

2nd meeting of the LDI's ISAB

The [International Scientific Advisory Board \(ISAB\)](#) will make its second visit to the LDI on June 21 and 22. Last year they conducted in-depth reviews of the Cancer, Psychosocial and HIV-AIDS Axes. This year the focus will be on the remaining Axes: Clinical Epidemiology, Hemovascular, and Aging.

Sir John Bell, Regius Professor of Medicine at Oxford University, has stepped down after chairing the ISAB for two years. We are fortunate to have **Dr. Alan Bernstein**, President and CEO of the Canadian Institute for Advanced Research (CIFAR), replacing him. CIFAR is a remarkable organization that “connects the world’s best minds through global research networks addressing important and complex challenges.” Dr. Bernstein served as Director of Research at the Samuel Lunenfeld Research Institute in Toronto (1994-2000) before being appointed founding President of the Canadian Institutes of Health Research (2000-2007).

New to the Board is **Dr. Ronan Lyons**, Professor of Public Health at Swansea University, Honorary Consultant with Public Health Wales NHS Trust, and a Fellow of the Learned Society of Wales. He is Director of the Centre for Improvement of Population Health through E-records Research (CIPHER), Co-Director of the DECIPHer UK Public Health Research Centre of Excellence and Co-Director of the Health Information Research Unit for Wales. The focus of Dr. Lyons’ research is the use of routine data in cohorts, trials, and the evaluation of natural experiments and complex interventions. He replaces **Dame Valerie Beral**, for whose advice we are grateful.



**Dr. Alan Bernstein, Chair
ISAB**

New Canada Research Chairs announced

Two new Canada Research Chairs (CRC) have been awarded to LDI investigators. CRCs honor excellence in research and research training.



Dr. Susan Kahn (left) received a Tier 1 Chair in Venous Thromboembolism (\$1.4 million over 7 years); **Dr. Vahab Soleimani** (right) received a Tier 2 Chair in Stem Cell Epigenetics (\$500,000 over 5 years).

LDI researchers earn Quebec Breast Cancer Foundation grants

Four LDI researchers were among the recipients of strategic funding awards from the Quebec Breast Cancer Foundation worth \$500,000 over four years.

- **Dr. Moulay Alaoui-Jamali** is developing an innovative approach to prevent metastasis.
- **Dr. Mark Basik** is analyzing genetic data to predict the risk of post-surgery recurrence.
- **Dr. William Foulkes** is trying to identify mutations to explain why certain Quebec families are at higher risk of developing breast cancer.
- **Dr. Michael Witcher** is studying a new therapeutic target for preventing metastasis.

Breast cancer affects more women in Quebec than any other form of cancer. However, thanks to advances in science, the five year survival rate has reached 88%.

[See the video.](#)

New revelations on potential pathway to Alzheimer disease

Dr. Andr ea LeBlanc's lab has determined that elevated levels of the protein Caspase-6 in the first area of the brain responsible for memory and cognition is an early indicator for the onset of the cognitive impairment characteristic of Alzheimer disease. In a 2006 paper, her lab demonstrated that Caspase-1, which is involved in inflammation, activated Caspase-6. In her latest paper, [published in Cell Death & Differentiation](#), it is revealed that the inflammasome nod-like receptor protein 1 (NLRP1) activates Caspase-1 in neurons and is, itself, 25 to 30 times more highly expressed in an Alzheimer brain than in one that is not afflicted.



Identifying NLRP1 as a trigger for Caspase-1 is an important finding and holds the potential of moving the search for the cause of Alzheimer's further upstream. The bad news, she acknowledges, is that NLRP1 is the least studied of inflammasomes.

"With the discovery that Caspase-1 activates Caspase-6 in the Alzheimer-afflicted brain, we naturally sought to understand what activated Caspase-1," she explains. "In general, we hadn't thought of neurons having inflammasomes, which are fundamental to immunity against, and react to, pathogens like bacteria or viruses, by recruiting a complex of proteins, including Caspase-1.

Caspase-1 activation in neurons initiates two parallel pathways of neurodegeneration that are involved in Alzheimer disease. One is Caspase-6-mediated axonal degeneration. The other involves the production of interleukin-1 beta, a protein that activates a particular inflammatory response that is highly toxic to neurons.

"You have to attack the process before inflammatory and axonal degeneration are initiated, otherwise irreversible damage may occur," Dr. LeBlanc said. "Among our objectives is identifying the optimal point along the pathway at which a novel inhibitor might intervene to prevent the onset of dementia. Going forward, we will try to figure out what is upstream of NLRP1, what condition in the brain could activate this pathway."

New Genomics Innovation Network

Genome Canada announced a \$15.5 million investment in a new national [Genomics Innovation Network \(GIN\)](#), comprised of ten nodes that will push the boundaries of technology in genomics, metabolomics, proteomics, and related sciences. One of the nodes is the Proteomics Centre, led by **Dr. Christoph Borchers**, which includes a joint initiative between the Segal Cancer Centre and Genome BC. The selection was the result of a competitive process involving peer review by an international review committee.

The novel technologies developed by Dr. Borchers at the University of Victoria for protein identification and quantitative proteomics will spur proteomics research in Canada. In collaboration with the Segal Cancer Centre, these technologies will be applied to clinically testable hypotheses for biomarker discovery and validation at the JGH's Molecular Pathology Centre and, ultimately, to therapeutic evaluation at the Clinical Research Unit.

By studying protein expression within genes, more detailed data can be gleaned about the active mechanisms triggered within a patient's tumor. Thus, proteomics holds the promise of providing deeper insights into the biological processes underlying cancer, thereby addressing currently unmet medical needs and advancing the application of more effective personalized treatment strategies. The GIN will also support important work in the area of bioinformatics and computational biology, including major challenges associated with the storage and analysis of "big data."

"Genome Canada's new GIN will provide leading Canadian researchers with new knowledge and new tools necessary to make breakthrough discoveries," said Minister of State for Science and Technology Ed Holder in making the announcement.

Canadian Cancer Society Innovation Grants

Awarded Innovation Grants to support "unique and creative research" by the Canadian Cancer Society are:

- **Dr. Chantal Autexier** (\$200,000) for "A haploid genetic screen in human cells to identify genes regulating chromosome end protection."
- **Dr. Nathalie Johnson** (\$200,000) for "Optimizing therapy for STAT6-mutant DLBCL."
- **Dr. Kostas Pantopoulos** (\$200,000) for "Targeting cancer by small molecule inhibitors of iron regulatory Protein 2 (IRP2)."

New discovery links epigenetics and metabolism in cancer

In a paper [published in PNAS \(Proceedings of the National Academy of Sciences\)](#), **Dr. Michael Witcher** reveals an intricate link between genomics and metabolism. Specifically, he found that changes to the genome may lead to metabolic disruption giving cancer cells a survival advantage.

CTCF is a key protein in organizing nuclear architecture. Dr. Witcher shows that it operates in collaboration with TFII-I to activate genes involved in metabolism. Both of these proteins are known to be mutated in a variety of cancers. “We believe that the mutation disrupts the functional interaction between these two proteins, leading to the deregulation of genes controlling cell metabolism. This aberration is conducive to the formation of cancer,” he explains, “by enabling cancer cells to thrive even under conditions where they are deprived of nutrients, which gives them a distinct advantage.”

Currently, there are anti-cancer therapeutics aimed at restoring genomics to normalcy in the hope this will stop the high rate of cancer cell growth. In the long run, it is hoped that targeting the genome with new drugs will also bring about normal metabolism to cancer cells, thus limiting their potential for growth.

“Linking metabolism and epigenetics is really a new concept,” Dr. Witcher said. “The idea is that extra-cellular signals impact genomics and will feed back to alter cell metabolism.”

His lab has identified two genes – in liver and kidney cancer – that are turned off when CTCF and TFII-I don’t function properly. He expects that the capacity to screen for whether these genes are on or off could eventually hold promise for novel therapeutic interventions.

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Tungsten and the tumor microenvironment

Tungsten is a metal with the admirable qualities of strength and flexibility. However, its effects on human health are unclear. **Dr. Koren Mann’s** is one of few labs in the world that are exploring this issue.

“While the risk for the average person is probably quite low,” she allows, “it is likely more a concern for people whose exposure is high. Tungsten is on the emerging toxicant list produced by the Environmental Protection Agency in the United States, meaning that it is suspicious and worthy of further study.”

She recently published [a study in Toxicological Sciences](#) that revealed how the use of tungsten-based shields to minimize off-target toxicity on a group of women receiving intraoperative radiotherapy for breast cancer left residual tungsten in the body. In this case, there was a defect in the shield whereby tungsten remained in the system following the procedure – it was

Two members of **Dr. Koren Mann’s** lab, PhD candidate Fernando Negro Silva and post-doctoral fellow Alicia Bolt, took first place in their respective categories for outstanding presentations in the Metals Section at the 2015 Society of Toxicology Annual Meeting.

detectable in the patients’ urine years later. Furthermore, in mouse studies conducted with **Dr. Josie Ursini-Siegel**, tungsten actually altered the tumor microenvironment in such a way as to support metastasis.

“It serves to alter the immune system and how the body responds to a tumor,” Dr. Mann said. “In this case, it made the metastatic site in the lung much more hospitable to the cancer.”

Tungsten is used in computers, cell phones, jewelry, light bulbs, and, medically, in some stents and drug delivery devices. Interestingly, it is also now being used in the manufacture of bullets. This is an increasingly important issue because fragments of armaments are frequently left in the body when they do not threaten vital organs or are situated in a position where surgical removal would be more dangerous than leaving them in place. Tungsten is now the most concentrated metal found in the urine of wounded veterans. The long-term repercussions are not yet known.

Long-term impact of chemotherapies on childhood cancer investigated

With more cancer survivors living longer, the sometimes debilitating long-term effects of chemotherapies are becoming more evident. For example, treatments that are highly effective against childhood acute lymphoblastic leukemia (ALL) are now implicated as a cause of impaired muscle function and increased rates of chronic diseases, many years later. **Dr. Thomas Jagoe** led a research team that examined the long-term effects of cancer treatments on skeletal muscle in non-tumor bearing mice. [The findings were published in *Scientific Reports*.](#)

The study demonstrated that repeated treatments with a combination of chemotherapeutic drugs caused profound impairment of muscle mitochondrial function long after all treatment had ceased. “Our results provide the most complete functional assessments of the effects of chemotherapy treatment on muscle mitochondria to date,” he and his co-authors wrote. Furthermore their analysis of mitochondrial function disproved the conclusions of prior studies that skeletal muscle was resistant to any long term damage by anti-cancer drugs such as the anthracyclines. “We can’t yet define the underlying molecular mechanism,” Dr. Jagoe elaborates, “but we do know that it is different from that which is active in cardiac muscle.”

The five-year survival rate for ALL is now upward of 85%, as compared with 5% in the 1970s, so there is no arguing the achievements of the anti-cancer agents for this type of cancer.

“The magnitude of the successes in therapeutics over recent years in pediatric cancer and many adult cancers is now creating new priorities, one of which is the need to consider how we can maximize the health of people many years after successful cancer treatment,” he adds. “What we have revealed in this paper is just one more type of treatment toxicity that needs to be taken into account.”

Future studies will focus on confirming the findings in longterm cancer survivors treated with similar drug regimes, and will define more completely the underlying mechanisms.



The Montreal Cognitive Assessment (MoCA), developed by a team including Drs. **Howard Chertkow**, **Ziad Nasreddine**, and **Natalie Philips**, was immortalized in pop culture when it was administered to a character who suffered a traumatic brain injury in an episode of the hit Netflix series *House of Cards*.

Dr. Andréa LeBlanc, Professor of Neurology and Neurosurgery, had her James McGill Professorship renewed for a seven year term. This award recognizes a senior scholar’s status as an outstanding and original researcher of world-class caliber and an international leader in their field.

Dr. Brent Richards, Associate Professor of Medicine, Human Genetics, and Epidemiology and Biostatistics, has been appointed a William Dawson Scholar for a five year term. The award recognizes a scholar developing into an outstanding and original researcher of world-class caliber.

Dr. Chantal Autexier was appointed by McGill University to serve on the Senate Pool for Statutory Selection Committees, for a three-year term. She will participate in the appointment of academic staff to tenure track positions and the granting of tenure at the University.

McGill University produced two videos on behalf of Canal Savoir for a show called *Un regard sur l'avenir de la médecine personnalisée*: one features **Dr. Gerald Batist** discussing personalized therapies for cancer patients, the other features **Dr. Carmen Loiselle** discussing psychosocial interventions for people coping with cancer.