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CNODES success affirmed in five year renewal

Every year, 150,000 Canadians are hospitalized and 10,000 die from adverse reactions to prescription drugs. This may sound shocking for a country with a rigorous drug approval procedure. But the fact is that no clinical trials of the safety and efficacy of novel therapies can possibly foresee all the variable comorbidities and interactions with other medications to be encountered in real world use. These include long-term effects that only appear after a drug has been consumed by many people over years.

Five years ago, the **Canadian Network for Observational Drug Effect Studies (CNODES)** was launched as a national collaboration of researchers to monitor after-market drug safety and effectiveness. Its achievements, under the leadership of **Dr. Samy Suissa**, Director of the Centre for Clinical Epidemiology, convinced the Canadian Institutes for Health Research (CIHR) to renew its mandate for another five year term.

"Our team has exceeded all expectations ," said Dr. Suissa. "By pooling the expertise of some of the best minds in Canadian pharmacoepidemiology, we have optimized the quality and quantity of research we can accomplish. We have substantially improved the study of drug safety and effectiveness by our ability to access and mine big databases."

CNODES studies questions posed by Health Canada and the Canadian Agency for Drugs and Technologies in Health (CADTH). Its findings have been published in high impact journals and have attracted a worldwide audience among clinicians and regulators.

"We have answered some very important questions with regard to commonly used medications for cardiovascular disease, diabetes, Parkinson's disease, gastrointestinal conditions, and others," Dr. Suissa points out. "Our work has had a direct impact on clinical practice." One example he cites is the case of isotretinoin. A popular and effective acne medication, it can lead to malformed fetuses when given during pregnancy. Consequently, using data from across Canada, CNODES reported that such improper usage still occurs and reminded clinicians against its prescription to women at risk of becoming pregnant.

Asked to identify results he found surprising, Dr. Suissa referred to the proton-pump inhibitor (PPI) study led by Dr. Kristian Filion, an investigator in the LDI's Centre for Clinical Epidemiology, that contradicted many previous findings that the use of these drugs was associated with a heightened risk for pneumonia. Since most patients using PPI are elderly, the danger of contracting pneumonia is especially severe. Debunking this side effect allows doctors to prescribe this very effective gastrointestinal reflux medication with greater confidence.

As compared with pre-approval clinical trials that engage hundreds of patients, CNODES has access to medical records of more than 102 million people in databases from Canada, the United Kingdom, and United States. Moreover, it is creating new methodologies for biostatistical and epidemiological analysis. One innovation being piloted is to employ real time monitoring of data so that, in addition to historical records, researchers can observe effects as they occur. A rapid response unit has been created to react quickly in the event of an urgent public health issue.

Other investigators from the LDI's Centre for Clinical Epidemiology actively involved in CNODES research include Drs Pierre Ernst, Laurent Azoulay and Christel Renoux. Forthcoming studies include the new anticoagulants being employed against venous thromboembolism and atrial fibrillation; new biologic agents to treat rheumatoid arthritis; and quetiapine, an antipsychotic used to treat schizophrenia, bipolar disorder and major depressive disorder.

CNODES major highlights: the first five years

- High potency statins and the risk of acute kidney injury – *BMJ*
- PPIs and the risk of community acquired pneumonia – *Gut*
- High potency statins and the risk of diabetes – *BMJ*
- Incretin-based therapies and pancreatic cancer – *BMJ*
- Isotretinoin use in pregnancy – *CMAJ*
- Domperidone use and sudden cardiac death in Parkinson's disease— *British Journal of Clinical Pharmacology*
- Incretin- based therapies and the risk of heart failure – *New England Journal of Medicine*
- Incretin-based therapies and the risk of pancreatitis – *JAMA Internal Medicine*

Gerald Batist appointed to Order of Canada and National Order of Quebec

Congratulations to **Dr. Gerald Batist**, Deputy Director of the Lady Davis Institute and Director of the Segal Cancer Centre at the Jewish General Hospital, on the dual honours of being appointed a Member of the Order of Canada and a Knight of the National Order of Quebec.

Dr. Batist has worn four hats simultaneously and with distinction: professor, researcher, clinical oncologist, and senior health care manager. He has earned an international reputation for conducting cancer research. He is a pioneer in the field of personalized medicine, ensuring that patients receive the precise therapies designed to treat their particular cancers. He has championed care for the "whole person," which emphasizes optimal nutrition as well as psychosocial support, to go along with the best medical treatment. Dr. Batist is a co-founder of the Quebec Clinical Research Organization in Cancer (Q-CROC), which has for its mission ensuring that all Quebecers diagnosed with cancer have access to the best available care.

"Gerry has been an outstanding researcher and a truly exceptional leader of scientists. Not only has he built the Segal Cancer Centre into one of Canada's leading cancer research and cancer care institutions, he has led many national and international research groups whose overall impact on health care extends well beyond his own work. He has brought great honour to the the Lady Davis Institute, Jewish General Hospital, McGill, Quebec, and Canada," said Dr. Roderick McInnes, Director of the Lady Davis Institute.

Dr. Mark Wainberg, Director of the McGill AIDS Centre, was presented with a D'Arcy McGee Citizenship Medal by MNA David Birnbaum for enriching lives within the riding and beyond through his work and community engagement. Click for more details.

$3.3 million project to analyze cancer-related proteins

A $3.3-million dollar project, co-led by University of Victoria and McGill University biochemist **Dr. Christoph Borchers**, is analyzing the expression and functionality of cancer-related proteins. In some instances, this analysis can significantly inform the effectiveness of drug therapies.

"Our technology uses antibodies and mass spectrometry to look for multiple forms of the Akt protein in a single test and hopes to identify where an anti-cancer drug is effective and where it is not," says Dr. Borchers, Director of the UVic-Genome BC Proteomics Centre and inaugural appointment to the McGill-Segal Chair in Molecular Oncology. "We are using the anti-cancer drug AZD536m, which is in clinical development by AstraZeneca, as evidence that this test works. AZD536 has been shown to stop tumor growth by inhibiting Akt but only in some people. This project can guide its best use"

The research is being co-led with Dr. Gerald Batist, Director of the Segal Cancer Centre. AstraZeneca is also a partner in this research.

Ultimately, the project will help identify patients with specific types of protein and a pathway to identify those most likely to benefit from AZD536. If successful, it will lead to the development of a diagnostic test that can be commercialized by Victoria-based MRM Proteomics Inc. This test could be used in clinics to screen patients with colorectal cancer, as well as other tumor types, to determine who will respond best to Akt inhibitors such as AZD536.

The ability to use cutting-edge proteomics to identify those most likely to benefit from particular treatments could also help Canada attract biopharma investment dollars to further develop protein-based biomarkers.

Prepared by the Research Communications Office, Lady Davis Institute at the Jewish General Hospital. Any suggestions with respect to content are welcome. Not to be reproduced without attribution.

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The Consortium pour l'Identification précoce de la Maladie d'Alzheimer - Québec (CIMA-Q), a network of more than 90 clinicians and scientists, held its annual Science Day at the Jewish General Hospital. Its missions are to develop new diagnostic tests for dementia, to detect those early biological changes that signal the onset of Alzheimer disease, and to identify promising pathways by which the progression of the disease may be slowed or stopped. Conference participants included: (back, left to right) Drs Stephen Cunane (Sherbrooke), Louis Collins (McGill), Serge Gauthier (McGill and Douglas Hospital), Naguib Mechawar (McGill and Douglas Hospital), Frederic Calon (Laval), Howard Chertkow (McGill and LDI), Remi Quirion (Chief Scientist of Quebec); (front, left to right) Drs Nicole Leclerc (Montreal and Centre Hopitalier de l'Universite de Montreal), Pierrette Gaudreau (Montreal and CHUM), and the co-directors of CIMA-Q, Drs Andrea LeBlanc (LDI, McGill) and Sylvie Belleville (Montreal and l'Institut universitaire de gériatrie de Montréal).

Cell Labelling via Photobleaching: a precious ally for scientific research

Dr. Claudia Kleinman and a multidisciplinary team of collaborators have created a unique methodology that enables instant, specific labeling of individual cells called Cell Labelling via Photobleaching (CLaP). The data are published in *Nature Communications*.

A laser is used as a paint brush to tag cells one by one. Unlike previous technologies for which one needs to either know molecular details of specific cells or label large numbers of cells in a non-specific way, this one permits painting cells based simply on observation. Researchers can, for example, paint only the big, the fast or the elongated cells. Next, they use the latest technology to investigate at the molecular level what was special about these selected cells. This technology allows for the retrieval of a few special cells within millions of normal cells.

This technique will be instrumental in pioneering next-generation sequencing applications for single-cell genomics. It has the advantages of versatility, efficiency, and non-invasiveness, as well as being simple, inexpensive, and accessible to any researcher with a standard confocal microscope. It can be automated to achieve high-throughput. It does not involve any cell damaging intervention, thus preserving the integrity of the cell for more accurate analysis.

“Single-cell genomics is a powerful new generation of technologies that could transform our understanding of diseases, like cancer, where unique cells, hidden within millions, play a major role,” said Dr. Kleinman. “This method will allow us to select those specific cells, enabling a wide range of experiments not previously possible. It will help us understand cell-to-cell variation and to study those specific cells responsible for disease progression.”

Chinese medicine under clinical study at Peter Brojde Lung Cancer Centre

A clinical study of QiGong, a traditional Chinese system of postures, breathing exercises, and meditation used to promote physical and spiritual health, undertaken at the Peter Brojde Lung Cancer Centre was honored for best clinical abstract at the International Conference on Cachexia, Sarcopenia, and Muscle Wasting in Paris.

“We found that regular cardiovascular and strength exercises kept patients stronger and helped more with symptom management than the practice of QiGong,” allows **Dr. Thomas Jagoe**, Co-Director of the Centre and senior author of the study, along with Brandy Vanderbyl, a nurse with the Cancer Nutrition Rehabilitation Program.

Dr. Jagoe has launched a new feasibility trial on a classical formula of 23 Chinese herbs produced with the strictest quality control. All participants are stage 4 lung cancer patients for whom oncology treatment is aimed at controlling symptoms. The first phase of the study is to check the safety of the herbs and to confirm that patients are able take the regimen for six weeks. Follow up studies to measure any beneficial effects will then be pursued.

“There is considerable literature coming out of China that this particular formula eases the symptoms of cancer and side effects from treatment, including fatigue and nausea,” he said. “Our focus is on making people feel better, filling in a gap between the treatment of disease and the management of symptoms.”

Novel therapy for patients with diffuse large B-cell lymphoma

A phase 2 clinical trial of a novel therapy for patients who have experienced a relapse of diffuse large B-cell lymphoma (DLBCL) resulted in extended remission, averaging 14.5 months, and longer than three years in exceptional cases. The drug, which targets histone-modifying enzymes (HME), was effective against a particular genetic mutation. The trial was initiated, designed, and coordinated by **Dr. Sarit Assouline**, a hematologist oncologist. The results were published in *Blood*.

"Following relapse, there are no effective standards of treatment for DLBCL and life expectancy averages six months," she said. "Our challenge is to identify new biomarkers and target specific mutations in order to improve the prognosis."

As many as 40% of patients with diffuse large B-cell lymphoma cannot be cured with standard chemoimmunotherapy or combinations of existing treatments and stem cell transplantation. Consequently, novel approaches that delve deeper into the molecular structure of their disease are needed. Since most DLBCL tumors contain mutations in histone-modifying enzymes, drugs known as histone deacetylase inhibitors suggested a potential pathway to significantly improve patient outcomes. Participants in the trial were given panobinostat orally in 30 mg doses three times a week.

Genomic analyses of the mutations presented in each patient's tumor revealed who was most likely to respond, as well as distinguishing those who would not. Overall, 28% of the patients in the trial experienced a positive response to the treatment. A mutation in the gene MEF2B was found to be significantly associated with this effect (approximately 11% of patients with DLBCL have this mutation). Moreover, the patients who responded remained in remission upon terminating the therapy. At the same time, increased levels of circulating tumor DNA (ctDNA) observed in plasma samples were strongly associated with a failure to respond.

This study revealed that panobinostat impacted a variety of proteins, suggesting that collecting biopsies and blood samples for analysis at intervals during treatment is a useful means for monitoring how a cancer evolves over time. This reinforces the importance of precision medicine in cancer.

"This trial has generated considerable data regarding methodology for processing samples from a clinical study, the genetic mutations associated with DLBCL and how they evolve over time, on ctDNA, and mechanisms of resistance to histone deacetylase inhibitors," said Dr. Assouline. "Our success is attributable to the tremendous synergy between clinical and research facilities at the JGH and Segal Cancer Centre. Having all the facilities and access to collaborators with different expertise, including the Molecular Pathology Centre, is what enables us to make the most of clinical and translational opportunities."

New approach dramatically reduces *C. difficile* infections in hospital

Testing patients to detect asymptomatic carriers of *Clostridium difficile* (commonly known as *C. difficile*), and taking appropriate steps to isolate these carriers being admitted to hospital, resulted in significant decreases in *C. difficile* infection in a recent clinical study led by **Dr. Yves Longtin**, of the Infection Prevention and Control Unit at the Jewish General Hospital. The results were published in *JAMA Internal Medicine*.

C. difficile is the leading cause of hospital-acquired infection. A half-million cases are reported annually in the United States, resulting in 29,000 deaths. The emergence of a hyper-virulent strain in the early 2000s made control of *C. difficile* an urgent priority, particularly in Quebec where it is thought to have originated.

"We prescribe a lot of antibiotics in hospital and this microbe is resistant to most antibiotics," Dr. Longtin explains. "Carriers of the hyper-virulent strain are contagious, and their own prospects for developing infection increase with the length of their hospitalization."

For 15 months, patients admitted to the Quebec Heart and Lung Institute in Quebec City – where the clinical study was performed –were screened for the presence of *C. difficile*. The results were dramatic. Of 7,599 patients who were screened, 368 (4.8%) were identified as *C. difficile* carriers and placed under isolation. During the study period (November 2013 to March 2015), the incidence rate of hospital acquired *C. difficile* infection decreased by more than 50%, to 3.0 per 10,000 patient days compared to 6.9 per 10,000 patient days before the intervention. As a result, Dr. Longtin and his collaborators estimate that approximately 63 cases of infection were prevented. The cost of the intervention was placed at US$130,000, far less than that of treating that number of patients for infection, not to mention having safeguarded them against the risk to which they would have been exposed.

Dr. William Foulkes has been elected a Fellow of the Royal Society of Canada (RSC), Canada's senior collegium of distinguished scholars, artists, and scientists. Dr. Foulkes is a cancer geneticist with clinical and research appointments at the Lady Davis Institute, Jewish General Hospital, and McGill University Health Centres.