



# Lady Davis Institute

## Research Newsletter



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### New Axis promises to inspire novel approaches to research

On April 1, three research axes – Aging, Hemovascular, and HIV/AIDS – were merged to form the Molecular and Regenerative Medicine (MRM) Axis. This evolution is the result of a recommendation of the International Scientific Advisory Board (ISAB) of the LDI, which noted that the former axes share a broad interest in the molecular basis of disease or its treatment, but lacked the critical mass of scientists necessary for a maximally effective and interactive research group.

The overall focus of the new Axis is to understand the causes and pathogenesis of common diseases (other than cancer), and to develop novel treatments. In particular, because stem cell research is a strategic priority for the LDI, this axis will be the home to the LDI's stem cell researchers, whose work is critical to the development of cell replacement therapies for damaged tissues and organs.

**Dr. Koren Mann** has been appointed to head the Axis. "Bringing these researchers together will enhance creativity and the interdisciplinary exchange of ideas," she said. "I have no doubt that unexpected new collaborations will develop, spawning true innovation. This is particularly important in Canada's increasingly competitive funding environment. We also believe this alignment will attract new faculty and inspire the best trainees with the opportunity to do really unique research."

The Director of the LDI, Dr. Roderick McInnes noted that while it may not be immediately evident how, for example, a microbiologist working on antiretroviral targets might benefit from interacting with a geneticist exploring the molecular mechanisms governing stem cell activity, it is through such unorthodox exposures that the most novel discoveries are often made.

"The cross-fertilization of concepts and technologies resulting from this new admixture of investigators will, in my view and that of the ISAB, substantially enhance the research of the members of this new axis and of the LDI as a whole," affirmed Dr. McInnes.

### Major new investment to advance personalized cancer care

A total of \$4 million has been invested in the Exactis Innovation "Personalize My Treatment" (PMT) initiative to help bring innovative precision medicine to Canadians living with cancer. Merck is contributing \$2 million, with the Cancer Research Society and New Brunswick Health Research Foundation each giving \$1 million.

"The Exactis vision is to build a Canadian Centre of Excellence in Cancer Precision Therapeutics. This project takes a giant step forward today with the partnership of New Brunswick's medical scientific community. Together we will accelerate discoveries and expand treatment opportunities so that we can really make a difference", said **Dr. Gerald Batist**, Co-Founder and Scientific Director of Exactis Innovation and of the Quebec – Clinical Research Organization in Cancer (Q-CROC), Co-Director at the Lady Davis Institute, and Director of the Segal Cancer Centre at the Jewish General Hospital.

Exactis is leading a pan-Canadian network to create a comprehensive cancer database of tissue samples, genomic data and clinical data from the cancer patient population. The main goal of PMT is to match patients to available clinical trials based on the molecular profile of their cancer and defined study inclusion criteria. The initiative aims to reduce barriers to personalized medicine by making Canada's rich scientific resources accessible to the research community. This project was first initiated at the JGH in November 2015, with **Dr. Mark Basik** as the Principal Investigator. Other Quebec sites will be opening shortly.

Established in 2014 with funding from the Canadian Networks of Centres of Excellence (NCE), the Canadian Institutes of Health Research (CIHR), the Natural Sciences and Engineering Research Council (NSERC), and the Social Sciences and Humanities Research Council (SSHRC), Exactis is a public-private collaboration that represents a strong and agile research network to provide patients with access to novel therapeutics and to accelerate drug development such that lab bench research moves more efficiently to bedside care. The Molecular Pathology Centre at the JGH, led by **Drs. Alain Spatz** and **Leon van Kempen**, serves as a core lab for Exactis.

## ***Anti-diabetic incretin-based drugs not associated with increased heart failure***

Incretin-based drugs, a type of medication used to treat type 2 diabetes, do not increase the risk of being hospitalized for heart failure relative to commonly used combinations of oral anti-diabetic drugs, according to a study led by epidemiologist **Dr. Kristian Filion** and published in [the \*New England Journal of Medicine\*](#).

“This landmark study highlights the importance of the CNODES pan-Canadian initiative in addressing questions of prescription drug safety. Such important research requires that we study very large numbers of patients, and this can only be achieved by participation of all Canadian provinces,” said Dr. Samy Suissa, the Principal Investigator of CNODES

ing to a study led by epidemiologist **Dr. Kristian Filion** and published in [the \*New England Journal of Medicine\*](#). “Clinical trials have provided inconsistent findings regarding the risk of heart failure with these drugs,”

said Dr. Filion. “By using health records from multiple Canadian provinces, the United States, and the United Kingdom, we were able to study this potential drug safety issue in a large number of patients seen in a real world setting.”

Incretin-based drugs (which include the DPP-4 Inhibitors Galvus, Jalra, Januvia, Nesina, Onglyza, Trajenta, and Xiliarx, as well as the GLP-1 analogs Bydureon, Byetta, Saxenda, Trulicity, and Victoza) are commonly prescribed to help reduce blood sugar in patients with type 2 diabetes. Approximately 12% of these patients are prescribed this class of drug. Concerns regarding their heart safety were raised following an unexpected finding of an increased risk of heart failure in a recent clinical trial. This finding was not replicated in subsequent clinical trials.

The study was conducted by the Canadian Network for Observational Drug Effect Studies (CNODES), a pan-Canadian, multi-center drug safety network.



## **Mark Wainberg Inducted into Canadian Medical Hall of Fame**

**Dr. Mark Wainberg**, Director of the McGill AIDS Centre at the Lady Davis Institute, was among six giants of health care to be inducted into the [Canadian Medical Hall of Fame](#).

“With the Induction Ceremony we honour excellence, preserve history and connect generations,” said Dr. Jean Gray, chair of The Canadian Medical Hall of Fame, of the 2016 laureats. “These Canadian heroes have not only furthered health, but they serve as an inspiration to all Canadians and to our future health leaders.”

The Canadian Medical Hall of Fame, the only such establishment in the world, is dedicated to celebrating the contributions of medical heroes who have impacted the lives of Canadians and others around the globe. It is located in London, Ontario. Laureates are individuals whose outstanding contributions to medicine and the health sciences have led to extraordinary improvements in human health.



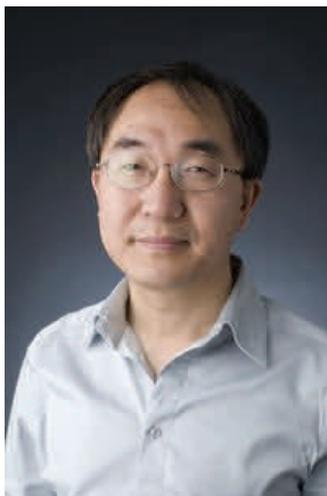
## Promising antiviral target in search for an HIV cure shows surprising resilience

Research led by Dr. Chen Liang, published in [Cell Reports](#), revealed that even a tiny mutation can allow the HIV virus to become resistant to therapies using the CRISPR/Cas9 gene-editing platform. Using CRISPR/Cas9 to mutate HIV-1 within cellular DNA, researchers found that while single mutations can inhibit viral replication, some also led to unexpected resistance. They believe targeting multiple viral DNA regions may be necessary for the potential antiviral aspect of CRISPR/Cas9 to be effective.

Upon entry into a cell, HIV's RNA genome is converted into DNA and becomes entwined with the cellular DNA. From here, CRISPR/Cas9 can be programmed to target a DNA sequence and cleave viral DNA. The problem is that HIV is notoriously good at surviving and thriving with new mutations, so while many viruses are killed by the targeted approach, those that escape the CRISPR/Cas9 treatment become more difficult to target.

"When we sequence the viral RNA of escaped HIV, the surprise is that the majority of the mutations that the virus has are nicely aligned at the site where Cas9 cleaves the DNA, which immediately indicates that these mutations, instead of resulting from the errors of viral reverse transcriptase, are rather introduced by the cellular non-homologous end joining machinery when repairing the broken DNA," says Dr. Liang. "Some mutations are tiny—only a single nucleotide—but the mutation changes the sequence so Cas9 cannot recognize it anymore. Such mutations do no harm to the virus, so these resistant viruses can still replicate."

Dr. Liang doesn't believe the effort to apply CRISPR/Cas9 as an antiviral is futile, as there are strategies that could overcome this limitation. For example, targeting multiple sites with CRISPR/Cas9 or using other enzymes aside from Cas9. Once a solution is identified, the next barrier will be identifying ways to deliver the treatment to patients.



## Countering inflammatory response in hypertension

A paper produced by the lab of Dr. Ernesto Schiffrin, published in the [Journal of Hypertension](#), definitively demonstrates that T-regulatory lymphocytes (Treg) are part of a mechanism that maintains a proper balance over inflammatory response in the vascular system in animal models of hypertension.

The Schiffrin team used a mechanistic strategy with Treg deficiency and replacement in a murine model of hypertension and vascular injury, finding that vascular injury and inflammation were much greater in mice deficient in Treg, whereas this was prevented by Treg replacement. The paper offers evidence of the benefits of immunotherapy in treating cardiovascular disease.

"The implication is that approaches allowing us to activate the Treg anti-inflammatory pathway with immune therapy devoid of adverse side effects caused by existing medications may improve the pro-inflammatory state that occurs in many cardiovascular diseases, including hypertension," Dr. Schiffrin said.

It is essential to be able to parse through potential pathways in order to identify those which optimize positive effects without the negative consequences. "We know that immunotherapy works; we have to be cautious in how we make it work," he points out, "particularly in chronic disease where treatments must be taken over long periods."

While emphasizing that there is no magic bullet, immunotherapy promises to be another potential weapon in the clinician's arsenal. "We are dealing with enormous complexity and multiple feedback loops and delicate balances between beneficial and adverse effects," Dr. Schiffrin emphasizes. "We must remember that inhibiting inflammatory mechanisms may open the way for infections, including tuberculosis. We must make sure that this is not a risk with immunotherapy of hypertension. Our quest is to discover new interventions that can deliver better outcomes for patients."

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## New therapeutic approach to rickets

Uncontrolled production of the protein fibroblast growth factor 23 (FGF23) is associated with rickets, a crippling skeletal condition. Rickets is among the most common inherited skeletal diseases, but can also be acquired in adulthood, when it is usually caused by an FGF23 secreting tumor. Rickets results in bones failing to grow, softening and weakening, as well as fusion between the bone and ligaments and tendons. **Dr. Andrew Karaplis**, Director of the Metabolic Bone Disease and Post-Fracture Clinics at the JGH, recalls treating a patient whose jaw was so thoroughly immobilized that his teeth had to be broken so that he could suck liquid sustenance through a straw.

Rickets is conventionally treated by supplementing vitamin D and phosphorus. This is not a cure, but can serve to offset the worst physical deformities.

“Some patients find this treatment difficult to tolerate and it is necessary to take these supplements for a lifetime,” Dr. Karaplis points out. “Phosphorus frequently causes severe diarrhea, so it is very difficult to get children to comply with their medication and, therefore, the condition persists into adulthood.”

His research, published in [The Journal of Clinical Investigation](#), reveals that phosphorous replacement is not necessary to improve the skeletal condition. “This is contrary to the conventional wisdom,” he said. “Using animal models, we manipulated vitamin D levels directly in the bone and this alone brought about dramatic improvement.”

He then administered a drug currently targeted for use in chronic kidney disease to rachitic mice. It acts by inhibiting the CYP24 enzyme, and improves vitamin D metabolism in the bone. The result was near complete recovery of the rachitic bone abnormalities. It will need to be determined whether such an intervention in children with rickets would prevent the development and progression of the skeletal deformities. Since the drug’s pharmaco-kinetic properties are understood and it is well tolerated, clinical trials for rickets could be initiated in the near future.



## Exceptional responder may reveal genetic secrets for cholesterol control

A patient of **Dr. Morris Schweitzer**, an endocrinologist and LDI investigator, had an exceptional response to the LDL-cholesterol adsorption inhibitor ezetimibe. Whereas a normal responder will see LDL-cholesterol reduction of 18%, the exceptional responder experienced reductions of 65%. The exceptional responder has familial hypercholesterolemia, which is due to a mutation in the LDL cholesterol receptor gene. These mutations are prevalent in the French Canadian population because of a founder gene effect. The patient in question had a LDL-cholesterol receptor mutation which is present in 65% of French Canadian hypercholesterolemic individuals and which results in very high LDL-cholesterol levels. The patient had her first coronary bypass surgery at age 38, followed by a second at 55. Her father died of a heart attack at 42, and her brother also died of a heart attack when he was only 31. With 80mg of Lipitor she reduced her LDL-cholesterol from 12.4 to 9.5mmol/L. When ezetimibe 10mg was added the LDL-cholesterol was further reduced to 3.8mmol/L which significantly reduced her risk for future coronary events.

This, Dr Schweitzer, in collaboration with **Dr. Lorraine Chalifour**, discovered was due to two mutation in Niemann-Pick C 1-like 1 (NPC1L1), the gene which reduces intestinal cholesterol transport protein targeted by ezetimibe. They performed extensive experiments which involved cholesterol uptake in cultured cells, immunofluorescent localization of NPC1L1 in cultured cells, molecular dynamic modeling of the mutant and wild type protein and identified new NPC1L1 binding partners in the mutant protein. The results were published in [Atherosclerosis](#).

“Exceptional responders give unique insights into how the drug functions,” said Dr. Chalifour. “We sequenced the patient’s DNA and identified a number of mutations responsible for significant changes in the uptake of cholesterol.”

“Nothing like this has ever been seen before. The novel mutations we identified made the patient very sensitive to the drug, which is why it was so effective,” affirmed Dr. Schweitzer. “Future drug development may focus on simulating the actions of these particular mutations so as to produce a more effective cholesterol lowering therapy.”

NPC1L1 is also a factor in carrying hepatitis C into cells, so future drug development may target this gene for treating and preventing this disease as well.

Quebec has among the highest mutation rates in the world for familial hypercholesterolemia – as high as one in eighty in the Lac St Jean region – compared with one in 500 globally.