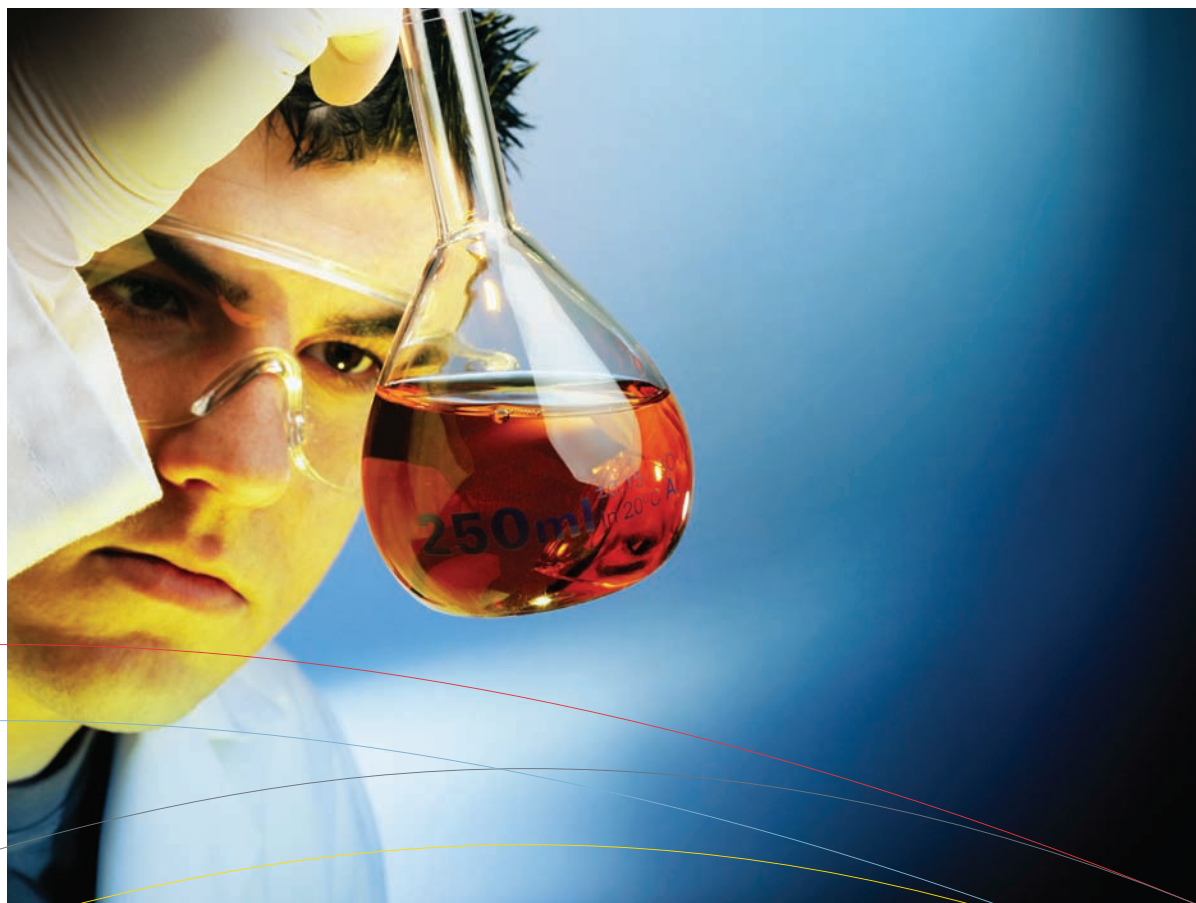


Muscular Dystrophy Canada
Research in the Works 2008



Research in the Works 2008

Improving lives, progressing towards a cure



In 1954, when Muscular Dystrophy Canada was established, people with muscular dystrophy lived short and painful lives. Today, while there is still no cure for this debilitating disorder, people with muscular dystrophy live longer, and with a much improved quality of life. The reason lies in research. Canadian scientists have made important discoveries about the causes of, and treatments for, muscular dystrophy. And, one day, they fully expect to find a cure.

Muscular Dystrophy Canada has supported these scientists throughout its existence. And, since 2000, it has done so in partnership with the Canadian Institutes of Health Research (Institute of Musculoskeletal Health and Arthritis, Institute of Genetics, and Institute of Neurosciences, Mental Health and Addiction) and the ALS Society of Canada.

The Neuromuscular Research Partnership (NRP), which is approaching its 10th anniversary, is the cornerstone of Muscular Dystrophy Canada's research program. By pooling our research funds, both the volume and the quality of the research we support have increased. For every dollar that Muscular Dystrophy

Canada contributes to the Partnership, more than three times that amount is invested in research. And all research funded through the Partnership has passed through CIHR's rigorous peer review process, ensuring that only the very best research is funded.

In 2008, the NRP awarded \$4.54 million to 11 new research projects, and continued to support 20 ongoing research studies.

In addition to the NRP, Muscular Dystrophy Canada, through the Rachel Fund for Myotonic Dystrophy, supported research to better understand myotonic dystrophy, the most common form of muscular dystrophy that begins in adulthood.

Muscular Dystrophy Canada's active research grants projects, which are described below, share many common elements. In particular, they focus on genes and proteins – discovering the genes and proteins whose mutations lead to neuromuscular disease, exploring their properties, and developing ways to restore the genes to their normal functioning. While this work takes place in the laboratory, often in animal models, the researchers carrying it out share a larger vision: they are all committed to one day discovering how to prevent and/or cure these devastating diseases. And, until that day comes, they share a commitment to slowing the onset and progression, and enhancing the lives of those affected by neuromuscular disorders.

Muscular Dystrophy Canada, and the researchers whose work is being supported, also share a strong sense of gratitude to the donors whose contribution makes all of this activity possible. We cannot say it often enough: thank you.

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Neuromuscular Research Partnership / Active Grants

Jane A. Batt (*St. Michael's Hospital, University of Toronto*)

Nedd4 regulation of skeletal muscle atrophy and regeneration

Dr. Batt is investigating the molecular mechanisms underlying skeletal muscle atrophy. This atrophy significantly increases the incidence of disease and requires more health resources at a greater cost. Understanding the biological signalling networks that mediate loss of muscle mass could lead to treatments for muscle atrophy.

Bernard Brais (*Centre Hospitalier de l'Université de Montréal*)

Developing molecular, cellular and mice models for Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS)

ARSACS is a recessive disease more frequent in the French-Canadian population. Dr. Brais is studying two genetic mutations that are tied to more than 96% of Quebec cases. The gene involved expresses a protein called sarsin; Dr. Brais' work will provide insights into its function and advance knowledge about ARSACS.



Avijit Chakrabartty (*University Health Network*)

Interplay of oxidative stress and protein misfolding in ALS

A mutation in the gene for the protein superoxide dismutase (SOD1) has been shown to cause ALS. Dr. Chakrabartty has demonstrated that an accumulation of oxidative injury causes aggregation of SOD1. Now he is investigating whether oxidative injury plays a role in ALS. If so, it could mean that antioxidants could hold potential for treating ALS.

Wayne S. Chen (*University of Calgary*)

Understanding the molecular defects and treatment of human malignant hyperthermia and central core disease

Mutations in the calcium release channel gene cause two human muscle disorders: malignant hyperthermia and central core disease. Dr. Chen and his team are defining the molecular basis of both disorders, looking in particular at the potential causes of the disorder. By better understanding the causes, the team hopes to lead to the development of new therapies for the disorders.

F. Jeffrey Dilworth (*Ottawa Hospital Research Institute*)

Elucidating the mechanisms directing temporally ordered gene expression by MyoD

Dr. Dilworth is studying the processes by which stem cells develop into mature muscle tissue, with a focus on how the muscle-specific pattern of gene expression is established during development, so that it can be reproduced exactly in stem cells. His work could lead to improved therapy for Duchenne muscular dystrophy.

Neuromuscular Research Partnership / Active Grants

Heather Durham (*Montreal Neurological Institute*)

The role of protein chaperones and proteasome-mediated proteolysis in the pathogenesis of motor neuron diseases

Dr. Durham is studying why motor neurons are vulnerable to damage in ALS, in order to identify therapies that can protect against the damage. Normally, when cells are subjected to stress, they synthesize families of proteins called stress proteins or heat shock proteins, whose role is to “chaperone” abnormal proteins to a degradation site. Her laboratory has shown that, in motor neuron diseases, the function of the waste degradation sites, called proteasomes, is disrupted. Her laboratory wants to know why this happens and whether increasing the chaperones can prevent or compensate for the poorly functioning proteasomes.



Stephen Gee (*University of Ottawa*)

Investigating the role of diacylglycerol kinase-zeta in the assembly and maintenance of the myofibrillar apparatus in skeletal muscle

Myofibrillar myopathy (MFM) is a group of neuromuscular disorders resulting in slow but progressive weakening of the limb muscles. The initial change is disintegration of the myofibrils, or long fibres that run the length of muscles. Dr. Gee is investigating the molecular mechanisms that control the assembly of the proteins that constitute myofibrils. His work could reveal signalling mechanisms that malfunction in MFM, and help identify targets for the design of therapies to slow or prevent myofibrillar destruction in MFM.

Renald Gilbert (*McGill University*)

Development of an integrated adenoviral vector for gene therapy of DMD

A promising approach to treating Duchenne muscular dystrophy (DMD) is to introduce a functional version of dystrophin, a muscle component whose mutation causes DMD, into muscle tissue – a process known as gene therapy. Dr. Gilbert is constructing a vector that could safely introduce the gene for dystrophin into living tissues.

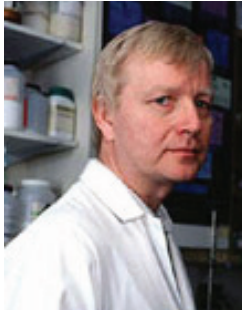


Anthony Gramolini (*University of Toronto*)

Molecular basis of ryanodine receptor regulation and function in skeletal muscle

Muscles contract when calcium is released into muscle cells from a storage compartment called the sarcoplasmic reticulum, and they relax when the calcium is returned to that compartment. Calcium release channels are the main protein responsible for the release of calcium. Dr. Gramolini and his team are studying the mechanisms regulating proper calcium release and uptake in muscle to understand how altered function can lead to disease. The knowledge gained from their work could lead to new ways to treat or prevent inherited and even acquired muscle defects.

Neuromuscular Research Partnership / Active Grants



Paul Holland and Josephine Nalbantoglu (*Montreal Neurological Institute*)
Combinatorial use of viral vectors for the gene therapy of muscle

Gene therapy is a promising treatment for genetic diseases such as Duchenne muscular dystrophy. However, the genes that are mutated in these diseases are too large to fit into the modified viruses that are used to introduce the corrected gene into the muscles of patients. Large genes can be delivered through adenoviruses, but only to cells with adenovirus receptors on their surfaces, which muscle cells lack. Dr. Holland proposes to first introduce the adenovirus receptor gene into muscle cells, and then to test whether these “pre-treated” muscle cells are better substrates for gene therapy.

Jean-Pierre Julien (*Université Laval*)
Pathogenic mechanisms associated with neurofilament disorganization

Evidence indicates that abnormal accumulations of neurofilaments (found in the axons that conduct signals away from nerve cells) are a hallmark of neuro-degenerative disorders such as ALS. Dr. Julien is examining the molecular mechanisms that underlie the toxicity of neurofilament disorganization using genetically modified mice.

Jean-Pierre Julien (*Université Laval*)
The role of inflammation in pathogenesis and immunotherapy of ALS

Dr. Julien is studying the contribution of the inflammation process to ALS onset and progression. As part of the project, he will use real-time imaging to study the effects of immunotherapy on inflammation and on pathological changes in ALS mouse models.

George Karpati* and Josephine Nalbantoglu (*McGill University*)
Molecular therapies for dystrophin deficiency

This team is pursuing a gene therapy strategy for Duchenne muscular dystrophy (DMD), by increasing the level of utrophin. Utrophin is a very similar protein to dystrophin (the gene whose mutation is responsible for DMD). The project involves testing two promising methods of augmenting utrophin levels in dog and mouse models of DMD, in order to determine if the methods will prove to be safe and effective for eventual use in humans.

**Dr Karpati passed away in February 2009. Dr Nalbantoglu will continue as the Principle Investigator for this grant.*



Jasna Kriz (*Université Laval*)
Live imaging and analysis of disease onset and progression in ALS

Recent studies suggest that glial cells (brain cells that, unlike neurons, do not carry electrical impulses) play an important role in the development of ALS. However, it is not clear where the starting point of the disease is and how it progresses. Dr. Kriz will be working with mouse models for live imaging of the activation of glial cells, to better understand the onset and progression of the disease. She and her team will also directly apply novel therapies to study how they affect the disease.

Neuromuscular Research Partnership / Active Grants

Susan Meakin (*University of Western Ontario*)

Nesca, a novel signalling adapter that regulates neuronal growth and regeneration

Dr. Meakin and her team have discovered a novel protein called Nesca. They believe this protein facilitates the growth and survival of brain cells (or neurons) that are involved in the coordination of motor control. Their work could lead to strategies to facilitate the survival, growth and functioning of brain cells in degenerative diseases such as ALS.

Elizabeth Meiering (*University of Waterloo*)

Folding and aggregation of ALS-associated mutant superoxide dismutases

Dr. Meiering and her team are focusing on mutant forms of a protein called superoxide dismutase (SOD). Disease can result when variant or mutant forms of a naturally occurring protein, such as SOD, misfold to form toxic aggregates. Because mutant SOD aggregates are observed in mice well before the onset of disease symptoms, Dr. Meiering and her team believe that mutant SOD aggregation is a possible cause of ALS. Her work could lead to strategies for treating ALS by preventing or reversing toxic protein aggregation.

Jean-Marc Renaud (*University of Ottawa*)

Mutation of the mouse NaV1.4 muscle sodium channel: Understanding hyperkalemic periodic paralysis (HyperKPP)

Patients with Hyperkalemia Periodic Paralysis experience periods of paralysis, lasting from a few hours to a few days or, in extreme cases, up to a year, during which they are unable to move. In between these periods, they experience myotonic discharge (muscle spasms, inability to relax muscles). Dr. Renaud is investigating the mechanisms that cause the disease, with the goal of developing new treatments to prevent both the myotonic discharge and paralysis.

Janice Robertson (*University of Toronto*)

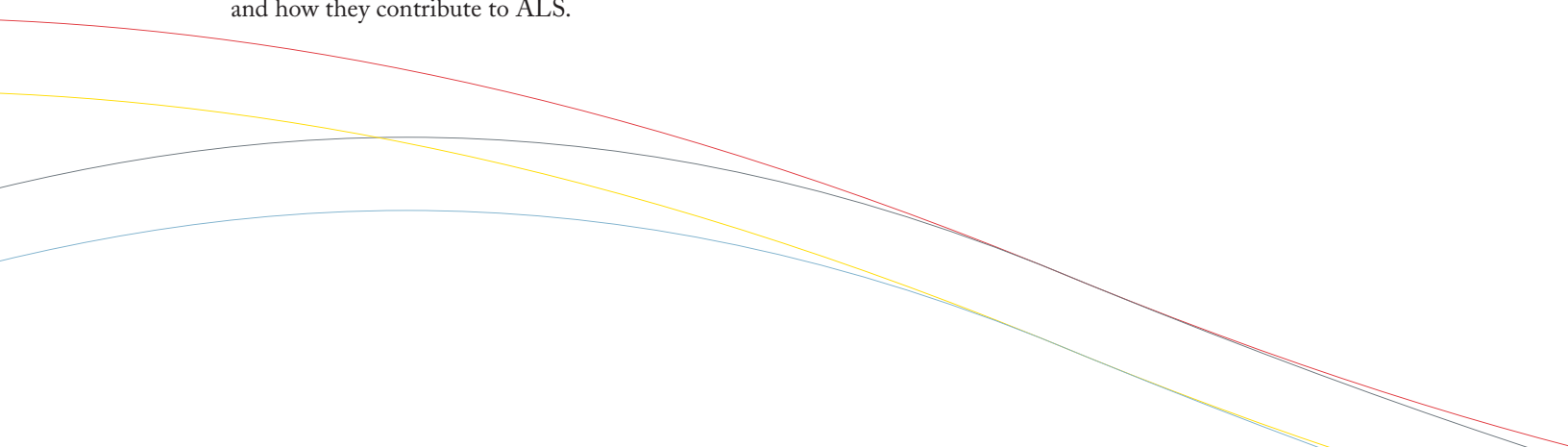
Peripherin abnormalities in ALS

Dr. Robertson is studying the molecular mechanisms underlying motor neuron degeneration in ALS. Her particular focus is a protein called peripherin that is deregulated in ALS. Her work could lead to a better understanding of the origin and development of the disease.

Janice Robertson (*University of Toronto*)

The TAR-DNA-binding protein-43 and ALS

Clumps of an abnormal protein, called TAR-DNA-binding protein-43 (TDP-43) are found inside the nerve cells that are affected by ALS. Dr. Robertson is studying these clumps to determine how they occur, and how they contribute to ALS.





Guy Rouleau (*Centre Hospitalier de l'Université de Montréal*)
Cellular and biochemical impact of TDP-43 mutants in ALS

Dr. Rouleau and his team have found that the mutation of a protein called TDP-43 is the likely cause of ALS in a subset of patients. Now they are working to determine the negative impact of TDP-43 mutations in ALS and the motor neuron degeneration of the disease. In doing so, they will also learn more about the roles the protein plays in normal motor neuron biology. This could open the way for the development of therapies that could delay or prevent disease onset and progression in patients with ALS.

Guy Rouleau (*Centre Hospitalier de l'Université de Montréal*)
Characterization of PABPN1 for the development of an oculopharyngeal muscular dystrophy (OPMD) treatment

Oculopharyngeal muscular dystrophy most often affects people over the age of 45, characterized in the early stages by difficulties swallowing and drooping eyelids. The highest prevalence of OPMD is found among French Canadians, where one out of every 1,000 people will develop the disease. Dr. Rouleau and his team have identified PABPN1 as the gene responsible for the disease. They are now testing different models to determine how the malfunctioning of this gene leads to the disease. By developing a better understanding of the disease mechanisms, Dr. Rouleau could help to develop treatments to improve the quality of life of people with OPMD.

Michael Rudnicki (*Ottawa Hospital Research Institute*)
Satellite stem cells from skeletal muscle for the treatment of neuromuscular disease

Dr. Rudnicki and his team have isolated satellite cells closely associated with muscle fibres, including a subpopulation that displays the characteristics of stem cells. Now, the team is investigating the potential of using these cells for therapy, by analysing their ability to give rise to new stem cells as well as muscle cells, particularly after injection into diseased muscle. Their work will provide important new information about how stem cells contribute to the regeneration of muscle and open new avenues for treating diseases such as muscular dystrophy.

Michael Sinnreich (*Montreal Neurological Institute*)
Development of therapeutic strategies for dysferlin deficiency

Mutations in a protein called dysferlin are a frequent cause of some types of muscular dystrophy, such as Limb-Girdle. There is, at present, no treatment available for people with these mutations. Dr. Sinnreich believes that dysferlin gene replacement therapy holds potential as a treatment; he is carrying out studies to design functional micro-dysferlin molecules and to test their functionality, as the groundwork for future gene transfer experiments.

Neuromuscular Research Partnership / Active Grants



Stefano Stifani (*Montreal Neurological Institute*)
Motor neuron differentiation, connectivity and regeneration

An important part of ALS research involves investigations into why motor neurons are selectively lost and how they can be replaced to restore motor functions in people with the disease. Dr. Stifani is studying the mechanisms that govern the development and connectivity of selected motor neurons known to be vulnerable to ALS, looking at the contribution of a transcription factor called Runx1 to the development, connectivity and regeneration of specific types of motor neurons. His work could provide insights into strategies to promote the generation of motor neurons from stem cells.

Michael Strong (*University of Western Ontario*)
The role of TDP-43 in regulating NFL mRNA metabolism

Dr. Strong is examining whether ALS is associated with a fundamental change in RNA metabolism. He is building on his earlier work, in which he found that people with ALS lack a protein that binds to the RNA and modulates its stability.



Tanja Taivassalo (*McGill University*)
Exercise-induced upregulation of mitochondrial gene expression: Therapeutic strategies for mitochondrial disease

Dr. Taivassalo is studying two forms of exercise training – endurance and resistance training – in patients with mitochondrial myopathies. Currently, no treatment exists for this progressively debilitating condition relating to the accumulation of mutations in skeletal muscle mitochondrial DNA. Dr. Taivassalo will compare patients with mutations in their skeletal muscle mitochondrial DNA who undergo no training, resistance training alone, or resistance and endurance training to determine their effects. Her work will have a potential impact on the health and well being of patients.

Jacques Tremblay (*Laval University*)
Development of immunological tolerance in monkeys for therapies for muscular dystrophies based on cell transplantation

Dr. Tremblay and his team have been working on the transplantation of myoblast cells to treat Duchenne muscular dystrophy. One of the problems of this type of cellular therapy is that the myoblasts are obtained from a donor and are thus rejected by the patient unless the patient's immune system is suppressed by drugs. The sustained use of an immunosuppressive drug induces adverse effects. This research is aimed at preventing the rejection of myoblasts transplanted into monkeys from different monkeys by developing a host specific immunological tolerance - to allow the immune system of the host to tolerate these genetically different cells.

Neuromuscular Research Partnership / Active Grants



Jacques Tremblay (*Laval University*)
Improving MPC transplantation by increasing IGF-1 or MGF stimulation

Dr. Tremblay's long-term goal is to develop a way to transplant stem cells that form muscle fibres in order to increase muscle strength in patients with recessive muscular dystrophies. Stem cells would be obtained from a donor, or could be the patient's own stem cells that have been genetically corrected. This project's goal is to increase the effectiveness of stem cell transplantation through the use of growth factors such as Insulin Growth Factor 1 (IGF-1).

Panayiotis Vacratsis (*University of Windsor*)
Molecular mechanisms regulating myotubularin-related lipid phosphatases mutated in neuromuscular diseases

Three myotubularin genes have been found to be mutated in the neuromuscular diseases myotubular myopathy and Charcot-Marie-Tooth disease. Dr. Vacratsis and his team are focusing on the molecular details of the mechanisms that regulate these diseases. Their work could be used as a platform for developing strategies to inhibit the mutated genes.



Christine Vande Velde (*Centre Hospitalier de l'Université de Montréal, Hôpital Notre-Dame*)
Identification of the mechanisms of motor neuron degeneration in ALS

Many types of neuromuscular diseases, such as ALS, feature degeneration of the nerves that control movement, also known as motor neurons. The biological basis for this degeneration is not known. Dr. Vande Velde is focusing on the role of mitochondria in motor neuron degeneration to better understand the development of ALS and contribute to a foundation on which to build effective therapies.

The Rachel Fund

Mani Mahadevan (*University of Virginia*)
Developmental aspects of RNA toxicity in myotonic dystrophy

Dr. Mahadevan's long-term goal is to understand the molecular mechanisms underlying myotonic dystrophy and to establish model systems to develop and test new treatments for the disease.