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Lady Davis Institute
Research Newsletter

McGill

July 2013 Vol. 2 No. 4

Trainees earn FRQS and CIHR research awards

A number of emerging scientists at the LDI earned the support of the Fonds de recherche Québec – Santé (FRQS) and the Canadian Institutes of Health Research (CIHR) in those agencies' latest rounds of peer reviewed funding.

FRQS post-doctoral fellowships were granted to **Yannick Auclair** in Dr. Stéphane Richard's cancer lab; **Linda Kwakkenbos** for her research on scleroderma with Dr. Brett Thombs; and **Christine Zelenak** for her work on breast cancer in Dr. Volker Blank's lab.

Isabelle Sirois, of Dr. Mark Basik's lab, won the Eileen Iwanicki Fellowship in Breast Cancer Research.

CIHR doctoral research awards were won by **Vanessa Delisle** for her work on depression screening with Dr. Thombs; **Sonia Grandi** for her study of treatment of heart attack patients with Dr. Mark Eisenberg; **Matthew McCallum** for research on drug resistance in HIV with Dr. Mark Wainberg; **Ilya Razykov** for a study on suicide among sufferers of chronic disease with Dr. Thombs; **Jennifer Wu** for work on drug safety and effectiveness with Dr. Samy Suissa; and **Lisa Jewett** for an assessment of anxiety from disfigurement caused by illness with Dr. Thombs.

FRQS doctoral training awards were given to **Elaheh Ahmadzadeh**, who studies breast cancer with Dr. Basik; and to **Mathieu Neault** for his work on cancer in Dr. Richard's lab.

FRQS Master's training awards went to **Samantha Burugu** of Dr. Anne Gatignol's HIV/AIDS lab; **Priscilla Hirst**, studying breast cancer with Dr. Basik; and **Vladimir Khanassov** for a health services study under Dr. Isabelle Vedel.

CIHR Master's scholarships were awarded to **Amanda Lovato** for work on breast cancer in Dr. Michael Witcher's lab; and **Anna MacKinnon** for a study on pre-natal anxiety with Dr. Phyllis Zelkowitz.

JGH Foundation raising funds to support research

As part of its $250 million capital campaign, the JGH Foundation is working to raise $45 million in support of medical research at the LDI.

"The Jewish General Hospital continues to expand its focus on, and commitment to, research," said Myer Bick, the Foundation's President and CEO. "Research has been a powerful driver enabling us to recruit outstanding physicians, while advancing the frontiers of medical knowledge and contributing to the international effort to combat disease. Private support will be the driving force behind our success."

With donor support, the LDI will be able to:

- Establish a Stem Cell Centre, which will be Quebec's leader in unlocking the potential of adult stem cells as a treatment for many diseases;
- Pursue new areas of research, including studies to identify the genetic predispositions underlying diseases; and health services, to identify the most effective ways to organize and deliver high quality care and improve patient safety and outcomes;
- Ensure the continued excellence and growth of existing research programs, especially those that focus on the diseases associated with an aging population, such as Alzheimer's disease, and other unsolved conditions such as cancer and AIDS;
- Recruit additional top ranking investigators and support their research in priority areas;
- Provide critical support to foster new ideas, and hasten the development of, and access to, novel treatments and therapeutics.
- Support translational and early clinical research, which are not typically funded by government or industry.

Donations can be made to the JGH Foundation directly from www.ladydavis.ca.

Effect of mutation in rare bone marrow disease identified

In the course of her research to better understand the mechanisms regulating the function of telomeres – the end of the chromosome that controls DNA replication each time a cell divides – **Dr. Chantal Autexier** has identified a likely cause for certain gene mutations that are key to a rare and fatal premature aging syndrome. Dyskeratosis congenita (DC), commonly known as Zinsser-Engman-Cole Syndrome, is an inherited progressive failure of the bone marrow that emerges between the ages of five and thirteen and induces infection and cancer by early middle-age.

Unless telomeres function properly, cells that divide frequently (i.e. blood, bone marrow, and skin) will lose more and more DNA with each division, resulting in their premature death. Problems with telomeres can cause premature aging or, in cancer cells, has been associated with uncontrolled multiplication.

Dr. Autexier's lab has discovered that modification of the dyskerin protein (encoded by the DKC1 gene) by small ubiquitin-like modifiers (SUMOs) – a process known as SUMOylation – can lead to defects in telomere maintenance, which are characteristics of DC. The results appear in *Human Molecular Genetics*.

"We actually set out to compare a normal telomerase enzyme to one that would add different sequences to the ends of chromosomes in order to test its effect on the telomere function of the cell," she explains. "We found that the mutant enzyme leads to a decrease in SUMO expression. When we looked at dyskerin, we found the first indication that SUMOylation may regulate the telomerase enzyme."

Dr. Autexier's student, Marie-Eve Brault, discovered that every amino acid found at one of the predicted SUMOylation sites in dyskerin is mutated in patients with DC. In addition to DC, conditions such as idiopathic pulmonary fibrosis – a progressive scarring or thickening of the lungs – also exhibit mutations in genes responsible for telomere maintenance.

Dr. Autexier hopes to study actual cells from patients with the mutations affecting telomere function in order to check for defective SUMOylation, as opposed to cell lines, which would further validate the importance of SUMOylation in telomerase function.

"The more we can learn about the mechanisms underlying a disease, the better our chances of eventually developing applicable therapies," she said.

Structural insight into cancer and inflammation

In a paper published in *Nature Structural & Molecular Biology*, **Dr. Marc Fabian** and his colleagues have advanced knowledge of the tumor suppressor protein, tristetraprolin (TTP). Using X-ray crystallography, they revealed – for the first time – TTP's crystal structure, a significant achievement because the development of drug compounds that can affect a protein often depends upon this fundamental knowledge.

Understanding how TTP acts at the molecular level is critical because several cancers, including breast cancer, as well as chronic inflammatory disorders, are linked to impaired TTP action.

TTP is an RNA-binding protein that controls the body's inflammatory response by limiting the expression of several pro-inflammatory cytokines, such as tumor necrosis factor, which has shown promise for destroying cancer cells. Specifically, Dr. Fabian's findings relate to TTP binding to a cellular machine called CCR4-NOT. This machine controls the activity of genetic material (messenger RNA), which in turn serves as the template for the synthesis of proteins in human cells.

"The major contribution of our team is that we successfully mapped at atomic resolution how TTP interfaces with the CCR4-NOT to bring about messenger RNA destabilization. Importantly, this is the first time that the crystal structure of any RNA-binding protein in complex with CCR4-NOT has been deciphered," he said.

TTP activity is regulated via its phosphorylation – a chemical modification for activating or deactivating the protein – although it is not yet clear how these phosphates impair TTP function. Thus, aberrant TTP phosphorylation may also contribute to disease.

"Several regions of TTP can be phosphorylated, including one that links TTP to the CCR4-NOT," Dr. Fabian went on. "Our work suggests that this phosphorylation event would impair TTP recruitment of CCR4-NOT to target mRNAs; however, this work is still at an early phase."

There is a complex choreography that goes on between post-transcriptional control networks that utilize both microRNAs and RNA-binding proteins, such as TTP, and Dr. Fabian's lab is seeking to understand how they work in concert or opposition, in order to identify important molecular defects in cancer cells.

Non-invasive treatment may help stroke patients recover language

Patients given transcranial magnetic stimulation (TMS) within four weeks of a stroke event, in conjunction with traditional speech and language therapy, exhibited three times better recovery from aphasia – loss of the ability to grasp language, read, write, or speak – than did those treated with speech and language therapy alone, according to a study led by **Dr. Alexander Thiel**, published in the journal *Stroke*.

"Speech and language therapy has been the only therapeutic option for stroke survivors with aphasia," said Dr. Thiel. "We are entering exciting times where, in the near future, we might be able to combine conventional therapy with non-invasive brain stimulation earlier in the recovery to bring about better outcomes."

Researchers treated 24 stroke survivors with several types of aphasia at a rehabilitation hospital in Cologne, Germany. Thirteen received TMS – a handheld magnetic coil that delivers low intensity stimulation and elicits muscle contractions when applied over the motor cortex – while 11 got sham stimulation. The patients received 20 minutes of TMS or sham stimulation and 45 minutes of speech and language therapy for 10 days.

Researchers, in essence, shut down the working part or the brain so that the stroke-affected side could relearn language. "This is similar to physical rehabilitation where the unaffected area is immobilized with a splint so that the patients must use the affected area during the therapy session," Dr. Thiel said. "To me, the most significant finding of our study is the fact that we can modulate brain activity after stroke in a favourable way to support our conventional rehabilitation efforts."

More than one-third of stroke survivors suffer from aphasia. TMS had the biggest impact on improvement in anomia, the inability to name objects, which is one of its most debilitating symptoms.

"We believe brain stimulation should be most effective early, within about five weeks after stroke, because genes controlling the recovery process are active during this time window," Dr. Thiel suggested.

The results of this study have opened the door to a larger, multi-center trial, funded by the Canadian Institutes of Health Research, under way at four Canadian sites and one in Germany. The current study was funded by the Walter and Marga Boll and Wolf-Dieter-Heiss Foundations.

Review of a key motif with wide-ranging implications

Dr. Stéphane Richard's lab has an on-going interest in arginine methylation, a process involved in regulating gene expression and protein function. Among the important regulating motifs are those that are rich in arginines and glycines, so-called RGG/RG motifs, which are found in more than 1,000 human proteins. Its effects are wide-ranging and implicated in several diseases, including cancer, cardiovascular disease, and neurodegenerative conditions, such as ALS (commonly known as Lou Gehrig's Disease), and Fragile X syndrome, which is second only to Down's syndrome as a cause of mental retardation. The RGG motif is also critical in various aspects of RNA metabolism, and can regulate this function.

"We undertook a comprehensive review of the RGG/RG motif in the literature," Dr. Richard explained of his recent publication in *Molecular Cell*, co-authored with PhD candidate Palaniraja Thandapani, "but where we went beyond the conventional review article was to engage colleagues in Australia to perform genome-wide bioinformatic searches to identify all the proteins that contain this motif."

This paper represents the first ever attempt to classify this particular motif. The fact that it is found in humans, as well as lesser species, including rodents, is a strong indication that it has some functional relevance, otherwise it would not be so ubiquitous.

Dr. Richard's review article provides a framework for further research into the role of the RGG/RG motif in different diseases.

"We divided them into four categories, the fourth of which is a bit speculative," Dr. Richard said, "in that we painted with a broad brush, including some proteins where we aren't sure if the motif plays any role, but we think there is promise for pursuing further inquiry. It could end up being proven that RGG/RG is even more prevalent and important than we are currently aware. We are hoping to open up new avenues for research."

As the Richard lab pursues this line of inquiry, the paper also concludes, "We hope that this review provides a framework for our colleagues studying this widespread and functionally important motif. We predict and hope that the emergence of the functional and biochemical properties of the RGG/RG motif will contribute to defining its role in disease states."

Distinguished Lecture Series

The Distinguished Lecture Series and Distinguished Lectureships in Human Genetics, the latter of which is co-sponsored with the McGill Univeristy - Génome Québec Innovation Centre, are important components of the LDI's educational mission. This past academic year's series included an eclectic and fascinating mix of scientists who shared their research with faculty and students.

Among the distinguished lecturers were:

David Streiner, Professor of Psychiatry at McMaster University and the University of Toronto, on why the results of Phase III trials differ from reality; **Michael Julius**, Vice President for Research at the Sunnybrook Research institute and Professor at the University of Toronto, on the role of the protein Fyn in immunology; **Benjamin Alman**, Senior Scientist at the Hospital for Sick Children and Professor of Orthopaedics at the University of Toronto on targeting beta-catenin; **Warren Chan**, of the Institute of Biomaterials and Biomedical Engineering at the University of Toronto on nanotechnologies in cancer and infectious disease diagnosis; **Michael Tyers**, of IRIC at the Université de Montréal, on chemical biology of the ubiquitin system; **Jeff Wrana**, Senior Investigator at the Samuel Lunenfeld Research Institute, University of Toronto on cell fate determination and cancer; **John Ioannidis,** of Stanford University on assessing biomedical evidence; **Roland Lill,** of the Institute of Cell Biology and Max-Planck-Institute in Marburg, Germany, on iron-sulfur protein biogenesis; and **Richard Lloyd**, of the Baylor College of Medicine, Houston, on mechanisms of cell stress.

The distinguished lectures in human genetics included **Tim Hughes**, Professor at the Donnelly Centre for Cellular and Biomolecular Research of the University of Toronto, exploring gene regulatory mechanisms; and **Yusuke Nakamura,** of the Center for Personalized Therapeutics at the University of Chicago, on identifying variations in immune cells in cancer research.

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Honours for Dr. Brett Thombs

Dr. Brett Thombs, of the Psychosocial Research Axis, has received two significant honours. The Academy of Psychosomatic Medicine will present him with its 2013 Research Award in Novemeber at its conference in Tucson, Arizona where he will deliver a plenary lecture related to his work on depression screening in medical settings.

He has also been awarded $300,000 from the Arthritis Society in support of his work as Director of the Scleroderma Patient-centered Intervention Network (SPIN), an international network dedicated to the development, testing, and delivery of psychosocial and rehabilitation services of sufferers of this rare rheumatic disease. This award is given to an investigator who has already earned a national reputation and has made outstanding contributions and demonstrated leadership in arthritis research. It is intended for those who, early in their careers, have developed a reputation for excellence in arthritis research.

"This award is not only a great honour, but the funding will go a long way to ensuring that we can ultimately bring better services to those with scleroderma," Dr. Thombs said.

LDI Student Travel Awards

LDI travel awards are given on a competitive basis to supplement the cost for students to attend major conferences in their fields, where they make oral or poster presentations. Honourees from the spring 2013 competition were: doctoral candidates **Meghedi Aghourian** and **Francois Bertin**, both from Dr. Mark Blostein's lab, who will attend the International Society of Thrombosis and Haemostasis conference in Amsterdam; and Master's candidates **Saeid Asgharizadeh** from Dr. Slobodan Devic's lab and **Joel Mullins** from Dr. Alasdair Syme's lab, both of whom will attend the American Association of Physicists in Medicine conference in Indianapolis.

The deadline for the next travel awards competition is September 20, 2013. Applications are available on the LDI intranet. For further information, contact Janik Jacmain at jjacmain@jgh.mcgill.ca or 514-340-8222, ext. 4846.