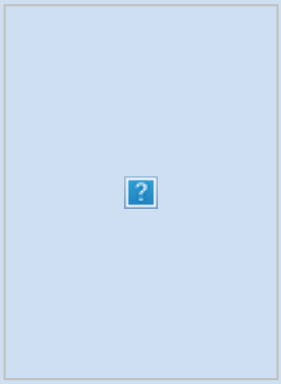
June 2008

Immune System: Taking Apart the 'Engine'

A new level of control for interferon-gamma (IFNgamma)—an important 'engine' of the immune system involved in a variety of human diseases including cancer, multiple sclerosis, heart disease and arthritis—has been recently uncovered by a Krembil team.



"We've discovered a whole new level of regulation of IFNgamma targets," says Dr. Rod Bremner, study author. "It's a bit like discovering that your car needs more than an ignition switch to start."

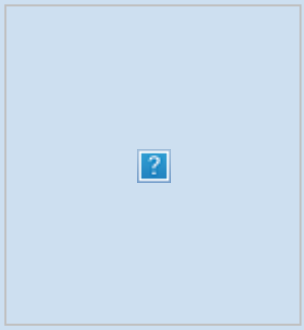
Using a variety of molecular and biochemical strategies, Dr. Bremner and his team have been able to demonstrate that the BRG1 protein works with at least five other remote switches to activate the CIITA gene, a gene responsible for mobilizing a very important class of molecules involved in ramping up the immune response.

Dr. Bremner notes, "In cancer, the goal is to 'fix the engine' by reactivating a broken IFNgamma pathway. But, in arthritis, the goal is to turn the engine down to reduce an overactive immune system. Ours is a critical finding towards the development of novel treatments that will have significant impacts on diseases requiring either level of control."

Nature Immunology [Epub ahead of print]. [Pubmed abstract]. *Research supported by the National Cancer Institute of Canada, the Canadian Cancer Society, the Krembil Foundation Seed Fund, the Vision Science Research Program, the Frank Fletcher Memorial Fund, Dr. R. Dittakavi & Dr. P Rao Graduate Award, and the Krembil Foundation.*

Diabetes and Cardiology: Tracking Fat in Disease

People who have insulin resistance or type 2 diabetes who experience dyslipidemia—unhealthy blood fat profiles increasing the risk for cardiovascular disease—now have a better understanding of how the body accumulates unhealthy levels of fat in the blood thanks to the efforts of Dr. Gary Lewis and colleagues.



The TGRI team examined the metabolism of 12 healthy men during a constant fed state and found that elevated levels of free fatty acids stimulate production of 'bad' cholesterol not only in the liver, but also in the intestine.

Comments Dr. Lewis, "Our evidence leads us to believe that chronic high levels of free fatty acids are likely to play an important role in the overproduction of intestinal fats that has been seen in these conditions."

Killam Prize Awarded to UHN Researcher

UHN congratulates Krembil Director Dr. Peter St. George-Hyslop on receiving the prestigious Killam Prize—governed by the Canada Council for the Arts—for his seminal research into the causes and mechanisms of neurodegenerative diseases which have radically improved the understanding of the molecular mechanisms of Alzheimer's disease.

The Prize also recognizes him for his contribution to the community through his presentations to lay audiences on Alzheimer's disease and as founder of two successful biotechnology companies.

OCI Welcomes Dr. Laurie Ailles

The Ontario Cancer Institute is pleased to welcome Dr. Laurie Ailles who has returned to Canada after nine years of research abroad, to join the division of Stem Cell and Developmental Biology.

Dr. Ailles' research focuses primarily on the characterization of cancer stem cells (CSC) from head and neck cancer. Answers to these questions could lead to the development of therapies that target the CSC population and stop tumors from growing, invading, and seed metastatic lesions.

Her laboratory is located on the 8th floor of the Toronto Medical Discovery Tower.

Circulation. 2008; 117: 2369-2376. [Pubmed abstract]. *Research supported by the Canadian Institutes for Health Research, the Heart and Stroke Foundation of Canada, the Canadian Diabetes Association, and the National Institutes of Health.*

Cancer: Clinical Trial Findings Merit Continued Research

Phase I trials of a member of a new family of anti-cancer drugs have cleared it to proceed to advanced testing.

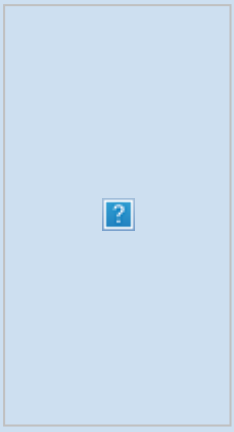
The new compound—which targets structural elements of DNA which control gene activation—was administered to a small group of people with cancer to test its safety in human subjects. The study team, led by Drs. Lillian Siu and Eric Chen and involving patients at PMH and John Hopkins, showed that the drug is tolerated at the doses tested. Interestingly, assessment of patients' blood cells on this trial has demonstrated indirect evidence of this drug inhibiting its target at a molecular level.

"Phase I studies are the key first steps in the path to introducing new drugs in the clinic. Our tests, done on patients within a wide range of cancer types, show that this drug is safe to proceed to phase II."

J Clin Oncol. April 2008. 26(12): 1940-1947. [Pubmed abstract]. *Research supported by MethylGene Inc.*

Neurology: Mapping Disease Origin

New evidence from UHN points to potentially harmful consequences of a type of mild brain degeneration observed in 50% of those 60 and older.



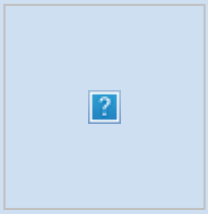
Leukoaraiosis—a white matter disease—is associated with cognitive dysfunction and potentially dementia. A UHN team led by Dr. David Mikulis used fMRI technology to map regions of blood flow change in the brains of 28 healthy volunteers during measured carbon dioxide administration.

Increased blood flow was observed in the gray matter but reduced blood flow—descriptively called a "steal" phenomenon—was observed in deep brain white matter regions located at distant ends of long blood vessels. Blood flow in these vessels may be more vulnerable to changes in blood pressure than the much shorter interconnected gray matter vessels.

"In essence, it appears that the ability of the brain's blood vessels to respond to blood pressure changes, or other blood flow challenges, is not equal. Blood flow to the gray matter is favored over the white matter, potentially harming the white matter over the long run. This white matter vulnerability may explain why leukoariosis develops. Since people in this age group are often treated for high blood pressure, it's important to understand the effects of lowered blood pressure."

Stroke. 2008 May 1 [Epub ahead of print]. [Pubmed abstract]. *Research*

supported by the Ontario Research Fund.



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