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Research Newsletter

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New mechanism of drug resistance in acute myeloid leukemia identified

Patients under the supervision of Drs. **Sarit Assouline** and **Wilson Miller** at the Segal Cancer Centre were part of a multi-centre clinical trial of ribavirin that revealed a novel mechanism of anticancer drug resistance in acute myeloid leukemia (AML), one of the deadliest forms of leukemia. The research team, led by Dr. Kathy Borden of the Institut de recherche en immunologie et cancer (IRIC), published its findings in *Nature*.

This discovery constitutes a major breakthrough because it suggests strategies to overcome drug resistance. Moreover, this type of drug resistance is likely implicated in other cancers. Therefore, a successful new treatment regimen based on these findings could have broad applications.

"A first clinical study yielded extremely promising results in most patients, including remissions, with no significant treatment-related toxicity. However, as is often the case when using a single drug, all patients eventually relapsed," recall Drs. Assouline and Miller.

A study of drug resistant cancer cells from AML patients and head and neck tumors revealed that the GLI1 gene is dramatically overactive. Researchers were able to show that this results in a chemical change to the drugs that prevents their toxicity against the cancer cells.

Fortunately, drugs that inhibit the activity of GLI1 are currently available and the scientists showed that, in the laboratory, these drugs could switch the cancer cells back into a ribavirin-sensitive state. It is hoped that, when used in combination-therapy with ribavirin (or more standard chemotherapy), these drugs will prevent the development of drug resistance in these patients. The team has now received approval from Health Canada to undertake a new clinical trial to test this novel drug combination on AML patients.

New Quebec consortium for early identification of Alzheimer's disease

A Quebec consortium for the early identification of Alzheimer's disease (known as CIMA-Q, Consortium pour l'identification précoce de la maladie d'Alzheimer – Québec) has been launched under co-directors Dr. Sylvie Belleville, Director of Research at the Institut universitaire de gériatrie de Montréal, and **Dr. Andréa LeBlanc**, James McGill Professor in the Department of Neurology and Neurosurgery, thanks to a $2.5-million investment from the Pfizer-FRQS Innovation Fund, a program of the Fonds de recherche du Québec – Santé funded by Pfizer Canada.

The ninety researchers and clinicians within CIMA-Q are actively recruiting 350 people over the age of 60 to undergo regular exams that will help with efforts to identify the early signs and the cause of Alzheimer's.

CIMA-Q will create a central database of clinical, cognitive, neuroimaging and biological measurements and materials that researchers will study to determine the early markers of Alzheimer's disease. Participants will undergo regular assessments to see if they are developing symptoms or maintaining their cognitive health. CIMA-Q experts will also study lifestyle aspects to determine which ones predispose individuals to, or protect them from, the disease.

Dr. LeBlanc encourages participation in this important province-wide initiative, "We need a large pool of volunteers. Whether you are healthy or worried about your memory, you can help advance science. This is a chance for people to take concrete action, as we all know someone who is suffering, or has suffered, from Alzheimer's. We all want to do something to prevent or treat Alzheimer Disease in the aged and to protect our children from this disease."

For more information, go to www.cima-q.ca or call 514-340-3540, extension 4599.

Novel findings on hemoglobin regulation

Dr. Prem Ponka published findings in *Blood* that, according to an accompanying *Inside Blood* commentary (Brousse and El Nemer), "advance(s) the field of heme regulation" by "address(ing) for the first time the role of the inducible HO-1 during murine erythroid differentiation." That is to say, the process by which red blood cells (RBC) differentiate themselves in the bone marrow from their progenitors.

Heme is a complex of iron with the molecule protoporphyrin IX, which is essential for the function of all cells that depend on oxygen. It serves as an essential component of many hemoproteins (eg, hemoglobin, myoglobin, cytochromes, and innumerable enzymes with regulatory functions). However, when left unguarded, non-protein-bound heme promotes free radical formation and lipid peroxidation, resulting in cell damage and tissue injury. Hence, the body maintains tight controls on cellular heme levels, the highest amounts of which (approximately 80%) are present in circulating RBC.

The only physiological mechanisms for degrading heme are heme oxygenases (HO), of which HO-1 has been extensively studied. Virtually nothing is known about the expression and potential significance of HO-1 in developing RBC.

"In our study, we have demonstrated that HO-1 is present in erythroid cells and, somewhat surprisingly, that its expression is upregulated during erythroid differentiation", explained Dr. Prem Ponka.

"Overexpression of HO-1 in erythroid cells impairs hemoglobin synthesis suggesting that this enzyme could play a role in some pathophysiological conditions such as unbalanced globin synthesis in thalassemias, genetic disorders characterized by a reduced amount of hemoglobin in RBCs associated with severe anemia," Dr. Ponka said.

Based on these results, the authors conclude that HO-1 controls the regulatory heme pool at appropriate levels for any given stage of erythroid differentiation. The results indicate that HO-1 plays an important role as a co-regulator of the erythroid differentiation process. They propose that targeted inhibition of erythroid HO-1 may be a future consideration for the treatment of some types of thalassemias.

5th Annual LDI Scientific Retreat

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Dr. Morag Park, James McGill Professor of Biochemistry and Oncology and Director of McGill's Goodman Cancer Research Centre, delivered the keynote address on cancer research in the post-genomic world.

Research Grants Officer **Janik Jacmain** was named LDI Employee of the Year.

First prize for trainee oral presentations was awarded to **Michael Dahabieh** of Dr. Wilson Miller's lab in the cancer axis for "Identification and targeting of autophagosome proteins in Vorinostat -sensitive and -resistant histiocytic lymphoma." Second prize went to **Leora Witkowski** of Dr. William Foulkes' cancer lab for "Germline and somatic SMARCA4 mutations characterize small cell carcinoma of the ovary, hypercalcemic type."

The best poster presentations were prepared by: **Ryuhjin Ahn** of Dr. Josie Ursini-Siegel's cancer lab, **Robert Scarborough** of Dr. Anne Gatignol's HIV/AIDS lab, **Sandrine Laurance** of Dr. Mark Blostein's hemovascular lab, and **Maud Jacques** of Dr. Michael Witcher's cancer lab.

Principal investigators who gave talks on their research included: Drs. **Prem Ponka** of the hemovascular axis, **Lawrence Kleiman** from the HIV/AIDS axis, **Susan Kahn** from epidemiology, **Marc Fabian** from the cancer axis, **Howard Chertkow** from the aging axis, and **Robin Cohen** of the psychosocial axis. Dr. **Colin Crist** of the cancer axis gave the new PI talk.

Rare, aggressive pediatric tumor linked to mutations in a single gene

Upon studying blood and/or tumor samples from virtually every known case of pituitary blastoma (PitB), a very rare, potentially lethal early childhood tumor of the pituitary gland, **Dr. William Foulkes**, head of the Cancer Genetics Laboratory at the LDI, and his collaborators have concluded that a germ-line (or heritable) mutation of DICER1 is the major, and possibly sole, predisposing genetic contributor. The finding was published in *Acta Neuropathologica*.

"If you have PitB, you essentially have to have a germline mutation in DICER1," said Dr. Wiiliam Foulkes. "It's quite rare to attribute all cases of a cancer to mutations in a single gene. Compare that to colon or breast cancer, where mutations account for only about 5% or 6% of cases, about 10% for ovarian cancer."

Notwithstanding that only thirteen cases of PitB have been reported, it is intriguing to have uncovered a unique genetic cause. Even among individuals with a DICER1 mutation, however, the risk of PitB is much less than 1%. "So, it isn't just a DICER1 mutation, but perhaps some other genetic factor that brings on this tumor," Dr. Foulkes specifies.

Dr. Foulkes, along with Dr. John Priest of Minnesota, combed the literature to identify patients and then succeeded in acquiring blood or tumor samples from almost all of them. With the help of Dr. Pierre Lepage from the McGill University Genome Quebec Innovation Centre, they were able to perform a Fluidigm array, which allows for the screening of the whole DICER1 gene in extremely small samples (they were, after all, working with tiny biopsies taken from a child's brain). This allowed them to finalize the mutation analysis.

"What is malfunctioning DICER1 doing that hijacks the normal development process? Learning the control mechanisms that are disrupted will reveal something about pituitary development. Endocrinologists are becoming very interested in our work," he reports.

"Pituitary Blastoma: a pathognomonic feature of germline DICER1 mutations" by Leanne de Kock, John R. Priest, William D. Foulkes and colleagues is published online in *Acta Neuropathologica.*

AmorChem offering up to $500,000 to fund innovative science

AmorChem is hosting its second KNOCK-OUT™ Event at BioContact 2014, in Québec City. Academic life science researchers developing innovative projects with strong commercial potential may be among the participants chosen to duke it out in the *Dragons' Den* inspired event for the chance to win AmorChem financing of up to $500,000.

Interested researchers must be able to describe their technology, its clinical applications, relevance to human disease, as well as its commercial potential. Selected contenders will make their case before a live audience at BioContact on October 8, 2014.

Deadline for application is July 14, 2014. Contact Nadia Nour for full details at 514-340-8222, ext. 8321 or nadia.nour@mcgill.ca.

First Canadian Alzheimer's Disease Research Symposium—October 2014

Dr. Andréa LeBlanc is among the organizers of the 1st Canadian Alzheimer's Disease Research Symposium to be held October 2-4, 2014 in Quebec City. Dedicated to finding a cure for Alzheimer's disease and related dementia, the meeting will be devoted to Canadian research, including fundamental, imaging and biomedical research. Researchers from coast to coast will have the opportunity to share the latest discoveries and breakthroughs from molecular mechanisms to preclinical trials. The organizers aim to provide a national official event for Canadian Alzheimer's disease research. Deadline for registration: August 15, 2014.
Click here for details and registration..

Sanofi BioGENEius Challenge National Finalist

Julien Sénécal, a first year student at Collège Jean-de-Brébeuf, placed fifth nationally in the Sanofi BioGENEius Challenge Canada. He was mentored in the development of his project by Yann Le Duff, a post-doctoral fellow in Dr. Chen Liang's HIV/AIDS lab. He was exploring the potential of the bacterial defense system CRISPR/Cas9 as a novel technology for inhibiting HIV-1 replication.

Higher death rates for weekend hospital stays

People hospitalized with chronic obstructive pulmonary disease or pneumonia are more likely to die during a weekend stay in hospital, according to research led by **Dr. Samy Suissa**, Director of the Centre for Clinical Epidemiology, and published in the *European Respiratory Journal*. This is the first study to assess death rates among patients staying in hospital over the weekend, irrespective of the day of admission.

Previous studies have identified the so-called *weekend effect*, where patients admitted to hospital at the weekend have an increased risk of dying. While this could be related to a shortage of staff, it could also be due to the fact that more severe patients will admit themselves to hospital during a weekend, while those with milder symptoms would wait to speak to their doctor the following week.

Dr. Suissa's study showed increased risk of death for patients who stay in hospital over the weekend.

Dr. Suissa's study analyzed the weekend effect in a different way by assessing whether patients who stayed in hospital over the weekend, even if they were admitted earlier in the week, also experienced an increased risk of death.

The results demonstrated that, irrespective of when patients are admitted, if they stay in hospital over the weekend the risk of death is increased. During the weekday, the death rate was 80 per 10,000 per day. On a Friday, the risk of death increased by 5%, suggesting an additional 4 deaths per 10,000. On a Saturday and Sunday the risk increased by 7% suggesting an additional 5.6 deaths per 10,000 for each weekend day.

The findings, therefore, suggest that the increase in the risk of death is due to a reduced quality of care or reduced access to high quality care at the weekend, an effect that appears to begin on Friday.

Dr. Suissa said, "Our study is the first to report an increase in mortality for patients staying in hospital over the weekend. There are huge implications for the way healthcare is delivered across the globe. It may be time to reconsider the weekend concept in the healthcare calendar to avert a significant number of likely preventable deaths."

Graduate Student Poster Award for Psychosocial Axis

Stephanie Coronado-Montoya, a master's student in Dr. Brett Thombs' group, received the Graduate Student Poster Award for the best graduate student poster at the 2014 Canadian Cochrane Collaboration Symposium in Ottawa, for her presentation that employed a novel statistical test to examine published clinical trials of mindfulness-based therapies for mental health problems. The purpose was to assess whether published results likely represent what actually occurs in trials or whether positive results that appear to support the therapy may have been reported to the exclusion of negative results raising questions about the therapy's effectiveness.

LDI organized conferences

- **Dr.Andrew Mouland** co-organized the First International Symposium on Stress-Associated RNA Granules in Human Disease and Viral Infection at Dalhousie University, Halifax in June. The initiative brought together leaders in the field of RNA granule biology.
- **Dr. Stephanie Lehoux** co-organized the 9th International Symposium on Biomechanics, Vascular Biology and Cardiovascular Disease in April at McGill. The meeting brought together vascular biologists, biomedical engineers, and clinicians to explore the effects of flow and shear stress on cell signaling and function and the role of fluid and solid mechanics in the genesis and fate of atherosclerotic plaques and vascular aneurysms.

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