Now more than ever is the time to invest in research for treatments and cures. Through your support, you can accelerate the timeframe for diagnosis, and bring more promising clinical trials and drugs to families faster. Whether through targeted research into specific disorders, or investments in key research areas like cardiac care and stem cells, together we can turn hope into answers.

“Research is providing us with a greater understanding of what causes neuromuscular disorders, leading to new approaches to treatment. As we continue to test potential new treatments in clinical trials I expect that we will see a direct improvement in the quality of life for people with neuromuscular disorders.”

—Dr. Lawrence Korngut, Donor and Chair, Canadian Neuromuscular Disease Network, Member, Medical and Scientific Advisory Committee for Muscular Dystrophy Canada
15–16 Research in the Works

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As the new Chair of Medical and Scientific Advisory Committee for Muscular Dystrophy Canada I am proud to be able to introduce the latest edition of Research in the Works.

For the past several years, Muscular Dystrophy Canada has made it a priority to raise awareness about respiratory care in order to give people affected by neuromuscular disorders the information, services and supports that they require. Our recently released Guide to Respiratory Care for Neuromuscular Disorders is part of that education and advocacy effort. However, it has become increasingly apparent that there is a need for greater investment in research that enhances the scientific evidence used to inform respiratory care decisions.

To address this gap, and as part of a diversified overall research funding strategy adopted in 2013, in 2014 we launched a "Seed Grant" program with an initial focus on fostering knowledge and increasing research investment in the area of respiratory health of people with neuromuscular disorders. In particular, the initiative sought to address respiratory issues, influence partnerships between researchers and users of evidence, and provide the opportunity to gather evidence that can help support other components of the respiratory care plan (such as education, advocacy or services).

From this program, we have awarded $191,067 to four new respiratory research projects this year. For a deeper dive into the
subject, please read our feature on respiratory care on page 6, and learn more about the specific research being conducted with this year’s respiratory seed grants in the Current Grants section, starting on page 12.

In addition to the seed grant program project, we continue to participate in the support of major biomedical research projects in partnership with the Canadian Institutes of Health Research and the E-Rare research program on rare diseases, and in other key initiatives.

While Muscular Dystrophy Canada has always supported leading research, the current Strategic Plan expresses that commitment in very clear terms: to provide research funding in areas related to neuromuscular disorders, leverage resources even more effectively than ever before, and encourage research-related partnerships within Canada and around the world. This edition of Research in the Works continues to highlight our emphasis on research—and strong partnership can be seen in both our innovative new projects, and in the continuation of our existing programs.

One such new project we are particularly excited about is called “Neuromuscular Nation”—a virtual social community for patients, family, caregivers and other community members interested in neuromuscular diseases. Launched in 2016 as an initiative of the Canadian Neuromuscular Diseases Network (CAN-NMD), a national research, clinical, and community networking program initiated through Muscular Dystrophy Canada's support and funding from the Canadian Institutes of Health Research, the platform will provide Canadians affected by these diseases the opportunity to share their experiences, obtain the latest updates from researchers and clinical care providers, and have a single source for health information in a secure environment. Read more about this portal on page 10.

I would like to take this opportunity to thank all the generous supporters of Muscular Dystrophy Canada, who have made this work possible. I would also like to thank my fellow members of our Medical and Scientific Advisory Committee. Their guidance and insight is crucial to our continued efforts to support promising research leading to new and improved therapies—and ultimately cures—for people living with neuromuscular disorders.

Dr. Ken Hastings, PhD, McGill University
Chair, Medical and Scientific Advisory Committee,
Muscular Dystrophy Canada
People affected by neuromuscular disorders today are living longer than ever before—which is very positive news. But the challenge of these disorders becoming more of a chronic disease state is that while many of these people are living longer into adulthood, they continue to face major quality-of-life challenges.

One of the key things having a negative impact on the quality of life in these individuals is their respiratory health. Although neuromuscular disorders do not impair the lungs directly, they often affect the muscles involved in breathing, coughing and swallowing.

Empowering both patients and their healthcare professionals with the tools and knowledge to help them live better and lengthen the time between emergency room visits is crucial, says Dr. Janice Richman-Eisenstat, Neuropulmonary Rehabilitation Medicine and Palliative Respiratory Care Specialist, Associate Clinical Professor with the Pulmonary and Neurology Divisions of the Department of Medicine at the University of Alberta.

“Imagine if you are coughing and choking all the time,” she said. “I'm sure I don't need to tell you that people don't really have fun when they have to go to the hospital. You are being looked after by doctors that usually are not informed about neuropulmonary conditions and they may not know how to help people cough or clear their airway.”

Educating patients and caregivers on tips and tools that they can use at home, such as swallowing techniques, breath stacking and lung volume recruitment devices, is vital, she said.

Four years ago, she and her colleagues started the first multidisciplinary neuromuscular clinic for adults in North America. Although a common model in pediatrics, the holistic multidisciplinary approach is still rare to find in adult care. This approach allows people to see different specialists, ranging from a dietician to a rehabilitation medicine specialist, in the same place on the same day.

“More and more, chronic illness is about working with a team. This is the model we need to aspire to in chronic disease management,” she said. “I learn from my colleagues, they learn from me and I feel that together we are moving the field forward in improving patient care and patient support - to live as best as possible in their homes and in their communities.”
Looking toward the future, while we search for cures, Dr. Richman-Eisenstat stresses the importance of framing research and care strategies around ways in which to make an immediate and positive impact in patients’ lives.

“There is always something that can be done. Maybe we cannot achieve goal one, but maybe we can reframe goal one into an achievable goal two. And if we can’t achieve that, maybe we can reframe it further,” she said. “We have to take all approaches to help our patients live as best as possible today as well as tomorrow.”

The quest for improved quality of life for these patients is a research priority for Muscular Dystrophy Canada—which is why we continue to award seed grants into respiratory health research areas. Four new grants were awarded this year:

- A grant awarded to a team led by Dr. Reshma Amin at the Hospital for Sick Children in Toronto (page 12) looks at assessing tests that predict the respiratory risks of air travel for those with Duchenne Muscular Dystrophy. Because of respiratory muscle weakness, these individuals are at risk of decompensation due to respiratory muscle fatigue, elevated carbon dioxide levels and even respiratory failure in the low air pressure environment of airplane flight cabins.

- A grant awarded to a team led by Dr. Marta Kaminska at the McGill University Health Centre in Montreal (page 16) investigates the validation of home portable monitoring for diagnosis of sleep-disordered breathing in patients with neuromuscular disorders. Home portable monitoring is a potentially viable alternative for those who might otherwise be unable to undergo in-laboratory sleep studies.

- A grant awarded to a team led by Dr. Hans Katzberg at the University Health Network in Toronto (page 18) seeks to evaluate factors associated with nocturnal hypoventilation in patients with myasthenia gravis, and help identify patients in neuromuscular clinics who would benefit from interventions.

- A grant awarded to a team lead by Dr. Louise Rose at the Sunnybrook Research Institute in Toronto (page 22) seeks to describe current practice related to monitoring cough effectiveness and clinician recommendations for airway clearance strategies.
Neuromuscular disorders cause progressive muscle weakness, which can affect the muscles used in breathing and coughing. Weak respiratory muscles can increase the risk of respiratory failure, a common cause of death in people with neuromuscular disorders. That is why Muscular Dystrophy Canada has made it a priority to raise awareness about respiratory care in order to give people affected by neuromuscular disorders the information, services and supports that they need.

While there are preventative measures and interventions that can help people with neuromuscular disorders maintain their respiratory health, there also is a need for greater investment in research that enhances the scientific evidence used to inform respiratory care decisions. To address this need, Muscular Dystrophy Canada launched its Respiratory Care Grants initiative in 2014 to support research related to improving respiratory care among people living with neuromuscular disorders. Over time, these “seed grants” will increase research capacity and overall investments in respiratory care research.

Research proposals on a broad spectrum of issues related to respiratory health and health-care services were accepted, with an emphasis on applied (not basic) research. After a rigorous peer review process, four projects were awarded funding for 12 months. The total value of the grants awarded for 2015 was $191,067.
**Research Programs**

**Rare Disease Collaboration**

The *Strategic Plan* outlines our commitment to collaboration with other research organizations in order to effectively and efficiently maximize our investments. Collaboration has other benefits, too: the presence of partners in the funding process ensures higher-quality projects and rigorous review of applications.

Muscular Dystrophy Canada is proud to participate (along with CIHR’s Institute of Genetics) in the E-Rare research program on rare disease. Led by ERA-NET (which works to increase cooperation and coordination among researchers and institutions in different countries), E-Rare is dedicated to linking research funding organizations to extend and strengthen transnational cooperation on research into rare diseases.

Over the past four years, we have contributed more than $700,000 to fund collaborative research projects on spinal muscular atrophy (SMA), Duchenne muscular dystrophy (DMD) and fascioscapulohumeral muscular dystrophy (FSHD).

**Neuromuscular Research Partnership**

Between 2000 and 2012, Muscular Dystrophy Canada collaborated with the ALS Society of Canada and CIHR to form the Neuromuscular Research Partnership. Together the partners invested more than $43 million into 177 Canadian basic, focused or applied neuromuscular research grants.

While this partnership is no longer evaluating and funding new grants, it does continue to fund several ongoing projects. You can read the profiles of some of these projects in the Current Grants section beginning on page 12.

For a complete list, please visit [muscle.ca/research/current-grants](http://muscle.ca/research/current-grants).
Traditionally, online peer-support communities for people with neuromuscular disorders have been somewhat limited, with the ability to communicate with each other only available through social media sites such as Facebook and other public, unsecured web support groups. That is, until now.

Introducing Neuromuscular Nation—a virtual social community for patients, families, caregivers, donors, researchers, and other community members interested in neuromuscular diseases. This portal is an exciting new initiative of the Canadian Neuromuscular Diseases Network (CAN-NMD), led by Dr. Lawrence Korngut (MD, FRCPC), University of Calgary clinical researcher and Associate Professor of Neurology.

Just launched this spring, Neuromuscular Nation provides Canadians affected by these diseases the opportunity to share their experiences, obtain the latest updates from researchers and clinical care providers, and have a single source for health information within a secure domain.

While some other online communities do exist internationally, they don’t offer the benefit of providing Canadian-specific information. This new password-protected platform features private messaging and chat capabilities, opportunities to share multi-media content such as photos and videos, and the ability to save and share documents such as research articles.

Neuromuscular diseases affect how muscle and nerve cells function and interact with the body, usually resulting in weakness which can often be disabling, and at times fatal. An estimated 50,000 Canadians are affected by these diseases, which include muscular dystrophy, ALS, and nearly 150 other conditions.

“The effects of these diseases are direct and life-limiting for the patients,” says Dr. Korngut. “They also impact the family including significant caregiver burdens and changes in employment. Sharing of experiences and experiential knowledge from patient to patient and family to family is known to have significant impacts on quality of life and feelings of support.”
In addition to benefitting patients and families, Neuromuscular Nation will also allow researchers to share findings and raise awareness of clinical trials and studies directly with the patient/family community.

“We hope that in addition to patient benefit, this will become an incredible tool for researchers and clinical care providers to ensure patients are getting access to important and correct information with respect to their care,” says Dr. Korngut.

Two years ago, Muscular Dystrophy Canada—in partnership with the Canadian Institutes of Health Research (CIHR) Institute of Musculoskeletal Health and Arthritis—provided three years of funding to CAN-NMD. The goal of this group is to provide a sustainable national network bringing together all interested stakeholders across neuromuscular diseases.

For more information on CAN-NMD, please visit www.neuromuscularnetwork.ca.
Oculopharyngeal muscular dystrophy (OPMD) is an adult-onset form of the disease that, while found worldwide, affects French Canadian and Jewish populations more frequently. Symptoms include drooping eyelids, difficulty swallowing and limb weakness. While the genetic mutation responsible for OPMD is understood, nothing is known about the underlying mechanism through which the mutation causes OPMD. Dr. Bachand and his team are investigating the function of the responsible gene, which is called PABPN1. Their work could address why OPMD is limited to specific muscles and open the way to new treatments.

Dr. François Bachand  
(Université de Sherbrooke)


Dr. Reshma Amin  
(The Hospital for Sick Children)

Neuromuscular disease (NMD) presents unique respiratory risk during air travel. Individuals with Duchenne Muscular Dystrophy (DMD) develop pulmonary restriction secondary to progressive neuromuscular weakness which compromises ventilation and/or oxygenation, upper airway muscle tone, and the ability to compensate for any stress to the respiratory system. With the need to increase ventilation in face of the hypoxic stress of air travel, these individuals are at risk of decompensation due to respiratory muscle fatigue, resulting in elevated carbon dioxide levels and respiratory failure. Dr. Amin and her team will investigate if a prolonged high altitude simulation test (HAST), lasting two hours, identifies more patients at risk of respiratory failure than the standard HAST, lasting 20 minutes, in patients with DMD and severe pulmonary restriction. The secondary aim of the study is to evaluate the safety of supplemental oxygen administered in those with a positive HAST in the DMD population.
Myotonic dystrophy type 1 (DM1) is caused by an expansion of the CUG-triplet repeats in the mRNA of the DMPK gene (the gene affected by DM1). The RNA-binding protein Muscleblind-like 1 (MBNL1) causes mutant CUG-repeat RNA to aggregate into nuclear foci, but it is unclear why MBNL1 (which also serves several normal functions in the cell) behaves this way with disease mRNA. Using several different methods, Dr. Chartrand and his team will clarify the mechanism of MBNL1 and CUG-repeat RNA aggregate formation in DM1; they also will attempt to define the role of MBNL1 in the spatial and temporal production of mRNA in the cytoplasm (the material—excluding the nucleus—within a living cell). They believe the results will allow for the development of new drugs that will inhibit the nuclear retention of mutant DMPK mRNA in patients with DM1 or restore the normal properties of mistargeted mRNAs.

Co-funded by CIHR’s Institute of Musculoskeletal Health and Arthritis

Myogenin regulates gene expression and plays a critical role in deciding which genes to turn on in muscle cells. Dr. Dilworth is determining how this decision is made. His work will shed light on the developmental process that gives rise to muscle cells, including identifying cellular proteins that collaborate with myogenin, in hopes of contributing to the development of stem cell-based therapies for muscular dystrophy.
Nearly 65% of our body weight is made of bones and skeletal muscles. They control many important functions in the body, including movement, breathing and the production of blood cells. Aging, injury and neurodegenerative diseases, however, can cause muscle to atrophy. Building on exciting advances in bone biology and disease, Dr. Frenette and his team want to bridge the physiopathology (the study of bodily disturbances caused by disease) of bones and muscles. Their early results indicate that a pathway that plays a role in bone homeostasis also features in muscle wasting and muscular diseases in some skeletal muscles, notably those essential for brief and powerful movements. Dr. Frenette and his team believe that the Rank/RankL/OPG pathway (as it is known) is an important actor in skeletal—and possibly even cardiac—diseases.

Despite years of study, the molecular mechanism that causes FSHD remains largely unknown. The research team, however, recently identified DBE-T, a long non-coding RNA (also known as an IncRNA, a type of non-protein coding transcript) that is produced preferentially in people with FSHD. They feel that DBE-T is a promising candidate for developing therapeutic approaches to normalize the 4q35 gene expression, where important repeated elements are deleted in people with FSHD. First, they want to answer more questions about DBE-T, including its role in activating FSHD candidate genes (genes that are thought to be relevant to FSHD).
Dr. Anthony Gramolini

Molecular basis of ryanodine receptor regulation and function in skeletal and cardiac muscle (2012–2015)

Dr. Anthony Gramolini’s research is aimed at providing a detailed study of the mechanics of skeletal muscle function and the role played by calcium regulatory proteins in normal muscle function and skeletal muscle diseases. By understanding the ryanodine receptor (RyR) calcium release channel (which regulates the movement of calcium ions that are involved in muscle contraction and relaxation), Dr. Gramolini and his team hope to increase their knowledge of calcium release in muscle. That information could prove crucial to identifying new cellular targets for therapeutic intervention in RyR-based muscle diseases, such as central core disease and malignant hyperthermia.

Dr. Marc Grynpas

Growth arrest and osteoporosis in Duchenne muscular dystrophy patients treated with glucocorticoids (2012–2017)

Children with DMD are often treated with high-dose glucocorticoids that substantially reduce mortality rates, but which also result in disordered bone health. This potentially can cause fractures, bone pain and vertebral compression. While a number of factors contribute to poor bone health in children—including nutrition, genetic factors and growth—studies in adults are of limited use. Dr. Grynpas and his team believe that by understanding the cause of osteoporosis, growth arrest (an interruption of normal bone growth), and the signalling pathways in bone, they can develop an approach to prevent and treat disordered bone health in DMD, thereby alleviating the additional burden that it causes.
DMD is the most prevalent inherited neuromuscular disorder, but there is still no effective cure or treatment for the disease. Resulting in mutations or deletions in the X-linked dystrophin gene, DMD prevents the production of full-length dystrophin, the protein that is crucial to muscle function. One possible therapy is the use of utrophin, a protein similar to dystrophin that might compensate for the lack of the other protein. Building on his previous research on the subject, Dr. Jasmin seeks to decipher the mechanisms involved in controlling utrophin in normal and DMD muscle fibres, information that one day might form the basis for the design of a pharmacological intervention that increases the expression of utrophin in DMD muscle fibres.

Ventilatory impairment is a leading cause of morbidity and mortality in patients with neuromuscular disorders (NMD). The development of daytime respiratory failure is generally a late event which occurs after sleep-disordered breathing (SDB). Access to diagnostic testing is challenging for many patients. Home portable monitoring (PM) is a potentially attractive alternative in patients with NMD who might otherwise be unable to undergo in-laboratory sleep studies due to logistical difficulties, such as impaired mobility. Early recognition of SDB leading to timely treatment may prevent clinical deterioration and improve quality of life. In Dr. Kaminska's pilot study, the team’s objectives are to validate a PM recording device for home diagnosis of SDB in patients with NMD, and to optimize clinical definitions—thus improving diagnostic accuracy of SDB in the patient population.
Participants at the 2015 Surrey Walk for Muscular Dystrophy.

I Can! inspire others to never give up.
Myasthenia gravis (MG) is an autoimmune neuromuscular disorder characterized by fatigable weakness of skeletal muscle. In addition to limb, facial, neck and bulbar weakness, involvement of diaphragmatic and accessory muscles can lead to respiratory dysfunction. Previous studies have made attempts at identifying patients at risk for sleep apnea; however, these studies have been limited by small sample sizes, omission of pediatric patients, and incomplete assessment of both daytime and nocturnal respiratory dysfunction. The objective of Dr. Katzberg’s current study is to evaluate factors associated with nocturnal hypoventilation in patients with MG, and help identify patients in neuromuscular clinics who would benefit from interventions such as BiPAP and napping, which have been shown to improve quality of life, prevent neuromuscular fatigue and mitigate medical complications of nocturnal hypoventilation.

Thanks to landmark studies performed by Drs. Michel and Jasmin and their teams, we know calcineurin, an enzyme that orchestrates muscle growth, has a significant effect on utrophin, a protein that can compensate for the lack of dystrophin (another protein) in dystrophic muscle fibres. Drs. Michel and Jasmin now intend to take the next logical step to define further the role of calcineurin in rescuing damaged dystrophic muscles and to identify other novel players involved in this rescue. They believe these experiments will contribute to our understanding of the biochemical and molecular regulatory events that are involved in this disease, thereby providing potential therapeutic targets and strategies to reverse its damaging effects.
One possible avenue for treating DMD is to increase the activity of a protein called utrophin (which is similar to dystrophin, the protein that is missing in people with the disease) so that utrophin becomes present throughout the surface membrane of muscle fibres (instead of its normal, very restricted, localization). Dr. Nalbantoglu and her team have already developed a protein to increase the amount of utrophin in mouse muscle, and this project will use the same approach to design artificial transcription factors that target the human utrophin gene to increase its expression. This approach could eventually be used to treat DMD.

At least 14 neuromuscular and neurodegenerative diseases, including myotonic dystrophy and Huntington’s disease, are caused by mutations in repeated DNAs. Not only do these mutations become more evident through family generations, but they worsen as patients age. If we think of a gene as a sentence where some repetition is normal—THE CAT ATE THE FAT RAT—typical mutations are spelling errors (“THE GAT” instead of “THE CAT”). In repeat-associated diseases like myotonic dystrophy, however, the mutation would be THE CAT ATE THE FAT FAT RAT, and children would inherit further repetition, resulting in their disorder becoming more severe. The mutations can also continue through the life of a person, making symptoms worse as they age. Dr. Pearson hopes to understand this mutation better, with the ultimate goal being the ability to modulate the mutation. If the mutation can be arrested or reversed, therapies for reducing disease progression and severity may be possible. For myotonic dystrophy, this includes identifying drugs that can lead to therapies that stop or reverse the mutations.

Co-funded by CIHR’s Institute of Musculoskeletal Health and Arthritis
Affecting approximately 1 in 3500 males, DMD is the most frequent disorder linked to the X chromosome. Patients often die of respiratory failure as the disease progressively destroys muscle (such as the diaphragm and other respiratory muscles) and prevents its normal repair. Dr. Petrof and his team want to better understand the factors that regulate muscle damage and repair in DMD in order to identify new therapeutic strategies for the disease. By examining the role of the immune system in balancing muscle damage and repair, they hope to determine whether manipulating an individual’s innate immunity could provide a way of treating respiratory muscle failure that is caused by DMD.
DM1 is the most common adult form of muscular dystrophy, and the second form, DM2, shares several manifestations with DM1. While neither form has a treatment, several different therapeutic approaches have been developed over the past few years, including two strategies that make use of antisense oligonucleotides (AO), single strands of DNA or RNA that complement a chosen sequence. In collaboration with Dr. Matthew Wood of the University of Oxford, who recently developed peptide-AO that are capable of restoring many of the dystrophin-positive fibres in the skeletal muscles and hearts of mice carrying a mutation in the dystrophin gene responsible for Duchenne/Becker muscular dystrophy, Dr. Puymirat’s research will evaluate the use of those peptide-AO in therapy for myotonic dystrophy. Not only might this facilitate the development of a gene therapy for DM, but it also will help researchers understand the causes of the disease.

Co-funded by France’s AFM-Téléthon

SMA is an incurable paralytic neuromuscular disorder that mainly affects children. It is characterized by the selective degeneration of spinal motoneurons, nerves that carry signals from the spinal cord to muscles to produce movement. Recent work has shown that SMA and amyotrophic lateral sclerosis (ALS) share certain mechanisms, and that it is the motoneuron-restricted death pathway triggered by Fas (a cell surface receptor protein) and its ligand FasL that contributes to the loss of motoneurons in ALS.

Preliminary data from the research team shows that Fas is markedly increased (or upregulated) in the spinal cord motoneurons of mice with SMA, suggesting that Fas may contribute to SMA. Additional preliminary data, however, shows that while Fas may induce motoneuron death, it also promotes neuronal outgrowth. As a result, the researchers propose to further dissect this functional duality and investigate the contribution of the Fas pathway in SMA pathogenesis. Their ultimate goal is to generate common therapeutic strategies for SMA, ALS and other motoneuron diseases.
Characterized by periods of uncontrolled muscle contractions in the limbs, hyperkalemic periodic paralysis (HyperKPP) can leave patients confined to bed for hours or even days. While the contractions and paralysis may cease after the age of 30, patients continue to suffer muscle weakness, making walking difficult or even impossible. Currently, none of the treatments for HyperKPP are fully effective. Dr. Renaud has now found the mechanisms that make the diaphragm asymptomatic, and he hopes to upregulate these mechanisms in limb muscles as a potential therapeutic approach for treating HyperKPP.

For individuals with neuromuscular disease (NMD), acute respiratory failure due to respiratory infection is the most frequent reason for unplanned hospital admission. Regular monitoring combined with early and appropriate use of airway clearance strategies reduces unplanned hospital and ICU admissions. In current Canadian practice, prescribing of airway clearance strategies is variable and not based on systematic monitoring of peak cough flow recommended by the 2011 Canadian Thoracic Society (CTS) Home Ventilation (HMV) Guidelines. Dr. Rose’s research seeks to describe current practice related to monitoring cough effectiveness and clinician recommendations for airway clearance strategies. Secondary objectives include developing an understanding of existing barriers to implementation of the CTS HMV guideline recommendations for airway clearance, and to identify potential strategies to mitigate these barriers.
The growth and repair of skeletal muscle in adults is linked to “satellite cells,” a group of cells that associate with muscle fibres. Dr. Rudnicki and his team have not only discovered another group within that satellite cell grouping that they have named “satellite stem cells,” but they have also identified Wnt7a, a protein that stimulates activity in those stem cells. By investigating these satellite stem cells and their interaction with Wnt7a, Dr. Rudnicki hopes to gain information about how muscle stem cell function is controlled and how those cells contribute to the regeneration of skeletal muscle. Ultimately, this knowledge could open new avenues for the treatment of diseases like muscular dystrophy.

 Appearing in early childhood, DMD is a devastating inherited muscular disorder that leads to progressive and debilitating muscle weakness and wasting, ultimately resulting in death. Dr. Rudnicki proposes to investigate the basis for the altered function of muscle stem cells in DMD. He is investigating whether muscle stem cells have undergone epigenetic changes, alterations in chromosomal structure caused by the disease environment that change the expression of genes involved in regulating stem cell function. Dr. Rudnicki believes that such insight into the factors that contribute to the cause of DMD will lead to new modes of therapeutic intervention.
DMD is a genetic disease of childhood that manifests in progressive debilitating skeletal muscle weakness and wasting, ultimately resulting in death. The research team recently identified a way of using a particular kind of signaling (the complex system of communication that governs basic cellular activities and coordinates cell actions) to stimulate the regeneration of muscle. The aim of their current project is to learn more about this signaling—known as Wnt7a/Fzd7—and its operation in muscle, with the goal of determining its therapeutic potential as a way of stimulating intrinsic muscle repair in a muscle-wasting disease like DMD.

Dr. Tremblay intends to develop a completely new therapeutic avenue for DMD by targeting specific sequences in the dystrophin gene with engineered endonuclease proteins (enzymes that cleave the DNA chain). By using these specifically engineered endonucleases, Dr. Tremblay believes that the reading frame (i.e. groups of three nucleotides that code for one amino acid) of the dystrophin gene can be corrected, thus restoring dystrophin expression, which is lacking in patients with DMD. The objective of the project is to inject these meganucleases—fused with a cell-penetrating peptide—into the blood of DMD patients so that the proteins can enter in the muscle fibers and potentially correct the dystrophin gene. In time, genetic corrections like this may also be eventually used to treat other neuromuscular diseases.
Charcot-Marie-Tooth (CMT) disease is a common group of disorders of the peripheral nervous system that is characterized by demyelination (where the myelin sheath of neurons is disrupted) that leads to the progressive decrease of muscle tissue and touch sensation across parts of the body. The gene encoding MTMR2 (part of the MTM family of enzymes) is mutated in a certain aggressive form of CMT disease (CMT4B). Dr. Vacratsis’ research group wants to understand why the loss of a functional MTMR2 enzyme causes CMT. Moreover, a detailed understanding of MTMR2 biology will provide the necessary framework to identify and develop novel therapeutic strategies for CMT disease.
Spotlight on a Landmark discovery: DMD is a stem cell disease

Late last year, a breakthrough study out of Ottawa made headlines around the globe as the first to show that Duchenne muscular dystrophy (DMD) directly affects muscle stem cells—findings that are already changing long-held beliefs around the causes of the disease.

The study, entitled “Dystrophin expression in muscle stem cells regulates their polarity and asymmetric division” was published in *Nature Medicine* on November 16, 2015. The research concluded that muscle wasting in DMD not only is caused by myofiber fragility, but also is made worse by impaired regeneration due to satellite cell dysfunction.

“For nearly 20 years, we’ve thought that the muscle weakness observed in patients with Duchenne muscular dystrophy was primarily due to problems in their muscle fibres,” said Dr. Michael Rudnicki, senior author of the study, and director of the Regenerative Medicine Program at The Ottawa Hospital. “But
Our research shows that it is also due to intrinsic defects in the function of their muscle stem cells.”

According to Dr. Rudnicki, who is also a professor at the University of Ottawa, these research findings “completely change our understanding of Duchenne muscular dystrophy, and could eventually lead to far more effective treatments.”

DMD is caused by genetic mutations that result in the loss of the dystrophin protein, leading to progressive muscle weakness, and death by the second or third decade of life.

For many years, dystrophin was thought to be a simple structural protein only found in muscle fibres. But in this study, Dr. Rudnicki and his team discovered that muscle stem cells also express the dystrophin protein, and without this protein, they produce tenfold fewer muscle precursor cells—which in turn generate fewer functional muscle fibres. They also discovered that dystrophin is a key piece of the molecular machinery that enables muscle stem cells to sense their orientation in surrounding tissue.

“Muscle stem cells that lack dystrophin cannot tell which way is up and which way is down,” said Dr. Rudnicki. “This is crucial because muscle stem cells need to sense their environment to decide whether to produce more stem cells or to form new muscle fibres. Without this information, muscle stem cells cannot divide properly and cannot properly repair damaged muscle.”

This research was conducted in mouse cells, but it is expected that the findings will hold in humans, as the dystrophin protein is very similar in all mammals.

Current treatments for Duchenne muscular dystrophy are limited to steroids and physical therapy that slow disease progression and lessen symptoms. Experimental approaches such as gene therapy are also being investigated, but Dr. Rudnicki’s research suggests that these approaches will need to be modified so that they target muscle stem cells as well as muscle fibres.

“We’re already looking at approaches to correct this problem in muscle stem cells,” said Dr. Rudnicki. “I’m not sure if we will ever cure Duchenne muscular dystrophy, but I’m very hopeful that someday in the future, we will have new therapies that correct the ability of muscle stem cells to repair the muscles of afflicted patients and turn this devastating, lethal disease into a chronic but manageable condition.”

The study was funded by the U.S. National Institutes of Health, the Canadian Institutes of Health Research, Muscular Dystrophy Canada, the Muscular Dystrophy Association (U.S.), the Stem Cell Network, the Canada Research Chairs program, the Ontario Ministry of Research and Innovation, Deutsche Forschungsgemeinschaft, the Swiss National Science Foundation and The Ottawa Hospital Foundation.
The **Dr. George Karpati Award** was established by Muscular Dystrophy Canada to recognize the contributions of a clinician or scientist working to improve the health and well-being of people with neuromuscular disorders. The award was renamed in 2010 to honour the memory of Dr. George Karpati, whose life’s work was dedicated to advancing neuromuscular research and clinical care in Canada.

- **2015/2016** Dr. Ronald Cohn
- **2014/2015** Dr. Craig Campbell
- **2013/2014** Dr. Douglas McKim
- **2012/2013** Dr. Jean Mah
- **2011/2012** Groupe de recherche interdisciplinaire sur les maladies neuromusculaires (GRIMN)
- **2010/2011** Dr. Lawrence Korngut
- **2009/2010** Dr. Rashmi Kothary
- **2008/2009** Dr. Douglas Biggar
- **2007/2008** Dr. Louise Simard
- **2005/2006** Dr. Jack Puymirat
- **2004/2005** Dr. Mark Tarnapolski
- **2002/2003** Dr. Klaus Wrogemann
- **2001/2002** Dr. Michel Vanasse
- **2000/2001** Dr. George Karpati
- **1999/2000** Dr. Ronald Worton

Dr. Ronald Cohn is the recipient of the Dr. George Karpati Award for Researcher of the Year for his work on a genome-editing technology known as CRISPR that corrects DNA errors in the cells of a patient with muscular dystrophy.
Our Medical and Scientific Advisory Committee (MSAC) is comprised of dedicated volunteers from across Canada who generously share their expertise in neuromuscular disorders. Members include physicians, neurologists, scientists and clinician-researchers, as well as patient and family representatives. Together, they represent various perspectives from the health professional and patient communities.

The Committee provides strategic advice and makes recommendations to the Board of Directors on research policy, granting programs and funding. That input plays a crucial role in ensuring that Muscular Dystrophy Canada’s research program is dedicated to scientific excellence and ensuring that we leverage our investments by continuing to use granting processes that are transparent and efficient.

Join us in thanking the MSAC volunteers past and present who have provided us with invaluable advice and strategic guidance.

2015–2016 Committee Members

Kenneth Hastings PhD, Chair
Craig Campbell MD
Debra Chiabai
Ronald Cohn MD
Jonathan Mesiano-Crookston
Cynthia Gagnon PhD
Phil Gardiner PhD
Lawrence Korngut MD
Hugh McMillan MD
Daniel McNamara MD
Robin Parks MD
Toshifumi Yokota PhD
It is because of thousands of donors—and our major corporate partner, Safeway—that we are able to support researchers who tirelessly seek treatments and a cure for neuromuscular disorders.

The following named funds were utilized in support of the projects described in this publication:

Emily Elizabeth Stoneham Fund
Fonds Jessica Chami
Friends of Fraser Earle
Ilsa Mae Research Fund
Lawrie Goldlist Memorial Fund
Rachel Fund
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Shad’s R&R

We wish to extend our gratitude to the determined volunteers, donors and researchers who make it all possible.
For the past seven years, Safeway and Muscular Dystrophy Canada have partnered to run the *Make Muscles Move* campaign at Safeway stores across western Canada. The 2015 campaign raised a total of $258,667 to fund leading research and mobility grants across western Canada and northern Ontario.

Since 2008, Safeway, its employees and its customers, have donated over $7 million dollars to support Muscular Dystrophy Canada, allowing us to purchase 707 pieces of mobility equipment, medical devices and home modifications (valued at $4.1 million) for more than 300 families, and to invest in neuromuscular research projects across Canada.

Safeway has also been a generous contributor to events like the 2014 Empowerment in Action conference and the Walk for Muscular Dystrophy events in western Canada and northern Ontario. We would like to thank them for their important and ongoing partnership.

We extend our gratitude to the determined volunteers, donors and researchers who make it all possible.

Are you passionate about finding a cure for muscular dystrophy?

Innovative and effective research is expensive, and we need your help. Please consider making a donation to Muscular Dystrophy Canada—your gift supports scientific research projects and partnerships that will make tomorrow brighter. Help us find the answers, and together we can *make muscles move*.

Donate online at muscle.ca, or call Lisa Pottie, National Campaign Director at 1-866-687-2538 ext. 1120.
I Can! transform lives.

Muscular Dystrophy Canada’s mission is to enhance the lives of those affected with neuromuscular disorders by continually working to provide ongoing support and resources while relentlessly searching for a cure through well-funded research.