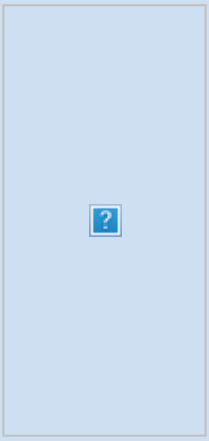
February 2009

Structural Biology: New Method of Investigation

Exciting findings from an OCI team published in this month's *Science Signaling* highlight the development of a new methodology that will allow investigators the ability to view changes in protein structure and activity in 'real-time'. Applied to an important molecule responsible for relaying cancer promoting signals, the G protein Rheb, the study reveals unprecedented insight into its regulation.



Explains co-lead Dr. Vuk Stambolic, "Rheb is a key regulatory switch in many human cancers, including those of breast, prostate, brain and kidney. Our team investigated the mechanics of how Rheb works and how it responds to inputs that promote tumor growth."

With Dr. Mitsuhiko Ikura, the team has shown that nuclear magnetic resonance (NMR)—a technique used to study the structural features of molecules—can be applied to monitor changes in Rheb structure over time. Such information is essential for a detailed understanding of how cancer-specific, abnormal Rheb signals govern tumor progression.

"With real-time NMR, we were able to examine how Rheb responds to its immediate regulators, products of the Tuberous Sclerosis Complex tumor suppressors. When genetically altered, these molecules drive cells to grow with little restriction," says Dr. Chris Marshall, the first author of the study.

Dr. Ikura proudly commented, "Here, NMR has given us a breadth of information on the biology of Rheb. It is also very exciting that our method can be used to examine the function and regulation of G proteins in general, including the other ones implicated in human cancers."

Sci Signal. 2009 Jan 27;2(55):ra3. [Pubmed abstract]. *Research supported by the Cancer Research Society, Canada Foundation for Innovation, Canadian Institutes of Health Research and the US Army.*

CIHR Milestones: UHN Recognized in 2008 List

UHN congratulates TGRI's Dr. Tony Lam for being recognized by the Canadian Institutes of Health Research (CIHR) as one of the important 2008 "Milestones in Canadian Health Research".

Dr. Lam is recognized for his April 2008 *Nature* paper where his work identified a new signaling pathway between the gut, the brain and the liver that lowers blood sugar when activated. These findings have created the possibility for new treatments for people with diabetes.

Accelerating Neuroscience Drug Discovery: Dr. Barry Greenberg

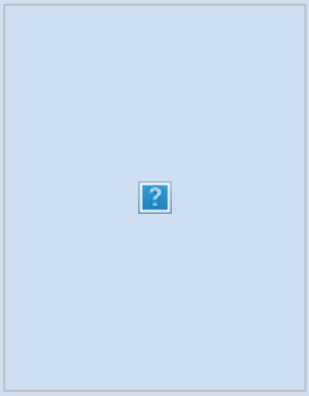
Dr. Barry Greenberg has recently joined UHN as the Director of Neuroscience Drug Discovery and Development.

He will work to enhance drug development capacity by developing an integrated platform across the research institutes and clinical programs to promote the discovery and development of new therapeutic compounds.

His background in the pharmaceutical and biotechnology sectors will help identify and develop alliances with external collaborators and industrial partners. Dr. Greenberg will work collaboratively with UHN's Technology Development and Commercialization office to develop all private sector contractual relationships.

Regenerative Medicine: Discovering New Lung Repair Methods

A new population of cells from the bone marrow, discovered by a team of TGRI investigators, have the potential to reconstruct damaged airways and to be developed as a new method of cell-based or regenerative therapies for lung disease.



Led by Dr. Thomas Waddell and colleagues Amy Wong (PhD student) and Dr. Armand Keating, the team discovered the population of cells expressing the Clara cell secretory protein (CCSP)—a marker of airway progenitor and stem cells—through a series of experiments. When these CCSP-expressing cells were injected into naphthalene-damaged lungs, they preferentially migrated to the damaged areas and developed into multiple airway cell types.

"For the first time we've been able to show that these CCSP-expressing cells are able to engraft in the lung and grow into different lung epithelium," explains Dr. Waddell. "With continued research, these bone marrow CCSP cells may have substantial value as a cell replacement therapy for lung epithelial diseases. We know these cells do exist in humans and are currently determining if they change in a variety of lung diseases".

J Clin Invest. 2009 Jan 26 [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Canadian Cystic Fibrosis Foundation and the Canadian Institutes of Health Research.*

Cardiology: Tackling the Challenge of Kidney Risk Factors

A TGRI team led by Dr. Keyvan Karkouti with colleagues Drs. Terrence Yau, Stephen Fremes, Stuart McCluskey, Scott Beattie, and Duminda Wijeysundera has identified modifiable risk factors of acute kidney injury (AKI) following cardiac surgery that could greatly affect patient outcome.

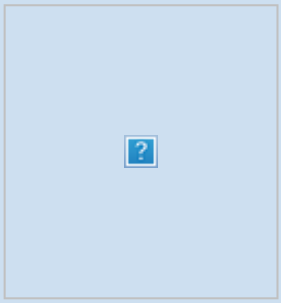
"AKI is a common complication of cardiac surgery and by understanding how these risk factors play a role in the onset of this condition, health care teams can tweak current practices to try and avoid it," comments Dr. Karkouti.

Looking at a group of over 3400 patients at seven hospitals who had undergone cardiac surgery, the team showed that several independent risk factors—including comorbidities diabetes mellitus, preexisting kidney disease, and left ventricular dysfunction—contributed to AKI.

"Of particular interest, the three factors independently associated with AKI that can be controlled by the healthcare team are preoperative anemia (or low red blood cell counts), red blood cell transfusions and surgical reexploration," says Dr. Karkouti. "Knowing the important role these factors play in the development of this complication, we can now look at therapies aimed at mitigating these factors to decrease the chances of AKI in patients."

Circulation. 2009 Jan 19. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Canadian Institutes of Health Research, the Canadian Blood Services, and Novo Nordisk.*

Leukemia: Harnessing Genetics to Understand Susceptibility



Results highlighted in recent work from a team of Korean and UHN investigators is providing important information on variations in genes from an apoptosis pathway—a pathway responsible for causing cell death—and the implications each of these variations have in terms of susceptibility to chronic myeloid leukemia (CML).

Leukemia occurs when too many white blood cells are being produced in the bone marrow, and unlike acute leukemia, CML usually progresses slowly over time. Comments study senior author Dr. Jeffrey Lipton, "We're trying to simultaneously look at single DNA base changes in multiple pathways known to be involved in the development of CML."

Former UHN fellow Dr. Dennis Kim with Dr. Lipton and co-investigators Drs. Katherine Siminovitch and Hans Messner, conducted a series of genetic and molecular analyses on blood taken from CML patients receiving or not receiving therapy at the Princess Margaret Hospital and compared results to patients that did not have CML. Regardless of treatment, individuals with a specific DNA change in the gene Bcl-2 (which is involved in the survival of blood stem cells) had increased susceptibility to CML.

"This single DNA base change was significantly associated with susceptibility to CML," comments Dr. Lipton. "Our approach could be useful to predict the risk of CML, an uncommon leukemia in the general population, and future studies will work on further validating current results with larger numbers of cases from different ethnic groups."

Blood. 2009 Jan 13. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Friends to Life fund of the Princess Margaret Hospital Foundation.*

Ankylosing Spondylitis: Translating Gene Findings into Biomarkers

Ankylosing spondylitis (AS) is a chronic inflammatory arthritis that primarily affects the spine, and a recent TWRI initiative has discovered that a broad screening of changes in gene activity may be an effective tool for determining treatment response.

"We see significant changes in gene expression when patients with AS are administered a monoclonal antibody against Tumor Necrosis Factor. We then used a global screening tool to analyze gene activity. This could give us insights into disease development," comments Dr. Nigil Haroon, Research Fellow in Rheumatology.

Drs. Haroon, Florence Tsui, Robert Inman and colleagues analyzed the blood of patients with AS for changes in gene activity at the onset of the study, and again at two weeks following infliximab treatment. The team found six genes, related to changes in other known markers of inflammation that significantly differed in activity.

"For those patients who were treated with infliximab, we detected activity change in four genes," says Dr. Inman. "The sLIGHT gene was most significantly down regulated, or 'turned down' with treatment and was clinically associated with a decrease in inflammation. This particular strategy could be used in future studies to look at a larger patient population. The study highlights the strengths of integrating a clinical database with a bioprofiling database to develop new insights into basic mechanisms of disease."

Ann Rheum Dis. 2008 Dec 22. [Epub ahead of print]. [Pubmed abstract].