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New Research Breakthroughs at UHN

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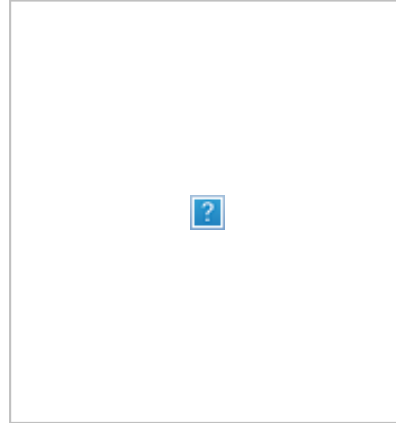
Dendritic Cells Dominate in Atherosclerosis-Prone Regions

Drs. [Myron Cybulsky](#), Jenny Jongstra-Bilen and their colleagues have discovered that, of the different blood cells known to accumulate at vessel branch points and curvatures, dendritic cells are most likely the culprits that predispose these regions to the development of atherosclerotic lesions.

Vulnerable vessel regions—including branch points and curvatures—have 100 times more dendritic cells than other regions. Mice genetically susceptible to atherosclerosis harboured more of these cells in the inner layer of their vessels.

"Our results suggest that these dendritic cells are part of the foundation of the plaque build-up that causes atherosclerosis," explains Dr. Cybulsky. "It's possible we could use dendritic cells as predictive markers for atherosclerosis in the future."

J. Exp. Med. 2006 Aug 7; [Epub ahead of print] [[Pubmed abstract](#)]
Research supported by Heart and Stroke Foundation of Ontario and the Natural Sciences and Engineering Research Council.



Bone Marrow Molecule Signals Repair "Troops"

UHN regenerative medicine researchers Drs. Shafie Fazel, Massimo Cimini, Liwen Chen, Shuhong Li, Denis Angoulvant, Paul Fedak, [Richard Weisel](#), [Armand Keating](#), and [Ren-Ke Li](#) have identified the SOS distress signal that mobilizes specific repair cells to the heart after a heart attack.

C-kit, a molecule located on the surface of a subset of bone marrow cells, is turned on by the SOS signals sent by the damaged heart. C-kit binds to another molecule, activating c-kit to signal bone marrow cells to home in on the heart to help stimulate new blood vessel growth.

"Each year, 70,000 Canadians suffer from a heart attack and many of them are left with crushing disabilities, mainly because the heart muscle is not able to regenerate after a heart attack," says Dr. Li. "This study identifies how the body naturally repairs the heart and provides new potential therapies to stimulate cardiac regeneration and prevent heart failure in these patients."

J. Clin. Invest. 2006 Jul;116(7):1865-77. [[Pubmed Abstract](#)]
Research supported by Heart and Stroke Foundation of Ontario, Canadian Institutes of Health Research and Physicians' Services Incorporated Foundation.

Fusion Protein Structure Reveals Potential Leukemia Target

Dr. [Mitsu Ikura](#) and postdoctoral fellow Dr. Michael Plevin have revealed the three-dimensional solution structure of the TAFH domain—a domain critical for E protein interactions—of the AML1-ETO fusion protein using NMR spectroscopy.

AML1-ETO is generated by a translocation between chromosomes 8 and 21, an event that occurs in up to 15% of acute myeloid leukemias (AML). AML1-ETO can silence E protein activation of transcription factors that are involved in regulating cell growth, differentiation and apoptosis. By mutating AML1-ETO, this activity is reduced.

“Resolving the structure of protein domains and doing mutational analysis is key to understanding protein function,” says Dr. Ikura. “This domain of AML1-ETO showed a surprising similarity to another cancer gene regulator Sin3. Our findings help us to obtain deeper insights into leukemia and to design chemical inhibitors based on similarities and differences in their protein structures.”

Proc. Natl. Acad. Sci. U S A. 2006 Jul 5;103(27):10242-7. [[Pubmed abstract](#)]

Research supported by Canadian Institutes of Health Research, National Institutes of Health, Leukemia and Lymphoma Society, Cincinnati College of Medicine, and the Canada Research Chairs Program.



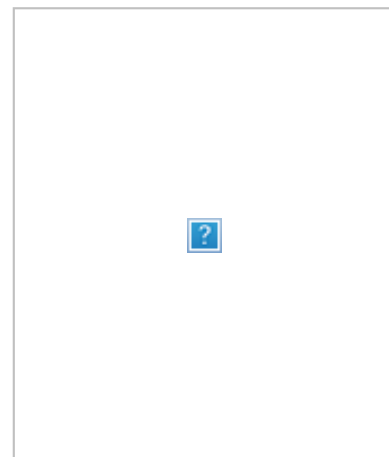
Infectious Disease Enzyme Blocked by Novel Inhibitors

Orotidine monophosphate decarboxylase (ODCase), an enzyme that produces DNA and RNA precursors, has been revived as a target for drugs directed against RNA viruses, such as pox and West Nile virus, as well as various bacteria.

This is the result of a recent study by a UHN team led by Drs. [Lakshmi Kotra](#) and [Emil Pai](#) who integrated medicinal chemistry and structural biology approaches to devise novel inhibitors.

“ODCase is a good potential drug target since its enzyme characteristics are not the same in humans and bacteria. We can take advantage of these differences to specifically target the pathogenic enzyme,” says Dr. Kotra, a recent UHN recruit featured below.

One of the new compounds the research team designed and tested was



found to be an especially potent inhibitor of the reaction, a preliminary indication of its ability to block reproduction of pathogens.

J. Med. Chem. 2006 Aug 10;49(16):4937-4945. [[Pubmed Abstract](#)]
Research supported by Canadian Institutes of Health Research and Ontario Innovation Trust.

New Faces in UHN Research

Lakshmi Kotra, PhD

Scientist, Division of Cell and Molecular Biology, Toronto General Research Institute

Medicinal chemist Dr. [Lakshmi Kotra](#) is bridging the gap between biological discoveries and clinical therapeutics by designing small molecule drugs. His approach is interdisciplinary using three-dimensional computer modelling, biochemistry and structural biology to design compounds that can be developed into pills or injections that can be used to treat different diseases, including cancer and infectious and metabolic diseases.

Dr. Kotra, recruited from the University of Toronto, is already working closely with the UHN Research Business Development Office to patent the compounds and further develop them into therapeutics.



Tony Lam, PhD

Scientist, Division of Cell and Molecular Biology, Toronto General Research Institute

Dr. [Tony Lam](#), the new John Kitson Mclvor (1915-1942) Chair in Diabetes Research, is investigating how the brain senses nutrients in the blood to determine how obesity progresses to type II diabetes. Dr. Lam and his colleagues have shown that the brain responds not only to glucose, but also to lipids.

When rats predisposed to insulin resistance were overfed, they were unable to sense circulating lipids and the balance of glucose levels in the liver was disrupted. When lipid sensing was restored pharmacologically, the glucose homeostasis returned.



“We may be able to translate this finding to a clinical setting by targeting the brain biochemically to prevent insulin resistance,” says Dr. Lam.

Breaking News

Krembil Research Day Attracts Crowds

Krembil held its annual research day at 89 Chestnut where over 150 staff, scientists and trainees enjoyed the day of talks and poster sessions.

The keynote address was given by Dr. Adriana Di Polo from the Université de Montréal who is interested in discovering the molecular mechanisms and signaling pathways that regulate neuronal survival and axon regeneration *in vivo*.

UHN Research congratulates the following postdoctoral fellows and graduate students who won awards for their research day presentations (awards financed by the Nadler Fund):

Postdoctoral Fellow Awards

Oral Competition

Joan Forder (1st)

Julio Furlan (Runner-up)

Poster Competition

Eftekhar Eftekharpour (1st)

Kim Dorval (Runner-up)

Nan-Hua Chang (Honorable Mention)

Graduate Student Awards

Oral Competition

Jill Couto (1st)

Christina Loh (Runner-up)

Janet Parsons (Honorable Mention)

Poster Competition

Ann Parr (1st place)

Miron Derchansky (Runner-up)

Sherri Robins (Honorable Mention)

Upcoming Events

Symposium To Celebrate New McLaughlin-Rotman Centre

On September 28, UHN researcher and centre director [Dr. Kevin Kain](#) is hosting an international symposium on global infectious disease threats as part of the launch of the McLaughlin-Rotman Centre (MRC).

Guest speakers will include Drs. Rip Ballou (Brussels, Belgium), Dan Carucci (Washington, DC), Dr. Marty Cetron (Atlanta, Georgia), Dr. Rick Steketee (Seattle, Washington), and Abdallah Daar (University of Toronto), who will talk about topics ranging from malaria and cervical cancer vaccines to how the vast connections among the global community will affect global health.

MRC, part of the McLaughlin Centre for Molecular Medicine, was made possible due to a generous donation from Mrs. Sandra Rotman. Its mission is to bring together new minds, novel ideas, and innovative solutions to solve problems associated with resurging infectious disease threats.

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