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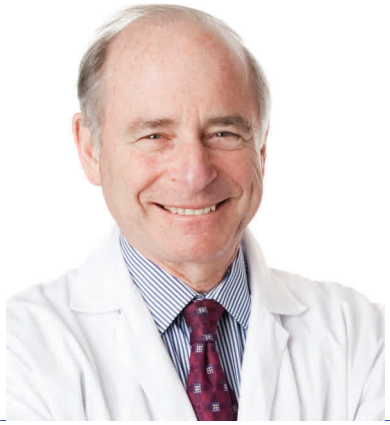
Ernesto Schiffrin awarded Prix Galien Canada – Research Award

Dr. Ernesto Schiffrin, Canada Research Chair in Hypertension and Vascular Research at the Lady Davis Institute, Physician-in-Chief at the Jewish General Hospital, Professor and Vice-Chair (Research) in the Department of Medicine at McGill University has been conferred the 2017 Prix Galien Canada – Research Award.

The Prix Galien is the most prestigious award in the field of Canadian pharmaceutical research and innovation. Referred to as the Nobel Prize of pharmaceutical research, it recognizes the efforts and achievements of pharmaceutical research and development and is presented to the researcher judged to have made the most significant contribution to pharmaceutical research in Canada.

"I feel honored and delighted at being chosen as this year's recipient of the Prix Galien Canada," said Dr. Schiffrin. "I have been fortunate that my work and that of my team has allowed the development of biomarkers and pharmaceuticals that contribute to improve outcomes of patients with hypertension and heart failure."

Dr. Schiffrin studies mechanisms and treatment of hypertension, vascular intracellular signaling and oxidative stress and remodeling of resistance arteries in animals and humans with hypertension, diabetes and chronic kidney disease.



Largest genetic study identifies potential targets for osteoporosis

The largest study ever conducted on the genetics of common age-related bone disease has resulted in the identification of 153 new gene variants associated with the loss of bone mineral density, the strongest clinical risk factor for osteoporosis, and a frequent cause of fractures. This effectively triples the number of genes known to be implicated in osteoporosis, and the new gene variants account for 12% of the heritability of the disease, which is double the previous level.

"There is a strong inherited component with bone health, but osteoporosis often goes undetected until a fracture occurs," said **Dr. Brent Richards** of the Centre for Clinical Epidemiology, and one of the senior authors of the paper, which appears in *Nature Genetics*.

Particularly exciting is the discovery of a previously unknown link between the gene GPC6 and osteoporosis.

The genome wide study involved more than 140,000 individuals whose records are included in the UK Biobank database. A qualitative ultrasound of the heel was employed to measure for bone mineral density.

"Trying to identify causal factors at novel loci, we were able to implicate GPC6 as a determinant of bone mineral density," explains John Morris, a doctoral candidate in human genetics being supervised by Dr. Richards. "We found that knocking out this gene in an animal model resulted in increased bone density. GPC6 is a cell surface protein making it easier to target, enhancing the prospects for successful drug development."

The sheer statistical power of this study is impressive, explaining why so many new gene variants were revealed. Dr. Richards' group is part of the Genetic Factors of Osteoporosis Consortium, which includes nearly every major bone density research team in the world.

CIHR Awards

Dr. Stéphane Richard received a CIHR Foundation Grant worth $3.5 million over seven years for "Molecular and Genetic Analysis of Arginine Methylation and RNA Binding proteins in Health and Disease." He was also awarded a project grant, which he was required to decline.

LDI researchers awarded project grants in the most recent round of CIHR funding are:

Dr. Jonathan Afilalo, $1.1 million for a four-year clinical study, "Protein and Exercise to Reverse Frailty in Older Men and women undergoing Transcatheter Aortic Valve Replacement: The PERFORM-TAVR Trial."

Dr. Mark Basik, $952,000 over five years for "Innovative pre-clinical models to overcome drug resistance in triple negative breast cancer."

Dr. Andréa LeBlanc, $925,000 over five years for "Validation of the Nlrp1-Casp1-Casp6 pathway as an early therapeutic target of age-dependent cognitive impairment and Alzheimer Disease."

Dr Alexandre Orthwein, $850,000 over five years for "Regulation of DNA double-strand break repair pathways in multiple myeloma."

Dr. Volker Blank, $800,000 over five years for "Regulation and function of NFE2L3: linking transcription factor activity to tumorigenesis."

Dr. Kristian Filion, $175,000 over two years for "Tramadol and the Risk of Adverse Cardiovascular Events: A Population-based Study."

Dr. Antonis Koromilas, $100,000 for one year for "Mechanisms and therapeutic implications of PKR and eIF2 phosphorylation in HER2 breast tumor suppression."

Dr. Michael Pollak, $100,000 for one year for "Direct targeting of translation machinery in cancer treatment."

Dr. Brett Thombs, $75,000 for one year for "Improving Depression Screening in Geriatric Patients by Reducing Bias and Generating Individualized Accuracy Estimates: An Individual Patient Data Meta-Analysis of the Geriatric Depression Scale (GDS)."

FRQS Grants

Ten LDI researchers were granted salary awards funding from the FRQS:

Dr. Céline Gélinas, Chercheur-boursier Senior for "Innovation dans l'évaluation et la gestion de la douleur dans les unités de soins intensifs adultes."

Dr. Brent Richards, Chercheur-boursier clinicien Senior for "La génomique de l'ostéoporose et de la vitamine D: Des corrélations à la causalité jusqu'à l'application Clinique."

Dr. Brett Thombs Chercheur-boursier Senior for "L'amélioration de la santé mentale et la qualité de vie des Canadiens souffrant de maladies chroniques: des preuves empiriques à l'action."

Dr. Josie Ursini-Siegel Chercheur-boursier Senior for "Les réseaux de signalisation des récepteurs tyrosine kinase gouvernant la progression du cancer du sein."

Dr. Kristian Filion, Chercheur-boursier Junior 2 for "Pharmacoépidémiologie cardiométabolique : Une évaluation de l'innocuité des médicaments à l'échelle population."

Dr. Yves Longtin, Chercheur-boursier clinicien Junior 2 for "Une approche globale et intégrative pour mieux comprendre et prévenir les infections associées au C. difficile."

Dr. Ivan Topisirovic Chercheur-boursier Junior 2 for "Rôles de la synthèse protéique et du métabolisme énergétique dans le cancer."

Dr. Michael Witcher Chercheur-boursier Junior 2 for "Dérèglement épigénétique dans le cancer du sein."

Dr. Arezu Jahani-Asl, Chercheur-boursier Junior 1 for "Glioblastome Pathogenesis: cibles et thérapies moléculaires."

Dr. Soham Rej, Chercheur-boursier clinicien Junior 1 for "Comorbidité Physique chez les Personnes Âgées avec Trouble Bipolaire: Investigations Pharmaco-épidémiologique. "

Dr. Roderick McInnes, Director of the Lady Davis Institute and Acting President of the Canadian Institutes of Health Research, is being honoured with the 2017 Distinguished Scientist Award by the Canadian Society for Clinical Investigation (CSCI). Dr. McInnes, who holds the Alva Chair in Human Genetics and a Canada Research Chair in Neurogenetics at McGill University, is being recognized for significant and innovative contributions in the field of human genetics.

"It is a particular honour to receive the CSCI's Distinguished Scientist Award because of the Society's focus on the physician scientist, who plays such a crucial role in building the bridges between bench and bedside," said Dr. McInnes. "The CSCI does so much to promote clinical research, which is the key to advancing medicine and improving health care."

Dr. McInnes will receive the Award at the CSCI's annual meeting this month in Toronto, where he will deliver a keynote address.

Le Spécialiste, the official magazine of the Fédération des médecins spécialistes du Québec, profiled **Dr. Susan Kahn**, head of the Canadian Clinical Research Network on Venous Thromboemolism (CanVECTOR) and Director of the Centre of Excellence in Thrombosis and Anticoagulation Care (CETAC) at the Jewish General Hospital, in its "Great Names in Quebec Medicine" series. Download the September issue here.

Searching for the "signature" causes of BRCAness in breast cancer

Breast cancer cells with defects in the DNA damage repair genes BRCA1 and BRCA2 have a mutational signature, known as "Signature 3." But not all breast tumor cells exhibiting Signature 3 have BRCA1 or BRCA2 mutations. Therefore, some consider Signature 3 a biomarker for "BRCAness," a sign of a breakdown in BRCA-related DNA repair (a process called homologous recombination), in general, and not BRCA damage, in particular.

An international team featuring **Dr. William Foulkes**, reporting in *Nature Genetics*, hint that mutational signatures like Signature 3 might fuel a precision medicine approach that uses a tumor's full scope of mutations to guide risk and treatment decisions, instead of focusing on individual genes.

"The defects associated with Signature 3 may make patients more responsive to certain treatments," said Dr. Foulkes, a cancer geneticist at the LDI and Segal Cancer Centre. "By undertaking a comprehensive genomic and epigenomic analysis of breast cancer, we have identified alterations that were not previously known to be associated with Signature 3. We are also better able to determine whether certain types of genetic variants are associated with disease, as opposed to simply being innocent bystanders."

And what of Signature 3's clinical utility? The team found that they could combine the signature's presence or absence in breast cancer cells with other data to classify rare BRCA1 and BRCA2 mutations as harmful or not, a finding they noted needs to be investigated further. The researchers also suggested that Signature 3 might one day factor into treatment decisions for women with breast cancer, or help guide development of future "BRCAness"-targeting therapies.

Dr. William Foulkes, at left

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Exploration of Gas6 as a target in VTE therapy

As a Centre for Excellence in Thrombosis and Anti-coagulation Care, the Jewish General Hospital and Lady Davis Institute are leading the search for improved and novel therapies for patients with venous thrombo-embolism (VTE). Anticoagulants have been the standard of care for VTE, however their association with severe bleeding makes them an imperfect remedy.

Dr. Mark Blostein and Dr. Catherine Lemarie explore the potential of manipulating the protein Gas6 to better control blood clots. In their most recent paper, published in *Arteriosclerosis, Thrombosis, and Vascular Biology*, they show that Gas6 is required for the recruitment of inflammatory white cells in the clot. They determine that reducing Gas6 undermines this process.

"Our lab is interested in delving down into the cellular components of VTE in order to discover alternative treatments that will minimize the complications of VTE and the use of blood thinners," Dr. Blostein explains.

"Our hypothesis is that the development of an inhibitor to Gas6 will interfere with the accumulation of white cells that are contributors to the damage caused by VTE, including post-thrombotic syndrome, chronic lung disease, and death from pulmonary embolism. It has been shown in animal models that targeting Gas6 does not cause bleeding, making it promising for adjuvant therapy to anticoagulants that may have a positive impact on the long-term complications of VTE."

The paper concludes, "Deciphering the role of Gas6 and precise function of inflammatory monocytes in venous thrombosis occurrence can be a powerful tool for the identification of new targets for future antithrombotic therapy."

An editorial accompanying this paper cites several of Dr. Blostein's earlier publications as "milestones" in the discoveries of Gas6's signaling function in thrombosis.

Dr. Blostein's research is part of the national Canadian Venous Thromboembolism Clinical Trials and Outcomes Research (CanVECTOR) network, headed by Dr. Susan Kahn, which conducts basic and clinical research in VTE.

Two distinct mechanisms identified in classical Hodgkin's lymphoma

In a paper published in *Laboratory Investigation*, **Dr. Hans Knecht** identifies two distinct mechanisms that lead to mononuclear Hodgkin cells and their progression to multinucleated Reed-Sternberg cells, the diagnostic cells of classical Hodgkin's lymphoma.

Employing a unique combined quantitative 3D TRF2-telomere immune fluorescent *in situ* hybridization technique, he revealed: a) massive attrition of telomere signals and a considerable increase of TRF2 (telomere repeat binding factor 2) signals not associated with telomeres; and b) telomere de-protection due to a loss of TRF2 signals, physically linked to telomeres.

"In Western countries, Epstein-Barr virus is associated with classical Hodgkin's lymphoma in about 40% of cases. These cases show clear evidence of an association with the activation of the latent membrane protein 1 (LMP1) oncogene, which mediates chromosomal abnormalities primarily through downregulation of TRF2," said Dr. Knecht, Chief of Hematology at the Jewish General Hospital. The progressive breakage-bridge-fusion (BBF) cycles during the transition of a Hodgkin to a Reed-Sternberg cell result in increasing genomic instability, leading to new long BBF "zebra" chromosomes.

"We had been looking for the mechanism responsible for this process," he goes on. "The Reed-Sternberg cell is a cytokine secreting end-stage tumor cell that continues to recruit other precursor lymphocytes. We were surprised to discover two molecularly disparate mechanisms. It reveals that this process is more complicated than we had anticipated. The telomeric zinc finger-associated protein (TZAP), discovered this spring, is probably a new player in the field."

Though the sample size was too small to draw definitive conclusions, Dr. Knecht suspects that massive over-expression of TRF2 is characteristic of more aggressive disease, resulting in rapid progression to Reed-Sternberg cells and a poorer prognosis.

"We need to examine more cases and further explore how these mechanisms are associated with relapse and aggressive disease," Dr. Knecht says. "We need better understanding of the basic mechanisms underlying Hodgkin's lymphoma in order to cure the about 15% of patients who still succumb to finally refractory disease."

Upcoming Grants and Awards Deadlines

November 24, 2017 Oncopole Multi-Institutional teams against cancer. A unique public-private partnership which will operate under the auspices of the Fonds de recherche du Québec – Santé.

November 29, 2017 FRQS AUDACE Program to support bold research that offers a departure from traditional approaches.

March 1, 2018 FRQS Étudiants-chercheurs étoiles

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