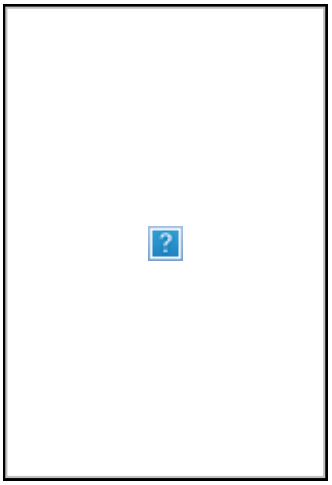
New Research Breakthroughs at UHN

Digestive System Disease: Defining Treatment Criteria for Swallowing Disorder



Patients with the rare swallowing disorder achalasia are unable to relax the muscular ring that links the esophagus to the stomach. They experience difficulty swallowing and moving food from their mouth to their stomach through their esophagus—sometimes leading to pain, regurgitation and dangerous weight loss.

There are two common surgical treatments for achalasia; however, it is not clear which treatment is less likely to result in the need for subsequent interventions. To address the controversy, UHN health services researcher Dr. David Urbach performed a retrospective study using data records from 1461 achalasia patients in Ontario.

“Our study shows that although both methods commonly result in the need for subsequent intervention, less than 40% of patients treated with surgical dissection of the muscle had to be treated again compared to more than 60% of patients treated by enlarging the contracted opening using an air-filled balloon,” says Dr. Urbach.

“Knowing that surgical dissection is slightly more efficient overall, we suggest that doctors consider the patient’s attitude toward surgical procedures and the desire to avoid further treatments when making recommendations.”

JAMA. 2006 Nov 8;296(18):2227-33. [Pubmed abstract] *Research supported by Society of American Gastrointestinal and Endoscopic Surgeons and Canadian Association of General Surgeons.*

Brain Injury: Research at the Forefront of New Therapies

A new UHN finding is the first step towards developing new multi-pronged strategies for traumatic brain injury (TBI).

Damage to a brain cell sets off a cascade of internal and external events that combine to create a toxic environment, killing neighbouring cells over a large area.

While neuroscientists are starting to understand this complex mechanism, treatments which address a single component of the cascade have proven unsuccessful in clinical trials. Thus researchers are moving to a multi-pronged paradigm to address two or more components simultaneously.

A pioneering study led by Dr. Michael Tymianski and graduate student Anthony Lau has shown that due to the effects of a lethal by-product of cell

damage called peroxynitrate, TBI therapy should include both anti-oxidant and anti-apoptotic compounds.

"If we can use molecular approaches to prevent the oxidizing process, which forms hazardous reactive oxygen molecules in the brain, and the apoptosis process, which leads to programmed cell death, we may be able to reduce cell death in these injuries," explains Dr. Tymianski.

J Neurosci. 2006 Nov 8;26(45):11540-53. [Pubmed abstract] *Research supported by Canadian Institutes of Health Research, National Institutes of Health, and Canadian Stroke Network.*

Degenerative Disc Disease: Notochord Cells Help to Regenerate Disc Cartilage

Drs. Mark Erwin and Robert Inman have discovered that notochord cells—which are primitive organizing cells of the developing embryo—release a factor called connective tissue growth factor (CTGF) that may be responsible for providing certain strains of dogs with their remarkable resistance to degenerative disc disease.

Degenerative disc disease is one of today's most common and costly medical conditions, marked by a progressive loss of disc height, mechanical properties and tissue degradation. However, in resistant dog strains it does not occur or occurs much later in life.

To find out why resistant dogs are protected, the UHN team obtained notochord cells from the discs of the dogs and determined the identity of some of the proteins secreted by these cells. They then used the proteins secreted by these cells to determine what disc cell genes are turned on by these notochord cells.

“Our results suggest that certain breeds of dogs are protected against this disease because their discs contain an abundance of notochord cells that are releasing CTGF,” says Dr. Inman. “This research will likely provide the groundwork to regenerate disc cartilage for patient treatment in the future.”

Arthritis Rheum. 2006 Dec;54(12):3859-67. [Pubmed abstract]

Thyroid Cancer: CEACAM1 Signals Potential to Spread

Drs. Sylvia Asa and Shereen Ezzat have discovered that a cell adhesion molecule called CEACAM1 could be a potential marker for identifying thyroid tumours that are more likely to metastasize.

The UHN researchers modified the quantity of CEACAM1 in thyroid cancer cells and used a variety of assays to determine whether these changes promoted tumour growth or increased the likeliness of invasiveness—a key indicator of the potential of cancer cells to metastasize.

When CEACAM1 was increased, they found that tumour size was not significantly affected but tumours had more invasive properties. Correspondingly, when they decreased the amount of CEACAM1 in cells, they found that tumour growth was significant but they were less likely to invade. These findings were corroborated in primary human samples where CEACAM1 was found mainly in small tumours that metastasized at an early stage.

“Few thyroid cancers metastasize—only about 20%—so it is important for doctors to have the tools to identify which ones will spread to avoid unnecessary treatments,” explains Dr. Asa. “The excessive presence of CEACAM1 in a tumour could be a flag for doctors to treat it more aggressively.”

Oncogene. 2006 Oct 23; [Epub ahead of print] [Pubmed abstract] *Research supported by Toronto Medical Laboratories and the Rita Banach Thyroid Cancer Research Fund.*

Liver Disease: New Target for Hepatitis C Treatment

Recent UHN research has shed light on the antiviral activity of a molecule which may lead to improved treatments for a serious public health problem.

Current therapy for the viral disease hepatitis C, which infects 170M people worldwide and can lead to liver disease and liver cancer, involves a powerful antiviral compound called interferon. However, half of hepatitis C patients are characterized as "non-responders" to this treatment.

New work by UHN's Drs. Ian McGilvray and Jenny Heathcote, along with graduate student Limin Chen, has shown that interferon's activity can be enhanced by inhibiting a specific protease, USP-18, identified in earlier work by the group.

“We've shown for the first time a relationship between USP-18 and interferon effectiveness against hepatitis C virus,” notes Dr. McGilvray. “As a result, USP-18 is a prime target for potentially improving the value of interferon treatment for the millions who have non-responsive forms of the infection.”

Gastroenterology. 2006 Nov;131(5):1584-91. [Pubmed abstract] *Research supported by National Institutes of Health, Ellison Medical Foundation, Greenberg Medical Research Institute, American Cancer Society, National Cancer Institute and Physicians' Services Incorporated Foundation.*

SARS: Model to Test Treatments Developed

A UHN team led by Drs. Gary Levy, Gregory Downey, Reginald Gorczynski, Ian McGilvray, James Phillips and Eleanor Fish have developed an animal model for severe acute respiratory syndrome (SARS) that is suitable for studying potential therapeutic strategies for humans.

The researchers created the model by infecting a specific strain of mice with a virus in the same family as the SARS virus called mouse hepatitis virus-1. These mice developed typical symptoms of SARS such as lung inflammation and an increased presence of immune cells while other mice strains showed only mild disease.

Using this model, the group has also shown that the antiviral compound interferon—a potential treatment option for SARS—improved outcomes in these mice.

"Although some compounds have shown promise, there are currently no effective treatments for SARS. During the outbreak in 2002, approximately 8000 people were affected globally and 700 died from the disease," says Dr. Levy. "With this model, we have a tool to test new ways to treat and prevent the disease in the future."

J Virol. 2006 Nov;80(21):10382-94. [Pubmed abstract] *Research supported by Canadian Institutes of Health Research, Ontario Research and Development Challenge Fund and National Institutes of Health.*

Breaking News from UHN Research

UHN Investigators Named to Order of Ontario

UHN congratulates OCI's fathers of stem cell research Drs. Ernest McCulloch and James Till as well as retinoblastoma expert Dr. Brenda Gallie who were among the twenty-nine newest appointees to the Order of Ontario. This honour is the province's highest award for excellence in any field of endeavour.

Drs. Till and McCulloch laid the foundation for stem cell science with their pioneering work more than 45 years ago. Dr. Gallie's research into the rare childhood eye tumour has led to insights into the genetic development of cancer.

Congratulating UHN's Five Latest Canada Research Chairs

Drs. Gordon Keller, Igor Jurisica, Thomas Kislinger, Shuzo Sugita and Elisabeth Tillier (pictured clockwise from top left) were awarded a total of $3.4M from the Canada Research Chairs program.

Embryonic stem cell biologist and new McEwen Centre Director Dr. Keller won a new Tier I CRC, which is awarded to outstanding researchers acknowledged by their peers as world leaders in their fields.

Drs. Jurisica, Kislinger and Tillier received new Tier II CRCs—given to exceptional emerging researchers, acknowledged by their peers as having the potential to lead in their field—and Dr. Sugita's existing Tier II CRC was successfully renewed.

Drs. Jurisica, Keller and Kislinger were awarded a further $1M in infrastructure funding associated with their CRC awards from the Canada Foundation for Innovation.
