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New Research Breakthroughs at UHN

Regenerative Medicine: New Stem Cell Fix

McEwen Centre for Regenerative Medicine Director Dr. Gordon Keller and colleagues have identified the human equivalent of a well-known mouse locus that will open new directions for studying human development while also providing a source of cells for replacement therapy.

Using a series of orchestrated molecular tests, the study identified the human equivalent of the *Rosa26* locus in mice—the site used to introduce foreign genes into the genome—and confirmed that the inserted pieces of DNA were functional.

"This human locus has the same 'plug-and-play' capabilities as have been used in the mouse analogue for many years. It will enable us to assess the effects of novel genes in human embryonic stem cells, dramatically expanding our ability to manipulate these for medical purposes," says Dr. Keller.

Nat Biotechnol. 2007 Dec. 25(12):1477-82 . [Pubmed abstract]. *Research supported by the National Institutes of Health.*

Liver Cancer: Treating in Three Dimensions

Results from a recent UHN Phase I study indicate that radiotherapy treatment may be an effective treatment option in the future for individuals with inoperable hepatocellular carcinoma (known as liver cancer) and cholangiocarcinoma (known as bile duct cancer).

The study led by Dr. Laura Dawson and colleagues Drs. John Kim, Bernard Cummings, Jennifer Knox and Morris Sherman followed forty-one patients treated with stereotactic body radiotherapy—the delivery of potent radiation in few fractions. The treatment was highly individualized, with the doses delivered to tumors based on the volume of liver irradiated and estimated risk of liver toxicity. The combination of hypofractionated radiotherapy with individualized tumor dosing resulted in a better-than-expected 13.4 month median survival with a 1-year survival rate of 51%.

"These early results are quite exciting because many patients with primary liver cancers who are not suitable candidates for other therapies may benefit from this short-course radiation treatment strategy," says Dr. Dawson. "The results have motivated us to start Phase II trials of stereotactic body radiotherapy in liver cancer."

J Clin Oncol. 2008 Jan 2 [Epub ahead of print]. [Pubmed abstract].

Research supported by Canadian Cancer Society, National Cancer Institute of Canada, and Elekta Oncology Systems.

Lupus: Antibody Manufacture Malfunctions

New findings by Krembil researchers Drs. Joan Wither, Murray Urowitz, Dafna Gladman and Paul Fortin have revealed the mechanics behind how the immune system B cell population is activated in people with systemic lupus erythmatosus (SLE).

"B cells are 'antibody factories'. When normal regulatory processes go awry, they can produce antibodies against body tissues, leading to autoimmune disorders like lupus," explains Dr. Wither.

By comparing blood cell markers—characteristic flags of the disease—from SLE and non-SLE patients, the research team found that more B cell populations were activated in SLE patients than in healthy controls, and that activation occurs very early in B cell development.

"Knowing how and when B cells are programmed to produce rogue antibodies is one step towards ultimately deprogramming or deactivating them in people with SLE," concludes Dr. Wither.

J Immunol. 2008 Jan 15;180(2):1276-84. [Pubmed abstract]. *Research supported by the Canadian Institutes for Health Research.*

Cerebral Malaria: Informatics Implicates Immune Genes

Cerebral complications can be fatal in one particularly vicious type of malaria. A TGRI research team has used microarray and informatics technologies to pinpoint clusters of immune genes responsible for the brain's response to malarial infection in a mouse model.

The team, led by Drs. Conrad Liles and Kevin Kain, showed that mice resistant to cerebral malaria have, paradoxically, a reduced immune response to the malarial parasite. In mice susceptible to infection, the immune system responds more dramatically, likely leading to cell death and tissue injury.

"This study demonstrates that the host response plays a pivotal role in determining the clinical outcome in malaria," says Dr. Liles. "Our analysis has revealed a number of therapeutic targets that may be exploited for the development of innovative immunomodulatory strategies to improve clinical outcome in severe malaria."

Am J Pathol. 2007 Nov 8; [Epub ahead of print]. [Pubmed abstract].*Research supported by the Canadian Institutes of Health Research, Genome Canada*

Irritable Bowel Syndrome: How Brain Structure Affects Pain

A recent Krembil study conducted in the lab of Drs. Karen Davis and Nicholas Diamant has, for the first time, linked anatomic and functional brain abnormalities in patients suffering from chronic pain diagnosed with irritable bowel syndrome (IBS). Individuals with IBS suffer from long-standing abdominal pain and disturbed bowel habits.

Led by Dr. Davis, the research team recruited patients from the TWH Gastrointestinal Unit and used brain imaging technology to study the structural differences in the brain that exist between patients suffering from IBS and healthy controls. Surprisingly, the study revealed anatomic brain abnormalities (cortical thinning of the insular cortex and anterior cingulate cortex) that coincide with their previous findings (Kwan et al., Neurology, 2005 Oct 25;65(8):1268-77) of functional abnormalities in key regions of the brain in IBS patients.

“There are two possible explanations for our finding,” explains Dr. Davis. “Prolonged pain may greatly affect brain structure, or pain is a result of this change in structure. Understanding the development and role of these brain structure changes may ultimately help us develop an intervention to manage pain in IBS patients.”

Neurology. 2008 Jan 8;70(2):153-4. [Epub 2007 Oct 24]. [Pubmed abstract].
Research supported by the Canadian Institutes of Health Research.

Diabetes: Examining the Anti-Oxidant Effect

A new study by TGRI researchers has shown that taurine, a type of antioxidant, may protect against the toxic effects of blood fats called free fatty acids in type 2 (adult onset) diabetes in humans.

“What we’ve seen so far with this small study group is very interesting,” comments study lead and TGRI researcher Dr. Gary Lewis, but he stresses that these findings in no way prove that the antioxidant is an effective treatment or prevention for diabetes.

The research team followed a group of non-diabetic, overweight men who were orally given one of two types of the antioxidants. Blood tests revealed an improvement in both insulin sensitivity and beta cell (the pancreatic cells that make insulin) function in men taking the over-the-counter, taurine for 2 weeks.

“This study is an important first step, but further research is needed to confirm the effect in a larger population,” says Dr. Lewis.

Diabetologia. 2007 Nov 17; [Epub ahead of print]. [Pubmed abstract].
Research supported by the Canadian Diabetes Association.

Breaking News from UHN Research

UHN Scientists Named to Order of Ontario

UHN's own Drs. Tak Mak and Frances Shepherd were two of the 27 prominent Ontarians named to the Order of Ontario. The honours recognize Dr. Mak's discovery of the T cell receptor, his work in molecular biology and his pioneering contributions in the genetics of immunology, as well as Dr. Shepherd's discovery of new treatment options for lung cancer patients in Ontario and throughout the world.

OCI Team Awarded $3M From National Institutes of Health

A $3M U.S. National Cancer Institute Phase I grant headed by Senior Scientist Dr. Lillian Siu, co-Director of the Robert and Maggie Bras and Family New Drug Development Program, will ensure patients have access to the most promising treatments for cancer while continuing to bolster clinical and translational research at the institute.

The application was one of only two new applications awarded in this cycle and the only non-U.S. site to receive a U.S. National Cancer Institute Phase I grant.

Some images adapted from the image archives of stock.xchng.ca. and National Institutes of Health, and the National Cancer Institute.