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NFL funding pan-Canadian research on concussions in youth sport

The National Football League's Scientific Advisory Board is funding a pan-Canadian research initiative that aims to reduce concussions and their consequences in youth sport. **Dr. Ian Shrier**, a sports medicine physician and senior investigator at the Centre for Clinical Epidemiology, is a co-principal investigator and national co-lead of analysis on the project.

SHRed Concussions, short for *Surveillance in High Schools to Reduce Concussions and Consequences of Concussions in Youth,* will provide a national platform for concussion surveillance in high schools to evaluate novel and sustainable solutions for concussion prevention that will have significant impact in reducing the risk of sport-related concussions and their consequences in youth. Some 6,000 high school athletes between the ages of thirteen and fifteen across five provinces will be followed over a three-year period in order to evaluate the causes, recovery, and treatment of concussion. Youth account for more than half of the annual burden of more than three million concussions annually in North America.

"Few studies have looked at the mechanisms of concussion in teenagers, and certainly none with the depth of data we will be gathering in SHRed," said Dr. Shrier, "so we don't have a full understanding of their physiological effects on the adolescent brain, which is what makes this study so important."

The research team has more than 35 scientists from nine Canadian universities and more than 30 community, government, and industry partners. Research involves a variety of youth sports, including ice hockey, rugby, football, lacrosse, wrestling, soccer, basketball, volleyball and cheerleading.

"We hope to determine factors that make kids more susceptible to concussions," said Dr. Shrier, "so that, hopefully, we can reduce the incidents of concussion."

Common treatment for type 2 diabetes associated with rare, aggressive cancer

A large-scale population based cohort study led by **Dr. Laurent Azoulay,** senior investigator with the Centre for Clinical Epidemiology, and published in *The BMJ*, reveals an association between incretin-based drugs used to treat type 2 diabetes and cholangiocarcinoma, a rare, but highly fatal cancer of the bile duct.

There are two types of incretin-based drugs: dipeptidyl peptidase-4 (DPP-4) inhibitors and GLP-1 receptor agonists. These drugs have proven to be highly effective in treating type 2 diabetes. Large trials have shown that they can be cardio-protective and help with weight loss, both of which are important for individuals with type 2 diabetes. However, their long-term association with important potential adverse events such as cancer requires further study.

Using the UK Clinical Practice Research Datalink, Dr. Azoulay and his team observed 105 cases of cholangiocarcinoma among more than 154,000 adults treated with anti-diabetic drugs over the ten-year period since the incretin-based drugs were first introduced. Their study reveals that DPP-4 inhibitors are significantly associated with a 77% increased risk of this cancer. An association of similar magnitude was observed with GLP-1 receptor agonists, but this analysis did not achieve statistical significance.

"All incretin-based drugs are associated with an increase in GLP-1 levels, which we believe is the main mechanism responsible for this association. Normally GLP-1 is in the system for a matter of minutes during digestion. However, for those taking these drugs, GLP-1 remains active for hours," reports Devin Abrahami, lead author and doctoral student working with Dr. Azoulay. "Fortunately cholangiocarcinoma is a rare cancer, but studies such as this one provide important insight on the effects of these drugs on various tissues."

Dr. Nancy Feeley, of the Centre for Nursing Research at the JGH and Associate Professor at the Ingram School of Nursing, is the recipient of the 2018 *Excellence in Nursing Research Award* from the Canadian Association of Schools of Nursing (CASN), as part of its mission to promote nursing research and recognize individual accomplishments in the research arena. Deeply engaged in training and mentoring nursing students and in developing their research skills, she is also an exceptional mentor for her colleagues. Dr. Feeley has been the Co-Director of the Quebec Network on Nursing Intervention Research (RRISIQ) since 2010.

A locally, nationally and internationally recognized expert, Dr. Nancy Feeley has advanced knowledge and practice in neonatology and neonatal nursing. She is a leading Canadian researcher in the area of parenting of preterm infants, a worldwide pioneer in the study of fathers' experiences in the neonatal intensive care unit, and was instrumental in shining a light on the methodological issues related to pilot randomized controlled trials. Her research has been funded by the Canadian Institutes of Health Research (CIHR), the Social Sciences and Humanities Research Council of Canada (SSHRC), Fonds de la recherche en santé du Québec (FRQS) and Fonds de Recherche du Québec – Société et Culture (FRQSC), among others.

Nancy Feeley (left) with CASN Board member Donna Murnaghan

The Canadian Society for International Health released its first list of Canadian women leaders in global health. Among the eight McGill faculty members represented was **Dr. Christina Greenaway** of the LDI. The Canadian list was inspired by a broad global movement to recognize the achievements and expertise of women in global health.

Potential new treatment options for anemia of inflammation

Anemia of inflammation is a common side effect of chronic inflammatory disorders, such as rheumatoid arthritis, inflammatory bowel disease, chronic kidney disease and some cancers, and its effective treatment remains an unmet medical need. In a paper that appeared in *Blood*, **Dr. Kostas Pantopoulos** proposed a new targeting pathway with therapeutic potential.

Iron balance is maintained by hepcidin, a liver-derived peptide hormone that inhibits iron entry into the blood-stream. Iron-dependent induction of hepcidin is critical for preventing excessive dietary iron absorption and depends upon signaling via bone morphogenetic protein 6 (BMP6) and hemojuvelin (HJV), a BMP coreceptor. Disruption of this pathway leads to hepcidin deficiency that causes hereditary hemochro-matosis, a disease of systemic iron overload. During infection, hepcidin is induced by the inflammatory cytokine interleukin 6 (IL-6); this promotes hypoferremia to prevent iron utilization by invading bacteria. If inflammation remains unresolved, persis-tent hypoferremia due to aberrant overexpression of hepcidin limits iron's availability for erythropoiesis and contributes to the anemia of inflammation.

Using an HJV knock-out mouse model, this paper reveals a critical role of BMP6/HJV in the inflam-matory response of hepcidin, in crosstalk with IL-6. Consequently, phar-macological targeting of BMP6/HJV may prevent over-production of hepcidin and thereby offer new options for treating anemia of inflammation.

Prepared by the Research Communications Office, Lady Davis Institute at the Jewish General Hospital. Any suggestions with respect to content are welcome.

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Deploying gene editing technology against HIV

CRISPR-Cas9 is an extraordinary technology that permits specifically targeted sequences of genetic code to be edited at precise locations within DNA. By enabling the modification of genes, it holds the promise of correcting mutations in the human genome that will allow for treatment of the genetic causes of disease. **Dr. Chen Liang**, acting director of the McGill AIDS Centre, is exploring how CRISPR can be employed against HIV in collaboration with **Dr. Michael Witcher** and other researchers.

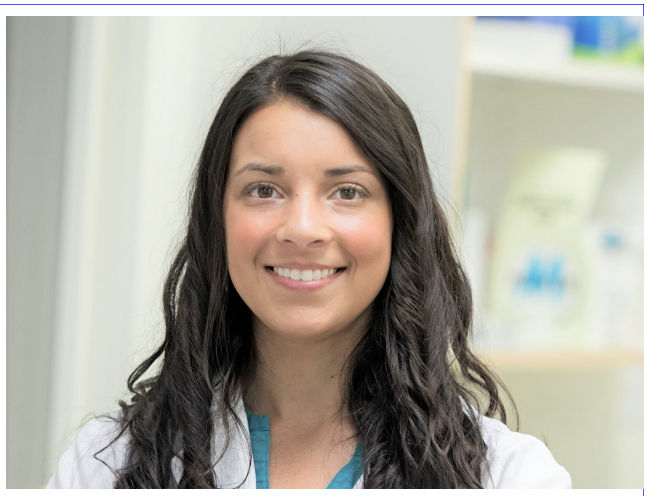
"We believe that we can program the CRISPR enzyme so that it will target the DNA sequence in HIV and edit it out of the human genome," Dr. Liang explains.

Current HIV therapies are so effective that they can reduce viral loads to levels where they are no longer detectable in the blood. However, they do not completely eradicate the virus, which remains in difficult to detect reservoirs. When those patients cease taking antiviral drugs, HIV reemerges.

"HIV can hide because it integrates its DNA with the cellular DNA," said Dr. Liang, "meaning that it becomes a part of the cell. If we can direct CRISPR-Cas9 to target the HIV DNA, we could splice out the viral DNA, restore the integrity of the cell's DNA and eliminate these reservoirs of virus."

The principal is deceptively simple; in practical terms, however, it is extremely complicated. Dr. Liang's lab has established the feasibility of deploying CRISPR-Cas9 against HIV in cell cultures. But, as he points out, there are millions upon millions of cells in humans and the objective is not for CRISPR to get into every cell because that might prove toxic. The challenge is how to deliver it only to latently infected cells.

"It's similar to the challenge of chemotherapy," he said, "in that you want the drugs to attack only malignant cells while sparing the healthy ones. Our lab is focused on developing the targeted delivery system that would allow CRISPR-Cas9 to hone in exclusively on HIV DNA and cure latently infected cells."



As the top-ranked student in McGill University's internal awards competition, **Constance Sobsey**, a PhD candidate in Dr. Gerald Batist's lab, was awarded the Charles James Patton, MD and Elizabeth Ross Patton Memorial Prize for excellence in medical research. Her research is focused on applying clinical proteomics approaches developed with Dr. Christoph Borchers at the Segal Cancer Proteomics Centre to analyze protein concentrations from tumour samples and determine their molecular features. If protein measurements are found to offer greater predictive power than the existing genomic screening alone, the data could form the basis of a new patient selection strategy. Improved specificity in patient selection will ensure that patients receive the best available treatment for their particular cancer type and will help avoid unnecessary side effects and lost treatment time.

The 2023 annual congress of the International Society on Thrombosis and Haemostasis will be held in Montreal at the Palais des congrès. The event, which will be attended by nearly 8,000 delegates, is organized by Drs. **Susan Kahn** and Marc Rodger, co-directors of the Canadian Venous Thromboembolism Clinical Trials and Outcomes Research Network (CanVECTOR). Dr. Kahn is the founder and director of the Centre of Excellence in Thrombosis and Anticoagulation Care at the Jewish General Hospital. Dr. Kahn was named an Ambassador to Montreal by the Palais des congrès for her part in bringing this major conference to Montreal and for advocating on behalf of the city.

Further refinement to recommended initial treatment of COPD

There are two recommended long-acting bronchodilators used as first-line treatments for chronic obstructive pulmonary disease (COPD). Both are effective, but, as **Dr. Samy Suissa** points out, are not interchangeable. He and **Dr. Pierre Ernst** undertook a large population-based cohort study to compare long-acting β2 agonists dispensed in fixed combination with inhaled corticosteroids (LABA-ICS) with long-acting muscarinic antagonists (LAMA). In a paper published in *The Lancet Respiratory Medicine*, they compared the effectiveness and safety profiles of the medications. This is the first such head-to-head comparison to employ real-world observational data.

While both treatments have proven effective, there are safety issues associated with ICS – namely, an increased risk of pneumonia. Moreover, it has been suggested that ICS-containing drugs may only be effective in patients with elevated blood eosinophil concentrations. Blood eosinophil is an important biomarker in COPD, with higher concentrations indicating increased incidence of COPD exacerbations and mortality.

This paper offers a more refined rationale for choosing between first-line bronchodilators. The authors studied a base cohort of almost 540,000 patients with prescriptions for LABA or LAMA from 2002 to 2015.

"By refining our understanding of how particular types of COPD will respond to different medications, our study provided evidence for the concept of precision medicine to treating patients with this condition," said Dr. Suissa. "A simple blood test can measure blood eosinophils and, based on the level, physicians can make a better-informed decision on which treatment to prescribe. In this way, we can avoid the potential harm of an ICS, unless it is justified as in the case of patients with high eosinophil levels."

Generally speaking, Dr. Suissa is skeptical about the unnecessary and widespread use of ICS in COPD.

"The evidence has suggested that ICS should be introduced only after a patient's symptoms have worsened," he said. "However, combination therapies have been promoted as a magic bullet. We are showing that this is not the case and that only a sub-group of patients will benefit."

No increased risk of death associated with overnight emergency surgery

A study conducted by **Dr. Michael Tessler**, an anesthesiologist at the Jewish General Hospital, concluded that patients who undergo emergency surgery during the overnight hours are at no greater risk of mortality than those who are operated upon during the day. Preliminary results of these findings were presented to the World Congress of Anaesthesiologists in Hong Kong and the American Society of Anesthesiologists in Chicago in 2016, and have now been published in *Anaesthesia*.

"Previous studies had detected an association between when surgeries began and mortality in non-emergency surgeries, but we questioned their methodology," said Dr. Tessler, who, along with his co-authors, assessed more than 10,400 emergency surgeries performed on more than 9,300 patients at the JGH over five years (2010-2015). They focused on emergency surgeries because those could not, by their very nature, be planned and needed to be performed whenever the cases presented. Thus, there was no element of choice in regard to the time of day at which they were performed.

The inquiry found no statistically significant connection between time of surgery, nor whether the emergency occurred on a weekday or the weekend, and mortality. Rather, mortality was associated with the patient's age, physical status, and urgency of surgery.

"Fatigue is recognized as a factor in performance in a number of disciplines, so it seemed important to investigate whether mortality statistics indicated that it was a factor in overnight surgery. Moreover, there is also the question of whether surgery at night might be affected by reduced on-site resources as compared with the day shifts," Dr. Tessler said. Surgeons working overnight or on call are accustomed to keeping alert and responding to situations when they arise. Thus, it isn't necessarily surprising that mortality rates are unaffected by time of surgery.

Dr. Lorraine Chalifour, Assistant Director for Graduate Students at the LDI and Associate Professor of Medicine has been appointed McGill's Associate Dean of Graduate and Postdoctoral Studies for Dentistry, Kinesiology and Physical Education, Management, and Medicine

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