

# RESEARCH IN THE WORKS



# 2005

## **Muscular Dystrophy Canada's Neuromuscular Research Partnership Grants**

**The Neuromuscular Research Partnership (NRP)** is a result of an agreement between the **ALS Society of Canada, Muscular Dystrophy Canada (MDC)** and the **Canadian Institutes of Health Research (CIHR)**. Collectively in 2005, the partners will contribute over **\$3,700,000** towards research aimed at identifying the causes, treatments and an eventual cure for neuromuscular disorders. The Partners are pleased to announce the results of the sixth NRP competition.

**Thank you to all of our donors. Without your generosity none of this research would be possible.**



# NEW RESEARCH GRANTS

## **Dr. Bernard Brais**

**Centre Hospitalier de l'Université de Montréal  
(CHUM)**

**CLONING AND CHARACTERIZATION OF THE MUTATED GENE  
RESPONSIBLE FOR A NEW FORM OF FRENCH- CANADIAN  
RECESSIVE SPASTIC ATAXIA**

**\$293,850** (2005 through 2008)

The recent detection of a unique form of spastic ataxia, a member of the group of neuromuscular disorders characterized by degeneration of the spinal cord and progressive damage of the peripheral nerves, has opened the doors for this research project. Dr. Brais and his team at the Centre Hospitalier de l'Université de Montréal are examining the history and prevalence of autosomal recessive spastic ataxia of Portneuf (ARSAP) that currently is understood to be responsible for more than 20% of recessive ataxias in Quebec, and also to locate the gene mutation that causes the disorder.

**This project will help build understanding of ARSAP and improve diagnostic accuracy for this newly distinguished disorder.**

## **Dr. F.J. Dilworth**

**Ottawa Health Research Institute**

**ELUCIDATING THE MECHANISMS DIRECTING TEMPORALLY  
ORDERED GENE EXPRESSION BY MYOD**

**\$645, 245** (2005 through 2010)

The myoD gene, that codes for the myoD protein molecule, is being studied for its role in the complex chain of

signals and reactions that changes a basic (progenitor or stem) cell into a muscle cell during the ongoing stages of embryonic development. This process is called myogenesis and Dr. Dilworth and his team at the Ottawa Health Research Institute are diving deeper into the puzzle of how and why this protein assists in changing the natural stem cells found in the embryo into a highly organized system of skeletal muscles. The complex chain reaction that involves the myoD protein could be an important part of future therapies and treatments that would involve transforming stem cells into muscle tissue, either inside or outside the body.

**It is the specific aim of this project to contribute to refining the stem cell research that holds significant hope for future treatments of many forms of muscular dystrophy.**

## **Dr. F.J. Dilworth**

**Ottawa Health Research Institute**



# NEW RESEARCH GRANTS

## Dr. H. Durham

McGill University & Montreal Neurological Institute

### THE ROLE OF PROTEIN CHAPERONES AND PROTEASOME-MEDIATED PROTEOLYSIS IN THE PATHOGENESIS OF MOTOR NEURON DISEASES

**\$512,285** (2005 through 2010)

Dr. Durham and her team are seeking to understand the unique vulnerabilities of motor neurons in order to help them live. In a continuation of their work from a previous NRP grant, this project is looking deeper at the specific methods by which a cell “cleans house”, removing proteins that are damaged or dangerous to the health of that cell. “Chaperones” would normally target and help transport these broken proteins to where they would be chopped up and recycled. But in familial ALS (fALS) this process seems to be impaired. After studying this process in their previous grant, Dr. Durham and her team at McGill University and the Montreal Neurological Institute continue to ask why, and look further at ways to compensate for this impairment.

**This project will lead to a deeper understanding of fALS and could offer potential drug therapies to treat the disorder.**



**Dr. H. Durham**  
McGill University &  
Montreal  
Neurological  
Institute

## Dr. K. Hastings

McGill University

### FIBER-TYPE SPECIFIC AND ACTIVITY-REGULATED GENE EXPRESSION IN FAST SKELETAL MUSCLE.

**\$298,992** (2005 through 2008)

Dr. Hastings is investigating how specific types of muscle fiber function so that we can better understand how neuromuscular disorders occur. Muscle is a complex tissue, composed of different cell types that are physically specialized for different roles. Dr. Hastings, and his team at McGill University, are interested in the differences between fast and slow muscle fibers, named for their relative rate of contraction when activated. Building on a previous NRP grant, Dr. Hastings' work continues to examine the elements that interact during genetic expression and muscle cell formation to cause muscle fibers to form into either the fast or slow variety. By understanding this process it will be possible to further understand how muscle tissue as a whole, composed of a variety of fiber types, is formed and maintained in the body.

**This project aims to refine our understanding of muscle growth and regeneration.**

## Dr. Jean-Pierre Julien

Université Laval

### PATHOGENIC MECHANISMS ASSOCIATED WITH NEUROFILAMENT DISORGANIZATION

**\$662,560** (2005 through 2010)

Amyotrophic Lateral Sclerosis (ALS) is a progressive and lethal neurodegenerative disorder. The disorder itself is associated with the build-up of neurofilament proteins (into protein collections called ‘spheroids’) but it is not well understood how or why these proteins are involved with the degeneration of neurons in

# NEW RESEARCH GRANTS

the brain and spinal cord. Dr. Julien and his team at the Université Laval are using mice that mimic the mutations found in humans to study this problem, trying to understand what role the neurofilament proteins play in the nerve cells.

**This project will shed light on ALS and its causes.**

**Dr. George Karpati  
& Joséphine Nalbantoglu**  
Montreal Neurological Institute & McGill University

#### **MOLECULAR THERAPIES FOR DYSTROPHIN DEFICIENCY**

**\$339,234** (2005 through 2008)

Building on past work supported by NRP grants, this project focuses on the area of gene therapy in two animal models of DMD, the *mdx* mouse and the golden retriever dystrophic dog. Dr. Karpati and his team are trying to increase the levels of utrophin, a protein that is similar in form and function to dystrophin (the mis-functioning protein in DMD and other neuromuscular disorders), inside the muscle tissue. This work encompasses two unique methods to achieve this goal. In one method, the team will introduce a new copy of the utrophin gene and cause it to produce the protein. In the other method, they will boost and stimulate an existing copy of the gene to produce extra utrophin.

**This project will help understand potential genetic therapies for DMD and many other types of muscular dystrophy.**



**Dr. George Karpati**  
Montreal Neurological  
Institute & McGill  
University

**Dr. Hakima Moukhles**  
University of British Columbia

#### **DYSTROGLYCAN FUNCTION IN GLIAL CELLS**

**\$266,433** (2005 through 2008)

Dr. Moukhles wants to understand why there is sometimes an effect on the brain when someone has a neuromuscular disorder. She, and her team from the University of British Columbia, are studying the protein dystroglycan, one of the many pieces that assemble to form the “dystrophin glycoprotein complex” implicated in several forms of muscular dystrophy. Their speculation is that, not only does the mutation have a direct effect on muscles, but also that it has an indirect effect on the central nervous system through glial cells. Dr. Moukhles is studying glial cells, the cells that form a protective insulating layer around nerve cells, and specifically what happens to their protective ability with a dystroglycan mutation.

**This project will lead to a better understanding of diminished mental function and structural abnormalities of the brain that occur in some forms of muscular dystrophy.**

**Dr. David Picketts**  
Ottawa Health Research Institute

#### **GENETIC DISSECTION OF ISWI FUNCTION DURING NEUROGENESIS**

**\$378,258** (2005 through 2008)

Two proteins, SNF2H and SNF2L, are being studied for their role in the complex chain of molecules and signals that help to turn stem cells into neurons in a developing embryo. Dr. Picketts and his team at the Ottawa Health Research Institute are studying these proteins in an effort to better understand their role in the growth and differentiation of both neurons and muscles. Using a customized mouse model to study

# NEW RESEARCH GRANTS

this system, Dr. Picketts is learning how SNF2H and SNF2L work, and what exactly is entailed by their influence on the cell and its growth.

**This project will help to define how stem cells work, and what steps are required to direct a stem cell to become a muscle or nerve cell.**

**Dr. Louise Simard**  
Hôpital Sainte-Justine

**CHARACTERIZATION OF "SURVIVAL OF MOTOR NEURONS" (SMN) GENE REGULATION**

**\$270,252** (2005 through 2008)

Spinal Muscular Atrophy (SMA), the second most common childhood neuromuscular disorder, is a neurodegenerative disorder that causes muscle weakness by disrupting the motor neurons in the spinal cord. Dr. Simard, and her research team at Hôpital Sainte-Justine in Montreal, continue their work (from a previous NRP grant) towards further understanding the genes that cause this disorder and potential therapies to control how these genes are expressed in the cell. Specifically, Dr. Simard continues to study "promoters", a kind of genetic ignition-switch, that control how the SMN genes associated with SMA are managed and regulated. Their research has been focused on specific molecules and genetic elements that have shown promise as important players in the processes leading to SMA.

**This project will contribute to the general understanding of SMA and may provide clues for future genetic therapies.**

**Dr. Michael Sinnreich**  
McGill University & Montreal Neurological Institute

**MODULAR FLEXIBILITY OF DYSFERLIN - POSSIBLE APPLICATIONS FOR GENE THERAPEUTIC STRATEGIES**

**\$91,947** (2005/06)

Dysferlin is a muscle protein thought to be involved in the repair of muscle damage caused naturally through exercise. Both limb-girdle muscular dystrophy type 2B (LGMD 2B) and Miyoshi myopathy, neuro-muscular wasting disorders, are considered to be linked to a mutation in the gene for dysferlin. Dr. Sinnreich, and his team at McGill University and the Montreal Neurological Institute, have been studying unique cases of LGMD 2B in an attempt to further understand dysferlin and uncover ways to replace its relatively large gene inside the cell. Their studies currently involve experiments with mice to replace the mutated dysferlin gene with a smaller, but fully functional version. It is hoped that this will lead to genetic tools and therapies using a gene that is small enough to be more easily and efficiently delivered to the muscles.

**This project will contribute to the further understanding of dysferlinopathies and will provide clues for future genetic therapies.**



# OTHER FUNDING

## FELLOWSHIP GRANT

**Dr. Brett Kaufman**  
Montreal Neurological Institute,  
McGill University

### IDENTIFICATION OF PROTEINS INVOLVED IN MITOCHONDRIAL GENOME MAINTENANCE AND SEGREGATION

**\$135,000** (2005 through 2008) Total funded by  
Muscular Dystrophy Canada

Fellowships in the Area of Neuromuscular Disease Mitochondria, the internal “power plants” of the cells, are unique in that they have their own set of genetic material, referred to as mtDNA. Dr. Kaufman is looking at the proteins that help to maintain this mtDNA inside the cell, and the role that these proteins play in the overall health of the whole cell. Dr. Kaufman hopes to apply the knowledge from this fellowship work towards further understanding the role of mtDNA in neuromuscular disorders.



## EW INVESTIGATOR GRANT

**Dr. Jeff Dilworth**  
Ottawa Health Research Institute

### EPIGENETIC REGULATION OF STEM CELL DEVELOPMENT INTO MUSCLE

**\$100,000** (2005 through 2007) A partnership grant  
with the stem cell network

Dr. Dilworth uses his knowledge of muscle growth and development to study some of the ways by which stem cells could be coaxed into changing from simple, unshaped cells into new muscles. This process, called myogenesis, is regulated by a complex series of hormones and genetic triggers. By further understanding and learning to replicate these molecular signals in the laboratory we may also learn how to better grow new muscles in people.

FOR MORE INFORMATION ABOUT OUR  
**RESEARCH PROGRAM** PLEASE VISIT  
**WWW.MUSCLE.CA.**

If you'd like to contribute to the  
Research Program, please e-mail  
**giving@muscle.ca**  
or write to:

**Muscular Dystrophy Canada**  
**2345 Yonge Street Ste 900**  
**Toronto ON M4P 2E5**

# ONGOING RESEARCH

**Dr. Vanessa Auld**  
University of British Columbia

**GLIAL CELL DEVELOPMENT AND FUNCTION AT THE DROSOPHILA NEUROMUSCULAR JUNCTION**

**\$401,922** (2004 through 2007)

Nervous system development and function is guided by control cells called glia. Dr. Auld and her team are studying the physiological basics of glia cells in fruit fly development. Fruit flies are a well-understood and highly useful animal model that will allow the research team to understand the fundamental elements of these cells. Understanding how these glia cells interact with neurons at a cellular level will set the stage for future investigations on neuron development and repair in vertebrates.

**Dr. J. Bain & Dr. M. Fahnstock**  
McMaster University

**MECHANISM OF SENSORY PROTECTION OF DENERVATED MUSCLE**

**\$217,247** (2003 through 2006)

The goal of the project is to understand how sensory protection prevents muscle atrophy and determine if sensory protection is a potentially valuable therapeutic approach to nerve damage following injury or disorders such as the muscular dystrophies, spinal muscular atrophies, and amyotrophic lateral sclerosis.

**Dr. B. Brais**  
University of Montreal,  
CHUM Research Centre

**OCULOPHARYNGEAL MUSCULAR DYSTROPHY AND POLYALANINE TOXICITY**

**\$277,698** (2003 through 2006)

Dr. Brais' study of polyalanine toxicity – the cause of oculopharyngeal muscular dystrophy— is focused on how polyalanine tracts disrupt muscle cell function?

**Dr. Avijit Chakrabarty**  
University Health Network,  
Ontario Cancer Institute

**PROTEIN MISFOLDING AND CONFORMATIONAL DISEASE**

**\$311,850** (2004 through 2007)

There are over one hundred point mutations in the gene for superoxide dismutase (SOD). Familial ALS is the result of one or more mutations in this gene. These mutations lead to incorrect “folding” of the completed protein, an effect that usually severely disrupts the protein's proper function and possibly adds new functions which can be harmful to the cell and the body. Understanding the results these misfolded proteins cause is a key element to understanding ALS and other disorders related to protein folding. Dr. Chakrabarty and his team is studying how protein folding affects cells and the entire body in order to better understand ALS.

**Dr. M. Ferns**  
Montreal General Hospital

**NEUROTRANSMITTER RECEPTOR LOCALIZATION AT THE SYNAPSE: REGULATION BY RAPSYN.**

**\$267,927** (2002 through 2005)

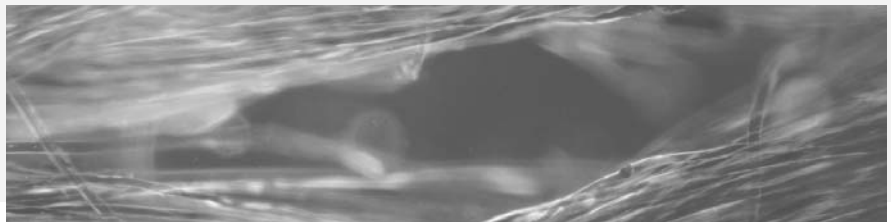
Dr. Ferns is seeking to elucidate the role of signaling factors in the neuromuscular junction's molecular formation. Understanding the basic biology of the junction is essential to understanding how nerve and muscle communication occurs.

**Dr. Jérôme Frenette**  
Université Laval

**INFLAMMATORY CELL RECRUITMENT AND FUNCTION IN SKELETAL MUSCLES FOLLOWING HIND LIMB UNLOADING AND RELOADING: NEW STRATEGIES TO PREVENT MUSCLE ATROPHY AND DYSFUNCTION.**

**\$262,978** (2004 through 2007)

For someone living with a neuromuscular disorder, muscle weakness often results in being confined to a bed or even a wheelchair for long periods of time. This can cause secondary atrophy of the muscles, compounding the original disorder. “Reloading” or trying to rebuild these muscles after atrophy has been shown to cause inflammation and further muscle damage. Using mice models, Dr. Frenette and his team hope to identify the proteins and processes involved in this damage.



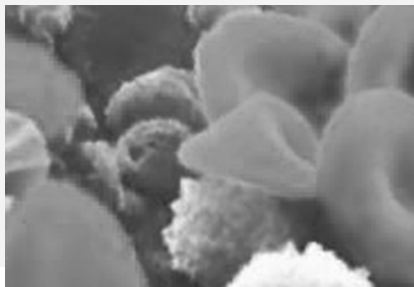
and also further understand the consequences of certain chemicals and stabilizing agents. Finally, they will consider possible therapeutic options. This project will provide insight into how secondary atrophy—a side effect of immobility—can be reduced or diminished.

**Dr. George Karpati**  
Children's McGill University

**EXTRASYNAPTIC ENDOGENOUS UTROPHIN UPREGULATION IN DYSTROPHIN DEFICIENT MUSCLE: A THERAPEUTIC APPROACH FOR DUCHENNE MUSCULAR DYSTROPHY.**

**\$216,720** (2004 through 2007)

Dr. Karpati and his team have had a great deal of experience working with genetic treatments for Duchenne muscular dystrophy (DMD) and related neuromuscular disorders. This grant deals with the “upregulation” or therapeutic increase in production of utrophin. Utrophin is a molecule very similar to dystrophin, the protein missing or damaged in DMD. Experimentally increasing the levels of utrophin in mice has decreased Duchenne-like symptoms. This study works towards the development of molecular tools to increase the safety and efficiency of utrophin upregulation. This project will help create therapies for Duchenne muscular dystrophy.



**Dr. Jiming Kong**  
University of Manitoba

**AMYOTROPHIC LATERAL SCLEROSIS: ROLE OF BNIP3 IN MUTANT SOD1-INDUCED MOTOR NEURON DEATH**

**\$211,830** (2004 through 2007)

Apoptosis, or programmed cell death is a genetically controlled mechanism for the body to eliminate cells that have outlived their usefulness. The hallmark feature of ALS is the excessive death of motor neuron cells. Dr. Kong and his team, using mice models of ALS, are studying a recently discovered protein (BNIP3) which appears to slow and control apoptosis in motor neurons. This project is examining ways to slow or decrease the symptoms of ALS.

**Dr. Robert Korneluk**  
Children's Hospital  
of Eastern Ontario

**THE X-LINKED INHIBITOR OF APOPTOSIS (XIAP): A THERAPEUTIC AGENT FOR THE TREATMENTS OF MUSCULAR DYSTROPHY**

**\$377,838** (2004 through 2007)

Neuromuscular disorders are often associated with excessive apoptosis, specifically disorders such as Myotonic Dystrophy (DM) where the mechanism for the disorder is related to untimely cell death. Dr. Korneluk and his team have spent years studying the effects of apoptosis and are now looking at naturally occurring factors that can control apoptosis. Using mice models, this study is looking at therapies for treating DM-like symptoms. This project is helping develop therapies for neuromuscular disorders.

**Dr. Charles Krieger & Fabio Rossi**

Simon Fraser University

**FUNCTIONAL ROLE OF HEMATOGENOUS INFLAMMATORY CELLS IN AMYOTROPHIC LATERAL SCLEROSIS**

**\$314,760** (2004 through 2007)

This project is investigating the causes of ALS and is providing information that will be useful in developing therapies for this disorder.

**Dr. A. Mackenzie**  
Children's Hospital  
of Eastern Ontario

**MODULATION OF APOPTOSIS IN MOUSE MODELS OF SPINAL MUSCULAR ATROPHY**

**\$270,900** (2003 through 2006)

Dr. Mackenzie is examining how cell death can be regulated in spinal muscular atrophy.

**Dr. Susan Meakin & John P. Robarts**  
Research Institute

**NESCA, A NOVEL INTRACELLULAR SIGNALING ADAPTER FACILITATES NEURITIC DEPENDENT NEURITE OUTGROWTH.**

**\$206,295** (2004 through 2007)

Neuromuscular disorders are one of many causes of damage to the nervous system, and there are many factors involved in the recovery, survival and regrowth of damaged nerves. This process involves a complex series of chemical events. Dr. Meakin and her team are studying a newly discovered molecule that seems to be an important signaling

element triggering the growth of neurites, hair-like projections of neurons stimulated by growth factors, and other molecules that are involved during development and after neuromuscular-related injury. This project is providing information that may help develop therapies and/or treatments for neuromuscular disorders.

**Dr. E. Meiring**  
University of Waterloo

**FOLDING AND AGGREGATION OF ALS  
-ASSOCIATED MUTANT SUPEROXIDE  
DISMUTASES**

**\$362,928** (2003 through 2006)

These studies are providing important information regarding the ALS disease mechanism and ultimately lead to new therapeutic approaches for treating ALS and potentially other protein conformational disorders.

**Dr. R. Michel**  
Laurentian University

**CALCINEURIN SIGNALING IN THE  
REGULATION OF SKELETAL MUSCLE  
FIBRE GROWTH**

**\$231,093** (2003 through 2006)

Dr. Michel was the first to demonstrate calcineurin's crucial role in the growth of adult muscle. With the hope that his research in muscle signaling may lead to new therapeutic approaches in neuromuscular disorders, Dr. Michel is now working to decipher the other factors affecting muscle growth.

**Dr. B. Minassian**  
Hospital for Sick Children

**UNRAVELING THE CAUSATIVE DEFECT IN  
THE X-LINKED MYOPATHY WITH EXCESSIVE  
AUTOPHAGY**

**\$310,665** (2003 through 2006)

Abnormalities in many genes can cause limb-girdle muscular dystrophy. Studying the mutations in these genes is providing insight into the functioning of muscle and is helping to develop future treatments.

**Dr. Robin Parks &  
Jonathan Bramson**  
Ottawa Health Research Institute

**ADENOVIRUS VECTORS FOR GENE  
THERAPY OF MUSCLE**

**\$388,545** (2004 through 2007)

Dr. Parks and her team have been working towards developing efficient and useful gene therapy vectors (elements that help carry genes into cells) to treat neuromuscular disorders, specifically Duchenne muscular dystrophy. Past studies have improved this knowledge and the current project will further refine the work that has been done to develop safe and efficient tools for future gene therapy approaches to neuromuscular treatment. This project is investigating treatments that will carry normal genes into cells to replace defective genes.

**Dr. J. Puymirat**  
Centre hospitalier  
de l'Université de Québec

**RIBOZYME AND ANTISENSE RNA AS A  
TOOL TO STUDY MYOTONIC DYSTROPHY**

**\$203,109** (2003 through 2006)

Dr. Puymirat is attempting to create gene therapies using "road blocks" that will stop the mutated genes that cause myotonic dystrophy from being read thereby reducing the symptoms of myotonic dystrophy

**Dr. J. Robertson**  
University of Toronto

**PERIPHERIN ABNORMALITIES IN  
AMYOTROPHIC LATERAL SCLEROSIS**

**\$142,647** (2003 through 2006)

Dr. Robertson is investigating the inflammatory reaction in the hopes of developing new therapies for treating ALS.

**Dr. F. Rossi**  
Biomedical Research Centre,  
Vancouver

**CIRCULATING MYOGENIC PROENITORS:  
A LINEAGE ANALYSIS**

**\$100,000** (2003 through 2006)

Dr. Rossi is examining how to regenerate damaged muscle. By studying a particular type of cell that plays a role in the regeneration of muscle, this project will lead to the creation of new therapies for muscular dystrophies.



**Dr. F. Rossi**  
Biomedical  
Research Centre,  
Vancouver

# ONGOING RESEARCH

**Dr. D. Schreyer**  
University of Saskatchewan

**REGULATION OF NEURONAL PHENOTYPE BY MUSCLE-DERIVED FACTOR**

**\$218,004** (2003 through 2006)

Dr. Schreyer is investigating the relationship between muscle cells and the motor neurons that target them, with the hope of identifying the factor that affects the way neurons react to injury. His findings will help to create new treatments for neuromuscular disorders.

**Dr. J. Tremblay**  
Laval University

**TREATMENT OF DUCHENNE MUSCULAR DYSTROPHY: CORRECTION OF MUTATED DYSTROPHIN MRNA WITH RIBOZYMES**

**\$247,350** (2003 through 2006)

Dr. Jacques Tremblay is growing myoblasts for transplantation in humans. He and his collaborators are making progress in the treatment of Duchenne and other muscular dystrophies. It has worked in a small trial, now Dr. Tremblay is working on how to make the process practical and effective.

**Dr. J. Tremblay**  
Laval University

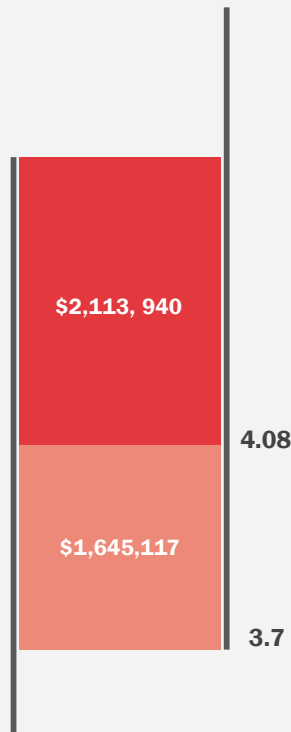


## HOW WE FUND RESEARCH

For decades, Canadian researchers have been world leaders in the search for the causes, cures and treatment of muscular dystrophy and other neuromuscular disorders. Since its inception in 1954, Muscular Dystrophy Canada has provided support to these scientists and we are dedicated to continuing this mandate in the future.

Muscular Dystrophy Canada has three main research programs: the Neuromuscular Research Partnership (NRP), Fellowships, and the Young Investigators grants. From time to time Muscular Dystrophy Canada may take part in awarding other grants deemed to have a great impact on neuromuscular research.

The NRP is a partnership between CIHR (Canadian Institutes for Health Research), ALS Canada and Muscular Dystrophy Canada. It follows CIHR's "winter cycle" for awarding grants. The competition is announced in the fall and includes a request for proposals. Interested researchers apply throughout the winter and CIHR convenes a committee and ranks the proposals in April and May.



CIHR ranks the proposals based on a set of strict and in-depth criteria. Muscular Dystrophy Canada convenes a committee to judge the relevance of the proposals to neuromuscular disorders and chooses to contribute on this basis.

All funds raised by Muscular Dystrophy Canada for research are given directly to the research institution (a university or hospital, for example) that holds the grant in trust for the researcher.

The NRP greatly reduces the administrative costs and time incurred for all parties and sets a high standard for the research conducted.

In 2005, the Canadian Institutes of Health Research funded 100% of projects deemed to be greater than a 4.08 on the ranking scale. In 2005, four projects met this standard for a total of \$2,113,940.

Muscular Dystrophy Canada, the ALS Society of Canada, and the Canadian Institutes of Health Research jointly fund projects that range between 3.7 and 4.08 on CIHR's ranking scale. In 2005, six projects received funding for a total of \$1,645,117.