



# Lady Davis Institute

## Research Newsletter



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### **\$21.1 million investment in personalized medicine for cancer**

\$21.1 million is being invested by the public and private sectors in a Personalized Medicine Partnership for Cancer (PMPC) to develop and implement clinical biomarkers and other personalized healthcare solutions to improve outcomes for cancer patients. The clinical driver behind this project is the Québec Clinical Research Organization in Cancer (Q-CROC), a multi-disciplinary network of clinicians, scientists, and other members of the medical community involved in clinical and translational cancer research. Q-CROC was co-founded by the Segal Cancer Centre.

Personalized medicine involves the use of patient-specific data to characterize disease subtype and to devise the optimal treatment plan. Among the projects supported through this partnership are state-of-the-art genomic, proteomic, bioinformatics and information technology platforms to develop and deploy novel biomarkers and targeted therapeutic strategies to treat lung, colon and breast cancers. The PMPC is a not-for-profit organization that aims at positioning Québec as a global leader in personalized medicine solutions for cancer patients.

“The rapid progress in clinical research enables us to decipher the underpinnings of cancer and to develop specific diagnostic tools and targeted drugs to treat specific subtypes of common cancers. It is critical that these new tools and medicines be deployed for the benefit of patients across Québec,” said Gerald Batist, Director of the Segal Cancer Center, and Co-director of Q-CROC. “While technology has been progressing rapidly, it is critical to prepare our healthcare system to integrate a wealth of new molecular information and educate professionals in the practice of personalized medicine.”

The broad network of partners and collaborators with expertise spanning molecular biology, genomics, proteomics, clinical management, pharmacoeconomics, ethics and information technology will deliver integrated solutions to be efficiently implemented in the healthcare system.

### **Researchers enjoy success in latest CIHR grant competition**

The following LDI researchers earned operating grants from the Canadian Institutes for Health Research (CIHR) after an intensive peer-review process:

Haim Abenheim to study the link between Cesarean deliveries and increased risk of bowel obstruction.

Laurent Azoulay to study the use of beta-blockers and the prevention of cancer-specific mortality.

Gerald Batist to explore novel strategies to selectively target tumor growth and chemo-sensitivity.

Colin Crist to look into the regulation of skeletal muscle stem cell activity.

Kristian Filion to study diabetes and the risk of incident cardiovascular disease.

Wilson Miller to examine responses and resistance to epigenetic therapy in hematological cancer.

Kostas Pantopoulos to study iron metabolism and cancer.

Prem Ponka to work on chelation, mobilization, and metabolism of stored iron.

Zeev Rosberger to address parental decision-making factors in giving HPV vaccines to their sons.

Hyman Schipper to examine a particular protein's role in aging and the on-set of Parkinson's disease.

Vicky Tagalakis to explore statin use and preventing recurrent venous thrombosis in the elderly.

Alexander Thiel to study non-invasive therapies for recovering speech in stroke patients.

Christel Renoux received a one-year bridge fund to launch her research into anti-epileptic medication and the risk of vascular incidents.

A Phase I proof of principle (POP) grant was awarded to Jonathan Afilalo for his research on a novel bio-marker for frailty. Lawrence Rosenberg received a Phase II POP grant for a novel drug therapy to restore natural insulin secretion in diabetes.

## SPECIAL PREVIEW – Fourth Annual Scientific Retreat, May 10, 2013

*The keynote speaker will be Dr. Brett Finlay of the University of British Columbia, one of the world's leading infectious disease researchers.*

*Trainees will give oral and poster presentations.*

*[See the program and register on-line.](#)*

*Among the principal investigators to present a talk are:*

### Dr. Antonis Koromilas on Cancer

Dr. Antonis Koromilas' lab is dedicated to understanding how normal cells transform into tumors. In particular, he is investigating the critical process within the cell that produces proteins. In a cancer cell, the process is deregulated, producing proteins that ought not to be present, or be present in very low amounts. He is trying to uncover how the cell begins to produce these rogue proteins and whether targeting this process might impede the development of cancer. The objective is to understand how to prevent the synthesis of malignant proteins without affecting healthy ones, which would mean that treatments could be more effective and provoke less side effects.

The LDI Scientific Retreat is an important opportunity to foster scientific interactions between faculty investigators and trainees.

“It takes a high quantity of a drug to kill cancerous cells, which is the conventional approach. But this can bring about serious side effects while taking a toll on healthy cells,” explains Dr. Koromilas. “It could be much better for the patient if we can develop drugs that stop the synthesis of rogue proteins.” Other research has demonstrated that once targeted tumor cells have stopped proliferating, the body's natural immune system has the potential to eliminate non-growing tumor cells.

Exploring genetic and pharmacological approaches, he is looking at the mechanisms for inducing senescence by targeting the machinery of protein synthesis. The drugs that are being examined are still in a pre-clinical phase and are not yet ready to be tried in humans, but they are exhibiting potential in both *in vivo* and *in vitro* experiments. A refined understanding of the mechanisms by which such inhibitors work holds the promise of enhancing targeting capabilities and developing their therapeutic potential.

Because the mechanism of protein synthesis that Dr. Koromilas is investigating occurs in all cancers, this avenue of inquiry should have broad applications in treating tumors.

### Dr. Pierre Ernst on Epidemiology

By design and necessity, clinical trials test new drugs on small and carefully selected population samples. They do not include, as Dr. Pierre Ernst emphasizes, “huge numbers of people who actually take the drug, often over an extended period, and who may have significant co-morbidities.” Hence, safety issues may only be revealed once a drug has a lengthy market history. This is the rationale behind the [Canadian Network for Observational Drug Effect Studies \(CNODES\)](#), a multi-centre national initiative of Health Canada headquartered at the LDI.

“You test a drug on 5,000 people, but then you prescribe it to 5 million people, which allows more opportunity for safety issues to emerge,” he goes on. “Most drugs involve a trade-off between adverse effects and benefit. Some of the adverse effects we find are relatively rare and may only impact very specific segments of the population to whom a drug is prescribed.”

With access to multiple national and international patient data bases, CNODES research teams employ sophisticated epidemiological methods to describe and explain associations between drugs and safety outcomes.

CNODES, headquartered at the LDI, can complete the analysis of a question concerning the safety of a medication and have a report ready within about six months.

“At CNODES, we can complete the analysis of a question concerning the safety of a medication and have a report ready within about six months,” said Dr. Ernst, who, as well as being an epidemiologist, is a clinical respirologist at the Jewish General Hospital.

The [first major CNODES study](#), recently published in *BMJ*, found that patients taking high potency statins were more likely to develop acute kidney injury than subjects receiving lower potency statins. Other ongoing projects include the risk of pneumonia in users of proton pump inhibitors, and the risk of diabetic ketoacidosis in users of newer anti-psychotic medications.

“We have to be careful when reaching conclusions because some things do occur by chance,” he cautions. “It is easy to do epidemiology wrong. When you're giving effective medication to the sickest people, they may appear to have more adverse effects since they are sicker than patients not getting such medications. The methodology is very complex because you have to tease out the cause and effect.”

## Dr. Joel Paris on psycho-social aspects of disease

Dr. Joel Paris, Past President of the Association for Research on Personality Disorders, has devoted twenty years to researching the biological and psychosocial causes, and the long-term outcomes, of borderline personality disorder, a particularly severe condition which can lead patients to attempt suicide, self-mutilation, substance abuse, and significant mood swings.

Everybody's personality fluctuates along a continuum. Generally speaking, a disorder begins where behaviour interferes with an individual's ability to function, hold a job, and maintain relationships.

"Years ago we thought of borderline personality disorder as untreatable," he said. "However, employing the proper methods, we have discovered that we can achieve considerable success with our patients, many of whom benefit from a degree of structure, including specific efforts to regulate their emotional life.

"Years ago we thought of borderline personality disorder as untreatable," Dr. Paris said. "However, employing the proper methods, we have discovered that we can achieve considerable success with patients."

"While pharmaceuticals are mostly ineffective, we have specialized clinics that provide the appropriate psychotherapy. Compliance is difficult because the process takes a lot of time and effort, and the more difficult a person is, the less compliant they tend to be. Younger people who are in school and may have stable relationships usually have better prognoses than individuals who have been on welfare for years and lack structure or reasonable life goals."

Along with his research at the LDI, Dr. Paris maintains a clinical practice at the JGH, teaches at McGill, and is editor-in-chief of the *Canadian Journal of Psychiatry*. Over forty years he has witnessed the continued marginalization of psychiatry. It remains stigmatized, both as a profession and from the patient's perspective. While the connections between mental illness and neurobiological changes have helped, therapeutic applications for genetic factors are, thus far, non-existent.

"The whole field of psychiatry scares people," he said. "How do you separate yourself from a psychiatric patient? It's easy when they're psychotic, but otherwise, we all have a fear of mental illness that causes people to be shunned in many circumstances. Improvement is slow to come."

## Dr. Anne Gatignol on HIV/AIDS

Dr. Anne Gatignol is searching for a pathway to halt or reverse the replication of the human immunodeficiency virus (HIV) in an effort to achieve a "functional cure" for AIDS, something which permanently suppresses the disease, even if it falls short of completely eliminating its presence.

Her focus is on how cells respond to HIV infection, distinguishing between those mechanisms that enhance or inhibit replication of the virus. She is exploring how components of the RNA interference machinery affect HIV and is developing RNA-based technologies to target HIV and prevent it from spreading.

"I am trying to understand the molecular interactions between the virus and the cell," she explains. Once the virus enters the cell, it exploits proteins within the cell in order to proliferate, integrating into the chromosome, where it is either latent or expresses itself and forms RNA, which can go on to arrange itself to produce HIV particles.

"We have found mechanisms that counteract the cellular reaction," she said. "In some cells, such as astrocytes, replication is blocked, while in others, replication occurs. We study which proteins are responsible for determining how the virus behaves. If we can isolate those proteins which inhibit replication, we may have the means to stop the progress of HIV."

RNA interference is a mechanism by which the cell regulates itself. Dr.

Gatignol is studying whether HIV is capable of influencing this process, or whether it could be RNA interference which might influence HIV's capacity to replicate. This gets to the heart of interaction between the virus and the cells it invades.

"If we can enhance this mechanism, it could be used to block the virus. Also, because of the variety of cellular functions controlled by RNA interference, we believe this could account for the co-morbidities that frequently accompany HIV, such as premature aging, cardiovascular disease, and some cancers," she said. "We have discovered some relatively minor modifications which could have significant impacts over time."

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## LDI / TD Bank Studentship Awards

Three Master's and three Doctoral candidates, who rank among the very best students at the LDI, have been awarded \$10,000 scholarships thanks to the generosity and vision of TD. These young scientists represent the breadth and creativity of research underway at the LDI.

The MSc winners are Leanne DeKock, who is exploring cancer genetics; Sylvia Josephy, who is trying to identify regulatory mechanisms of long-term memory; and Kristen Marcellus, who is investigating Alzheimer's disease.

The PhD winners are Elaleh Ahmadzadeh, who is looking at an aspect of resistance in triple negative breast cancer; Bahar Kasaai, who is studying the genetics and biomechanics of vascular development; and Luis Negro Silva, who is examining the role of arsenic in the accumulation of fatty plaques in arteries.

"The TD program has had a major impact on the LDI," affirmed Dr. Roderick McInnes, the Institute's Director. "At present, as research funding decreases nationally and provincially, the importance of the TD Studentship has increased greatly."

## LDI student is FRQS lauréat

Michelle Roseman's study "[Reporting of Conflict of Interest from Drug Trials in Cochrane Reviews: A Crosssectional Study.](#)" published in *BMJ* earned her selection as ÉTUDIANT-CHERCHEUR ÉTOILE for March by the FRQS. Roseman, a McGill medical student, raised important questions about how conflicts of interest between researchers and drug manufacturers may influence findings presented in systematic reviews and meta-analyses. The issue is critical because, when such information is not provided, users of evidence reviews are not able to truly evaluate the degree of risk in a drug trial. Indeed, there is robust empirical evidence that conflicts of interest can influence how results of drug trials are reported and interpreted. Co-authored with Dr. Brett Thombs, the study was highlighted as the LDI Paper of the Month in October 2012.

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## Study shows majority of smokers re-light following heart attack

A new study led by Dr. Mark Eisenberg, a cardiologist and epidemiologist at the Lady Davis Institute reveals that two-thirds of middle aged smokers who have been hospitalized for acute myocardial infarction resume smoking within twelve months, despite being treated with bupropion (sold as Zyban™), which is prescribed to help those trying to quit because of its demonstrated capacity to reduce nicotine cravings and withdrawal symptoms without increasing heart rate or blood pressure the way nicotine replacement therapies will. This surprising finding appears in the [Journal of the American College of Cardiology](#).

"Conventional wisdom was that suffering a heart attack served as a significant wake-up call inspiring smokers to quit. But," Dr. Eisenberg is quick to add, "nobody had ever studied this population a year after the event. In fact, it may be that even more than two-thirds return to smoking, because those who agreed to participate in our study were more motivated than those who didn't want to be involved in a cessation trial."

"There is no escaping the power of a nicotine addiction combined with the social and behavioural aspects of smoking," said Dr. Mark Eisenberg.

The study used a randomized sample of 392 patients, whose median age was 54 and who smoked an average of 23 cigarettes per day. Six months after beginning treatment, smoking abstinence was 39% in the bupropion group and 33% in the placebo group. At twelve months, the prevailing abstinence rates were 37% and 32%, respectively. One positive outcome among the persistent smokers was a dramatic reduction in their daily cigarette consumption to an average of eight per day, with no difference between groups.

"Notwithstanding the relapse rate we observed, the patients' significant decrease in consumption suggests that a subset could be effectively re-targeted for smoking cessation therapy," Dr. Eisenberg pointed out. "While any reduction is positive, the health benefits of complete abstinence are significantly higher than even modest smoking. However, there is no escaping the power of a nicotine addiction combined with the social and behavioural aspects of smoking. It is very tough to quit and there is no magic bullet, in the form of a pill, that will make quitting easy."