

## New researcher does novel stem cell work

Colin Crist's research aims to uncover the dynamics of skeletal muscle stem cell biology. The results could have a direct impact on novel treatments for muscular dystrophies (MD), diseases characterized by chronic degeneration of muscle.

"Specifically, my lab is looking at the skeletal muscle stem cells that reside along the muscle fibers in a quiescent state," Dr. Crist explains. "Our objective is to discover the mechanisms that waken them in a healthy body where they will proliferate to repair muscle damage. Skeletal muscle stem cells in patients with MD are unable to keep up with the chronic degeneration of muscle. The question is whether we can employ stem cell therapy to replace damaged muscle and the stem cells that contribute to their repair."

Dr. Crist's research could eventually have an impact on novel treatments for muscular dystrophies.

Stem cell therapy is promising for the treatment of MD because it is known that the appropriate satellite cells can be regenerated in adulthood.

"If we can understand how to replenish the stem cell pool for skeletal muscle, we hope to be able to overcome the genetic compromise that prevents people with MD from replacing the tissue that is wasting away," said Dr. Crist. "The two key questions for us are how the stem cells go from quiescence to an active state and back again; and how they regenerate muscle. Our findings will have wide-ranging implications for future research into all stem cell applications."

Dr. Crist completed his PhD at the University of Tokyo before spending the past six years as a post-doctoral research associate at the *Institut Pasteur* in Paris. He is now excited at the prospects of continuing his work at the LDI.

"I am very proud to have the opportunity to join such a vibrant research community," he said. "Though I am dedicated to basic biology, it is important to be connected with the clinical environment at the JGH because the culmination of our efforts comes when we succeed in advancing the cause of human health."

His latest publication appears in the July edition of [Cell Stem Cell](#).

## Diabetes drug linked to increased bladder cancer risk

Pioglitazone, a drug sold as Actos to control blood sugar levels in patients with type 2 diabetes, is associated with an increased risk of bladder cancer, according to findings from a study led by Dr. Laurent Azoulay, of the Centre for Clinical Epidemiology, along with Hui Yin, Kristian B. Filion, Jonathan Assayag, Agnieszka Majdan, Michael N. Pollak, and Samy Suissa, and published in the *BMJ*. It is attracting considerable international media coverage, as medical and legal news. Lawsuits had already been filed against the drug manufacturer in the United States.

The results show that more than two years of daily exposure to pioglitazone doubles the risk of bladder cancer. However, the authors stress, in absolute terms, the risks are low – up to 137 extra cases per 100,000 person years.

Using a data base from the United Kingdom, the authors studied 115,727 patients newly treated with diabetes drugs from 1988 to 2009. Results showed that 470 patients were diagnosed with bladder cancer during the average 4.6 years of follow-up (a rate of 89 per 100,000 person years). The rate of bladder cancer in the general UK population aged at least 65 years is 73 per 100,000 person years.

If patients had ever taken pioglitazone they were at an 83% increased risk of bladder cancer. This corresponds to 74 cases per 100,000 person years. This increased to 88 per 100,000 person years for patients who had taken the drug for two years or more, and increased further to 137 per 100,000 years for patients who had taken 28,000 mg or more. These findings remained consistent in several further analyses designed to check the results.

The authors conclude that their results "provide evidence that pioglitazone is associated with an increased risk of bladder cancer." They suggest that such associations may have been underestimated in previous observational studies and say doctors, patients, and regulatory agencies "should be aware of this association when assessing the overall risks and benefits of this therapy."

The paper, "The use of pioglitazone and the risk of bladder cancer in people with type 2 diabetes: nested case-control study," [can be found online](#).

## Neurologist develops promising model for schizophrenia

Dr. Hyman Schipper, a specialist in degenerative neurological diseases of aging, has created a mouse model that holds promise for unlocking some of the mysteries of schizophrenia, a serious mental illness characterized by varying degrees of disassociation from reality. Its causes are unknown and, though treatable, it remains incurable.

For the past fifteen years, Dr. Schipper's lab has been examining the influence of the protein heme oxygenase-1 (HO-1) on neuro-degenerative processes associated with Alzheimer's and Parkinson's diseases. HO-1 is of interest because it is over-expressed in the brains of subjects with these disorders and had been shown, in tissue culture, to contribute to pathologies common to both. About five years ago, his lab created a mouse model wherein human HO-1 is up-regulated in astrocytes of the brain.

At around forty-eight weeks, the HO-1 mouse displayed dramatic hyperkinetic behaviour. This motion – manifested, for example, by running around in circles – is not a feature of either Alzheimer's or Parkinson's, which diminish motor function. It is, however, characteristic of other human conditions, including schizophrenia, autism, and attention deficit disorder. Closer examination has revealed about a dozen neuropathological and neurochemical abnormalities that are attributes of human schizophrenia, including excessive dopamine levels in appropriate brain regions. Also evident was a decreased level of the protein reelin, which may be a factor in the abnormal brain development observed in schizophrenia.

“The indications are that if HO-1 is over-expressed early in life, we observe schizophrenic features,” said Dr. Schipper, “while we see parkinsonian symptoms when the transgene is induced later in life. It is fascinating that the same gene causes opposite outcomes depending on when the gene is expressed in the course of the life cycle. Also, we know that HO-1 expression is very sensitive to risk factors identified in schizophrenia, such as maternal infection. This could suggest that HO-1 acts as a funnel for a variety of stressors which may trigger schizophrenia in early life and Alzheimer's or Parkinson's in later life.”

From a clinical perspective, the successful development of a selective HO-1 inhibitor, a project underway in Dr. Schipper's lab, may prove important in blocking this particular pathway to disease. The results of his research are in press with the *Journal of Neuroscience*. [A video of the mouse model, illustrating hyperlocomotor activity, is available.](#)

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## New genetic markers open novel pathways to treating osteoporosis

A team of investigators, including Dr. Brent Richards, research scientist at the LDI and Assistant Professor of Medicine, Human Genetics, Epidemiology and Biostatistics at McGill University, has conducted the largest genome-wide meta-analysis into bone mineral density (BMD). They uncovered 56 genetic pathways – 32 of which are novel – associated with the architecture and physiology of bone density. BMD is the most important predictor of an individual's risk for fractures. Sufferers of osteoporosis, a disease characterized by low bone mass and the progressive deterioration of bone tissue, could benefit from the promise this discovery holds for identifying new and more effective drug targets. Their paper, entitled “Genome-wide meta-analysis identifies 56 mineral density loci and reveals 14 loci associated with risk of fracture,” has been published in *Nature Genetics*.

“That our extensive analysis succeeded in identifying six of eight existing drug targets for treating osteoporosis supports the evidence that the novel pathways we revealed are promising targets for new drug development,” said Dr. Richards.

Osteoporosis is a serious disease that accounts for approximately 1.5 million fractures annually. Associated health care costs are estimated to be \$17 billion in the United States alone, and are expected to rise a further 50% by 2025. While identifying the genes connected with bone density probably won't predict who will develop osteoporosis, previous studies have shown that approximately 80% of the clinical measures of BMD are tied to genetics.

This study points to hundreds of variants with small effects that play a role in the genetic architecture of BMD and fracture risk, thus underscoring the complexity of bone formation and integrity. As the most extensive undertaking of its type, it included more than 80,000 subjects on all continents and engaged the efforts of more than 100 researchers world-wide.

“By discovering new genetic links to BMD, we open the prospects that entirely new classes of drugs may prove efficacious in preserving bone density and preventing fractures,” said Dr. Richards. “Furthermore, having identified novel genetic markers associated with bone density, we can take any drugs that target those genes and test whether they are effective against osteoporosis.”

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## Research network to make Canada global leader in quality of care for seriously ill seniors

LDI researchers are playing major roles in the Technology Evaluation in the Elderly Network (known as [Tech Value Net](#)), a national enterprise between more than forty clinician researchers, nineteen universities and hospitals, and more than two dozen industry and non-profit partners, dedicated to positioning Canada as a global leader in providing quality care for seriously ill seniors. By conducting research in this population and translating findings into practice, researchers aim to save lives when possible, improve the quality of life, increase the quality of the dying process for seniors at the end of life, and increase patient and family satisfaction with the care they receive.

Dr. Bernard Lapointe, Chief of the Marjorie & Gerald Bronfman Palliative Care Division of the JGH, is on Tech Value Net's Board of Directors. Dr. Robin Cohen, Senior Investigator at the LDI and Research Director of the Program in Palliative Care at the JGH, is among its investigators, and will be co-leader of the end-of-life research group. Tech Value Net has received more than \$45 million in public and private funding, the former from the Network Centre of Excellence.

Under its auspices, Dr. Cohen is leading a multi-disciplinary team that will develop an evidence- and clinical experience-based program to improve the quality of life for caregivers to people at the end of life so that they, in turn, may offer better care. The Max Bell Foundation is providing more than \$170,000 in funding for the three-year project.

"If someone you love is dying, it is painful. Oftentimes, you are forced to take time off work to accommodate a new vocation for which you have no previous experience and for which you must be on call twenty-four hours a day," explained Dr. Cohen. "It is physically and emotionally exhausting. And while the caregivers' needs, understandably, come second to those of the patient, neglecting them comes at the expense of the patient's, as well as the family caregiver's, well-being."

Dr. Cohen's project has three specific objectives: to develop an evidence-based training program for volunteers to guide and support family caregivers, to implement a pilot project using this training program, and to collect data to evaluate its effectiveness.

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## Dr. Brett Thombs named William Dawson Scholar

Dr. Brett Thombs, Associate Professor of Psychiatry, has received a William Dawson Scholar Award from McGill University. The award recognizes a scholar developing into an outstanding and original researcher of world-class caliber who is poised to become an international leader in their field.

The Award will help support research that Dr. Thombs is pursuing in three fields. In the first instance, he will be expanding on evaluations he has undertaken of standardized depression screening tests applied in various medical settings. His findings indicate a lack of empirical evidence to support the therapeutic value of this widely endorsed practice. His second interest addresses the absence of effective psychosocial interventions for people with rare diseases, and promises to fill a glaring health care gap. Dr. Thombs is the founding director of the CIHR-funded Scleroderma Patient-centred Intervention Network (SPIN), which is developing innovative methods to help individuals cope with this condition. His third focus is to identify methodological and reporting biases that could result in inaccurate or misleading research reporting, such as when potential conflicts of interest are not documented.

"My research looks at problems faced by patients with a given disease, but, more broadly, examines issues that are generally relevant to providing better patient-centered care across disease groups," he explains.

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## LDI Scientific Retreat

The third annual LDI Scientific Retreat featured competitive oral and poster presentations by students. First prize for orals went to Frédéric Mallette of Dr. Stéphane Richard's lab for his talk on how the protein jumonji2 promotes cellular transformation by blocking cellular senescence. Second prize went to Stefania Simeone of Dr. Stéphanie Lehoux's lab for her presentation on how matrix metalloproteinase inhibition reverses shear stress-induced atherosclerotic plaque regression.

Best poster prizes went to the following students: Rahul Gawri (Mwale lab), Michelle Jasmine Ramcharitar (LeBlanc lab), Konstantinos Gkouvatso (Pantopoulos lab), Asia Rehman (Schiffirin lab), Samara Perez (Rosberger lab), Nicolas Garnier (Miller lab), Alexander Kelly (Mann lab), and Torsten Nielsen (Miller lab).

[Complete abstracts for all presentations are online.](#)

## Student Travel Award winners

LDI Travel Awards have been won by Ryen MacDonald, a third year PhD candidate, Hamed Bekerat, second year MSc, and Mathieu Neault, a second year PhD. Each will receive up to \$1,000 for travel expenses to make an oral or poster presentation of their research at a scientific conference.

LDI Travel Awards are conferred three times per year. Students employed at the LDI who are enrolled in the second or third year of a Master's program and in their second to fifth year of Doctoral studies are eligible. The next deadline for applications is September 20, 2012 for travel to be undertaken between November 2012 and February 2013. The deadline is January 20, 2013 for travel between March and June 2013; the May 20, 2013 deadline covers travel from July to October 2013.

Guidelines and applications are available on the LDI intranet.

## Dr. Howard Chertkow elected to board of international Alzheimer's research society

Dr. Howard Chertkow, Director of the Bloomfield Centre for Research in Aging has been elected to sit on the board of directors of the [International Society to Advance Alzheimer's Research and Treatment \(ISTAART\)](#), a professional society for individuals interested in Alzheimer's and dementia science. It includes research scientists, physicians and other professionals involved in the causes and treatments of Alzheimer's disease and related disorders. ISTAART is the first collegial group to represent all areas of Alzheimer's disease investigation.

Dr. Chertkow was also selected by the CIHR to sit as its representative on the [Alzheimer's Disease Neuroimaging Initiative \(ADNI\)](#) of the National Institutes of Health. The CIHR is a partner in ADNI, which is a \$60 million international initiative to elucidate the natural history of Alzheimer's Disease using scans and memory testing on a large group of subjects varying from the normal elderly to those with severe memory loss. ADNI has already had a major international impact in our ability to use biomarkers for early diagnosis of Alzheimer's Disease.

Dr. Howard Chertkow has been selected for the Board of Directors of the International Society to Advance Alzheimer's Research and Treatment.

## Health & Safety Officer is Employee of the Year

Alain Petit, who has been Health and Safety Officer for nearly two years and was recently designated Biosafety Officer, was honoured as the 2012 Employee of the Year. He has done much to create a culture of safety at the LDI, providing proper training and dissemination of information so as to ensure that all employees are aware of proper procedures and regulations.

Dr. Petit places a great deal of emphasis on prevention and preparedness, regularly inspecting labs in order to verify that hazardous materials are being properly stored or disposed, testing equipment such as showers and eyewashes so that they are functioning in the event of an emergency, and reminding employees of the need to wear appropriate protective gear.

"It's easy to become complacent when you are accustomed to working with dangerous goods," Dr. Petit acknowledged. "It's important to respect the potential for an accident in order to prevent them from ever occurring."

He gives training courses in transporting dangerous goods, biosafety and good laboratory practices, and workplace hazardous materials information systems. It is important to keep staff who come into contact with hazards in the research environment fresh and up-to-date in their training. After all, when an incident occurs, it is essential that those who are in proximity react quickly and appropriately to control the situation.

Given the presence of pathogens, biological and chemical agents, and radioactive materials, present in a modern medical research facility, the potential hazards are significant. It is a collaborative effort by all those who handle these materials that maintains a safe work environment.

## LDI student honoured

Dr. Tariq Roshan, a PhD candidate in the Ponka lab won an award of excellence (Silver Category) at the Canadian Institutes of Health Research National Research Poster competition in Winnipeg in June.

"Students such as Tariq bring great credit to the LDI and show our ability to turn out fine graduate students," commented his supervisor, Dr. Prem Ponka.

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