

Lady Davis Institute Research Newsletter



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Geriatric mental health highlighted at the JGH

Depression, anxiety, social isolation, coping with comorbidities such as dementia and physical illness, and fears of mortality are some of the mental health issues that affect older individuals.

"This is a really unique population about whom there is a need for better understanding and further research," explained **Dr. Soham Rej**, a leader in geriatric psychiatry within the CIUSSS West-Central Montreal, which serves one of the highest concentrations of older adults in Canada. "Therapies that are effective on younger people may not have the same impact on geriatric patients because of combinations of medications, frailty, dementia, as well as social factors such as the loss of long-standing support networks through death or incapacity. All of these factors contribute to the complexity of devising treatment plans."

In addition to his practice at the Jewish General Hospital and research at the Lady Davis Institute, Dr. Rej is committed to educating other front line service providers on the latest developments in the field. To this end, he organizes the Annual Geriatric Psychiatry Academic Day, now in its third year at the Institute of Community and Family Psychiatry.

This year's focus was on technology in geriatric health. "Technology holds great promise," Dr. Rej affirmed, "but psychiatry also requires a very human touch. So, we're searching for that optimum balance."

One significant way in which technology can have a huge impact is by enhancing the system's ability to cope with the increasing demands for service.

"Most Canadians with mental health issues never seek treatment," pointed out guest speaker Dr. Cheryl Forchuk of the University of Western Ontario, "and if they did, we have nowhere near the capacity to accommodate all of them."

Technology, then, might offer a solution: allowing patients to forego visits to hospitals or clinics except when necessary without losing connections to health care professionals. Skype might be a time-efficient alternative to face-to-face visits, and various apps could be developed for mobile monitoring of symptoms.

Dr. Ipsit Vahia, the keynote speaker from Harvard University, foresees a time when technology will facilitate monitoring patients and tracking their compliance with medication, which is a major problem in psychiatry. For example, he highlighted how mobility is being studied as a biomarker for psychiatric distress. Wearable fitness devices can inform health care professionals of a major depression by showing that a person is rarely rising from bed. "This sort of passive measurement is helpful because it can alert physicians without requiring the patient to do anything," he said.

Dr. David Benrimoh, a psychiatry resident at McGill, is exploring potential applications of artificial intelligence in mental health. "Because AI learns from the data it accumulates, we can create algorithms that will analyze a multitude of variables and predict the optimal therapy for a person's symptoms. This means that more patients will improve with initial treatment, rather than having to endure a lengthy trial and error process."

Dr. Rej believes that the more awareness that is raised within the health care system, the better the outcomes for patients. To this end, he will be co-hosting the upcoming annual <u>scientific meeting</u> of the Canadian Academy of Geriatric Psychiatry in Montreal in October.

Cellular origins of pediatric brain tumors identified

Dr. Claudia Kleinman and her collaborators discovered that several types of highly aggressive and, ultimately, fatal pediatric brain tumors originate during brain development. The genetic event that triggers the disease happens in the very earliest phases of cellular development, most likely prenatal. The findings represent a significant advance in understanding these diseases, and are published in *Nature Genetics*.

"We have determined that stalled development of progenitor cells in the pons and forebrain, where a large proportion of high-grade embryonal and pediatric tumors emerge, is responsible for several childhood brain cancers," said Dr. Kleinman. "Rather than developing normally, the cells' progress is arrested and they transform into malignancies. But they retain many features of the original cells, and we could pinpoint the tumor origins among the hundreds of different cell types present in the brain." This is called the Peter Pan Syndrome, as these cells are stuck in time, unable to age and this is what causes the tumors. The challenge is now to identify how best to unlock these cells, promote their differentiation, and allow for normal processes to take over.

Brain tumors are the leading cause of cancer-related deaths in children. For several of these tumors, there are no effective therapies and survival is often less than two years. Indeed, Dr. Kleinman points out, very limited progress has been made in treating afflicted children.

Applying sophisticated single cell sequencing techniques and large-scale data analysis, researchers compiled the first comprehensive profile of the normal prenatal pons, a major structure on the upper part of the brainstem that controls breathing, as well as sensations including hearing, taste, and balance. Dr. Kleinman's team performed the bioinformatics and established the molecular identity for cell types in this and other brain regions, as well as the dynamics underlying their differentiation. They created an atlas of more than 65,000 individual cells and defined the developmental dynamics for 191 distinct cell populations. They then mapped patient samples to this atlas, and identified the origins of WNT medulloblastomas, embryonal tumors with multilayered rosettes (ETMRs), and high grade gliomas (HGGs).

Roderick McInnes honored for contributions to research, education, and innovation

Dr. Roderick McInnes, Director of he LDI, has recently been bestowed several distinguished honours that reflect the high regard with which he is held in Canada's health sciences community.

He won the 2019 Leadership in Advocacy Award from Research Canada as an outstanding champion of health research and innovation at the national level – an advocate who educates policymakers, the media, and the public about the health, social, and economic benefits of health research and health innovation in Canada.

"Dr. McInnes has given us a new lease on embracing our premiere health research funding agency, the Canadian Institutes of Health Research (CIHR)," said Deborah Gordon-El-Bihbety, President and CEO of Research Canada.

He received the 2019 Paul Armstrong Lecture Award from the Canadian Academy of Health Sciences in recognition of leadership and commitment to advance health sciences through academic service and innovation at the local, national, and international levels and for achievements that are truly extraordinary.

The Friends of CIHR presented him their 2018 Award of Honour in recognition of his significant and sustained contribution to health research in Canada.

He had his appointment as Alva Chair in Human Genetics renewed by McGill's Faculty of Medicine.

"The honours that have been bestowed on Dr. McInnes acknowledge not only his dedication to research, but his commitment to ensuring that society benefits from his work and that of his colleagues," says Dr. Lawrence Rosenberg, President and CEO of CIUSSS West-Central Montreal. "In this respect, Dr. McInnes represents the overall approach of our CIUSSS in making education and research relevant to the needs of the public, while keeping the lines of communication open to policymakers, leaders and scientists around the world."

Dr. Ana Velly, Associate Professor in McGill's Faculty of Dentistry, has been appointed chair of a new working group on orofacial pain in the Network for Canadian Oral Health Research, which is Canada's primary resource on oral health research.

Therapeutic resistance in aggressive breast cancer

Using tumor biopsies from patients with chemotherapeutic resistant triple negative breast cancer (TNBC), researchers led by **Dr. Mark Basik** have identified changes to the form of the cancer cells that appear to be associated with their capacity to resist usual drug treatment. This discovery is featured on the cover of the December issue of *Molecular Cancer Research*, where it is highlighted for its importance.

"When patients with TNBC respond to treatment, their prognosis is very good," explains Dr. Basik. "However, resistance to treatment is quite common. Chemotherapy resistant TNBC constitutes the most aggressive form of breast cancer, and the prognosis for those patients is not that good. Therefore, it is critical that we determine the processes that promote resistance and target them directly to overcome its influence on the tumor."

The researchers observed that the onset of resistance to the two most common drugs deployed against TNBC is associated with changes in the shape of the cancer cells and the manner in which they process fat. The cells are able to store fat droplets that they can exploit as a source of energy to fight off the effects of chemotherapy. These cells were also seen to develop a dependence on the protein perilipin4, which is highly expressed in resistant tumors. The protein is used by the cancer cell to stabilize the fat droplet, which would otherwise leak free fat into the cell, which is toxic to it and would kill the cell. Dr. Isabelle Sirois, a postdoctoral fellow in Dr. Basik's lab and the first author on the paper, and her colleagues determined that targeting this protein caused nearly all of the resistant cells to stop growing, and most to die.

"This is very promising," said Dr. Basik, "because if we can eliminate the resistant cells, we will be able to successfully treat far more TNBC patients."

A key element in treating cancer is finding the active protein that makes possible the disease's unchecked growth. With that, the vulnerability of the cell is revealed, opening the door to new therapies and better patient outcomes.

Dr. Gerald Batist, Director of the Segal Cancer Centre, received the 2019 Award for Exceptional Leadership in Cancer Research from the Canadian Cancer Research Alliance. The Award recognizes his decades-long commitment to accelerating the translation of new discoveries from the research laboratory into clinical benefits for cancer patients by building unique collaborative and multidisciplinary research programs and networks in Quebec, across Canada and internationally and addressing the major challenges in cancer research and cancer care.

Dr. Brett Thombs has been accepted into the College of New Scholars, Artists, and Scientists of the Royal Society of Canada. Since 1882, The Royal Society has recognized excellence in intellectual achievement, promoted a culture of knowledge in Canada, and advised governments and the public. The RSC College is Canada's first national system of multidisciplinary recognition for the emerging generation of Canadian intellectual leadership.

Dr. Christel Renoux received the John-J-Day MD Award of Excellence at the Quebec Heart & Stroke event. This award of excellence in research is granted annually to the researcher from McGill University who receives the highest evaluation in the grant-in-aid competition in cardiovascular research.

Below, left to right: Kostia Pantazis, chair of the provincial board, Robert Cowling, Dr. Christel Renoux, and Dana Ades-Landy, senior vice-president, Quebec Heart & Stroke.



Rare pediatric liver disease linked to DICER1 mutation

For a decade, **Dr. William Foulkes** and his collaborators have been puzzling over various mutations and alterations of the gene *DICER1* in order to more fully comprehend its catalytic activity. In a report published in *The New England Journal of Medicine*, they examine the only two documented cases so far identified of *DICER1* mutations in mesenchymal hamartoma of the liver (MHL), the second most common benign liver tumor in children.

"We have been trying to find the extent of the phenotype associated with germline *DICER1* mutations and this adds another piece to the puzzle," said Dr. Foulkes. Prior to this discovery, there was nothing to suggest that this gene was implicated in MHL. He cautions that two cases are not definitive, but they do offer a new clue as to the effects DICER1 mutations may have.

This research is also noteworthy for employing refined biochemical techniques that improve the capacity to predict the functional effect of specific variants within the gene. Work done by Dr. Maria Apellaniz-Ruiz, a post-doctoral fellow in Dr. Foulkes' lab, in close collaboration with **Dr. Marc Fabian**, contributed the complex sequencing analysis.

The paper represents a far-ranging collaboration between the LDI and clinicians in Italy and Germany, where the two children were treated.

ClinGen, a National Institutes of Health (NIH) funded effort to build a centralized resource to define the clinical relevance of genes and gene variants, has formed a DICER1 group and Dr. Foulkes expects that the assay used in this paper could gain widespread recognition for screening other potential DICER1 effects. The Foulkes lab is internationally recognized for its DICER1 research and its web site, www.dicer1syndrome.ca, is regularly sought out by practitioners for its expertise.

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To submit information or for media enquiries, contact: Tod Hoffman at: tod.hoffman@ladydavis.ca; 514-340-8222, ext. 28661

Dr. Susan Kahn has been appointed to the advisory board of the CIHR Institute of Circulatory and Respiratory Health (ICRH). One of thirteen institutes of the CIHR, the ICRH supports research that focuses on cardiovascular health, respiratory health, blood and blood vessels, stroke, critical/intensive care, and sleep/circadian rhythms. Together, the disease areas covered under its mandate represent conditions with the largest health, societal, and economic burden of any of the other Institutes within CIHR.

Dr. Christoph Borchers, in collaboration with Drs. **Gerald Batist**, **Alan Spatz**, and **Mark Basik**, has been awarded a grant from the Institut TransMedTech to develop new assays that will improve the ability to predict patient response to Akt inhibitors in treating breast cancer. Though this particular treatment has proven effective, patient selection remains a particular challenge. More accurate tumor profiling will help to identify those who have the precise mutation that will engender a positive response to targeting this particular pathway. The Jewish General Hospital is one of the founding partners of TransMedTech, which supports interdisciplinary collaborations to develop new medical technologies.

The Quebec Clinical Research Organization in Cancer (Q-CROC) has launched a new web site to provide easy access to information about oncology clinical trials that are currently recruiting patients or are soon to be initiated. It includes all participating Q-CROC hospitals: the Jewish General, MUHC, CHUM, Sainte-Justine, Gatineau, Maisonneuve-Rosemont, Sacre-Cœur, Chicoutimi, Sherbrooke, IUCPQ- UL, Laval, Rimouski, Trois-Rivières and CHU de Québec.

OncoQuébec, as the site is called, is updated in real time as soon as a trial is activated or close to recruitment. Trials can be filtered by tumor site, PI, disease, disease stage, treatment type and treatment line, making it an excellent tool to use for screening patients during Tumor Board. It is extremely useful for physicians when screening patients for eligibility for clinical trials. Additionally, the name of the research coordinator and their contact details is provided for each trial. As well, there is an app compatible with desktop, Android and Apple phones.

https://oncoquebec.com/en

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