May 2010

UHN Captures $30M in New Ministry Funding

The Ontario Ministry of Research and Innovation has announced $30.1M in new funding to five UHN-led programs in genomics and gene-related areas of research spanning cancer, cardiology, lung transplant and computational biology. UHN awardees in the Ontario Research Fund--Global Leadership Round in Genomics & Life Sciences include:

OCI's Drs. Benjamin Neel and Bradly Wouters were awarded $10.1M for the "*Functional Genomics of Solid Tumours for Discovery and Development of New Biologics and Biomarkers*" project. With collaborators at the University of Toronto, the team will use state-of-the-art genetic screens, next-generation genome sequencing and high-throughput synthetic antibody development to accelerate the discovery of novel cancer therapies and biomarkers.

Dr. Igor Jurisica

Drs. Igor Jurisica and Gary Bader (University of Toronto) were awarded $10.02M for the "*Cancer Gene Encyclopedia (CGEP): Computationally optimized characterization of cancer genes, proteins, their structure, function and interactions*" project. It will provide an integrated database for systematic characterization of cancer proteins, their interactions and pathways; and will allow for the identification of new cancer targets in lung, prostate, breast, ovary and head and neck cancers.

Drs. Peter Liu and Gordon Keller will receive $6.6M towards the "*Cardiovascular Biomarker Discovery in Disease and Development through Predictive Precision Proteomics (CBD3P3)*" project. The team will develop new screening and diagnostic tools to identify patients in the early stages of heart disease and determine the most effective treatment on an individual basis.

OCI's Dr. Rama Khokha was awarded $2.1M towards her proposed "*Functional Oncogenomics for the Discovery of Cancer Drivers and Unique Subclasses (FOCUS)*" project that aims to understand how certain genes affect the development of osteosarcoma—a devastating form of bone cancer brought to the forefront by Terry Fox thirty years ago on his Miracle of Hope campaign.

UHN Researcher Wins CFI Award

UHN's Dr. Brian Raught was awarded $400K by the Canada Foundation for Innovation (CFI) in the most recent Leaders Opportunity Fund. The award will provide Dr. Raught with funds to establish infrastructure towards the "*Mass Spectrometry-Based Proteomic Studies of Cancer Models*" program, which will accelerate the development of new tools against leukemia, specifically acute promyelocytic leukemia, and other forms of cancer.

Congratulations Dr. Raught!

Investing to Accelerate New UHN Technologies

UHN congratulates Dr. Li Zhang on receiving new funding from the Ontario Institute for Cancer Research (OICR) towards accelerating the commercialization of her unique cellular immunotherapy for cancer technology. With OICR, UHN created a spin-off company to complete the pre-clinical requirements for testing Dr. Zhang's novel cellular therapy in patients with acute myeloid leukemia.

The technology involves growing a specific minor population of a patient's own cancer-killing T cells in the lab with subsequent reinfusion into the patient to fight their disease. Dr. Zhang has conducted extensive pre-clinical testing of these cancer-killing cells grown from AML patients and shown that they kill human leukemia cells in an animal model. The next step is a phase I clinical trial in leukemia patients.

Functional Genomics Symposium

On June 14, 2010, the UHN Microarray Centre will host the "Functional Genomics: Present & Future" symposium in the MaRS auditorium.

The event will run from 8:30 AM until 5 PM and will include ten presentations on

TGRI's Dr. Shaf Keshavjee was awarded $1.75M for his proposed "*Molecular and Genomic Diagnostics to Improve Outcomes in Lung Transplantation*" project that will work towards developing novel and accurate diagnostic strategies for donor lung injury and for the prediction and diagnosis of recipient rejection.

The one-time funding opportunity awarded 19 projects across the province.

Breast Cancer: Evidence Points towards Hormone-Driven Cell Growth

Reproductive history is one of the strongest risk factors for breast cancer after age, genetics and breast density. Thanks to recent findings from OCI's Dr. Rama Khokha and her team (Purna Joshi, Hartland Jackson, Alexander Beristain, Marco Di Grappa), we now know that progesterone—an ovarian hormone that functions to prepare the uterus to receive a fertilized egg—plays a critical role in changing breast stem cells. Breast stem cells have the potential to become any type of breast cell and can create multiple copies of themselves; however, until now, they were believed to remain inactive, except during puberty and pregnancy. These findings show a direct link between hormones and breast stem cells, adding important new knowledge to our understanding of breast cancer risk.

Using an animal model, the team discovered how and when hormones affect breast stem cells during the natural reproductive cycle. Through a series of experiments, the team mimicked the human menstrual cycle to show that as progesterone peaks in the second half of the menstrual cycle, it affects breast stem cells and neighboring cells causing normal breast stem cells to expand in number. It is this rapid cell expansion that could trigger an environment where cancer could begin, a finding that has sparked new areas of future research targeting stem cells and treatment.

As explained by Dr. Khokha, "Until now, breast stem cells were thought to be generally inactive in the adult female breast; however, for the first time we have been able to show progesterone-driven shifts in the breast stem cell pool. Understanding how hormones change these stem cells provides us with important new knowledge about how breast cancer growth begins and how, in the future, we can prevent it."

Joshi PA, Jackson HW, Beristain AG, Di Grappa MA, Mote P, Clarke C, Stingl J, Waterhouse PD, Khokha R. Nature. 2010 May 5. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Canadian Cancer Society Research Institute and the Canadian Breast Cancer Foundation.*

Irritable Bowel Syndrome: Changes in Brain Landscape Linked to Disrupted Brain-Gut Communication

TWRI's Drs. Karen Davis and Nicholas Diamant, and graduate students Udi Blankstein and Jerry Chen, have discovered that individuals with irritable bowel syndrome (IBS) have an altered brain structure that could provide insight into the mechanisms behind the chronic pain experienced by patients. Symptoms of IBS include abdominal pain, cramping, bloating and diarrhea, and are often associated with emotional stress.

Explains lead author Dr. Davis, "Our previous study revealed that patients with IBS have structural changes in specific regions of their brain, and in

topics ranging from clinical applications of array-based technology to new research technologies available such as nanostrings and the nCounter system.

For more information on the symposium and how to register, visit www.microarrays.ca/info/symposium.

this current study we were interested in determining if these changes are the result of suffering from IBS pain, the duration of IBS or are a result of a patient catastrophizing or excessively focusing on the pain they feel."

The team used structural magnetic resonance imaging (MRI) to take a 'look inside' the brain of 11 patients with IBS and compared that to 16 age-matched healthy subjects. MRI findings show that the patients with IBS have increased gray matter in the hypothalamus, which could be related to IBS, stress and a brain-gut communication axis responsible for regulating food intake, digestion, gut sensations and the control of bowel movements.

"We've also found abnormalities in a region of the brain that could be pre-existing and contribute to IBS vulnerability, and abnormalities in other brain regions may develop over time, possibly because of these chronic abnormal communication signals," explains Dr. Davis. "Our findings indicate that in IBS, the brain shows both pre-existing vulnerabilities as well as disease-driven abnormalities. Future studies will focus on the structural changes that specifically affect pain and IBS, as these changes can one day act as new therapeutic targets."

Blankstein U, Chen J, Diamant NE, Davis KD. Gastroenterology. 2010 May;138(5):1783-9. [Pubmed abstract]. *Research supported by the Canadian Institutes of Health Research, the Purdue Pharma OGSST scholarship and CIHR Strategic Training Program: Pain Molecules to Community Fellowship.*

Neurology: Deciding When to Re-Start Anticoagulation

Recent findings out of TWRI indicate that, for patients with brain or spinal cord hemorrhage (bleeding) that occurs as a complication of anticoagulant (AC) therapy —medications that thin the blood preventing it from clotting—it would be wise for health care teams to re-start these anticoagulation treatments earlier than previously thought. TEs occur when a clot travels through the blood, obstructing its flow through the circulatory system leading to complications such as heart attack or stroke.

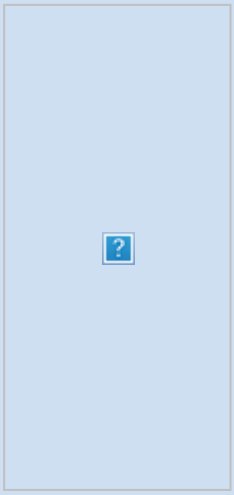
Graduate student Dr. Gregory Hawryluk, supervisor Dr. Michael Fehlings and other research fellows from the Fehlings lab including James Austin, Julio Furlan, Jang Bo Lee and Cian O'Kelly reviewed data from over 60 publications detailing greater than 490 patients from 1975 to 2009. Findings show that the majority of complications resulting from hemorrhage are seen within 72 hours of initially being detected by medical staff. Importantly, the study uncovered strong evidence showing that patients who were re-started on AC treatments after 72 hours were significantly more likely to have a TE complication than patients started before 72 hours.

"If patients were restarted before 72 hours, they were more likely to hemorrhage," explains Dr. Fehlings. "The take away message here is that patients with brain or spinal cord bleeding may have unique characteristics, such as low risk of bleeding and high risk of TE. It is important for medical teams to consider individual patient risk when selecting AC restart time and intensity."

Hawryluk GW, Austin J, Furlan JC, Bo Lee J, O'Kelly C, Fehlings MG. J Thromb Haemost. 2010 Apr 8. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the AO Spine North America.*

Diabetes: Locating the Brain's 'Sweet' Spot

TGRI's Dr. Tony Lam and his team have uncovered important findings that could help explain how glucose (sugar) production and blood sugar levels are regulated in healthy and obese/diabetic individuals. These findings have important implications for future therapies using glycine or a glycine analogue to lower blood sugar levels in diabetes and obesity.



"We've been able to show that delivery of glycine activates, or turns on, specific brain receptors and triggers a brain-liver axis of communication to lower sugar production," explains Dr. Lam. "Our studies demonstrated for the first time not only that a region of the brain called dorsal vagal complex (DVC) is sufficient to lower blood sugar levels, but that the signal(s) in the DVC can be activated by glycine."

Using animal model, the team used several approaches to show that activating the NR1 (glycine binding site) and NR2 subunits of NMDA receptors in the DVC—receptors responsible for brain cell communication—lowers sugar production and blood sugar levels. Future studies will look towards testing glycine effects in multiple diabetic and obese models as well as discovering new activators of NMDA receptors that could potentiate the glucose-lowering effect in diabetes and obesity. Clarifying the role of NMDA receptors in the DVC that relay gut signals to lower blood sugar levels is also important future research.

Lam CK, Chari M, Su BB, Cheung GW, Kokorovic A, Yang CS, Wang PY, Lai TY, Lam TK. J Biol Chem. 2010 May 6. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Canadian Institutes of Health Research, the Banting and Best Diabetes Centre and the University of Toronto, the John Kitson McIvor Endowed Chair in Diabetes Research,and the Canada Research Chairs Program.*