Active Limb-Girdle Muscular Dystrophy Research Grants

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<td>(CRTG)</td>
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AUSTRALIA
Parkville - The University of Melbourne

Gordon Stuart Lynch Ph.D.

RG                  Therapeutic potential of heat shock protein 72 induction in muscular dystrophy

$135,503.00  2/1/2013  1/31/2014  Year 1
$135,003.00  2/1/2014  1/31/2015  Year 2
$135,003.00  2/1/2015  1/31/2016  Year 3

Summary
Muscle wasting and weakness are major symptoms of many neuromuscular disorders, including Duchenne muscular dystrophy (DMD). Although considerable efforts are being directed to the development of gene therapies for DMD, these techniques are far from perfected. In the interim, it is essential that alternative therapies be developed, and research directed to preserving muscle tissue, enhancing muscle regeneration, and promoting muscle growth. Through MDA support, we have made major contributions to the field; demonstrating that growth factors have exciting potential for improving muscle function in the mdx mouse, an animal model for DMD (Am. J. Pathol. 161:2263-72, 2002; Muscle Nerve 30:295-304, 2004; Am. J. Pathol. 166:1131-1141, 2005; Exp. Physiol. 93:1190-8, 2008; Am. J. Physiol. 294:C161-8, 2008; and many other published papers and review articles).
We have recently discovered how Hsp72 induction (through transgenic manipulation, heat therapy and drug-induction) can protect dystrophic muscle against functional decline and improve lifespan in severely affected dko mice (Nature, 484, 394-398, 2012). Based on this novel and important biological discovery, this research proposal aims to examine the full therapeutic potential of Hsp72 induction in the skeletal and cardiac muscles of various models of muscular dystrophy, with the aim of developing a novel treatment for improving skeletal and cardiac muscle function and quality of life for patients with muscular dystrophy.

ISRAEL
Jerusalem - Hebrew University of Jerusalem

Yosef Gruenbaum Ph.D.

RG  The molecular basis of AD-EDMD

$100,003.00  8/1/2012  7/31/2013  Year 1
$100,003.00  8/1/2013  7/31/2014  Year 2
$100,003.00  8/1/2014  7/31/2015  Year 3

Summary  Autosomal dominant Emery-Dreifuss muscular dystrophy (AD-EDMD) is caused by mutations in lamins A/C; however, the mechanisms by which lamin mutations lead to this disease are currently unclear. Our laboratory has established Caenorhabditis elegans as a powerful system in which to study novel pathways regulated by lamin and its role in human disease. Lamins are evolutionarily conserved and many of the residues that are mutated in AD-EDMD are conserved in Caenorhabditis elegans lamin. Our results also define C. elegans as the only system in which changes in lamin filament assembly in vitro and in vivo can be correlated with the disease phenotypes in vivo. The goal of our current proposal is to expand our studies of the Y59C (Y45C in human) and T164P (T150P in human) lamin EDMD-linked mutations in order to elucidate the molecular mechanisms by which these mutations cause motility and muscle defects. The results of this study should elucidate the underlying mechanisms of the currently enigmatic human AD-EDMD disease, which could identify novel drug targets for developing therapy to treat AD-EDMD.

UNITED KINGDOM

London - Royal Veterinary College

Susan Carol Brown Ph.D.

RG  An animal model for studying therapeutic approaches in FKRP related disease

$118,946.00  8/1/2012  7/31/2013  Year 1
$118,946.00  8/1/2013  7/31/2014  Year 2
$118,946.00  8/1/2014  7/31/2015  Year 3

Summary  Mutations in any one of 6 genes leads to forms of muscular dystrophy collectively known as the ‘dystroglycanopathies’ the disease process of which is associated with a problem in the way alpha-dystroglycan is glycosylated or decorated with sugars. We previously generated mice which display a marked reduction in expression levels of Fukutin Related Protein or FKRP which is one of the genes that leads to a reduction in alpha dystroglycan glycosylation. These animals display a muscle, eye brain phenotype similar to that of patients with FKRP mutations at the severe end of the clinical spectrum. However, these animals die around the time of birth due to the reduction of FKRP in the central nervous system. In order to circumvent this we have now crossed these mice with lines that will replace FKRP in the CNS but not the muscle thus providing us with a model for LGMD2I. This model has an overt muscle pathology by 12 weeks of age and so will now be used to determine if some of the therapeutic approaches proposed for other forms of muscular dystrophy are appropriate for the dystroglycanopathies.

UNITED STATES

CALIFORNIA

Irvine - The Regents of the University of California (Irvine)

Tahseen Mozaffar M.D.

SG  Third Annual UC Irvine Neuromuscular Colloquium

$5,000.00  5/17/2013  5/20/2013  Year 1

Summary  The Third Annual UC Irvine Neuromuscular Colloquium is a national academic meeting of neuromuscular physicians, scientists and clinician-scientists. This conference has been a highly successful gathering of regional neuromuscular experts and allows an opportunity for these experts to network, discuss recent advances in the field, discuss challenging and interesting neuromuscular patients and develop research collaborations and ideas. This is a
one-day conference, with didactic lectures and case presentations, as well as short research talks. Preliminary agenda attached.

**La Jolla - The Regents of the University of California, San Diego**

**Masahiko Hoshijima M.D., Ph.D.**

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**Summary**

In patients with muscular dystrophies including the Duchenne/Becker Muscular Dystrophies and Limb-Girdle Muscular Dystrophies (LGMDs), both skeletal and cardiac muscles are severely affected. While progressive weakness of neck, trunk and limb muscles disables these patients, their major causes of death are cardiac and respiratory failure. Using adeno-associated viral vector-based gene therapy, we recently became successful to treat cardiac and respiratory failures of BIO14.6 hamsters, an animal model of muscular dystrophy and inherited cardiomyopathy, at their advanced disease stage and substantially elongate their lifespan. Notably, muscle defects in BIO14.6 hamster is caused by the genetic defect of the delta-sarcoglycan, a membrane protein, mutations of which have been linked to a sub-type of human LGMD. Nonetheless, previous studies including ours have not determined how therapies affect respiratory and cardiac failures interactively. The current project takes advantage of recent advancement in cell-type specific gene transfer technologies and investigates (1) how cardiac specific genetic correction affects respiratory function and (2) whether skeletal muscle selective gene replacement therapy alters heart function. The project will provide new knowledge that guides us to understand how pernicious cardiac and respiratory dysfunctions in muscular dystrophy should be collectively treated.

**Los Angeles - The Regents of the University of California, Los Angeles**

**Melissa Spencer Ph.D.**

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**Summary**

Limb girdle muscular dystrophy type 2A due to mutations in the gene encoding calpain 3 (n(C3)) is one of the most prevalent LGMDs. Our previous studies have created genetically modified mice to understand the biological function of calpain 3 and have demonstrated that muscles lacking calpain 3 do not grow properly. Concomitantly, we have identified a signaling pathway that is defective in muscles lacking calpain 3. In this investigation, we will determine whether loss of this signaling pathway is the basis for the impaired growth in LGMD2A, and we will determine if this pathway can be pharmacologically targeted for therapy.

**Palo Alto - Palo Alto Institute for Research & Education, Inc.**

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

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**Summary**

Fibrosis refers to the development of scar-like tissue in place of functional cells of that tissue. In skeletal muscle, fibrosis develops as muscles waste from degenerative disorders, such as muscular dystrophies, and muscle cells are replaced by connective tissue. This is associated not only with progressive weakness as functional muscle cells are lost, but also by progressive muscle stiffness since connective tissue is not as elastic as muscle tissue. The goals of the experiments described in this proposal are to understand why fibrosis occurs in the muscular dystrophies and to determine the biochemical mechanisms that lead to that
fibrosis. We have preliminary data that suggests that a specific biochemical pathway, known as the "TGF-beta signaling pathway", is activated in dystrophic muscle and affects muscle stem cells in a way that leads to the development of fibrosis. We will directly test whether blocking this pathway leads to a reduction of the fibrosis that develops in the mdx mouse. These studies have the potential to lead directly to new therapies that will reduce the amount of fibrosis in the muscles of boys with Duchenne muscular dystrophy.

San Francisco - The Regents of the University of California, San Francisco (Contracts & Grants)

Jianming Liu Ph.D.

DG Targeting Smad mediated signaling of TGFbeta family for stem cell therapy of DMD

$59,929.00 2/1/2012 1/31/2013 Year 2

$59,997.00 2/1/2013 1/31/2014 Year 3

Summary A hallmark of Duchenne muscular dystrophy muscle is the rapid depletion of endogenous muscle progenitor cells. Therefore, using normal stem cells to promote muscle regeneration represents a potential therapeutic approach. It has been known that the differentiation of cells into a particular tissue type is regulated by a group of proteins with TGF-beta as prototype. This research aims to increase the effectiveness of stem-cell-based therapy by decreasing the intrinsic effector molecules inside the cells that relay the signals activated by TGF-beta and a related molecule, myostatin, which are known to counteract the differentiation into muscle cells. We aim to achieve this goal by modulating these signals in both the donor stem cells and recipient dystrophic muscles.

COLORADO

Boulder - The Regents of the University of Colorado d/b/a University of Colorado at Boulder

Bradley Olwin Ph.D.

RG Identification and Characterization of Satellite Stem Cells

$123,055.00 2/1/2012 1/31/2013 Year 2

$123,055.00 2/1/2013 1/31/2014 Year 3

Summary Diseases that result in progressive loss of skeletal muscle tissue indicate that the normal regenerative processes in muscle are disrupted and are not capable of sustaining normal repair. If the cells responsible for normal repair could be augmented by drug therapies or cell replacement therapies, this might enhance regeneration and slow or halt loss of skeletal muscle function. We have identified a rare stem cell that we believe is a primary source of skeletal muscle stem cells. Since we know little concerning these cells we are proposing experiments to understand where these cells come from, whether they are a primary contributor of muscle stem cells and if we can enhance muscle repair in mdx mice by cell transplantation of the satellite stem cells.

CONNECTICUT

Storrs - University of Connecticut

David J Goldhamer Ph.D.

RG Regulation of satellite cell lineage commitment in regeneration and disease

$125,000.00 2/1/2012 1/31/2013 Year 2

$125,000.00 2/1/2013 1/31/2014 Year 3

Summary Satellite cells are muscle stem cells that are responsible for postnatal muscle growth and the repair of damaged muscle in injury and disease. In Duchenne muscular dystrophy, accumulation of intramuscular fat and connective tissue represent histological hallmarks of advanced disease, and this infiltration of non-muscle tissue significantly affects muscle structure and function. Satellite cells have been implicated as a possible cell of origin for the increased fat and fibrotic tissue, but their involvement remains uncertain and controversial.
Using mouse lines developed in the lab that allow specific and permanent labeling of satellite cells, we will directly assess the contribution of satellite cells to fat and connective tissue infiltrates in mouse models of muscular dystrophy. MyoD and Myf-5 are key regulators of embryonic myogenesis that have been implicated in satellite cell functions. Using a new mutant allele of MyoD that will allow the timing of MyoD deletion to be controlled, we will investigate the requirement for MyoD and Myf-5 in myogenic commitment in vivo. Further, we will determine whether double mutant satellite cells can engraft into injured and dystrophic muscle, foundational data that will assess the potential utility of this cell type for therapeutic use.

DISTRICT OF COLUMBIA

Washington - Children's Research Institute (CNMC)

Sebahattin Cirak Ph.D.

DG  Gene discovery of exome-negative muscular dystrophy patients by nextgen RNAseq.
$60,000.00  2/1/2013  1/31/2014  Year 1
$60,000.00  2/1/2014  1/31/2015  Year 2
$60,000.00  2/1/2015  1/31/2016  Year 3

Summary  The disease causing mutations are known in 50% of the patients with muscular dystrophies. The discovery of disease genes was in the past a time consuming process. It required mapping of the shared genomic region between affected individuals of the specific disease and then the sequencing (decoding) of the genetic code in these regions. Currently the so-called "Exome" sequencing has become available and enabled us in a single experiment to sequence about 80% of the coding region of the human genome. This is leading to the discovery of many disease genes. But still in a large number of patients the mutated genes are escaping discovery. One reason for this is that disease causing mutations can also occur in the so-called noncoding regions of the human genome. These are genetic variants that are involved in the regulation and processing of the genetic information. These so-called noncoding mutations are usually not accessible with exome sequencing. Very recently, a new technique called RNA sequencing has been developed. RNA sequencing is decoding of the entire RNA, the "working copies," or transcriptome, of the human genetic information in the cell. This technique allows us to identify the sequence of the RNA code and but also to determine its quantity. We will extract this RNA from the affected muscle or nerve biopsy of these patients and perform RNA sequencing. This will allow us to investigate the blueprint and identify the mutation.

Kanneboyina Nagaraju Ph.D., D.V.M.

RIG  Murine Preclinical Center for Neuromuscular Diseases (MPCNMD)
$100,000.00  3/15/2012  3/14/2013  Year 1
$100,000.00  3/15/2013  3/14/2014  Year 2
$100,000.00  3/15/2014  3/14/2015  Year 3

Summary  Recent advances in high throughput drug screening are facilitating identification of several drug candidates for muscular dystrophy. Currently there are very few murine preclinical facilities that can screen these therapeutic candidates in a reliable and reproducible manner in mouse models of neuromuscular diseases. The preclinical drug testing facility at Children's National Medical Center (CNMC) is one of the few facilities in the US that is equipped with state-of-the art equipment to comprehensively assess therapeutic efficacy of drugs/compounds in multiple models of myopathy in a robust and reliable manner. The Murine Preclinical Center for Neuromuscular Diseases (MPCNMD) at CNMC will use standardized protocols for skeletal, respiratory and cardiac endpoints in mouse models that will help to guide planning human clinical trials. The MPCNMD will maintain rare models of muscular dystrophy; develop new methodologies for phenotyping and screen therapeutics coming from both academic and industry groups. It will serve as a premier pre-clinical core facility for muscular dystrophies so that patients will have access to the best potential therapeutics.
A comprehensive approach to identifying novel genes associated with NMDs

GEORGIA
Atlanta - Emory University

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

RG  
A comprehensive approach to identifying novel genes associated with NMDs

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Summary
A comprehensive approach to identifying the causative gene and understanding the underlying mechanism associated with each disease genotype is inevitable to diagnose disease and eventual selection of effective therapeutic strategy. In this project we will screen a large set of patient samples with known and unknown forms of muscular dystrophies by whole exome sequencing and targeted array analysis to identify the causative gene and the associated genotypes. For each identified candidate gene and genotype, we will later perform confirmation studies by transcript expression analysis (qRT-PCR) and western blot analysis to understand the nature of substantial alterations in the expression patterns of the muscle proteins. Mutations in a single gene and altered levels of the corresponding protein may further alter the expression pattern of closely related proteins, especially in the case of muscle proteome where several proteins form structural complexes, thereby modifying of the severity the disease phenotype and showing overlapping features. By our comprehensive approach and confirmation studies we will better delineate the disease subtypes. Identification of novel genes and disease delineation will help effective disease diagnosis and choose appropriate therapeutic approach.

ILLINOIS
Maywood - Loyola University Chicago, Health Sciences Division

Renzhi Han Ph.D.

RG  Efficacy of complement inhibition as a therapeutic strategy for dysferlinopathy

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Summary
A subset of muscular dystrophy referred to as dysferlinopathies are caused by mutations in the gene encoding dysferlin, a protein shown to play an important role in the membrane repair process in striated muscles. At present, no therapy exists for dysferlinopathies. Our long term goal is to design a therapy for dysferlinopathies. Loss of dysferlin in skeletal muscle results in prominent muscle inflammation and muscle wasting. However, questions remain concerning what causes muscle membrane injury and whether immunological attack plays an active role in muscle injury in the absence of dysferlin. Resolving these questions may provide clues for the development of effective treatment strategies. This project focuses on exploring the effect of interfering the complement system on the muscle pathology associated with dysferlin deficiency. The overall results of these experiments will advance our understanding of the pathological mechanism underlying dysferlinopathies. Future studies will use this information for the development of therapeutic strategies to treat dysferlinopathies.

IOWA

Iowa City - The University of Iowa

Kevin Peter Campbell Ph.D.

RG  Protein O-mannosylation: Classification of new players in muscular dystrophy

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Summary
Protein O-mannosylation is a rare type of post-translational protein modification in
mammals, which when deficient can lead to progressive muscle wasting with potentially profound brain abnormalities. There is a critical need for better understanding of the enzymatic mechanism responsible for this modification to develop new treatment options for O-mannosylation deficient disease. Besides direct patient health benefits, identification of new players involved in protein O-mannosylation will open new avenues to understand O-mannosylation deficient muscular dystrophies.

Jennifer Rachel Levy Ph.D.

DG Pathways and consequences of non-dysferlin mediated membrane repair
$60,000.00 8/1/2012 7/31/2013 Year 2
$60,000.00 8/1/2013 7/31/2014 Year 3

Summary All cells have a plasma membrane that separates the intracellular content from the extracellular space. When the plasma membrane is damaged, it relies on molecular repair mechanisms to patch the sites of injury and prevent leakage of this content. Muscle-cell membranes undergo particularly frequent rounds of damage and repair due to exercise-associated plasma-membrane rupture. This repair is ineffective in dysferlinopathies, a class of muscular dystrophies caused by a defect in the protein dysferlin, which is a key player in the membrane repair process. Studies of mouse models of the dysferlinopathies have shown that plasma-membrane resealing in response to damage is defective in this context. However, muscle damage in dysferlinopathy is accompanied by inflammation, and the relationship between defects in dyferlin-mediated repair and this inflammation is not fully understood. In this project, I aim to identify the aberrant membrane repair mechanisms that compensate for loss of dysferlin in dysferlinopathy patients. Further, I seek to determine if dysferlin-independent membrane repair signals immune cells to augment inflammation at sites of muscle injury. Identifying new factors that contribute to muscle inflammation in dysferlinopathy patients is expected to lead to the discovery of new therapeutic strategies for additional muscular dystrophies that are also associated with inflammation.

MARYLAND

Baltimore - Hugo W. Moser Research Institute at Kennedy Krieger, Inc.

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

RG Myostatin Regulates Fate of Satellite Cells in Dystrophic Muscle
$117,513.00 8/1/2012 7/31/2013 Year 2
$117,513.00 8/1/2013 7/31/2014 Year 3

Summary In most muscular dystrophies and chronic myopathies, muscle regeneration becomes less effective over time and muscle is replace by fibrosis or scar tissue. The factors that govern establishment of fibrosis are not well understood. However, myostatin, a regulator of muscle growth, is one important factor in development of fibrosis. In the absence of myostatin, muscle regenerates more quickly and with less fibrosis. The studies described in this grant application will determine whether one of the cells that is important for muscle regeneration, the satellite cell, can become misdirected to contribute to muscle fibrosis. The studies will specifically evaluate whether myostatin is a cue that directs satellite cells away from forming new muscle and toward fibrosis. If this hypothesis is correct, then anti-myostatin therapies, currently in clinical trials for muscular dystrophy, will have an important role to play in stimulating muscle regeneration and reducing muscle fibrosis in a variety of clinical scenarios.

Baltimore - Johns Hopkins University School of Medicine

David A. Kass M.D.

RG Protein Kinase G inhibition of TRPC to Benefit the Dystrophin-deficient Heart
$105,309.00 2/1/2012 1/31/2013 Year 2

Summary Duchenne muscular dystrophy results from a genetic lack of the protein dystrophin, which leads to progressive and severe skeletal and heart muscle weakness. This gene defect also
results in depression of the function of the enzyme nitric oxide synthase (NOS), reducing localized levels of its primary downstream regulator, cyclic GMP and enzyme, protein kinase G. This is thought to generate a muscle nutrient supply/demand imbalance and contribute to muscle damage. Another feature of the disease is that ion channels located in the outer membrane, known as TRPC channels, become to be hyperactive, and this may increase calcium levels inside the cell that in turn can stimulate oxidative stress, and cause cell damage and/or death. We recently discovered that cyclic GMP dependent signaling can potently suppress TRPC channels directly. This suggests that treatments to increase cGMP levels such as sildenafil (Viagra), or activators of an enzyme called soluble guanylate cyclase, may be able to attack both the loss of normal NOS function, and hyperactive TRPC channels. The research we proposed in this grant will test the importance of cGMP/PKG activation to block stimulated TRPC channels in experimental models of muscular dystrophy, and determine if this modification can inhibit muscle damage associated with excess calcium and oxidant stress. This work would enable us to move forward with clinical trials – as these are drugs already used to treat other human diseases.

**Baltimore - University of Maryland, Baltimore**

**Robert J. Bloch Ph.D.**

**RG Cellular and Molecular Studies of Dysferlinopathy**

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**Summary**

Limb Girdle Muscular Dystrophy Type 2B (LGMD2B) and Miyoshi Myopathy are caused by mutations in the gene coding for the protein, dysferlin. Dysferlin is a large protein, but we have little information about what parts of it are important for its activity. We have found that most of the dysferlin in healthy muscle is associated with intracellular membranes that carry the electrical signal to initiate muscle contraction, but its role there is unknown. The work we propose will determine what parts of dysferlin are required for its function, and how the protein helps to stabilize the intracellular membranes of skeletal muscle. This information will be essential in designing and testing pharmacological or gene therapy approaches to treating muscular dystrophies linked to dysferlin.

**Andrew Ziman Ph.D.**

**DG Calcium Signaling in Dysferlinopathies**

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**Summary**

Dysferlinopathies are a family of recessive muscular dystrophies caused by mutations in the DYSF gene, which encodes the protein dysferlin. Clinical diagnosis of dysferlinopathies includes significant muscle weakness and biopsies showing signs of degeneration/regeneration, necrosis and inflammation. There are no therapies that slow the onset or progression of symptoms. While dysferlin has been associated with membrane repair mechanisms, little is actually known of its function in muscle. I hypothesize that dysferlin plays a significant role in maintaining the ability of muscle to function normally during and after muscle exercise and following injury. My results show that insults to muscle cells in tissue culture cause a rise in reactive oxygen (ROS) production and a disruption in Ca2+ regulation not seen in control fibers. Both can lead to pathogenic signals, including the activation of enzymes such as calpain, which cause death of the muscle fiber. Using this experimental paradigm, I will determine the dynamics of Ca2+ signaling and ROS activation in healthy and dysferlin-null muscle fibers. I will also test several prospective therapeutic compounds to learn if preventing the abnormal changes will preserve normal structure and function of dysferlin-null muscle. Finally, I will introduce either wild type or mutated forms of dysferlin in null muscle to determine which domains of the protein are necessary to convey protection from injury-induced pathology.
Bethesda - Society for Muscle Biology

Mary Baylies Ph.D.

SG  Development, Function and Repair of the Muscle Cell

$15,000.00  2/1/2012  1/31/2013  Year 1

Summary
This application requests partial support for the "Frontiers in Myogenesis" meeting, "Development, Function and Repair of the Muscle Cell", sponsored by the Society for Muscle Biology. Our objective is to bring together experts in developmental, cellular and molecular biology, adult muscle biology, human genetics to stimulate muscle disease research and foster new collaborations at both the basic and clinical levels. Our meeting will be held at the Kimmel Center at New York University in New York City, on June 4-8, 2012. We expect over 300 participants from all over the world. Seven plenary sessions, presenting sixty-three speakers (20 selected from submitted abstracts) at the senior, mid-career and junior levels, will address: Origins, Patterning and Behaviors of Muscle Progenitors; Transcriptional Control of Myogenesis and Muscle Progenitors’ Identity; Muscle Differentiation, Interaction of Muscle Cells with its Environment; Adult Muscle Progenitors, Satellite Cells: Specification and Contributions to Muscle Repair; Muscle Size Regulation; and Therapeutic Interventions to Human Muscle Disease. Three dedicated poster sessions will foster the exchange of ideas among all participants. A review of the meeting will be published in Skeletal Biology. This meeting will afford a comprehensive analysis and integration of recent discoveries and will emphasize how these advances inform our understanding of, and lead to potential therapies for, muscle disease.

MASSACHUSETTS

Boston - Children’s Hospital Boston

Alan H. Beggs Ph.D.

RG  Molecular Genetics of Congenital Myopathies

$133,978.00  8/1/2012  7/31/2013  Year 2

$129,034.00  8/1/2013  7/31/2014  Year 3

Summary
The congenital myopathies are a diverse group of inherited neuromuscular conditions that result in skeletal muscle weakness of variable onset and severity. To better understand the causes of these disorders, which are commonly seen in MDA neuromuscular clinics, we are building an extensive registry and biorepository of cases and specimens from patients and their families. Simultaneously, we have initiated a mutation screen in zebrafish to identify novel lines of mutant fish with genetic mutations that lead to muscle defects similar to those seen in patients with congenital myopathies. We are now mapping and identifying many of these new zebrafish mutations, and have already discovered several to be in genes with known relationships to human neuromuscular diseases. In this project, we will map these new genes, and determine their nature and relationship to the muscle defects seen in the fish. This information will then be used to identify human patients and families with analogous muscle findings from our registry and from related and complementary registries belonging to collaborators. The relevant genes will be screened in these human cases to identify new human neuromuscular disease genes. Identification of these genes will provide the information necessary to develop accurate carrier and prenatal testing, and will hopefully lead to new insights into therapies for these conditions.

Peter B. Kang M.D.

RG  Linkage analysis in limb-girdle muscular dystrophy

$99,938.00  2/1/2012  1/31/2013  Year 2

$99,914.00  2/1/2013  1/31/2014  Year 3

Summary
At least 18 different genes have been linked to the Limb Girdle Muscular Dystrophies (LGMDs). Individually, each LGMD is rare, but collectively they form a major class of inherited myopathies. Identification of new genes that cause LGMD would help expand our
knowledge of the muscular dystrophy disease process, and perhaps illuminate new therapeutic approaches for the muscular dystrophies in general. The candidate has accumulated and genotyped DNA samples from a number of families with LGMD. Known loci for LGMD have been excluded in 3 kindreds, raising the likelihood that novel genes are associated with the disease in these families. Mutations in known genes for LGMD have been identified in the other 14 families studied to date. The applicant will (1) continue to recruit new families with LGMD and perform linkage analysis; (2) identify potential mutations in novel genes using traditional and high-throughput sequencing technologies, as well as zebrafish morpholino suppression; and (3) determine which of the variants identified are likely to be causative mutations. This project has the potential to yield tangible and useful scientific knowledge in the study of muscular dystrophies.

**Boston - Harvard Medical School**

**Alfred L. Goldberg Ph.D.**

**RG**

Protein breakdown in muscle in normal and disease states

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**Summary**

Our studies during the past grant period have further clarified the common mechanisms of muscle wasting in a variety of pathological conditions including motor neuron disease (e.g. ALS), various myopathies, and systemic diseases. We showed that the ubiquitin-proteasome pathway is critical in destroying the myofibril during denervation atrophy. We made the unexpected finding that different components of the contractile apparatus are lost in a distinct order and that the enzyme, MuRF1, which is dramatically induced during all known types of atrophy, targets components of the muscle’s thick filaments for destruction by the proteasome. However, the components of the thin filament are targeted by distinct enzymes. Previously, we demonstrated that the transcription factor, FoxO3, is critical in various types of muscle atrophy by causing expression of a set of atrophy-related genes (e.g. MuRF1), and that activation of FoxO3 alone causes profound muscle wasting. We also discovered an important new role of FoxO in stimulating autophagy, which catalyzes the destruction of mitochondria during atrophy. FoxO3 increases expression of many components of the autophagy process, which we showed are also induced in mouse muscles atrophying in vivo. Finally, we have shown that exercise inhibits atrophy in part by inducing production of PGC-1alpha, which blocks the ability of FoxO to stimulate protein breakdown by these mechanisms.

**Boston - Trustees of Boston University**

**Jeffrey Boone Miller Ph.D.**

**RG**

CMD & LGMD therapeutic targets: Studies with patients’ myogenic cells

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**Summary**

Our studies are designed to identify new therapeutic strategies for a group of rare congenital and limb-girdle muscular dystrophies for which there currently are no effective ameliorative treatments. We have identified a molecular pathway that is abnormally activated within diseased muscle cells and thereby causes muscle cell death. Our goals in this project are to (i) further identify the mechanisms by which this muscle cell death occurs and (ii) develop therapeutic strategies that will ameliorate disease by preventing the abnormal cell death.

**MICHIGAN**

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

**Daniel E Michele Ph.D.**

**RG**

Reversing nitric oxide synthase dysfunction in muscular dystrophy
Muscular dystrophies are characterized by muscles that are weak, sensitive to injury, and fatigue rapidly during normal muscle activity. Recent work has focused on the role of loss of function of an enzyme nitric oxide synthase (nNOS) in muscle causing fatigue in muscular dystrophy. nNOS produces nitric oxide, which is required for maintaining increased blood flow to muscle during activity. Very little is known about how nNOS is regulated in muscle. Although nNOS localization to the cell membrane is disrupted in Duchenne muscular dystrophy, the broad disruption of nNOS localization in other muscular dystrophies with normal dystrophin expression, raises considerable questions about what causes NOS dysfunction in dystrophic muscle. An important regulator of nitric oxide synthase activity in whole animals is modified forms of the amino acid arginine, that circulate in the bloodstream and inhibit nitric oxide synthase. Our preliminary data show that methylated arginines are markedly elevated in serum of dystrophic mice, are acutely increased in result to direct skeletal muscle injury, and experimental elevation of methylated arginines is sufficient to reduce running exercise capacity in normal animals. This project will test if methylated arginines cause muscle fatigue, and test directly if reducing methylated arginines in dystrophic animals, reduces muscle fatigue/weakness and slows development of cardiomyopathy, and provides therapeutic benefit to dystrophic animals.

MINNESOTA

Minneapolis - Regents of the University of Minnesota - Twin Cities

David D. Thomas Ph.D.

RG Muscular dystrophy therapy based on small-molecule activators of Ca2+ transport

Summary Increased calcium influx, and reduced calcium removal from the sarcoplasm are thought to contribute to the muscular dystrophy (MD) phenotype. This suggests that activating Ca-transport (pumping) out of the sarcoplasm should benefit MD individuals. To test this hypothesis, we will use small-molecule compounds that specifically activate the calcium pump (SERCA) from the sarcoplasmic reticulum (SR), the intracellular reservoir of calcium. Our goal is to test whether compounds that activate SERCA in vitro can improve muscle contractility in vivo (and reduce MD pathology), in mouse MD models. The results of this research will provide proof-of-concept for a small-molecule strategy to treat MD and help select a set of lead compounds for drug development.

NEW JERSEY

Newark - UMDNJ-New Jersey Medical School

Diego Fraidenraich Ph.D.

RG Pluripotent stem cell-induced corrections in muscle and fat of mdx mice

Summary Interactions between adipose and muscle have attracted the attention of the scientific and medical communities lately. Recent published reports demonstrate that skeletal muscle and one type of fat have a common cellular ancestor, and our studies of developing mice show related changes in these tissues. We treated an embryonic mouse model of Duchenne muscular dystrophy with stem cells derived from normal mouse tissue in order to provide the missing muscle protein. New, normalized muscle developed, but there was also an increase in fat and a persistence of muscle markers in fat tissue that are not seen in normal mice. In
this project we will characterize this stem cell-derived fat and understand its role in the development of normal muscle. New determinants of muscle formation will provide mechanisms for future therapies. Key words: fat/muscle conversion, blastocyst injection, embryonic and induced pluripotent stem cells, mdx.

NEW MEXICO
Albuquerque - The Regents of the University of New Mexico
Richard Cripps D. Phil.
RG A Drosophila model for mammalian muscular dystrophy
$113,187.00 7/1/2012 6/30/2013 Year 3

Summary
We shall study muscle development in the fruit fly, Drosophila melanogaster, to help us understand muscle development and disease in humans. We use Drosophila as a model organism because the mechanisms of muscle development in this animal are very similar to those of vertebrates, yet the genetic processes are simpler and more well understood in flies. This project will study the function in Drosophila of a gene named abba, for which mutations in a related gene in humans have been identified to cause muscular dystrophy. We shall carry out experiments to understand how abba works in flies, including characterizing mutants for this gene, which we propose will develop muscular dystrophy in fly larvae. We shall also carry out experiments to define at the molecular level how the protein produced by abba functions in muscle, which will tell us a great deal about how the normal gene works in humans. These findings in Drosophila will therefore provide insight into normal muscle processes in humans; accordingly, our data will help us to understand how muscle development goes awry in diseased individuals, and will uncover potential mechanisms by which to generate rational therapies for muscle disease.

NEW YORK
New York - Memorial Sloan-Kettering Cancer Center
Mary Baylies Ph.D.
RG Myonuclear Positioning: links to Nuclear structure and Muscle Function
$137,331.00 8/1/2012 7/31/2013 Year 1
$133,304.00 8/1/2013 7/31/2014 Year 2
$128,634.00 8/1/2014 7/31/2015 Year 3

Summary
Emery Dreifuss Muscular Dystrophy (EDMD) has been linked to mutations in LMNA, a gene which encodes the Lamin A and C proteins. Lamin A and C are components of the nuclear lamina, a fibrous structure associated with the inner nuclear membrane via interactions with integral membrane proteins. Lamin A and C provide structural integrity and shape to the nucleus. They also interact with chromatin and transcriptional regulators to influence gene expression in myofibers and satellite cells. Recently, EDMD-linked mutations in Lamin A/C also have been shown to cause nuclear movement/positioning defects in tissue culture. Given the many functions of Lamin A/C, the reason why LMNA mutations cause muscle disease remains unclear. We previously identified a microtubule-associated protein, Ensconsin (Ens) as critical for nuclear movement in both Drosophila and mouse muscle. ens mutant larvae do not move as fast as wild-type larvae, indicating that improper nuclear localization has significant impact on muscle function. We find that Ens physically and genetically interacts with Lamin C. Lamin C mutants have mispositioned nuclei and defective muscle function. We hypothesize that Ens and Lamin C act together, linking nuclear positioning to gene expression and muscle function. We will determine the nature of the interaction, how they regulate muscle function, and provide new insights to both the cellular processes required for optimal muscle function and to different muscle diseases.

NORTH CAROLINA
Chapel Hill - The University of North Carolina at Chapel Hill
Joan M. Taylor Ph.D.
RG  Muscle development and repair mediated by the BAR-containing Rho GAP, GRAF  
$132,000.00  2/1/2013  1/31/2014  Year 1  
$132,000.00  2/1/2014  1/31/2015  Year 2  
$132,000.00  2/15/2015  1/31/2016  Year 3  

Summary  We published that depletion of a skeletal muscle selective protein from developing tadpoles led to mobility defects and progressive muscle degeneration that was reminiscent of the disease progression observed in several congenital muscular dystrophies. We subsequently found that this protein acts to promote muscle formation and injury repair will identify the underlying mechanisms. Moreover, we found that this protein interacts with receptors frequently mutated in patients with muscular dystrophies, and will test the possibility that mis-regulation of this protein contributes to the debilitating nature of these diseases. We have developed several novel mouse models that will now enable us to test these exiting possibilities. These studies will undoubtedly lead to new and important directions for therapies to target a multitude of congenital dystrophies.

Charlotte - Carolinas Medical Center  
Susan Sparks M.D., Ph.D.  
RRG  Longitudinal Assessment and Genetic Identification of Limb-Girdle Muscular Dystrophy  
$188,987.28  10/1/2012  9/30/2013  Year 1  

Summary  Limb-girdle muscular dystrophy (LGMD) is largely a descriptive term for a molecularly heterogeneous group of muscular dystrophies with onset in childhood or adulthood that is characterized by progressive muscle weakness. LGMD are classified into two groups based on the mode of inheritance, type 1 for autosomal dominant and type 2 for autosomal recessive. Each type is further subdivided depending on the molecular etiology, designated by a letter in the order they were discovered (i.e. LGMD1A-E and LGMD2A-N). Molecular clarification has resulted in the elucidation of common pathways of pathogenesis, as well as important differences between subtypes of LGMD. The community has identified lack of natural history studies as a major gap in our knowledge base and a significant barrier to the development of effective clinical trials in LGMD. In addition, the lack of validated clinical trial endpoints makes it near impossible to transition potential therapeutics through rigorous clinical trials into routine treatments for LGMD. This proposal aims to comprehensively evaluate individuals with genetically identified LGMD and follow potential outcome measures longitudinally in patients with LGMD. In addition, there is an aim to perform whole-exome sequencing on patients with clinically diagnosed LGMD without an identified genetic mutation.

Xiaohua Wu Ph.D., M.D.  
RG  Enhancing Laminin Binding to Treat Muscular Dystrophies  
$106,015.00  2/1/2012  1/31/2013  Year 2  

Summary  The long term goal of our research is to discover effective treatments for muscular dystrophies. Currently, there is no effective treatment for any forms of MD. A number of muscular dystrophies (MD) are associated with compromised linkage between basement membrane and myofibers due to various genetic defects. The linkage plays a key role in muscle function. Enhance the linkage through via over expression certain genes have been proved useful in MD mouse models. In this project, we plan to identify small compounds that can enhance the linkage. We recently developed a cell-based assay. We plan to screen large number of small compounds (100,000)to identify the compounds. Further, we plan to test the identified compounds in cell culture and MD mouse models to develop drug for MDs.

Durham - Duke University Medical Center  
Michael Hauser Ph.D.  
RG  The Genetic Basis of Autosomal Dominant LGMD  
$127,952.00  2/1/2012  1/31/2013  Year 2
We have collected a number of families in which limb girdle muscular dystrophy affects multiple family members. We will analyze the DNA from those affected individuals in order to find the specific mutations (DNA changes) that cause disease. The identity of these mutations and the genes that they affect will improve our understanding of the way these diseases damage muscle tissue, and will allow the development of new therapeutic strategies. Relevance to MDA Development of new treatments for autosomal dominant muscular dystrophies requires a clear understanding of the causative mutations and the mechanism by which those mutations cause disease. This proposal builds on a previously funded MDA grant 4090 "Genetic Studies in Unlinked Muscular Dystrophies" which supported the linkage analysis of a number of dominant LGMD families. That work successfully linked multiple pedigrees. In the present proposal, we will continue analysis of these families to identify the causative mutations.

**OHIO**

**Columbus - The Ohio State University**

**Noah Weisleder Ph.D.**

**RG** Protein therapy targeting limb girdle muscular dystrophy

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**Summary** Defective muscle cell membrane repair is associated with the progression of various types of limb girdle muscular dystrophy (LGMD) that is linked to mutations in many different genes in human patients. We recently discovered that Mitsugumin 53 (MG53), a muscle-specific TRIM-family protein (TRIM72), is an essential component of the acute membrane repair machinery in striated muscle. MG53 acts to nucleate recruitment of intracellular vesicles to the injury site for membrane patch formation. We showed MG53 can interact with dysferlin to facilitate its membrane repair function. Results that are recently published establish that MG53 protein can be used directly as a therapeutic approach to increase membrane repair in skeletal muscle fibers. Our studies found that membrane injury leads to exposure of a signal to the extracellular space that can be detected by purified recombinant human MG53 protein (rhMG53). We generated in vivo data to show that intravenous delivery of rhMG53 can ameliorate cardiotoxin-induced damage to muscle fibers. Furthermore, we demonstrated that subcutaneous injection of rhMG53 could reduce the severity of pathology in the mdx mouse model of Duchenne muscular dystrophy. In this project we will test the capacity for the MG53 protein to reduce the pathology in animal models of three forms of LGMD. This application will represent a first resubmission of our application from December 2011 and contains additional preliminary data and a revised research plan.

**Columbus - The Ohio State University (OSU)**

**Jill Rafael-Fortney Ph.D.**

**RG** Investigation of a new treatment target for heart failure in muscular dystrophy

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**Summary** At least 95% of Duchenne muscular dystrophy (DMD) patients develop cardiomyopathy. As therapies to protect respiratory function improve, DMD patients live longer, and the chance of heart failure will approach 100%. Supporting this prediction, Becker muscular dystrophy patients with milder skeletal muscle disease all develop severe cardiac disease. We have discovered that the claudin-5 protein is deficient specifically in heart muscle cells in a muscular dystrophy mouse model that exhibits heart failure. Claudin-5 reductions occur in a time-frame that makes it an excellent candidate as a therapeutic target. We have also identified specific reductions of claudin-5 in at least 60% of patients with heart failure, demonstrating the clinical relevance of this protein and further supporting that claudin-5 may be a key "switch" from many forms of cardiomyopathy to progression of heart failure.
Claudin-5 therefore represents a novel potential therapeutic target for treatment of DMD related cardiomyopathy and heart failure. In this study, we will define the mechanisms specific to claudin-5 deficiency, determine claudin-5 levels in other forms of muscular dystrophy, and determine whether exogenous claudin-5 expression is sufficient to prevent heart failure in muscular dystrophy mouse models. This study will directly address the potential of a novel protein as a treatment target for prevention of heart failure in muscular dystrophy patients.

Columbus - The Research Institute at Nationwide Children's Hospital

Paul Martin Ph.D.

**RG**  Protein-based GALGT2 therapies for Duchenne muscular dystrophy

$132,000.00  8/1/2012  7/31/2013  Year 2

$132,000.00  8/1/2013  7/31/2014  Year 3

**Summary**  This proposal seeks to develop two new therapies for the treatment of Duchenne muscular dystrophy (DMD). The investigators have shown that overexpression of a naturally occurring gene, called Galgt2, in skeletal muscles can inhibit the development of disease in the mdx mouse model for DMD. Here, they seek to translate this idea into a therapy for DMD. The approach is to test two new protein therapies in a DMD animal model that would increase the expression of Galgt2. One approach is to add a factor that stimulates the ability of skeletal muscles to increase their own expression of Galgt2. The other approach is to engineer a Galgt2 protein that can cross into muscle cells from the serum to directly increase expression levels. Because overexpression of Galgt2 has been shown to be therapeutic in other models of muscular dystrophy (Congenital muscular dystrophy 1A and Limb Girdle Muscular Dystrophy 2D), any approach shown to work in DMD may also apply to these other forms of the disease.

PENNSYLVANIA

Philadelphia - The Trustees of the University of Pennsylvania

Tathagata Chaudhuri Ph.D.

**DG**  Matrix Conditioning of Mesenchymal Stem Cells to Rescue Muscular Dystrophies

$60,000.00  8/1/2012  7/31/2013  Year 1

$60,000.00  8/1/2013  7/31/2014  Year 2

$60,000.00  8/1/2014  7/31/2015  Year 3

**Summary**  The specific goal of this study is to develop a novel technology which will direct human Mesenchymal Stem Cells (MSCs) to form muscle cells and therefore repair damaged skeletal muscle in muscular dystrophies, particularly, Duchenne Muscular Dystrophy (DMD). MSCs are commercially available and can be engineered to differentiate into muscle and our objective is to show that matrix based-conditioning of these MSCs can induce differentiation into muscle like cells. First, we will test if these preconditioned MSCs are capable of rescuing muscle defects and lead to myogenesis when injected into the damaged muscles of mdx mice, the mouse model of DMD. Secondly, to examine if this work can be clinically translated, we will also apply the same technology in the golden retriever muscular dystrophy (GRMD) dogs which exhibit a more severe dystrophic phenotype and closely resembles the human condition. We will determine if dog MSCs derived from GRMD dogs can also be programmed by matrix specification into a myogenic fate, similar to human MSCs. Finally, we will engineer these dog MSCs to express dystrophin, commit them into a myogenic lineage and inject them back into the same donor GRMD dog to examine if muscle repair and regeneration occur. These goals will determine if matrix elasticity alone can induce both human and canine MSCs to be committed into a myogenic lineage and whether this approach of utilizing preconditioned cells can be used for cellular therapy of muscular dystrophies.
RHODE ISLAND
West Kingston - Gordon Research Conferences

Peter David Currie Ph.D.

SG  Myogenesis Gordon Research Conference and Myogenesis Gordon Research Seminar
$10,000.00  7/1/2013  7/31/2013  Year 1

Summary  The central objective of the 2013 Myogenesis Gordon Research Conference (GRC) entitled "Models and Mechanisms in Myogenesis" is to stimulate discussion, scientific interchange and insight into the factors affecting muscle tissue formation and repair during muscle development and disease. The participants present new, unpublished research on a wide range of topics including muscle specification, cell interplay during muscle development, evolutionary mechanisms of muscle formation, insights into muscle stem cells, and regeneration and there will be a strong emphasis on advanced animal disease modelling to examine the genetic and morphogenetic basis for muscle formation and repair. There will be several sessions that deal directly with research targeted at generating treatments for a range of muscular dystrophies. These topics are central to the MDAs mission of funding research that seeks to understand the causes of, and effective treatments for, neuromuscular diseases. The meeting will bring together 50 speakers that represent critical areas of striated muscle research with a total of 180 participants for a five-day conference. A new component of the 2013 meeting will be the Gordon Graduate and Post-doctoral Seminar on Myogenesis, held immediately before the main meeting. Students and post-doctoral researchers will interact and present their research in an exciting, unintimidating environment consisting wholly of their peers before attending the more traditional GRC.

WASHINGTON
Seattle - University of Washington

Martin K Childers Ph.D.

RG  Dystrophin-deficient cardiomyocytes for high-thruput drug screening
$160,000.00  8/1/2012  7/31/2013  Year 2
$160,000.00  8/1/2013  7/31/2014  Year 3

Summary  Heart failure is a common and serious feature of Duchenne muscular dystrophy. The reason for this is because the heart muscle carries a genetic mutation that damages the normal operation of this all-important muscle. Our project will allow for the discovery of new drugs that might reverse, or prevent effects of the disease on the heart muscle in DMD patients. We will use two types of new technology to find potential new drugs. First, we will use a groundbreaking method called "cellular reprogramming". This method was first used to make stem cells out of skin cells from patients. In our project, we will first make stem cells from the skin cells of DMD patients, then we will use these stem cells to form beating heart cells. These newly "reprogrammed" heart cells will contain the same genetic mutation found in the patient's own skin cells. Many thousands of reprogrammed cells can be generated to form identical heart cells, and these cells can be individually examined. This remarkable new technology will allow us to study how a genetic mutation affects the heart cells of a specific patient. The second method we will use is a drug discovery "platform" that can screen individual cells against thousands of drug compounds available for testing. By marrying these two incredible technologies, this project will allow for the first time, the ability to test new drugs directly on the heart cells from an individual patient without carrying any risk to the patient.