HGJ | JGH

Lady Davis Institute
Research Newsletter

McGill

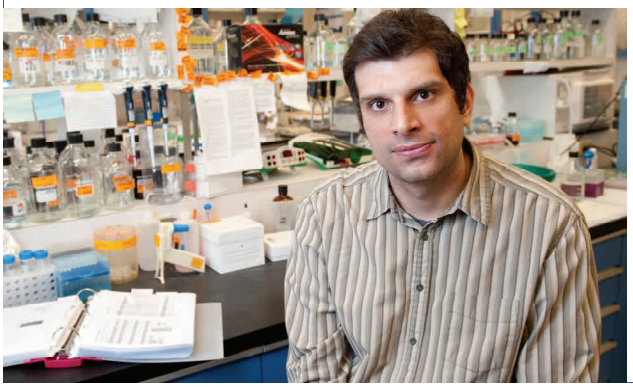
July 2017 Vol. 6 No. 4

Award for Excellence in Basic Research

Dr. Ivan Topisirovic of the Cancer Axis is the 2017 recipient of the Award for Excellence in Fundamental Research at the Lady Davis Institute. Dr. Topisirovic has been a principal investigator at the LDI and Assistant Professor in the Faculty of Medicine at McGill University since 2011.

He is a recipient of several awards including the Governor General Award for Leukemia Research, the CIHR Young Investigator Award and honorary membership in the Serbian Society for Molecular Biology. Dr. Topisirovic's current research focuses on uncovering the differences between the mechanisms that coordinate translatomes and metabolomes in normal versus cancer cells, with the aim to identify therapeutically exploitable metabolic vulnerabilities of neoplasia.

His laboratory is interested in studying the molecular mechanisms which underlie the role of mRNA translation in modulating growth (increase in cell volume) and proliferation (increase in cell number) of normal and malignant cells. Rates of cell growth and proliferation are modulated by signaling pathways in response to various extracellular stimuli and intracellular cues. The main focus of his studies will be to determine how the mammalian target of rapamycin (mTOR) – a pathway that is frequently disregulated in human diseases such as cancer, diabetes and heart disease – affects mRNA translational influence on cell growth and proliferation. He aims to elucidate post-transcriptional regulatory networks which play a role in coordinating the expression of genes that regulate cell growth and proliferation and investigate the mechanisms which lead to aberrant function of these networks in human disease.



Award for Excellence in Clinical Research

The 2017 Award of Excellence in Clinical Research was awarded to **Dr. Robert Platt** of the Epidemiology Axis. The inaugural Albert Boehringer I Chair in Pharmacoepidemiology and Professor in the departments of Pediatrics and of Epidemiology, Biostatistics and Occupational Health at McGill, Dr. Platt has been a principal investigator with the Canadian Network for Observational Drug Effect Studies (CNODES) at the LDI since its inception in 2011.

"I am particularly interested in developing more precise statistical methods so that we have the capacity to extract more exact information from the data at our disposal," Dr. Platt explains. "As medicine gets better at managing more complex comorbidities, we have to develop more sophisticated methodologies so that we are sure to compare like-with-like in order to be clear about the effects that drugs may have on different patient populations. Our challenge is to develop the most accurate statistical tools."

CNODES offers the opportunity to review drug effects on far larger samples of users than could ever be possible in a clinical trial. Big data collected over years is parsed and analyzed in order to ascertain whether any subsets of users may be susceptible to unexpected side effects that may only become evident through extensive usage.

"There is a real need to follow drugs for long periods of time in broad populations so that we can refine those circumstances where they will do the most good and those where there may be potential for harm," he says. "It is important for clinicians to be aware of the risks when they prescribe a drug so as to balance the possibility for an adverse effect with the benefits for the condition the drug is meant to treat."

He stresses the quality of the investigators and investigations underway at the LDI, "This is a remarkably collaborative environment in which to conduct research."

8th Annual Scientific Retreat

More than 300 researchers, trainees, and staff attended the 8th annual LDI Scientific Retreat. This year's keynote speakers were **Dr. Peter Zandstra**, Senior Scientist at the Institute of Biomaterials and Miomedical Engineering, Associate Director for Research & Development at the Ontario Institute for Regenerative Medicine, and Professor at the University of Toronto, who spoke on stem cell bioengineering; and **Dr. Jill Baumgartner**, Assistant Professor at the Institute for Health and Social Policy at McGill University, who spoke about her field work on air quality in China.

Bianca Di Iorio, (right) who is responsible for human resources at the LDI, was recognized as Administrative Employee of the Year.

Trainees are given the opportunity to present their research during the retreat. First Prize for oral presentation was awarded to Valerio Piscopo of Dr. Roderick McInnes' lab. Second Prize went to John Morris of Dr. Brent Richards' lab. Recognition for best posters went to Devin Abrahami (Dr. Laurent Azoulay's group), Suellen Coelho (Dr. Ernesto Schiffrin's lab), Husam Khaled (Dr. Alexandre Orthwein's lab), Tatiana Shorstova (Dr. Michael Witcher's lab), and Antoine Caillon (Dr. Schiffrin's lab).

Prepared by the Research Communications Office, Lady Davis Institute at the Jewish General Hospital. Any suggestions with respect to content are welcome.

To submit information or for media enquiries, contact:
Tod Hoffman at: thoffman@jgh.mcgill.ca;
514-340-8222, ext. 28661

The role of immune response in hypertension

A new paper by **Dr. Ernesto Schiffrin** advances understanding of how hypertension, and the ensuing vascular damage, develops by exploring the role of the immune response. The paper was published in *Circulation*. It was highlighted in *Nature Reviews Nephrology* to bring it to broad attention in the scientific community.

The investigators set out to test the hypothesis that gamma delta T lymphocytes play a key role in the development of hypertension, vascular injury, and inflammation.

"These gamma delta T cells, which account for only 1 to 4% of circulating lymphocytes, are unconventional T lymphocytes. They have a potential to bridge the innate and the adaptive immune system and, therefore, they might help us to understand some of the mechanisms by which the immune system is triggered to initiate blood pressure elevation, and to sustaining it, which characterizes hypertension," said Dr. Schiffrin by way of explaining why this was a significant area of inquiry.

Having demonstrated that gamma delta T cells are critical to blood pressure response to angiotensin II in an animal model, Dr. Schiffrin sought translational evidence in humans. Looking at whole blood TCR gamma constant region gene expression levels from 206 patients with a full range of blood pressures, he found 12% of variance in blood pressure is explained by gamma delta T cells, once correction for age and sex was factored into the equation, which is very significant for a small population of cells. This demonstrates a correlation between what was found in the animal model and humans. Thus, the finding represents an important breakthrough that promises to be useful both diagnostically and therapeutically.

"We should eventually be able to develop a diagnostic test for predisposition to hypertension, and thereafter a new therapeutic approach to blood pressure elevation and to vascular damage," said Dr. Schiffrin.

Immune modulation is becoming central in therapeutic development and, Dr. Schiffrin believes, this could be promising in cardiovascular disease, despite some reluctance to pursue such therapies over concern for potential side effects of long-term immune suppression.

New guideline recommends against routine screening for hepatitis C

The Canadian Task Force on Preventive Health Care has recommended against screening for chronic hepatitis C virus (HCV) in adults at low risk. Details were published in *CMAJ (Canadian Medical Association Journal)*.

"Given the lack of direct evidence that mass screening is beneficial, and that patients identified by screening will either never develop symptoms of hepatitis C or will remain well for decades after infection, we have recommended against screening for HCV in adults who are not at elevated risk," said **Dr. Roland Grad**, chair of the guideline work group. "This was not an easy decision, but a comprehensive assessment of the evidence led us to conclude that the disadvantages – over-diagnosis and the costs to the health care system of screening everybody regardless of risk profile – outweigh the benefit of the few additional cases that may be diagnosed."

The recommendation is based on the following:

- the low prevalence of hepatitis C in Canada, roughly 6 to 7 per 1000 adults;
- the lack of direct evidence on the benefits and harms of screening;
- many with chronic HCV identified by screening would not have timely access to anti-viral treatment;
- the potential for harms caused by screening could include labeling, stigma, and difficulties with insurance;
- the low risk of household and sexual transmission of HCV among individuals not at elevated risk, as well as the low risk of transmission through blood products given routine screening of blood and organs; and
- the anticipated increase in harm resulting from diagnosing and treating individuals who screen positive, but would have never developed HCV-related disease during their lifetime.

The Public Health Agency of Canada does recommend screening for those at increased risk, including people with a history of intravenous drug use, people engaged in high risk sexual behavior, those who have spent extensive time in countries where HCV is prevalent or received medical treatments in such countries, as well as pregnant women.

Listen to a podcast: https://soundcloud.com/cmajpodcasts/161521-guide

Neurofeedback: an effective placebo treatment?

Dr. Amir Raz, Canada Research Chair in the Cognitive Neuroscience of Attention, argues that, although neurofeedback seems to work, the therapeutic benefits largely stem from placebo effects rather than the brain-based mechanisms that practitioners suggest. His paper was published in *Brain*.

"Some people suffering from attention deficit disorders, depression, and insomnia, among other conditions, have turned to neurofeedback out of desperation," he explains. "Of the thousands of papers on the subject, barely half a dozen include adequate placebo controls and implement a double-blind procedure. Of those that do, the intervention and the placebo condition affect behaviour comparably. In other words, only sparse data exist to support claims of brain mechanisms in neurofeedback".

Neurofeedback is a non-invasive procedure where participants watch their brain activity in real-time. This technique promises to give patients control of a particular brain signal and, in turn, improve related symptoms. Very little evidence, however, suggests that regulating a particular brain signal leads to the expected changes in behaviour.

Neurofeedback is highly profitable, with a proliferation of clinics offering treatment that can cost anywhere from $4,000 to $10,000 for between a dozen and forty sessions. The field is largely free of regulatory controls. Many patients turn to neurofeedback after conventional medicine has not provided adequate relief. The procedure is also being marketed to people seeking greater concentration and to athletes looking to enhance their performance.

"While almost six decades of research has focused on understanding the brain-based mechanisms behind neurofeedback, very few studies focus on the underlying psychology at play," said Robert Thibault, a doctoral candidate. "Meanwhile, it appears that placebo effects likely drive the major benefits of this contentious therapeutic option".

See Dr. Raz's TEDx Talk on the placebo effect, "When can deception be good for you?"

Adaptor protein may be new target to activate anti-tumor immunity

Tyrosine kinases are a class of proteins that are often disregulated in breast cancers with poor outcomes. Several drugs targeting these proteins are approved or in clinical trials. While these drugs are initially effective, breast cancers rapidly develop resistance. Therapeutic resistance is due, in part, to the fact that many kinases converge on a common group of signaling molecules, called adaptor proteins, to elicit their tumorigenic properties. To overcome this effect, it may be necessary to target these adaptor proteins. Exciting new research published by **Dr. Josie Ursini-Siegel** and her research team in *Nature Communications* has identified the ShcA adaptor protein as a critical signaling molecule that plays an essential role in allowing breast tumors to escape the tumoricidal properties of the host immune system.

"We pinpointed a particular domain within this protein that is important in blocking the ability of a tumor to evade an immune response," Dr. Ursini-Siegel said. Her research has further shown that inhibiting the function of the ShcA adaptor protein could sensitize breast tumors to immunotherapies.

Nobody has yet considered targeting adaptor proteins because they don't display any enzymatic activity. "Trading a specific approach that targets individual kinases for a broader approach targeting adaptors may lead to more durable therapeutic responses and less resistance," she speculates. "The difficulty with this approach could be in getting enough inhibitor to the tumor site to be effective."

ShcA regulates a tumor's capacity to evade an immune response, which is essential for cancer to grow. No tumor survives without co-opting the immune system. If that process can be interrupted, the potential exists to have a greater therapeutic response.

- **Dr. Alexandre Orthwein was** granted a new Canada Research Chair (Tier 2) in Genome Stability and Haematological Malignancies. CRCs are granted to outstanding researchers acknowledged by their peers as world leaders in their fields.

- **Dr. Chen Liang** has been promoted to full Professor in the Department of Medicine at McGill University.

ADT not associated with Alzheimer's in patients with prostate cancer

A large-scale, population based study led by **Dr. Laurent Azoulay** has concluded that the use of androgen deprivation therapy (ADT) to treat advanced prostate cancer is not associated with an increased risk of Alzheimer disease. This result, published in the *Journal of Clinical Oncology* is important because it soothes fears raised by an earlier, very controversial study that asserted a significant and troubling connection.

ADT is a form of chemical castration that is prescribed to eliminate testosterone in men with advanced prostate cancer because the disease is fuelled by testosterone. It is widely used and so effective at halting the progress of the cancer that men are often treated with ADT for many years.

"Cognitive impairment is a known side effect of declining testosterone, in general, so it is naturally of concern with ADT," explains Dr. Azoulay. "However, there is a significant difference between cognitive limitations and the biological mechanisms associated with dementia."

Dr. Azoulay and Farzin Khosrow-Khavar, a doctoral candidate under his supervision, discovered some troubling methodological deficiencies in the studies that found the association. Thus, they undertook to study a cohort of nearly 31,000 men who were newly diagnosed with nonmetastatic prostate cancer over a twenty-seven year period from the United Kingdom's Clinical Practice Research Datalink, one of the largest data bases of its kind.

"Our group was alarmed to see the earlier study that proposed that ADT doubled the risk of Alzheimer disease," said Dr. Azoulay. "Such a dramatic finding called for further investigation and we found some important methodological problems in the study. Because ADT is so often given to older men, very careful statistical analysis is required to assert a causal relationship. Once we applied the correct methodology we found no statistically significant association. However, we would encourage additional studies to confirm our findings."

The American Society of Clinical Oncology (ASCO) was quick to highlight this study because of its immediate clinical importance.