



Lady Davis Institute Research Newsletter



May 2018 Vol. 7 No. 3

LDI Annual Research Awards

The Lady Davis Institute is proud to honour the achievements of its researchers.

Dr. Prem Ponka of the Molecular and Regenerative Medicine Axis received the Award for Excellence in Basic Research. An internationally recognized scientist who has been at the LDI for more than thirty years, the goal of his research is to enhance knowledge about iron metabolism and heme synthesis in erythroid cells, and to examine the pathophysiology behind some diseases caused by defective hemoglobin formation. Recently, his laboratory provided evidence for his novel hypothesis that, in erythroid cells, iron is directly delivered to mitochondria by endosomes in a “kiss and run” paradigm.

Dr. Kristian Filion of the Centre for Clinical Epidemiology was given the Award for Excellence in Clinical Research. A member of the Canadian Network for Observational Drug Effect Studies (CNODES) team, Dr. Filion uses large, population-based databases to study the safety of commonly prescribed medications, with a particular interest in cardiovascular medications and outcomes.



Award for Excellence in Basic
Research: **Dr. Prem Ponka**



Research Leadership Award:
Dr Bluma Blenner & Dr. Thibault Mesplède



The inaugural Research Leadership Award was shared by Drs. **Bluma Brenner** and **Thibault Mesplède**. This honour is intended to recognize their outstanding leadership and significant contributions to the institution, above and beyond their own research program or professional obligations. Specifically, it rewards their exceptional efforts in taking charge in the wake of Dr. Mark Wainberg's untimely passing and providing stability and continuity during a difficult time.



Award for Excellence in Clinical
Research: **Dr. Kristian Filion**

The LDI's annual research awards acknowledge the high regard in which the winners are held by all members of the Lady Davis community.

9th Annual Scientific Retreat

More than 300 researchers, trainees, and staff attended the 9th annual LDI Scientific Retreat. This year's keynote speakers were both from McGill University. **Dr. Edouardo Franco**, James McGill Professor and Chairman of the Department of Oncology, and Director of the Division of Cancer Epidemiology, spoke on new challenges in scholarly publishing. **Dr. Russell Jones**, Associate Professor in the Department of Physiology, spoke about novel mechanisms of LKB1-mediated tumour suppression.

Stephane Benhamou, (pictured), the IT manager at the LDI, was recognized as Administrative Employee of the Year.

Trainees have the opportunity to present their research during the retreat by giving talks and displaying posters. The prize for best oral presentation was awarded to **Nour Ghaddar** of the Koromilas lab for "*The adaptive trait of the integrated stress response promotes KRAS lung tumorigenesis.*"



Recognition for best posters went to:

Mingyi Lou (Orthwein lab);
Thomas Funk (Thiel lab) ;
Marisa Cressatti (Schipper lab);
Elizaveta Solomonova (Zelkowitz lab);
Michael Dahabieh (Miller/Del Ricon lab).

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.

To submit information or for media enquiries, contact:
 Tod Hoffman at: thoffman@jgh.mcgill.ca;
 514-340-8222, ext. 28661

.**Dr. Thibault Mesplède** was the inaugural recipient of an award from the Mark Wainberg Fund of the Canadian Association for HIV Research (CAHR) which supported his participation in the 2018 Conference on Retroviruses and Opportunistic Infections (CROI) in Boston. Dr. Mesplède presented two posters dealing with HIV drug resistance mutations.

CAHR created the Fund to honour Dr. Wainberg and provide financial support to enable researchers to present their work at Canadian and international conferences.

"It is important for us to show the scientific community that the work Mark started is continuing and advancing," he said. "One of the strengths of the lab has been to select and identify drug resistance in pre-clinical studies. Our intention now is to work more closely with infectious disease clinicians at the Jewish General Hospital to make our work more translational."

Dr. Mesplède has also been elected to the "Comité de Direction Scientifique du Réseau SIDA/MI" of the Fonds de recherche Québec – Santé for the next four years.

Smoking in patients with heart attack reduced with varenicline

Patients who smoke after an acute coronary syndrome, including a heart attack (myocardial infarction) or unstable angina (reduced blood flow to the heart) are at increased risk of another attack and death if they do not quit.

About 40% of participants in a randomized controlled trial who received varenicline were not smoking at one year, compared with 29% in the placebo group. Reductions in daily cigarette smoking of at least 50% were also higher in the varenicline group (57.8%) compared with the placebo group (49.7%). Rates of adverse events were similar in both groups. The trial was led by **Dr. Mark Eisenberg** and published in the [Canadian Medical Association Journal \(CMAJ\)](#).

The authors note that if varenicline was used as routine treatment in smokers after heart attack, it would reduce smoking in this group by about 10%.

MAY 31 IS WORLD NO TOBACCO DAY



13th annual JGH Department of Psychiatry

Research Day: featuring distinguished speakers from the Lady Davis Institute, focused on the theme *Connecting Mind and Body: Psychosocial interventions in the context of treating physical disease*. Pictured (left to right) are **Dr. David Dunkley** of the Institute of Community and Family Psychiatry at the JGH, who coordinates the research day; **Dr. Melissa Henry**, a psychologist with the Louise Granofsky Psychosocial Oncology Program at the Segal Cancer Centre and an Assistant Professor in the Departments of Oncology and Psychology at McGill University, who discussed her research on meaning-making interventions for patients with advanced cancer confronting existential distress; **Dr. Carmen Loiselle**, Senior Researcher at the Centre for Nursing Research, Co-Director of the Segal Cancer Center and Professor at McGill's Ingram School of Nursing, who served as the discussant;

Two LDI trainees—**Matthew Laaper** (of the Molecular and Regenerative Medicine Axis) and **Michael Dahabieh** (Cancer Axis) were finalists in McGill's 3-Minute Thesis competition. Fourteen grad students were given the opportunity to present captivating and concise summaries of their research.

Dr. Soham Rej, a geriatric psychiatrist at the JGH and Assistant Professor of Psychiatry at McGill University, who presented new clinical evidence on how mind-body treatments such as meditation, yoga, and Tai Chi can help to treat late-life depression and anxiety; **Dr. Karl Looper**, Chief of the JGH Department of Psychiatry; and **Dr. Brett Thombs**, Director of the Scleroderma Patient-centred Intervention Network (SPIN) and Professor of Psychiatry at McGill University, who addressed the unique challenges faced by those living with rare diseases and novel approaches for overcoming insufficient knowledge of their condition and lack of therapeutic options.

The conference is supported by a grant from the Gustav Levenschi Foundation.

Dr. Jackson Mwale has been selected to serve as a member of the National Institutes of Health's (NIH) Musculoskeletal Tissue Engineering Study Section, Center for Scientific Review for a 6-year term beginning July 1. Dr. Mwale has the distinction of being the only non-American on the panel.

President of the Canadian Orthopedic Research Society, Dr. Mwale is co-organizer of the 2019 Combined Meeting of Orthopaedic Research Societies in Montreal.

New therapeutic pathway explored in melanoma

The acral/mucosal subtype of melanoma – which accounts for between 5% and 40% of all cases of melanoma – is less responsive to standard therapies used against cutaneous melanoma. Noting that this variant of the disease is characterized by a mutation of the KIT gene and elevated levels of the MNK / eIF4E proteins has revealed a previously unexplored pathway holding potential for treatment, according to findings from **Dr. Wilson Miller's** lab, published in the *[Journal of Clinical Investigation](#)*.

"When mutated, KIT doesn't require any additional external signals to spawn malignancy," explained **Dr. Sonia del Rincon**, Assistant Professor of Oncology. "We showed that the MNK / eIF4E axis was critical to induce this activity. It facilitates downstream synthesis of proteins that have long been associated with cancer."

KIT mutant melanomas are particularly prevalent among people of Asian descent. Yao Zhan, who obtained her PhD in the lab, played a crucial role in accessing patient samples through the Beijing University Cancer Hospital. These particular melanomas are not associated with sun exposure and are frequently found on the palms and soles of the feet where they may go unnoticed. It is a very aggressive disease.

To this point, the MNK target has not been fully explored. "We propose that MNK1/2 inhibitors could be effective in a molecularly defined cohort of melanoma patients with KIT aberrations, which currently represents a pressing therapeutic challenge," write the authors.

An MNK inhibitor has been tested on an animal model with KIT mutations. While it doesn't destroy the melanoma, it was shown to slow its growth and reduce its invasive and metastatic properties. There are clinical trials underway using MNK inhibitors in combination with immunotherapies on different cancers. This is promising because immunotherapies have produced complications due to their toxicity, while the MNK inhibitors are not toxic.

"We see MNK1/2 as a valuable untapped drug target," said Dr. del Rincon. "We think this is a promising vulnerability in those cancer cells where it is expressed."

A potential new strategy for treating thalassemia

Thalassemias are a serious form of red blood cell disorder, in which a genetic mutation causes decreased production of hemoglobin. The resulting destruction of large numbers of faulty red blood cells causes anemia. Among genetic disorders, they rank as a major cause of mortality and morbidity, for which there is no optimal treatment or cure available. **Dr. Prem Ponka**, who is an international leader in the study of heme synthesis and the formation of red blood cells, together with his co-workers, have published the first investigation of heme oxygenase (HO) as a potential target for thalassemia therapy in *[Blood](#)*.

Since genetic therapy is still years away, Dr. Ponka's lab concentrates on the therapeutic potential of a specific pathway associated with the manufacture of hemoglobin and the regulation of its production.

"We thought we could take an approach that would address the consequences of malformation of globin chains on the health of developing red cells in the bone marrow", Dr. Ponka explains. "We contemplated that molecules of heme (red cell pigment) that are associated with free globin chains in excess, are targets for HO-1." Hence, Dr. Ponka's lab looked at HO-1, the enzyme that destroys heme and releases potentially toxic iron from this pigment in developing red cells. The investigators also considered a possibility that abundant HO-1 in macrophages, a type of white blood cell, could play a role in thalassemia pathogenesis. Red cells, after their 50-day (mice) sojourn in the circulation, are engulfed by macrophages that recycle hemoglobin iron.

Dr. Ponka and coworkers have confirmed their hypotheses by showing that blocking the degradation of heme with an inhibitor of HO-1 reduced toxicity and significantly improved the well-being of red cells in thalassemic mice. Additionally, administration of an HO inhibitor to thalassemic animals decreased the amount of iron available for erythropoiesis, consequently ameliorating ineffective erythropoiesis characterized by the premature death of developing red cells in the marrow.

As Dr. Ponka states, "This double-punch strategy stands out as an alternative and advantageous approach for treatment of thalassemia compared to other current procedures and deserves further investigation".

This article was featured in "**This Week in Blood**", a snapshot of the hottest studies from each week's issue, hand-picked by Editor-in-Chief of *Blood*.

Upcoming Grants and Awards Deadlines

- May 20, 2018 – LDI Students Travel Awards (up to \$1,000 each award), contact janik.jacmain@ladydavis.ca
- June 22, 2018 – [Cancer Quality and Innovation Research Fund, Rossy Cancer Network](#)

Selected Bibliography of Papers from the Lady Davis Institute (March—April 2018):

CANCER

[Afatinib in Osimertinib-Resistant EGFR ex19del / T790M / P794L mutated Non-Small Cell Lung Cancer.](#) **van Kempen LC**, Wang H, Aguirre ML, Spatz A, Kasymjanova G, Vilacha JF, Groves MR, Agulnik J, **Small D**. *J Thorac Oncol*. 2018 Apr 25. pii: S1556-0864(18)30548-3. doi: 10.1016/j.jtho.2018.04.020.

[High-Protein Hypocaloric Nutrition for Non-Obese Critically Ill Patients.](#) **Hoffer LJ**. *Nutr Clin Pract*. 2018 Apr 27. doi: 10.1002/ncp.10091.

[Cytology cell blocks are suitable for immunohistochemical testing for PD-L1 in lung cancer.](#) Wang H, Agulnik J, Kasymjanova G, Wang A, Cohen V, Small D, Pepe C, Sakr L, Fiset P, Auger M, Camilleri-Broet S, Alam El Din M, Chong G, van Kempen L, **Spatz A**. *Ann Oncol*. 2018 Apr 12. doi: 10.1093/annonc/mdy126.

[Atypical Tuberous Sclerosis Complex presenting as familial renal cell carcinoma with leiomyomatous stroma.](#) Bah I, Fahiminiya S, Bégin LR, Hamel N, D'Agostino MD, Tanguay S, **Foulkes WD**. *J Pathol Clin Res*. 2018 Apr 16. doi: 10.1002/cjp2.104.

[Signaling pathways involved in the regulation of mRNA translation.](#) Roux PP, **Topisirovic I**. *Mol Cell Biol*. 2018 Apr 2. pii: MCB.00070-18. doi: 10.1128/MCB.00070-18.

[Inhibition of CD45 phosphatase activity induces cell cycle arrest and apoptosis of CD45+ lymphoid tumors ex vivo and in vivo.](#) Perron M, **Saragovi H**. *Mol Pharmacol*. 2018 Mar 19. pii: mol.117.110908. doi: 10.1124/mol.117.110908.

[A screening algorithm for early detection of major depressive disorder in head and neck cancer patients post-treatment: Longitudinal study.](#) **Henry M**, Rosberger Z, Ianovski LE, Hier M, Zeitouni A, Kost K, Mlynarek A, Black M, MacDonald C, Richardson K, Zhang X, Fuhrmann F, Chartier G, **Frenkel S**. *Psychooncology*. 2018 Mar 13. doi: 10.1002/pon.4705.

[The Special Issue: Clinical Proteomics for Precision Medicine.](#) Parker CE, **Borchers CH**. *Proteomics Clin Appl*. 2018 Mar;12(2). doi: 10.1002/prca.201600144.

[Distinct homologous recombination gene expression profiles after neoadjuvant chemotherapy associated with clinical outcome in patients with ovarian cancer.](#) Kessous R, Octeau D, Klein K, Tonin PN, Greenwood CMT, Pelmus M, Laskov I, Kogan L, Salvador S, Lau S, Yasmeen A, **Gotlieb WH**. *Gynecol Oncol*. 2018 Mar;148(3):553-558. doi: 10.1016/j.ygyno.2018.01.017.

Epidemiology

[Observational studies of inhaled corticosteroid effectiveness in COPD: Lessons learned.](#) **Suissa S, Ernst P.** Chest. 2018 Apr 18. pii: S0012-3692(18)30574-9. doi: 10.1016/j.chest.2018.04.006.

[Making Sense of Triple Inhaled Therapy for COPD.](#) **Suissa S, Drazen JM.** N Engl J Med. 2018 May 3;378(18):1723-1724. doi: 10.1056/NEJMMe1716802. Epub 2018 Apr 18.

[First concussion did not increase the risk of subsequent concussion when patients were managed appropriately.](#) **Shrier I, Piché A, Steele RJ.** Br J Sports Med. 2018 Apr 16. pii: bjsports-2018-099104. doi: 10.1136/bjsports-2018-099104.

[Do not throw the baby out with the bathwater; screening can identify meaningful risk factors for sports injuries.](#) Verhagen E, van Dyk N, Clark N, **Shrier I.** Br J Sports Med. 2018 Apr 11. pii: bjsports-2017-098547. doi: 10.1136/bjsports-2017-098547.

[The effectiveness and cost-effectiveness of screening for latent tuberculosis among migrants in the EU/EEA: a systematic review.](#) **Greenaway C, Pareek M, Abou Chakra CN, Walji M, Makarenko I, Alabdulkarim B, Hogan C, McConnell T, Scarfo B, Christensen R, Tran A, Rowbotham N, van der Werf MJ, Noori T, Pottie K, Matteelli A, Zenner D, Morton RL.** Euro Surveill. 2018 Apr;23(14). doi: 10.2807/1560-7917.ES.2018.23.14.17-00543.

[Reduced Mortality With Sodium-Glucose Cotransporter-2 Inhibitors in Observational Studies: Avoiding Immortal Time Bias.](#) **Suissa S.** Circulation. 2018 Apr 3;137(14):1432-1434. doi: 10.1161/CIRCULATIONAHA.117.032799.

[Dipeptidyl peptidase-4 inhibitors and incidence of inflammatory bowel disease among patients with type 2 diabetes: population based cohort study.](#) Abrahami D, Douros A, Yin H, Yu OHY, Renoux C, Bitton A, **Azoulay L.** BMJ. 2018 Mar 21;360:k872. doi: 10.1136/bmj.k872.

[How I treat the post-thrombotic syndrome.](#) Rabinovich A, **Kahn SR.** Blood. 2018 Mar 15. pii: blood-2018-01-785956. doi: 10.1182/blood-2018-01-785956.

[Synthesizing risk from summary evidence across multiple risk factors.](#) **Shrier I, Colditz GA, Steele RJ.** Epidemiology. 2018 Mar 13. doi: 10.1097/EDE.0000000000000820.

[Risk of Intracranial Hemorrhage Associated with the Use of Antidepressants Inhibiting Serotonin Reuptake: A Systematic Review.](#) Douros A, Ades M, **Renoux C.** CNS Drugs. 2018 Mar 13. doi: 10.1007/s40263-018-0507-7.

[Non-Vitamin K Antagonist Oral Anticoagulants and Risk of Serious Liver Injury.](#) Douros A, Azoulay L, Yin H, Suissa S, **Renoux C.** J Am Coll Cardiol. 2018 Mar 13;71(10):1105-1113. doi: 10.1016/j.jacc.2018.01.009.

[Special issue: Late consequences of venous thromboembolism.](#) **Kahn SR, Pengo V.** Thromb Res. 2018 Apr;164:99. doi: 10.1016/j.thromres.2018.02.005.

[An analytic approach for interpretable predictive models in high-dimensional data in the presence of interactions with exposures.](#) Bhatnagar SR, Yang Y, Khundrakpam B, Evans AC, Blanchette M, Bouchard L, **Greenwood CMT.** Genet Epidemiol. 2018 Apr;42(3):233-249. doi: 10.1002/gepi.22112.

Molecular & Regenerative Medicine

[Deep Vein Thrombosis Induced by Stasis in Mice Monitored by High Frequency Ultrasonography](#). Rys RN, Blostein MD, Lemarié CA. J Vis Exp. 2018 Apr 13;(134). doi: 10.3791/57392.

[Update of the 6-Item Brief Geriatric Assessment Screening Tool of Older Inpatients at Risk for Long Length of Hospital Stay: Results From a Prospective and Observational Cohort Study](#). Beauchet O, Chabot J, Fung S, Launay CP. J Am Med Dir Assoc. 2018 Apr 26. pii: S1525-8610(18)30134-8. doi: 10.1016/j.jamda.2018.03.010.

[Succinate decreases bladder function in a rat model associated with metabolic syndrome](#). Velasquez Flores M, Mossa AH, Cammisotto P, Campeau L. Neurourol Urodyn. 2018 Apr 18. doi: 10.1002/nau.23488.

[ADAR1 and PKR, interferon stimulated genes with clashing effects on HIV-1 replication](#). Radetsky R, Daher A, Gatignol A. Cytokine Growth Factor Rev. 2018 Mar 26. pii: S1359-6101(18)30032-7. doi: 10.1016/j.cytofr.2018.03.007.

[The S230R Integrase Substitution Associated with Viral Rebound during DTG Monotherapy Confers Low Levels INSTI Drug Resistance](#). Pham HT, Labrie L, Wijting IEA, Hassounah S, Lok KY, Portna I, Goring M, Han Y, Lungu C, van der Ende ME, Brenner BG, Boucher CA, Rijnders BJA, van Kampen JJA, Mesplède T, Wainberg MA. J Infect Dis. 2018 Mar 29. doi: 10.1093/infdis/jiy175.

[Bladder overdistension with polyuria in a hypertensive rat model](#). Velasquez Flores M, Mossa AH, Cammisotto P, Campeau L. Neurourol Urodyn. 2018 Mar 31. doi: 10.1002/nau.23550.

[Cystatin C promotes tau protein phosphorylation and causes microtubule instability by inhibiting intracellular turnover of GSK3 \$\beta\$ in neurons](#). Duan J, Marcellus KA, Qin X, Wang Y, Paudel HK. Mol Cell Neurosci. 2018 Mar 22;89:1-8. doi: 10.1016/j.mcn.2018.03.009.

[Body position and motor imagery strategy effects on imagining gait in healthy adults: Results from a cross-sectional study](#). Beauchet O, Launay CP, Sekhon H, Gautier J, Chabot J, Levinoff EJ, Allali G. PLoS One. 2018 Mar 15;13(3):e0191513. doi: 10.1371/journal.pone.0191513.

[Effect of pre-pregnancy body mass index on respiratory-related neonatal outcomes in women undergoing elective cesarean prior to 39 weeks](#). Vincent S, Czuzoj-Shulman N, Spence AR, Abenhaim HA. J Perinat Med. 2018 Mar 15. pii: /j/jpme.ahead-of-print/jpm-2017-0384/jpm-2017-0384.xml. doi: 10.1515/jpm-2017-0384.

[Rare human Caspase-6-R65W and Caspase-6-G66R variants identify a novel regulatory region of Caspase-6 activity](#). Tubeleviciute-Aydin A, Zhou L, Sharma G, Soni IV, Savinov SN, Hardy JA, LeBlanc AC. Sci Rep. 2018 Mar 13;8(1):4428. doi: 10.1038/s41598-018-22283-z.

[CXCL1-CXCR2 lead monocytes to the heart of the matter](#). Paradis P, Schiffrian EL. Eur Heart J. 2018 Mar 8. doi: 10.1093/eurheartj/ehy114.

Psychosocial

[Training and support needs of scleroderma support group facilitators: the North American Scleroderma Support Group Facilitators Survey](#). Delisle VC, Gumuchian ST, El-Baalbaki G, Körner A, Malcarne VL, Peláez S, Carrier ME, Pépin M, Thombs BD; Scleroderma Support Group Project Advisory Team. Disabil Rehabil. 2018 Apr 26:1-6. doi: 10.1080/09638288.2018.1467970.

[Theory of mind as a link between oxytocin and maternal behavior.](#) MacKinnon AL, Carter CS, Feeley N, Gold I, Hayton B, Santhakumaran S, **Zelkowitz P.** Psychoneuroendocrinology. 2018 Jun;92:87-94. doi: 10.1016/j.psyneuen.2018.03.018.

[Micro-Meso-Macro Practice Tensions in Using Patient-Reported Outcome and Experience Measures in Hospital Palliative Care.](#) Krawczyk M, Sawatzky R, Schick-Makaroff K, Stajduhar K, Öhlen J, Reimer-Kirkham S, Mercedes Laforest E, **Cohen R.** Qual Health Res. 2018 Mar 1:1049732318761366. doi: 10.1177/1049732318761366.

[Understanding and communicating risk: Measures of outcome and the magnitude of benefits and harms.](#) Bell NR, Dickinson JA, Grad R, Singh H, Kasperavicius D, **Thombs BD.** Can Fam Physician. 2018 Mar;64(3):181-185.

[Factors associated with negative observer responses towards individuals with visible differences: A scoping review.](#) Jewett LR, Gumuchian ST, Pepin M, Rice DB, Kolorz F, Harrison P, **Thombs BD.** Body Image. 2018 Mar 8;25:103-132. doi: 10.1016/j.bodyim.2018.02.007.

[Use of the nominal group technique to identify stakeholder priorities and inform survey development: an example with informal caregivers of people with scleroderma.](#) Rice DB, Cañedo-Ayala M, Turner KA, Gumuchian ST, Malcarne VL, Hagedoorn M, **Thombs BD;** Scleroderma Caregiver Advisory Team. BMJ Open. 2018 Mar 2;8(3):e019726. doi: 10.1136/bmjopen-2017-019726.