



Lady Davis Institute Research Newsletter



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JGH Foundation Gala supports LDI

The [JGH Foundation's](#) 2015 gala succeeded in raising \$800,000 to support research at the Lady Davis Institute at the Jewish General Hospital. [See the video.](#)

"I want to thank everyone who donated to the gala for their extraordinary generosity and foresight in recognizing that research is the only way to improve health care," said Dr. Roderick McInnes, Director of the LDI. "I want to recognize the extraordinary effort of the JGH Foundation in raising donor awareness of research at the Lady Davis, in particular CEO Myer Bick, and the gala's organizing team led by Annette Goldman."

The funds will help the LDI continue with its leading edge contributions to basic, translational, and clinical research to develop novel approaches to treating cancer, diseases of aging, HIV/AIDS, hemovascular diseases, advances in epidemiology and psychosocial aspects of disease.

Thanks to the gala's lead sponsor, Desjardins Group.



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Cooperating in building the future

Pioneering research undertaken by Dr. Lawrence Rosenberg (right), President & CEO of West-Central Montreal Health, is behind a new clinical trial to treat type 1 diabetes



Landmark Clinical Trial of a Novel Treatment for Type 1 Diabetes

The JGH and MUHC have launched the first clinical trial that combines a specific agent to restore normal insulin secreting islets and a treatment to control autoimmune attack of the newly formed islets to treat patients with longstanding type 1 diabetes. Based largely on pioneering research by **Dr. Lawrence Rosenberg**, President and CEO of West-Central Montreal Health, the treatment combines INGAP Peptide (Exsulin™), which stimulates growth of the insulin secreting islets, and ustekinumab (Stelera™), an interleukin-12 inhibitor, which showed the islet restoring effect of INGAP peptide was enhanced by the addition of another IL-12 inhibitor.

In previous trials, INGAP Peptide demonstrated improvement in insulin secretion and glucose control in type 1 and type 2 diabetes patients.

Type 1 diabetes affects over 1.5 million people in North America, and its prevalence is also growing. Type 1 diabetes develops when the body's immune system destroys the beta cells within the pancreatic islets. All people with type 1 diabetes require insulin therapy to survive. Poorly controlled diabetes can lead to serious complications, including heart disease, blindness, kidney failure and death.

"My colleagues and I have invested our careers in demonstrating the potential for, and means of, restoring normal insulin secretion in people with diabetes. Though our study is small, we know that the return of significant insulin secretion in just one person could represent a major finding," said Dr. Rosenberg.

Alexandre Orthwein joins Cancer Axis

After graduating from the Université Louis-Pasteur in Strasbourg, **Dr. Alexandre Orthwein** pursued his graduate studies at the Institut de recherches cliniques de Montréal (IRCM) at the Université de Montréal, where he focused, first, on HIV pathogenesis, and, later, on immunology and lymphoma/leukemia. He is establishing his lab at the Lady Davis Institute as an Assistant Professor of Oncology at McGill having completed his postdoctoral work in the lab of Dr. Daniel Durocher at the Lunenfeld-Tanenbaum Research Institute in Mount Sinai Hospital, Toronto.

“For my postdoc, I concentrated on genome stability to understand how certain DNA breaks are repaired,” he explains. “DNA lesions are a major source for the development of cancer. My objective is to study how genome integrity is maintained, and how dysregulation can lead to cancer.” The Durocher lab, where Dr. Orthwein spent the past four years, is one of the larger labs in Canada researching how normal cells become cancerous by illuminating how genome integrity is maintained. DNA instability, in general, is associated with a broad range of diseases beyond cancer, including immune deficiencies, infertility, aging and some types of neurodegeneration.

“The mechanisms behind DNA instability remain complex, though we know in some detail the important proteins in the pathway that regulates genome stability,” he said. “It’s unclear how cancer emerges from genome instability due to the loss of these proteins or when they become over-expressed.”

Dr. Orthwein’s lab will explore genome stability in B-cells and its link to the emergence of immune deficiencies and B-cell malignancies. “What drew me to the Lady Davis is its connection to the Jewish General Hospital, which offers a direct route to impacting patient treatment efficiently, as part of a translational team in the clinic,” he said.



Commercialization of dry eye disease treatment developed at LDI

The discovery that tavilermide induces the production of mucin, a crucial lubricant in tears, offers hope of relief to people who suffer from chronic dry eye disease. The invention and the development of a drug based on this small molecule was made by the team led by **Dr. H. Uri Saragovi**.

“As there is currently no treatment available for dry eye disease, we are very excited that tavilermide, taken in the form of an eye drop, can help millions of patients who suffer from this disease,” said Dr. Saragovi.

Already completed Phase 2 clinical trials with 1% tavilermide demonstrated significant improvement in both signs and symptoms of dry eye over placebo, with absolutely no adverse side effects.

This technology has recently been licensed by Allergan, a leading global pharmaceutical company, from Mimetogen Pharmaceuticals, a Montreal biotechnology company, for an upfront payment of \$50 million, plus potential milestone and royalty fees.

Two phase 3 trials have been successfully completed. It is expected that the final phase 3 trial undertaken by Allergan should quickly confirm its designation as a treatment for all stages of dry eye disease, enabling it to be brought to market shortly thereafter.

Dry eye disease, which afflicts more than 25 million people in North America, first presents itself as an inability to produce moisture to lubricate the eye. The constant irritation that ensues is compounded by inflammation. Because there is no cure or effective treatment, the condition eventually leads to the degeneration of the sensory nerves in the cornea. By stimulating the production of mucin, tavilermide will keep the eye moist and avert inflammation. It may also stimulate re-innervation.

Dr. Ian Shrier, of the Epidemiology Axis, an elected member of the Society for Research Synthesis Methodology, has been named co-editor-in-chief of *Research Synthesis Methods*, the leading interdisciplinary journal in the field. It publishes papers on evidence synthesis from across the health, applied, and social sciences.

Varenicline promising for smokers trying to quit in the wake of a heart attack

A multicentre randomized placebo-controlled clinical trial, initiated and led by **Dr. Mark Eisenberg**, revealed that nearly half of the heavy smokers admitted to hospital following a heart attack successfully quit smoking six months after being given varenicline (sold as Champix in Canada and Chantix in the United States). This is an important achievement in a very high risk patient population. The results of the study (known as the EVITA trial) were published in [Circulation](#).

“This is a significant result because we know from previous research that less than a third of smokers hospitalized with a heart attack or chest pain quit smoking after they leave the hospital,” said Dr. Eisenberg. “This fact is rather surprising given our expectation that these patients are highly motivated to quit in the aftermath of an acute coronary incident. It is critical that we get these patients to quit because those who continue to smoke have substantially higher disease and death rates, whereas those who quit can reduce the risk by upwards of fifty-percent within a year.”

Researchers found that varenicline increased smoking abstinence rates at all follow-up visits. At six months, 47.3-percent of varenicline patients were still not smoking compared to 32.5-percent of placebo patients - a 14.8-percent difference.

The effectiveness of varenicline as a smoking cessation therapy has previously been demonstrated in young, healthy smokers, but this study is the first to verify its efficacy in a population that had already experienced a cardiac incident serious enough to require hospitalization.

“This is the first clinical study that points us to a pharmacotherapy that you can start in hospital that is going to reduce smoking among high risk patients after six months,” Dr. Eisenberg points out.

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To submit information or for media enquiries, contact: Tod Hoffman at: thoffman@jgh.mcgill.ca; 514-340-8222, ext. 8661.

New explanation for how protein Aven accumulates in leukemia

The protein Aven is found in increased quantity in certain types of leukemia cells – notably T-cell acute lymphoblastic leukemia. It is a key ingredient in their capacity to thrive and multiply. Reducing the level of Aven in leukemic cells would remove an important factor in their capacity to survive and replicate among healthy blood cells, ultimately causing them to die.

“What wasn’t clear,” points out **Dr. Stéphane Richard**, James McGill Professor and Senior Investigator in the Cancer Axis, “is the process through which Aven affects how leukemic cells develop.”

In a paper published in [eLife](#), his lab revealed that Aven binds to G-quadruplexes found in two particular messenger RNA (mRNA) molecules responsible for encoding proteins associated with leukemia. The G-quadruplex is a highly stable structure, about which little is known. This binding process increases the translation of these mRNAs most efficiently when a helicase, which remodels RNA, also binds to Aven.

“Our hypothesis was that Aven may be involved in translational regulation,” said Dr. Richard. “We showed that, in fact, it does regulate the protein production of several oncogenes.”

At the molecular level, the paper demonstrates, Aven recognizes a planar structure and binds the G-quadruplexes, escorting them to polyribosomes where the proto-oncogenes are produced. Aven is, therefore, a key element in this process. Reducing the amount of Aven in cells caused fewer of the leukemic proteins to be produced, which also reduced the growth and multiplication of these malignant cells.

“These findings raise the possibility that drugs that disrupt Aven could help treat leukemia,” Dr. Richard explains, adding, “The next challenge will be to identify the signalling pathways that communicate with Aven and to define all the G-quadruplex mRNAs that Aven regulates.”

This work was done in collaboration with Dr. Ivan Topisirovic’s lab, which has expertise in mRNA translation.

Cancer Research Society Grants

Four researchers competed successfully for [Cancer Research Society](#) operating grants worth \$120,000 over two years (2015-17):

- **Chantal Autexier** – “ALTEred telomere biology in breast cancer”
- **Mark Basik** – “Dissecting the tumour suppressive functions of SPEN in ER+ breast cancers” (funded with the Quebec Breast Cancer Foundation)
- **Walter Gotlieb** – “Sequential therapeutic targeting strategy of ovarian cancer harboring dysfunctional BRCA1”
- **Wilson Miller** – “Inhibiting the metastatic propensity of pregnancy associated breast cancer (PABC) with inhibitors of eIF4E function” (funded with the CURE Foundation).

[Dr. Andréa LeBlanc](#) was featured in *La Presse* as *Personnalité de la semaine* on November 29.

Rossy Cancer Network’s Cancer Quality & Innovation Research Fund Grants

Dr. Sarit Assouline was among the beneficiaries of the [Rossy Cancer Network](#)’s 2015 Cancer Quality & Innovation (CQI) Research Fund, which supports advancements in cancer care quality research by funding projects that rigorously evaluate the benefits of continuous improvement projects in cancer care.

Dr. Assouline and her team will be evaluating how health care professionals adhere to treatment guidelines in the management of chronic myeloid leukemia — a patient population where adherence can critically impact life expectancy.

“Such projects support the RCN’s goals of providing world-leading care to all patients in the network,” stated Dr. Wilson H. Miller Jr, the RCN’s Clinical Lead. “They provide a rigorous framework to assess quality improvement initiatives and to help transfer this knowledge across the McGill-affiliated hospitals.”



Dr. Gerald Batist, head of the Cancer Axis, co-chaired the scientific program committee of the Canadian Cancer Research Conference, held in Montreal in November. This three day event attracted nearly

1000 scientists and trainees. The conference is held bi-annually on behalf of the [Canadian Cancer Research Alliance](#), formed in 2004 to coordinate cancer research and document research activities on a pan-Canadian level.

Dr. Koren Mann, of the Cancer Axis, has been nominated to serve on a new Inorganic Arsenic Assessment Development Committee established by the National Academies of Sciences, Engineering, and Medicine in Washington, DC. The committee will meet to peer review the Environmental Protection Agency’s revised Integrated Risk Information System toxicological assessment of the health effects of oral, inhalation, and dermal exposure to inorganic arsenic.

Dr. Ernesto Schiffrin, head of the Hemovascular Axis, was awarded the 2015 Distinguished Scientist Award by the Canadian Society for Clinical Investigation at its annual meeting in Toronto. The President of Hypertension Canada (2013-2016) and immediate past President of the International Society of Hypertension, Dr. Schiffrin becomes editor-in-chief of the *American Journal of Hypertension* in January 2016.

Dr. Leon van Kempen, Scientific Director of the Molecular Pathology Centre, co-organized the *Melanoma Mini-Symposium: “Networking from bench to bedside.”* It convened melanoma investigators from McGill and the Université de Montréal, and affiliated institutions, to present their latest research. The goal of the meeting is to establish a Montreal Melanoma Research Network to foster collaborations and establish Montreal as a hub for basic science and clinical translation.