/03 Year 3

Summary Researchers will develop and test reagents that will aid the identification and production of the early precursor and stem cells which should provide the best material for myoblast.

Dominic Wells, M.A., VetMB, Ph.D.

(RG) Avoiding immune responses to dystrophin gene therapy

$ 90,000 7/1/02 - 6/30/03 Year 2

$ 90,000 7/1/03 - 6/30/04 Year 3

Summary Researchers will investigate a range of approacheds to the prevention of immune rejection of dystrophin following gene transfer. This is key to the development of effective therapy for DMD.

London - Kings College

Naveed Mustfa, MBBS, MRCP

(DG) Study to assess cough and sleep in amyotrophic lateral sclerosis (ALS)

$ 35,000 1/1/03 - 12/31/03 Year 3

Summary Researchers will study cough flow and pressures in ALS patients with different patterns of weakness and see which treatments improve these most. Researchers will also assess how patients' specific impairments affect their sleep.

London - King's College Hospital

Michael Rose, M.D.

(RG) US Validation of a neuromuscular disease quality of life measure

$ 64,530 1/1/03 - 12/31/03 Year 1

$ 51,840 1/1/04 - 12/31/04 Year 2

$ 53,946 1/1/05 - 12/31/05 Year 3

Summary Investigators wish to further develop a quality of life measure that can be used as a sensitive and reliable measure of the benefit of any treatment, taking into account its benefits and its side effects. This particular quality of life measure would be tailored to those with various muscle diseases and would be flexible enough to take account of individual life styles. It has been designed with major input from patients themselves. It could be used in clinical trials or in muscle clinics. In financially limited health service organisations the arguments for the provision of any type of treatment would be strengthened, were that treatment shown to have a major impact on the quality of life of those with muscle disease.

Nottingham - University of Nottingham

Jane Hewitt, Ph.D.

(RG) Abnormal glycosylation as a mechanism for muscular dystrophy

$	74,206	1/1/03 - 12/31/03	Year 2
$	78,633	1/1/04 - 12/31/04	Year 3

Summary The LARGE gene encodes a protein that adds sugar to proteins and is mutated in a mouse model of muscular dystrophy. Researchers will determine whether the human gene plays a role in muscular dystrophy.

Oxford - University of Oxford

Kay E. Davies, MA, DPhil.

(RG) Utrophin in therapy of Duchenne muscular dystrophy (DMD)

$	95,386	1/1/03 - 12/31/03	Year 3

Summary The long term aim of this project is to develop an effective treatment of DMD. Researchers are attempting to do this through the upregulation of the dystrophin related protein utrophin.

(RG) Analysis of the role of syncoilin in muscle disease

$	77,333	7/1/02 - 6/30/03	Year 1
$	82,406	7/1/03 - 6/30/04	Year 2
$	86,047	7/1/04 - 6/30/05	Year 3

Summary Researchers will determine the role of a recently identified protein which links the dystrophin associated protein complex and the intermediate filament network in normal muscle and disease.

Wrexham - North East Wales Institute

Glenn E. Morris, D.Phil

(RG) Interactions of the spinal muscular atrophy protein, SMN

$	62,832	7/1/02 - 6/30/03	Year 2
$	64,759	7/1/03 - 6/30/04	Year 3

Summary Understanding SMN's direct and indirect interactions with other proteins is the key to understanding its potential functions in FNA splicing, gene transcription and axonal transport. Interactions between SMN and other proteins will be studied by a novel biosensor method that enables quantitative measurements of binding in real-time. Interactions in vivo will be studied by immunolocalization, using specific antibodies and confocal microscopy, in transfected cell lines, in normal fetal and adult tissues and in SMN-depleted cell lines.