Muscular Dystrophy Canada

let's make muscles move

Summer 2004

RESEARCH IN THE WORKS:

Muscular Dystrophy Canada's Neuromuscular Research Partnership Grants

A graduate student at work in Dr. Heather Durham's (grant recipient in 2003) lab.

Muscular Dystrophy Canada, in partnership with the Canadian Institutes for Health Research and the Amyotrophic Lateral Sclerosis Society of Canada, is pleased to announce the following research grants.

Each of these projects underwent intense scientific review before being accepted for granting. These nine projects represent a total of $2,692,738 of targeted neuromuscular research.

Thank you to all of our donors whose generosity has made this possible.

Principal Investigator: Dr. Robert Korneluck
Children's Hospital of Eastern Ontario (Ottawa ON)

Title	Amount Funded
The X-linked inhibitor of apoptosis (XIAP): A therapeutic agent for the treatments of muscular dystrophy	$377,838
Explanation	**Relevance to neuromuscular disorders**
Apoptosis – or programmed cell death – is a genetically controlled mechanism for the body to eliminate cells that have outlived their usefulness. 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 will help develop therapies for neuromuscular disorders. **Duration** 3 years beginning Fall 2004

Principal Investigator: Dr. Vanessa Auld,
University of British Columbia (Vancouver BC)

Title	Amount Funded
Glial cell development and function at the Drosophila neuromuscular junction	$401,922
Explanation	**Relevance to Neuromuscular Disorders**
Nervous system development and function is guided by control cells called glia. Dr. Auld and her team will be 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 hopefully set the stage for future investigations on neuron development and repair in vertebrates	This project will help develop therapies for neuromuscular disorders.
	Duration
	3 years beginning fall 2004

Principal Investigator: Dr. Avijit Chakrabartty,
University Health Network, Ontario Cancer Institute (Toronto, ON)

Title	Amount Funded
Protein misfolding and conformational disease	$311,850
Explanation	**Relevance to Neuromuscular Disorders**
There are over one hundred point mutations in the gene for superoxide dismutate (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. Chakrabartty and his team will study how protein folding affects cells and the entire body in order to better understand ALS.
	Duration
	3 years beginning Fall 2004

Two students working in Dr. Eric Shoubridge's lab (former chair of Muscular Dystrophy Canada's Medical & Scientific Advisory Committee).

Principal Investigator: Dr. George Karpati,
Children's McGill University (Montreal, QC)

Title	Amount Funded
Extrasynaptic endogenous utrophin upregulation in dystrophin deficient muscle: A therapeutic approach for Duchenne muscular dystrophy.	$216,720
Explanation	**Relevance to Neuromuscular Disorders**
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.
	Duration
	3 years beginning Fall 2004

Another graduate student working in one of Dr. Eric Shoubridge's labs.

Principal Investigator: Dr. Jérôme Frenette,
Université Laval (Montréal, QC)

Title	Amount Funded
Inflammatory cell recruitment and function in skeletal muscles following hind limb unloading and reloading: New strategies to prevent muscle atrophy and dysfunction.	$262,978
Explanation	**Relevance to Neuromuscular Disorders**
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.
	Duration
	3 years beginning Fall 2004

Principal Investigator: Dr. Jiming Kong
University of Manitoba (Winnipeg, MB)

Title	Amount Funded
Amyotrophic lateral sclerosis: Role of BNIP3 in mutant SOD1-induced motor neuron death	$211,830
Explanation	**Relevance to Neuromuscular Disorders**
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 will examine ways to slow or decrease the symptoms of ALS.
	Duration
	3 years beginning Fall 2004

Principal Investigator: Dr. Robin Parks Co-investigator: Jonathan Bramson
Ottawa Health Research Institute (Ottawa, ON)

Title	Amount Funded
Adenovirus vectors for gene therapy of muscle	$388,545
Explanation	**Relevance to Neuromuscular Disorders**
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.
	Duration
	3 years beginning Fall 2004

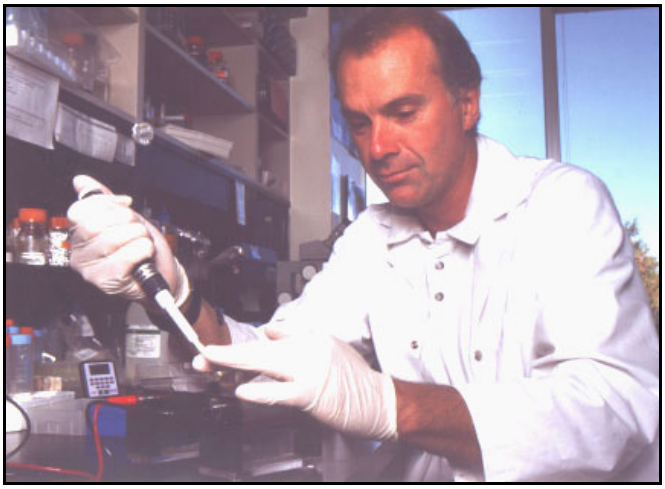
Principal Investigator: **Dr. Charles Krieger** Co-Investigator: **Fabio Rossi** *Simon Fraser University (Burnaby, BC)*	
Title	**Amount Funded**
Functional role of hematogenous inflammatory cells in amyotrophic lateral sclerosis	$314,760
Explanation	**Relevance to Neuromuscular Disorders**
Nervous system development and function is guided by control cells called "glia". Microglia are found in high numbers in people with ALS. Dr. Krieger and his research team are looking at the possible causes and resulting treatments of ALS relating to how high numbers of microglia find their way to the central nervous system and the consequences of their discovery there. Understanding how and why these cells are found in the central nervous system may have an impact on future therapeutic models for ALS	This project is investigating the exact causes of ALS. It will provide information that will be useful in developing therapies.
	Duration
	3 years beginning Fall 2004

Research Facts:

- Each year the Neuromuscular Research Partnership (NRP) provides approximately $2.5 million in research funding specifically targeted to neuromuscular research.
- The NRP leverages each dollar donated up to 4 times due to matching funds from the partners. It also lowers administrative costs because the program management is centralized.
- Last year, two scientists funded through the NRP made important breakthroughs. Please visit www.muscle.ca for details on Dr. Tremblay and Dr. Puymirats' successes.

For more information about our Research Program and to view our Research Updates, 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

Picture of Mr. Gordon Thiessen, Honorary Director of Muscular Dystrophy Canada (left) speaking with Dr. George Karpati (Recipient of a grant this year and long time friend of Muscular Dystrophy Canada) in the Vector Unit at the Montreal Neurological Institute



Picture of Dr. Alex McKenzie (grant recipient in 2003) at work in his lab.

Principal Investigator: **Dr. Susan Meakin** *John P. Robarts Research Institute (London, ON)*	
Title	**Amount Funded**
Nesca, a novel intracellular signaling adapter facilitates neurotrophin dependent neurite outgrowth.	$206,295
Explanation	**Relevance to Neuromuscular Disorders**
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 projects of neurons stimulated by growth factors, and other molecules that are involved during development and after neuromuscular-related injury.	This project will provide information that may help develop therapies and/or treatments for neuromuscular disorders.
	Duration
	2 years beginning Fall 2004

On-going Research

The following on-going projects receiving grants from the Neuromuscular Research Partnership in previous years.

Researcher	Project Title	Amount Funded	Timeline	Relevance
Dr. H. Antonicka; CFMA Montreal Neurological Institute	"Molecular basis of cytochrome c-oxidase deficiencies in fatal infantile neuromuscular disorders."	$114,000	2002-2005	Dr. Antonicka is focusing on the identification of genetic mutations that cause fatal infantile neuromuscular disorders. The information she uncovers will help with prenatal diagnosis and hopefully lead to therapies and treatments for these disorders.
Dr. J. Bain & Dr. M. Fahnestock; MacMaster University	"Mechanism of sensory protection of denervated muscle"	$217,247	2003-2006	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; & Dr. B. Banwell; Hospital for Sick Children	"Study of the clinically and pathologically diverse forms of CMD found in the French Canadian population and the more ethnically mixed population served by the paediatric neuromuscular clinic of The Hospital for Sick Children in Toronto."	$100,000	2003-2005	Dr. Brais and Dr. Banwell hope to genetically characterize congenital muscular dystrophy by: confirming linkage in a subset of families, uncovering the mutations, and characterizing the pathology and cell culture phenotypes. They also hope to design molecular diagnostic tests for the more common forms of Congenital Muscular Dystrophy in the French Canadian population. This will lead to more accurate diagnosis.
Dr. B. Brais; University of Montreal, CHUM Research Centre	"Oculopharyngeal Muscular Dystrophy and polyalanine toxicity "	$277,698	2003-2006	Dr. Brais hopes his study of polyalanine toxicity–the cause of OPMD– will lead to treatments for this disorder.

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Researcher	Project Title	Amount Funded	Timeline	Relevance
Dr. H. Durham; McGill University	"The role of protein chaperones and proteasome-mediated proteolysis in the pathogenesis of motor neuron diseases."	$317,988	2002-2005	Dr. Durham and her team are seeking to understand the unique vulnerabilities of motor neurons in order to help them live.
Dr. M. Ferns; Montreal General Hospital	"Neurotransmitter receptor localization at the synapse: Regulation by rapsyn."	$267,927	2002-2005	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 and treating neuromuscular disease
Dr. S. Gee; University of Ottawa	"The role of diacylglycerol kinase-zeta and syntrophins in neurite outgrowth"	$304,550	2002-2005	Dr. Gee is studying the molecules that interact with dystrophin to better understand the cognitive impairment associated with DMD.
Dr. T. Gordon; University of Alberta	"A possible link between motoneuronal death and sprouting in ALS"	$256,386	2002-2005	Dr. Gordon hopes that by examining the cause of death of motor neurons, she will be able to find a way to diagnose ALS before nerve damage begins so that preventative treatments and therapies will be more effective.
Dr. K. Hastings; McGill University	"Fiber-type specific and activity-regulated gene expression in fast skeletal muscle."	$334,104	2002-2005	Dr. Hastings is investigating how of a type of muscle fiber works so that we can better understand how neuromuscular disorders work.
Dr. J. Henderson; University of Toronto	"Role of EphB-family receptors in regulating motoneuron identity and somatotopic axon outgrowth"	$246,369	2002-2005	Dr. Henderson is examining how we may be able to achieve the goals of neuromuscular preservation and regeneration. This could lead to treatments and therapies for neuromuscular disorders.

On-going Research

The following on-going projects receiving grants from the Neuromuscular Research Partnership in previous years.

Researcher	Project Title	Amount Funded	Timeline	Relevance
Dr. J. Julien; McGill University	"Generation and analysis of a new mouse model for amyotrophic lateral sclerosis"	$61,000	2003-2004	As research on ALS progresses, the implications for drug discovery become more promising. Dr. Julien's new mouse model for juvenile ALS may bring another level to our understanding of how the disease works.
Dr. G. Karpati; Montreal Neurological Institute	"Development of efficient and safe gene transfer to skeletal muscle for the therapy of dystrophin deficiency"	$335,710	2002-2005	Dr. Karpati is among the leading experts in muscular dystrophy research. In his current project he is working to improve the safety and efficiency of gene transfer techniques for the treatment of muscular dystrophies, including Duchenne muscular dystrophy.
Dr. H. Klamut; University Health Network, Ontario Cancer Institute	"Telomerase-mediated lifespan extension applied to the development of autologous myoblast transplantation strategies for Duchenne Muscular Dystrophy"	$391,778	2002-2005	Dr. Klamut shared in the discovery of the gene that causes Duchenne Muscular Dystrophy (DMD). Today he is working towards developing effective treatment for DMD.
Dr. A. Mackenzie; Children's Hospital of Eastern Ontario	"Modulation of apoptosis in mouse models of spinal muscular atrophy"	$270,900	2003-2005	Dr. Mackenzie is examining how cell death can be regulated in spinal muscular atrophy. His findings will contribute to possible therapies for SMA.
Dr. E. Meiering ; University of Waterloo	"Folding and aggregation of ALS -associated mutant superoxide dismutases"	$362,928	2003-2006	These studies will provide important information regarding the ALS disease mechanism and ultimately lead to new therapeutic approaches for treating ALS and potentially other protein conformational disorders.

On-going Research

The following on-going projects receiving grants from the Neuromuscular Research Partnership in previous years.

Researcher	Project Title	Amount Funded	Timelines	Relevance
Dr. R. Michel; Laurentian University	"Calcineurin signaling in the regulation of skeletal muscle fibre growth ."	$231,093	2003-2006	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 signalling 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	2003-2006	Abnormalities in many genes can cause limb-girdle muscular dystrophy. Studying the mutations in these genes will provide insight into the functioning of muscle and help to develop future treatments.
Dr. J. Puymirat; Centre hospitalier de l'Université de Québec	"Ribozyme and antisense RNA as a tool to study myotonic dystrophy"	$203, 109	2003-2006	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	2003-2006	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 myogentic proenitors: a lineage analysis"	$100,000	2003-2005	Dr. Rossi is examining how to regenerate damaged muscle. He hopes that by studying a particular type of cell that plays a role in the regeneration of muscle, his project will lead to the creation of new therapies for muscular dystrophies.
Dr. D. Schreyer; University of Saskatchewan	"Regulation of neuronal phenotype by muscle-derived factor"	$218, 004	2003-2006	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

On-going Research

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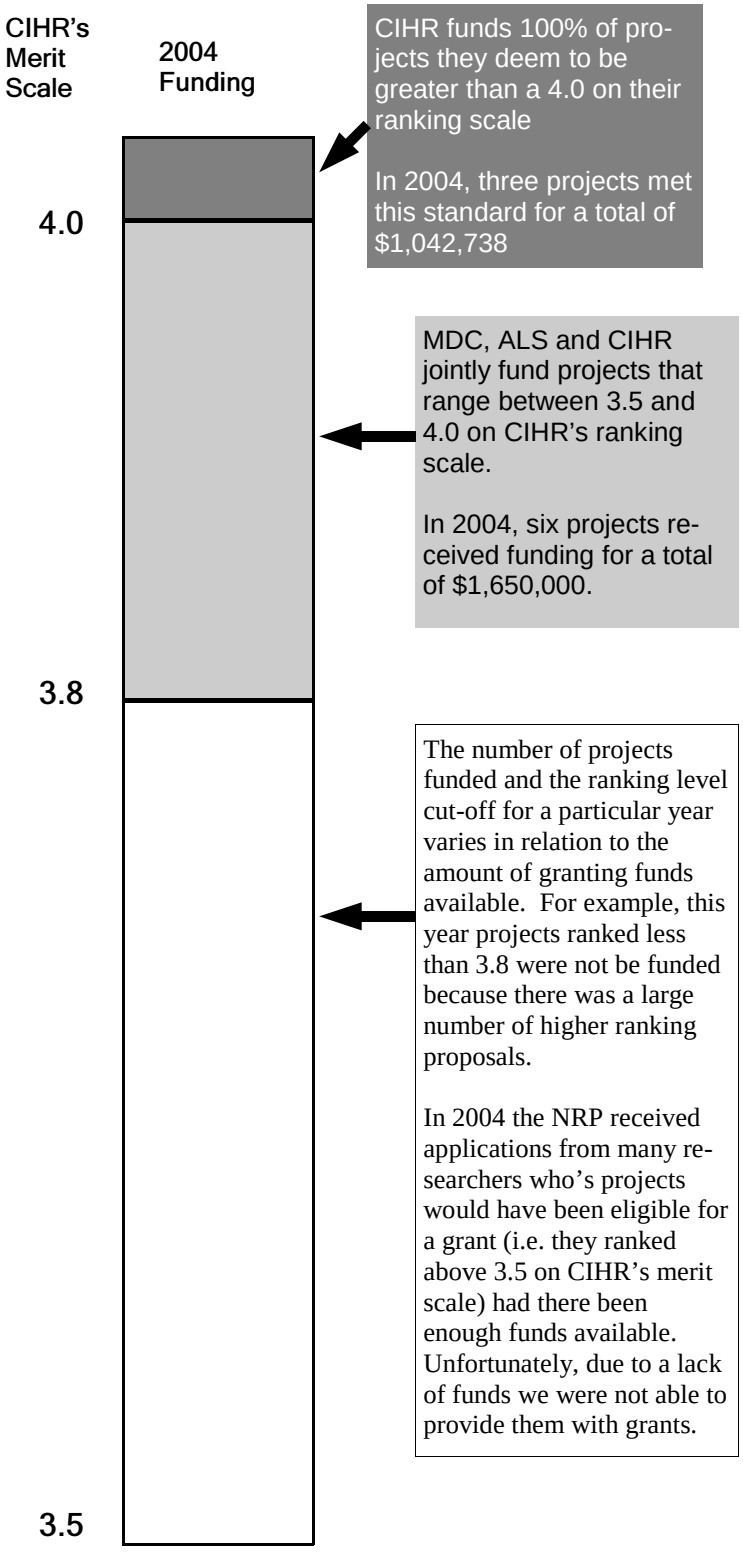
Researcher	Project Title	Amount Funded	Timelines	Relevance
Dr. S, Stifani; McGill University	"Regulation of neuronal development in the mammalian nervous system"	$456,015	2000-2005	Dr. Stifani is examining how the growth and development of neurons is controlled to enable us to better understand their function and develop possible treatments for neuromuscular disorders.
Dr. J. Tremblay; Laval University	"Treatment of Duchenne Muscular Dystrophy: Correction of mutated dystrophin mRNA with ribozymes"	$247, 350	2003-2006	For the first time in Canada, Dr. Jacques Tremblay is growing myoblasts for transplantation in humans. He and his collaborators are making exciting 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.

HOW WE FUND RESEARCH

Muscular Dystrophy Canada
let's make muscles move



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 our 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 3 main research programs: the Neuromuscular Research Partnership (NRP), Fellowships and the Young Investigators' Grant. 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.

The CIHR ranks the proposals based on a set of very 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.

Muscular Dystrophy Canada's committee consists of 2 scientists, a board representative and a staff member from each of Muscular Dystrophy Canada and ALS.

All funds raised by Muscular Dystrophy Canada for research is 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.