



Lady Davis Institute

Research Newsletter



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FRQS Chercheurs-boursiers named

Nine LDI researchers won career awards from the Fonds de recherche Québec – Santé (FRQS), the province's major funding agency for medical research.

John Antoniou was one of only four investigators in Quebec to be awarded Chercheur national, the highest title in the FRQS pantheon, for his research on, "The Importance of Link N as a Mediator in the Biological Repair of Inter-vertebral Disk Degeneration."

Slobodan Devic had his Chercheur-boursier Senior funding renewed for his study on "Optimization of Radiation Therapy Using Functional Imagery and Improved Dosimetry."

Brent Richards was awarded Chercheur-boursier clinicien Junior 2, for his project, "From Bench to Clinic: Understanding the Genetic Determinants of Common Medical Illnesses to Improve Patient Care."

Brett Thombs was also awarded a Chercheur-boursier Junior 2, to investigate "Improving the Mental Health and Quality of Life of Canadians Living with Chronic Disease: From Evidence to Practice."

Awarded Chercheur-boursier Junior 1 funding were:

Colin Crist, to investigate the "Molecular Mechanisms Regulating Activities of Skeletal Muscle Stem Cells."

Marc Fabian, for his research on the "Role of the CCR4-NOT Complex in Gene Regulatory Networks in Mammals".

Christel Renoux, for a "Neuro-Epidemiology Study on Adverse Drug Reactions."

Isabelle Vedel, to look at "Alzheimer's Disease and Comorbidities: Adjusting and Improving the Quality and Effectiveness of Front Line Services."

Michael Witcher, for his study on "The Epigenetic Impact of Poly(ADP) Ribosylation Deregulation in Breast Cancer."

4th annual LDI Scientific Retreat

On May 10, the LDI held its fourth annual Scientific Retreat, showcasing examples of research under way in each axis, as well as the work of some of its most promising trainees. This year's retreat attracted more than 100 abstract proposals for oral and poster presentations, and was attended by more than 300 scientists, lab assistants, and students.

Dr. Brett Finlay of the University of British Columbia, one of the world's leading cellular microbiologists, whose laboratory studies several pathogenic bacteria, including Salmonella and pathogenic E. coli interactions with host cells, gave the keynote address on the role of microbiota in enteric and allergic diseases. Because scientists realize that the microbiota population hosted by the human body outnumber human cells by ten times, they are paying increasing attention to the role of microbiota on human disease.

The best student oral presentation was by Valentina Gandin of Ivan Topisirovic's cancer lab, for "Degradation of newly synthesized polypeptides by ribosome-associated RACK1/JNK/eEF1A2 complex." In second place was Peter Quashie of Mark Wainberg's HIV/AIDS lab for "Evidence for the importance of the integrase mutation G118R in subtypes C and CRF02_A/G."

Gustavo Wendichansky was named LDI Employee of the Year. During this past year, he added the responsibilities of the chief operating officer to his already substantial duties as chief financial officer.

Principal investigators who gave presentations included Dr. Hyman Schipper (Aging) discussing a novel mouse model for schizophrenia; Dr. Antonis Koromilas (Cancer) on the EIF2a phosphorylation pathway and its connection to cancer; Dr. Joel Paris (Psychosocial) on what constitutes a personality disorder; Dr. Elizabeth Jones (Hemovascular) on vascular remodelling during embryonic development; Dr. Anne Gatignol (HIV/AIDS) on the interplay between complexes mediating the RNA interference pathway and HIV; and Dr. Pierre Ernst (Epidemiology) on multi-centre observational drug safety studies.

Exploring a Novel Approach to Hypertension and Cardiovascular Protection

A decade ago, in an influential and frequently-cited paper published in *Circulation*, Dr. Ernesto Schiffrin, head of hemovascular research at the LDI, broke new ground in identifying the protective qualities of the nuclear receptor peroxisome proliferator-activated receptor- γ (PPAR γ) with respect to some models of hypertension. Stimulating the particular PPAR known as gamma with glitazones, a class of drugs used to treat diabetes, showed promise for reducing inflammation and oxidative stress in blood vessels.

However, along with the benefits, some severe off-target side effects were eventually recognized, including the possibility for heart attacks and heart failure, especially in patients at high cardiovascular risk. Since the negative effects were so serious, the use of glitazones was largely abandoned.

Still intrigued by the therapeutic possibilities of PPAR γ , and unwilling to abandon the undeniably positive results it had demonstrated, Dr. Schiffrin's lab has continued its investigations and recently published new findings regarding its protective role in hypertension in the journal *Cardiovascular Research*.

"We know that stimulating PPAR-gamma has a positive effect," Dr. Schiffrin states. "What we need to do is tease out those benefits, while mitigating the harmful side effects, which is what we do in all drug development. I think it would be a pity to ignore the benefits simply because we don't yet have the means to overcome the risks."

Dr. Schiffrin's team generated a mouse model in which they were able, with Cre-lox technology, to inducibly knock down the gene of PPAR-gamma selectively in smooth muscle cells, including those of all the vasculature.

"Inactivation of the PPAR gamma gene confirmed its vascular protective effect," Dr. Schiffrin said of his latest study. "Thus, we believe that the negative side effects that have been observed with glitazones are a reflection of the design of these drugs, but does not negate the fact that PPAR gamma is protective and could serve as an effective target for cardiovascular protection. That is, of course, if the right drug can be developed to stimulate PPAR gamma, without the off-target adverse side effects which occur with currently available glitazones."

CNODES makes its annual report

[The Canadian Network for Observational Drug Effect Studies \(CNODES\)](#) established a national network of over 60 researchers, with headquarters at the LDI under the leadership of Dr. Samy Suissa, to review drug safety and effectiveness in the marketplace. Though all drugs are subject to rigorous, multi-phased clinical trials, many rare adverse effects only emerge after exposure to extremely large and diverse patient populations. The project was launched in late 2011 with a \$17.5 million grant from the Canadian Institutes of Health Research.

The first major study to emerge from CNODES was the revelation that high dose statins, which are used to lower cholesterol and are the most widely prescribed medication in the world, elevate the risk of acute kidney injury. This discovery was published in the highly respected

British Medical Journal and attracted widespread international media coverage. It revealed a previously unrecognized risk which physicians will now take into account when treating their patients.

The overarching aim of CNODES is to use collaborative, population-based approaches to provide rapid answers to questions about drug safety and effectiveness.

Two other projects have been completed, with the results to be published shortly:

1. Proton-pump inhibitors, drugs used to treat gastric-acid related conditions, and the risk of community-acquired pneumonia;
2. Atypical antipsychotic drugs and the risk of diabetic ketoacidosis.

Three investigations are currently in progress:

1. High potency statins and the risk of diabetes in patients with occlusive vascular disease;
2. Isotretinoin, a treatment for severe acne, use during pregnancy and the risk of congenital malformations;
3. Anti-depressant drugs and the risk of renal failure.

While launching this ambitious research agenda, CNODES set up an operating structure devised to provide quick and accurate answers, a major challenge for an organization with a presence across Canada.

"Our network provides access to the health records of over 40 million people, a database large enough to accurately assess therapeutic risks and benefits," said Dr. Suissa. "We use state-of-the-art research methods, ensuring that our studies find an audience in the best scientific journals and give health care professionals the confidence to use our findings to improve patient care."

Dr. Michael Pollak wins Canadian Cancer Society award

Dr. Michael Pollak, Director of Cancer Prevention at the Segal Cancer Centre, and holder of the Alexander Goldfarb Chair at McGill, has been awarded the [Canadian Cancer Society's O. Harold Warwick Prize](#) for his contributions to research on cancer control in Canada.

"This award is greatly appreciated, not just in the context of my own work, but also because it represents recognition of the truly excellent cancer research that is being done at the JGH, LDI and McGill, even at a time when resources are at a premium," said Dr. Pollak.

Treating patients while undertaking basic laboratory research, population studies, and clinical trials, he investigates prevention and treatment for cancers in general, as opposed to honing in on a particular anatomical site. He argues that global efforts to prevent cancer need to be advanced because cancer treatments are not always successful and are often very costly, and unavailable in the developing world.

"Everyone is at risk of cancer, but it has been estimated that by simply applying the knowledge we have in a concerted fashion we could reduce cancer, overall, by 25 %." he says. "For example, cervical cancer can be prevented with an HPV vaccine. We can predict a genetic predisposition in some cases, and take preventive action such as removing the at-risk organ, as with ovarian cancer. Not smoking, or quitting smoking, has a huge impact on preventing lung cancer."

Among the highlights of Dr. Pollak's career is a paper, published in *Science* in 1998, which showed that the risk of prostate cancer varies with the level of circulating insulin-like growth factor. This was one of the first studies to implicate peptide hormones in cancer biology, and is among the most-cited Canadian contributions to global cancer research. Subsequent work has shown that many cancers can be growth-stimulated by hormones. As the levels of these hormones vary with genetic, dietary, and lifestyle factors known to influence cancer risk, this line of research provides clues for novel cancer prevention and treatment strategies.

Another topic under study by Dr. Pollak's research group concerns hormonal control of energy metabolism by cancer cells. When cancer cells behave aggressively, their energy requirements are high, and they can become more sensitive than normal cells to treatment strategies that interfere with the use of compounds such as glucose to generate energy.

Honours for LDI

Dr. Mark Wainberg, head of HIV/AIDS research at the LDI and Director of the McGill AIDS Centre, was honoured with the Canadian Institutes of Health Research and *Canadian Medical Association Journal* 2012 Top Canadian Achievements in Health Research Award. Dr. Wainberg was cited for his role in the discovery of the anti-retroviral drug 3TC, and for his continuing contribution to understanding AIDS on the medical, epidemiological, and political levels. Dr. Wainberg was also the recipient of the Premio Venezia, awarded by the Italian Chamber of Commerce in Canada, for his collaborations with the Superior Health Institute of Rome in clinical trials that have been instrumental in the development of new drugs to fight HIV-related disease.

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Dr. Ernesto Schiffrin, Physician-in-Chief of the JGH and head of hemovascular research at the LDI, has been awarded the 2013 American Society of Hypertension's Distinguished Scientist Award for outstanding work in the field of hypertension. He was presented with the award at the ASH's Annual Scientific Meeting in San Francisco. Dr. Schiffrin currently serves as President of the International Society of Hypertension and is an editor of the American Heart Association journal *Hypertension*.

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Dr. Roderick McInnes, Director of the LDI, has been honoured with the Queen Elizabeth II Diamond Jubilee Medal, awarded to distinguished citizens who have contributed significantly to Canadian society. An internationally recognized geneticist, Dr. McInnes has made important discoveries leading to better understanding of the molecular basis of retinal and eye development, and to the identification of genes and processes associated with inherited retinal degenerations. Most recently, he and his collaborators identified an important protein required for learning and memory.

Scientists and trainees at the LDI are regularly recognized for their contributions on the national and international levels.

Student Cited for Best Poster

Oneeb Muhammad Mian, an MSc student in the hemovascular axis, was awarded best poster presentation in the cardiovascular and respiratory disease category for "T regulatory lymphocytes counteract angiotensin II induced vascular remodeling." at the 2013 Annual McGill Biomedical Graduate Conference.

LDI prominent at international AIDS symposium

Dr. Andrew Mouland is among the organizers of the 9th bi-annual International Retroviral Nucleocapsid Protein and Assembly Symposium to be held in Montreal, August 25 to 28. Dr. Mark Wainberg will present a keynote address. Among the world renowned scientists who will speak are the following members of the HIV/AIDS axis: Drs. Mouland, Chen Liang, Larry Kleiman, and Michael Laughrea.

The objective of this conference is to bring prominent researchers together to discuss evolving aspects of nucleocapsid protein function and assembly in retroviruses. The nucleocapsid protein represents an intriguing viral protein that is conserved in many retroviruses, as well as several other types of viruses. It is an essential viral factor involved in many aspects of the viral life cycle including viral assembly and budding, RNA chaperoning and transport, and in reverse transcription. Its role as a chaperone protein is perhaps its most important function as it promotes reverse transcription and coats the retroviral genomic RNAs. In the context of Gag, nucleocapsid promotes viral RNA assembly and dimerization and interacts with several host cell factors. It is therefore a prime target for anti-HIV-1 therapy.

“Because nucleocapsid plays such a critical role in various phases of the replication of the virus, researchers have been trying to identify small molecule compounds that could inhibit its activities,” explained Dr. Mouland. “Despite the existence of some thirty drugs to combat HIV, we still need new therapies to counter problems of resistance and toxicity.”

This conference has historically focused on the multiple roles of the nucleocapsid protein on retroviruses, which is involved in the synthesis, maintenance and integration of proviral DNA and in virus particle assembly. For this year’s meeting, the focus has been expanded to include the latest developments in viral RNA function, metabolism and trafficking, restriction factors, and the control of viral assembly.

[Click here for further information and registration.](#)

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New hope to resurrect anti-cancer drug

A pancreatic cancer patient being treated by Dr. Gerald Batist at the Segal Cancer Centre had a dire prognosis of one year to live, prior to joining a clinical trial for farnesyltransferase inhibitors (FTIs). Ten years later, she is in remission. This patient, however, stands out as an oddity, since FTIs proved to be a clinical failure and were subsequently abandoned by pharmaceutical developers.

“FTIs were very promising because they targeted mutated RAS, which is ubiquitous in many common cancers,” Dr. Batist explains. “However, we discovered that guanylation offered an alternate pathway that enabled the cancer to bypass the FTI. Our hypothesis is that this particular patient lacks that signaling pathway. If we can prove that guanylation is non-existent in a significant number of patients, FTIs could be resurrected as a very effective treatment.”

Dr. Batist doesn’t address cancer in the singular, but as a plural. “Cancers should really be redefined as a collection of rare diseases,” he asserts. This gets to the heart of personalized medicine, which aims to target the specific genetic mutation driving the run-away proliferation of malignant cells. The most effective, least toxic treatment can be ascertained by sequencing a tumor and identifying its underlying biology.

The LDI, which will inaugurate its Molecular Pathology Centre later this year, is partnering with the Moffitt Cancer Center in Tampa to collect tumor samples and build an extensive bio-bank where tissue can be sequenced for the purpose of determining genetic markers that could emerge as potential drug targets. This will help identify new drugs and repurpose existing ones, like FTI.

“Delving into the actual composition of a cancer to more accurately identify potential responders based on specific driver mutations lets us be far more effective in determining a treatment strategy,” he explains.

Abandoning a drug on the evidence of a failed clinical trial could well prove premature if more sophisticated screening and more comprehensive bio-banks can group patients according to common biomarkers. Exceptional responders – patients whose response to a particular treatment far exceeds expectations – are so common in cancer that the US National Cancer Institute is soliciting data that will help explain the phenomenon. Ultimately, this will reveal whether anecdotal evidence can be assembled to demonstrate unrecognized trends.

[News of exceptional responses was reported in *Nature*.](#)