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# Lady Davis Institute
## *Research Newsletter*

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## New Centre of Excellence in Thrombosis and Anticoagulation Care

The creation of the Centre of Excellence in Thrombosis and Anticoagulation Care (CETAC) builds upon the achievements of the JGH Thrombosis Program, under the directorship of Dr. Susan Kahn, that established the Jewish General Hospital's international leadership in patient care, teaching, and research in this critical field. Thrombosis is a frequent and important cause of disability and death in hospitalized patients and outpatients. On any given day, between 60% and 65% of inpatients at the JGH are on some form of anticoagulation medication, which must be closely monitored in order to combat side effects.

"Venous thromboembolism (VTE) is the third most common cardiovascular condition after heart attack and stroke," said Dr. Kahn. "In addition, pulmonary embolism causes more deaths each year than breast cancer, HIV and motor vehicle accidents combined. These complications are serious health issues, which must be addressed in a concerted fashion within a dedicated facility."

On the research side, fifteen peer-reviewed and five pharmaceutical funded studies are underway at the LDI on the diagnosis, prevention, and treatment of thrombosis. The Program has been awarded $4 million for principal investigators and more than $20 million for co-investigators. In addition, CETAC is the beneficiary of support from the JGH Foundation and a $1 million contribution from Sanofi Canada over three years. Along with clinical and basic science research activities, the Thrombosis Program has played a leading role in developing international treatment guidelines and knowledge transfer of evidence-based clinical practices for thrombosis care and anticoagulation management.

Thrombosis experts at the LDI are frequently sought as collaborators by researchers at other institutions. The JGH is a highly regarded site for participation in multi-centre clinical trials of thrombosis prevention and treatment by pharmaceutical and medical device companies.

CETAC will position the LDI as a magnet institution, attracting trainees as well as established scientists and financial resources. As a hub for thrombosis research, CETAC will act as a valuable resource for information and knowledge transfer for other institutions in fulfillment of the goal of reducing the incidence of VTE and improving patient safety and outcomes.

## Montreal Cognitive Assessment (MoCA) tops 1000 citations

The paper by Ziad Nasreddine, a cognitive neurologist, LDI Aging Axis Director Howard Chertkow, and LDI research neuropsychologist Natalie Phillips that introduced the world to the Montreal Cognitive Assessment (MoCA) in 2005 (Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J.L., & Chertkow, H. "The Montreal Cognitive Assessment, MoCA: A brief screening tool for Mild Cognitive Impairment." *Journal of the American Geriatrics Society*) recently surpassed 1,000 citations, a significant academic milestone.

"It's a number that represents a rare achievement," smiled Dr. Chertkow. "It demonstrates broad acceptance of the MoCA test, and we're thrilled to have developed an instrument that has had a real-world impact on how we go about assessing cognitive impairment, and, along the way, has enhanced the international reputation of the Memory Clinic at the JGH."

MoCA was devised as a simple-to-administer test that would differentiate elderly individuals who would be classified (after laborious clinical and neuropsychological assessment) as normal from those showing the earliest changes of memory loss that could lead to Alzheimer's Disease. It only takes twelve minutes to do the test, and it produces a valid result that distinguishes between the expected memory function of an elderly brain and mild cognitive impairment.

"There was really nothing that allowed doctors to make this particular distinction before MoCA," Dr. Chertkow said. "The only tools available were designed to pick up dementia, which is a much more severe condition. MoCA allows physicians to make an earlier and faster diagnosis of memory impairment."

The developers of MoCA decided to make the test freely available to all physicians to aid in diagnosis of memory problems. It has been translated into 32 languages, and has become a world standard for diagnosing cognitive decline across a range of conditions, including aging, AIDS, multiple sclerosis, and head injuries. Drs. Nasreddine and Chertkow received an award as "Most Cited paper in Mild Cognitive Impairment, 2006-2009" from the Thomson Reuters' Essential Science Indicators, 2009. The paper was also cited in the Canadian Institutes of Health Research's (CIHR) International Collaborative Research Strategy for Alzheimer's Disease (ICRSAD) plan as one of the seven top Canadian contributions to the dementia field.

## Trajectory of chronic obstructive pulmonary disease redefined

A paper co-authored by Dr. Samy Suissa, Director of the Centre for Clinical Epidemiology, Sophie Dell'Aniello, and Dr. Pierre Ernst has redefined the trajectory of chronic obstructive pulmonary disease (COPD) by revealing that patients experience a rapid decline following their second acute exacerbation and run an increased risk of mortality in the weeks immediately following every subsequent severe exacerbation.

In its year-end review, the editors of *Thorax* awarded this paper its gold medal for research on adult lung disease, calling the authors "the best sort of epidemiologists . . . They ask important and highly clinically relevant questions and provide answers that change the way we think about disease."

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Though it was accepted that COPD decreased life expectancy, the wisdom prevailing since the 1960s had been that it worsened gradually. It took this broad-based investigation of more than 73,000 patients from 1990 to 2005 to chart an accurate picture of the course it follows and to evince a new paradigm.

"It was very clear that with each hospitalization, the deterioration of the patient's health was dramatic," Dr. Suissa said. "Thus, the pattern was not one of gradual decline over time, but a step progression of sharp descents with each acute lung attack."

Studies such as this clearly illustrate how epidemiological research contributes to our understanding.

"The clinical implications are huge," Dr. Suissa noted. "This study tells us that when a patient is hospitalized for an exacerbation of COPD, they are at very high risk of death for the first month. Therefore, we know they must be closely monitored over this period. We also learned that experiencing a second exacerbation marks a patient for a very rapid decline. It is crucial to stave off this second exacerbation as long as possible through medication if we are to extend the patient's life."

The best way to handle COPD, Dr. Suissa points out, is simply not to get it. The good news is that the condition can be avoided easily enough: do not smoke, as the most common cause is prolonged exposure to cigarettes.

## Promising target to prevent thrombosis without bleeding risk

The challenge in treating venous thromboembolism is to dissolve the clot without inducing bleeding. It is a delicate balancing act that specialists like Dr. Mark Blostein are trying to achieve when managing patients, and which he is trying to perfect in his lab at the LDI.

Since establishing his lab in 1999, his research has focused on growth arrest specific 6 (Gas6), a protein that has shown itself to be important in promoting thrombosis. What is unique about Gas6 is that it can inhibit thrombosis without causing bleeding. Drs. Blostein, Catherine Lemarié, et al recently published an important paper on the subject in *Blood*.

"We treat thrombosis with anti-coagulants, which are all associated with a risk of bleeding because they thin the blood in order to dissipate the clot," he explains. "In Gas6, we have a potential drug target that could treat thrombosis without this side effect of bleeding. This could be an ideal anti-thrombotic."

Another interesting characteristic of Gas6 is the manner in which it promotes thrombosis without having anything to do with coagulation, per se. Thus, it is important to understand how it works because the capacity to inhibit clot formation without interfering with the coagulation cascade of the blood would represent a new pathway in treating thrombosis.

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"For the past fifty years we have been prescribing warfarin, which has been a very effective anti-coagulant. However, it has been effective because it inhibits coagulation, which, in turn, can bring on bleeding," he said. "The ideal situation is to prevent thrombosis without affecting coagulation because this would remove a considerable risk factor in treating these patients."

Whether being used to treat venous thrombosis or as a prophylaxis against stroke, anticoagulants must be closely monitored because of this potential for severe bleeding. If a causative agent for thrombosis that does not carry the threat of bleeding, i.e. Gas6, could be targeted, patients would be relieved of this potentially serious side effect.

The paper by Richard S. Robins, Catherine A. Lemarié, Sandrine Laurance, Meghedi N. Aghourian, Jianqiu Wu, and Mark D. Blostein. "Vascular Gas6 contributes to thrombogenesis and promotes tissue factor upregulation following vessel injury in mice," can be found online in *Blood*.

## Research Excellence Award from Quebec Heart & Stroke Foundation

Dr. Caroline Paquette received the 2011-12 Stroke Research Excellence Award from the Québec Heart and Stroke Foundation (HSF) for a project that will employ a novel imaging technique to quantify how a person's brain functions while walking and navigating turns.

"We used to have people lie in a scanner and imagine walking, which gave us only a limited picture of all the complex brain activity that goes into the real action," she explains. "By injecting a tracer, we can have a patient actually walk and then put them in a scanner so that we will have a more accurate picture of how the brain manages this function."

She hopes to map the brain circuitry that controls walking and turning and to ascertain the neuroplastic changes that occur as the result of a stroke. This could identify those areas that need to be stimulated during rehabilitation to teach the brain how to restore functionality. Once approved, her clinical research will recruit patients at the Jewish General Hospital.

"I am especially pleased to see that the HSF has chosen to honor a young researcher who has just started her academic career based on research accomplishments during her post-doctoral fellowship," said Dr. Alexander Thiel, who supervised Dr. Paquette's post-doc. "The research that Caroline does is only possible because of the unique connection between the clinical stroke unit and research infrastructure here at the JGH."

This is the second time in a row that the stroke research program at the JGH has been recognized by the Heart and Stroke Foundation (Dr.Thiel received this award for 2010-2011).

## Bell Mental Health Award to Child Psychiatry Service

A transitional care program for families of children being discharged from Child Psychiatry Day Hospital Services, created by Dr. Phyllis Zelkowitz, Dr. Jaswant Guzder, and head nurse Rosemary Short, has won a Bell Mental Health Award in the amount of $230,000. The program is designed to help children successfully return to the community and to their regular schools. The project involves the development of a manual to document this novel approach, which will allow it to be shared with schools and other community partners to support them in assisting these vulnerable children and their parents.

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## LDI features Quebec's only NanoString™ gene expression profiling

The newest core facility at the LDI is a NanoString™ nCounter® Analysis System for high throughput gene expression profiling. This state-of-the-art technology, which permits for gene expression analysis of archival material without loss of accuracy even once the tissue begins to degrade, exists nowhere else in Quebec.

"While it takes several years before gene samples show deterioration, this technology is very important because we are interested in tracking the progression of disease over long periods of time," explains Dr. Leon van Kempen, scientific director of the facility. "We can go back and analyze samples taken from biopsies at different stages of disease to see changes in gene expression."

Such analysis can prove valuable for a variety of conditions, including cancer, degenerative, inflammatory, or cardiac diseases for which a researcher may wish to compare gene expression within a patient, or in groups of patients, over time. Changes in gene expression will lead investigators to isolate those genes that seem to be playing an essential role in disease progression.

The NanoString™ eliminates the need for gene amplification, thereby making it much faster than is possible with older technologies. It can target 800 genes or 3,000 cells at one time in a tissue sample as small as 100 nanograms. Moreover, the analysis can be completed in far less time (normally a two day turn-around) than would otherwise be the case. Taking into account time and resources, NanoString™ is less expensive than other modes of gene expression profiling.

The technology can be used to measure any form of gene expression. While there are pre-existing code sets available, custom code sets can be designed and accommodated. A limitation of NanoString™ technology is that it is biased, and only looks for code sets for which it has been programmed. Therefore, the researcher has to approach an analysis with a good idea of the genes which are likely to be of interest and to narrow down their searches by process of elimination.

## Honorable Mention from Society of Toxicology

"Exposure to Moderate Arsenic Concentrations Increases Atherosclerosis in ApoE$^{-/-}$ Mouse Model," by Dr. Koren Mann and Maryse Lemaire, which appeared in *Toxicological Sciences*, was selected as one of four papers for "Honorable Mention" by the Society of Toxicology Board of Publications. Posters announcing the Honorable Mention papers will be displayed at the 2013 SOT Annual Meeting in San Antonio, Texas.

## 2012 Segal Cancer Centre retreat

The Segal Cancer Centre (SCC) hosted its sixth annual retreat, where scientists, clinicians, and students gathered to share the latest developments in cancer care at the Jewish General Hospital. The emphasis was on innovation and the quest for novel interventions that will, ultimately, improve outcomes for patients.

As has been the case every year, new investigators were given the opportunity to discuss the research they are initiating at the LDI. Ivan Topisirovic spoke on post-transcriptional coordination of gene expression in cancer. Melissa Henry addressed a psychosocial clinical trial of an intervention designed to enhance the quality of life for patients coping with a new diagnosis of advanced cancer. Marc Fabian spoke of his work on understanding microRNA-mediated gene silencing in normal and cancer cells.

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Collaboration beyond the JGH and LDI was highlighted, with presentations about the Rossy Cancer Network, which was established in 2012 to improve the quality of cancer care across the McGill University network and Q-CROC, which coordinates clinical research throughout Quebec.

The importance of clinical research for the further development of personalized medicine was noted. Data being collected from biopsies and analyzed in next-generation bio-banks is refining molecular profiling of tumors. Already an international leader in this domain, the SCC's capabilities will be expanded next year with the opening of the Molecular Pathology Centre. It is important to enlist patients in this effort, as their collaboration is critical. To this end, Dr. Gerald Batist, Director of the Centre, urged, "We must improve awareness within the clinic of what is to be gained from this research. Patients must be educated on the benefits they may realize if the genetic composition of their tumor reveals a mutation that we have the capacity to target, and of the contribution they can make by providing us with the material to enhance our overall understanding of cancer by expanding our genetic database."

The most impressive aspect of the retreat is the discovery of the breadth of basic and clinical research underway in the LDI's cancer axis.

## National colon cancer clinical study

Under the leadership of colorectal specialist Dr. Carol-Ann Vasilevsky, patients at the Jewish General Hospital have the opportunity to participate in a large-scale colon cancer prevention study. The purpose of the study is to determine whether the drug rosuvastatin prevents the recurrence of polyps in people with a history of the disease. Polyps can become malignant, and individuals who have once had colon cancer have a heightened probability of developing polyps and another cancer in the future.

Rosuvastatin is being tested because evidence suggests that statins, which are widely used to lower cholesterol, may also reduce the risk of certain cancers, including colorectal.

"We're always looking for new ways to prevent the formation of polyps because 95% of colon cancers develop from polyps," said Dr. Vasilevsky. "This particular study is taking a population with a higher risk of polyp occurrence in order to gather evidence for whether statins can effectively reduce that risk."

The National Surgical Adjuvant Breast and Bowel Project (NSABP) is overseeing this national study. The JGH is a longstanding member of this group, which has pioneered breast cancer research.

Patients who have had a Stage 0, I, II, or III colon cancer surgically removed within the last twelve months are being actively recruited. Anyone who is interested in participating can call 514-340-8222, ext. 4830.

## SPIN web site launched

The web site for the Scleroderma Patient-centred Intervention Network (SPIN) is now on-line. SPIN is a collaboration between patient organizations, clinicians, and researchers, who share the goal of developing an infrastructure that can be used on an ongoing basis to test accessible, low-cost interventions to reduce disability and improve health-related quality of life for people with scleroderma, a rare, chronic autoimmune connective tissue disease. An effort of international scope, SPIN is directed by Dr. Brett Thombs and the program coordinators are based at the LDI.
The SPIN homepage is: www.ladydavis.ca/en/SPIN.