

Lady Davis Institute Research Newsletter



April 2021 Vol. 10 No. 2

Identification of a protective protein that reduces the severity of COVID-19

The Richards lab discovered that increased levels of the protein OAS1 are associated with reduced mortality and less severe disease requiring ventilation among patients with COVID-19. Using drugs that boost OAS1 levels could be explored to try to improve these outcomes. The findings are published in <u>Nature Medicine</u>.

"Our analysis shows evidence that OAS1 has a protective effect against COVID-19 susceptibility and severity," explains **Dr. Brent Richards**. "This is a very exciting development in the race to identify potential therapies to treat patients because there are already medicines in pre-clinical development that boost OAS1 and could be explored for their effect against SARS-CoV-2 infection."

From genetic determinants of 931 circulating proteins, Dr. Sirui Zhou, first author on the paper, found that increased OAS1 levels were associated with reduced COVID-19 death or ventilation, hospitalization, and susceptibility in up to 14,134 COVID-19 cases and 1.2 million controls. The results were consistent in multiple sensitivity analyses. They proceeded to measure OAS1 levels in 504 patients with different COVID-19 outcomes from the Biobanque Québec COVID-19, and found that increased OAS1 levels in post-infection patients were associated with protection against very severe COVID-19, hospitalization, and susceptibility.

"The protective effect was particularly large," points out Dr. Zhou, "such that we observed a 50% decrease in the odds of very severe COVID-19 per standard deviation increase in OAS1 circulating levels. Interestingly, for non-African peoples, this protective effect is likely inherited from a Neanderthal derived form of OAS1 called p46."

This form of OAS1 likely emerged in people of European ancestry through interbreeding with Neanderthals tens of thousands of years ago. Evolutionary pressure slowly increased the prevalence of this OAS1, such that it is now detectable in more than thirty-percent of people of European descent. It is likely that the form of the protein has served as protection against earlier pandemics.

Pan-Canadian research platform to boost stroke recovery

Brain Canada and the Heart & Stroke Foundation Canadian Partnership for Stroke Recovery have awarded \$1.9 million over three and a half years, through the Brain Canada Platform Support Grant program to the Canadian Platform for Research in Non-Invasive Brain Stimulation (CanStim), a national network that will accelerate discovery and move new research on stroke recovery into clinical practice. Co-led by Dr. Alexander Thiel, CanStim is the first platform of its kind in the world.

CanStim features a unique translational approach towards stroke rehabilitation and recovery research by integrating pre-clinical and clinical research from the project's inception. The platform will provide the necessary research capacity in non-invasive brain stimulation methods, such as repetitive transcranial magnetic stimulation (rTMS), to develop and optimize novel approaches for people living with stroke disabilities and other neurological disorders.

Additionally, CanStim will provide opportunities to trainees across Canada to explore new interdisciplinary approaches to studying stroke recovery.

"CanStim will bring developed devices to the patient faster by accelerating clinical trials and it will offer our expertise in pre-clinical research to develop new tools with industry partners," said Dr. Thiel. CanStim's integrated design will encourage rapid advances in optimizing the protocols for using TMS in the clinic for stroke rehabilitation.

Stroke recovery is a huge public health issue in Canada. According to a 2015 study published in the journal *Stroke*, there are more than 405,000 Canadians living with long-term disability from stroke – and the number is expected to almost double by 2038.

Roderick McInnes completes his term as Director of the LDI

Over the course of **Dr. Roderick McInnes**' twelve year tenure as Director, the national and international stature of the Lady Davis Institute, and of the Jewish General Hospital (JGH) as a leading clinical and fundamental research facility, grew markedly.

Having served for a decade as the inaugural Scientific Director of the Institute of Genetics of the Canadian Institutes of Health Research (CIHR), he came to the LDI from the University of Toronto and the Hospital for Sick Children (SickKids) in 2009. Dr. McInnes was the first Director in the LDI's history to be recruited from outside of McGill. His internationally recognized expertise in genetics and his reputation as a leader introduced many fresh perspectives.

Under his guidance, the LDI has been streamlined, with cardiovascular, aging, and viral disease researchers now grouped together to create a critical mass of scientists who study disease biology and treatment. Dr. Koren Mann has led this new group, the Molecular & Regenerative Medicine (MRM) Axis from its inception. To keep the LDI at the forefront of innovation, a cadre of stem cell researchers was recruited to the MRM axis. In addition, the McGill AIDS Centre at the LDI has evolved to become part of the McGill Centre for Viral Diseases, to expand the scope of its efforts to combat viral diseases, including COVID-19.

When asked what being Director has been like, Dr. McInnes said "Well, the job is really all about helping people to get where they want to go. That has been hugely rewarding."

The Cancer Axis, the largest at the LDI, enhanced its national stature under the leadership of Dr. Gerald Batist as Axis Head and Dr. Josie Ursini-Siegel as Head of Molecular Oncology. The emphasis on personalized approaches to care, together with clinical trials of novel therapeutics, advanced knowledge of cancer biology, and cancer genetics have combined to improve patient outcomes. The emergence of sophisticated genomic and proteomic explorations in oncology, as well as virology, promise to bring exponential benefits to cancer care.

The Clinical Epidemiology Axis, led by Dr, Samy Suissa, established the LDI as a national hub for sophisticated pharmaco-epidemiological inquiry. The LDI became the headquarters for the Canadian Network for Observational Drug Effects Studies (CNODES) and a key member of the McGill Ludmer Centre for Neuroinformatics and Mental Health. The LDI's growing capacity in computational

bio-informatics was led by this axis, a growth that has benefited the entire institution.

The Psychosocial Research Axis, led previously by Dr. Phylis Zelkowitz and now by Dr. Ashley Wazana, has also thrived. New faculty have been recruited and the research program has expanded to examine mental health across the lifespan, developmental psychopathology, and novel approaches to mental health. These include pioneering telehealth options and digital health initiatives to improve access to care. Long a world leader in cultural psychiatry, the axis is also developing a new theme, Social and Cultural Neuroscience, that will include neuroimaging, computational methods and artificial intelligence.

In 2015, Dr. McInnes also assembled an International Scientific Advisory Board of renowned experts to review the Institute's operations and output. The Board's assessments of the LDI's science have been glowing.

To his great credit, Dr. McInnes was tapped by the Canadian government to serve as Acting President of the CIHR in 2017-2018. In that role, he oversaw the national health research funding agency through a challenging transition. For this and his other contributions to health research, he received the 2018 the Award of Honour of Friends of CIHR, the 2019, Research Canada Leadership in Advocacy Award, and the 2019 Paul Armstrong Lecture Award of the Canadian Academy of Health Sciences, which recognizes "leadership and commitment to advance academic health sciences . . . through achievements that are . . . extraordinary."

Throughout his time at the LDI. Dr. McInnes maintained an active lab research program and supervised trainees as a Professor of **Human Genetics** and Biochemistry at McGill. Last year, his Alva Chair in Human Genetics was renewed for a second term and he will continue to pursue his research and



other academic activities at the LDI, McGill and nationally.

Dr. Ernesto L. Schiffrin, Distinguished James McGill Professor and Vice-Chair in the Department of Medicine, McGill University, Physician-in-Chief of the Jewish General Hospital, and Director of the Vascular and Hypertension Research Unit at the Lady Davis Institute and



Director of the Cardiovascular Prevention Center, has been selected as the recipient of the International Society of Hypertension ISH Franz Volhard Award and Lectureship for Outstanding Research for 2021.

This award and lectureship was endowed by Farbwerke Hoechst in 1972 to commemorate the centenary of the birth of Franz Volhard. Awardees are to have initiated in the field of hypertension, or in a related discipline, a concept which remains of current interest.

The 2021 Award is presented to Dr. Schiffrin in particular in recognition of the ground-breaking research on the role of vascular remodelling and role of endothelin, angiotensin II, aldosterone, inflammation and T regulatory lymphocytes in hypertension. He is "recognized widely in the hypertension community for his trail blazing research and curriculum vitae that provides testament to outstanding contribution to the biology of hypertension, its causation as well as clinical research that affected guidelines and practice."

Dr. Schiffrin will be presented the award at the virtual ISH Awards Ceremony and Presidential Lecture on April 13, 2021 during the Joint Meeting ESH-ISH2021 ON AIR.

In addition to the Award, Dr. Schiffrin will deliver a lecture during the Awards Ceremony on his work related to hypertension.

Dr. Susan Kahn has been appointed to the position of Associate Chair, Research, in the McGill Department of Medicine. In this role, Dr. Kahn will focus on capacity building in basic/clinical research, the growth in Department of Medicine research publications/impact and in research grant funding and will develop mechanisms to ensure the regular measurement and reporting on the Department's research metrics. The Associate Chair will work in close collaboration with internal (McGill and partner institutions) and external (e.g. FRQS, CIHR) research organizations to help McGill reach an even higher level of excellence. Part of Dr. Kahn's stated goals as Associate Chair, Research are to develop robust research mentorship and to further the planning, development and expansion of Medicine's research mission across all sites.

Dr. Arezu Jahani-Asl has been promoted to Associate Professor in the Gerald Bronfman Departement of Oncology and Integrated Program in Neuroscience by McGill University. As a result, she has earned the title of Senior Investigator at the Lady Davis Institute. Her lab's efforts are focused on identifying the molecular mechanisms that underlie brain tumors, in particular, adult glioblastoma, a particularly aggressive cancer of the brain for which, presently, there is no cure.

Dr. Mark Eisenberg, Professor of Medicine and Director of the joint MD-PhD Program at McGill University has co-edited, The Essential MD-PhD Guide [McGraw-Hill Education, 2021]. It is a complete guide to MD-PhD success, with practical tips and insights from MD-PhD students, recent graduates, and practicing physician-scientists. It is intended to provide the prospective or current MD-PhD students with all they need to choose the right program or succeed in their current program. It serves as a resource to guide them through the process of choosing a program, navigating the early years of medical school, selecting a research laboratory and PhD project, and making the transition between medical and graduate studies. It also provides invaluable guidance on choosing clinical rotations, residency programs, and fellowships that open doors to various career options.

Quebec's primary care model for Alzheimer's disease

Answering a call from the World Health Organization for the development of regional plans to address Alzheimer's disease, Quebec has adopted a model anchored in primary care. The Quebec Alzheimer Plan (QAP) is being implemented in family medicine and primary care clinics across the province. An overview of the QAP has been published in *Santé publique* by the Research on Organization of Healthcare Services for Alzheimer's (ROSA) team. ROSA is based in McGill University's Department of Family Medicine and is led by co-founder and Scientific Director, **Dr. Isabelle Vedel**, a Senior Investigator at the Lady Davis Institute and Associate Professor of Family Medicine at McGill.

"The QAP takes a holistic approach to the patient, but does not define them according to their disease," said Dr. Geneviève Arsenault-Lapierre, Senior Research Associate at the LDI and first author on the paper. "Patients and their caregivers are included in the process of providing care as their needs evolve, always with an emphasis on dignity and respect."

The plan emphasizes flexibility and adaptability, incorporating multidisciplinary teams focused on detection, diagnosis, treatment, and follow-up according to the progression of the disease. An evaluation of Phase 1 of the QAP revealed higher quality of care since it was adopted for patients and caregivers, as well as positive attitudes, knowledge and practices from doctors, nurses, social workers, and other health care professionals.

"The patient-centered approach is what distinguishes the Quebec plan," said Dr. Vedel. "It allows Alzheimer's patients to be treated by primary care professionals, who are their first point of contact with the health care system. Those in primary care have a broader appreciation for the complexity of their patients' overall situation and how best to manage their condition within the community. They can then assure access to a range of specialized services, including, for example, memory experts and geriatric psychiatrists."

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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New book addresses the impact of prenatal stress on child development

The complex impact of prenatal stress, the mechanisms by which it is transmitted from mother to child, and how it can impact a child's development and future well-being are the subjects of the new book *Prenatal Stress and Child Development*, edited by Drs. **Ashley Wazana**, Eszter Székely, and Tim F. Oberlander., published by Springer.

"The book offers an overview of the various ways in which prenatal stress affects cognitive, affective, behavioral, and neurobiological development in children, while pinpointing core processes of adaptation, resilience, and interventions that may reduce negative behaviors and promote optimal outcomes in children," said Dr. Wazana, interim head of the Psychosocial Research Axis at the Lady Davis Institute. "Our objective in assembling this collection of current research and thinking on the subject aims to inform clinical strategies and future research targeting prenatal stress and its cyclical impact on subsequent generations."

The volume looks at multiple mechanisms of prenatal stress, including prenatal programming, epigenetics, inflammatory processes, and the brain-gut microbiome. It reports findings on prenatal stressors affecting pregnancy, such as preconception stress, prenatal maternal depression, anxiety, and pregnancy-specific anxieties.

Key areas of coverage include:

- The developmental effects of prenatal maternal stress on children.
- Intergenerational transmission of parental early life stress.
- The effect of prenatal stress on parenting.
- Gestational stress and resilience.
- Prenatal stress and children's sleeping behavior.
- Prenatal, perinatal, and population-based interventions to prevent psychopathology.

Prenatal Stress and Child Development is an essential resource for researchers, professors, and graduate students as well as clinicians, therapists, and related professionals in infancy and early childhood development, maternal and child health, developmental psychology, pediatrics, social work, child and adolescent psychiatry, developmental neuroscience, and related behavioral and social sciences and medical disciplines.

Dr. Brett Thombs of the Psychosocial Axis was awarded a Tier 1 Canada Research Chair in Patient-Oriented Disease Management and Preventive Health Care. Tier 1 Chairs, valued at \$200,000 annually for seven years with one opportunity for renewal, are for outstanding researchers, acknowledged by their peers as world leaders in their field.

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