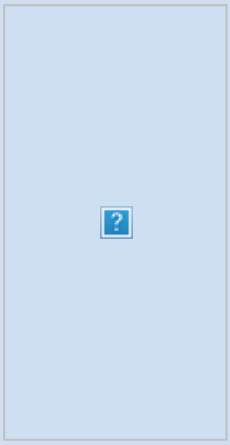
November 2008

Regenerative Medicine: Directing Cell Growth

Researchers at the McEwen Centre for Regenerative Medicine have discovered that signals passing through the Notch pathway—involved in embryogenesis—can affect heart cell development, providing insight into a novel approach to generating large numbers of heart cells for regenerative therapies.



Comments study lead Dr. Gordon Keller, "The molecular tools we've used in this project will provide us with greater knowledge of signaling pathways that regulate the development of cardiac cells from human ES cells."

Using mouse ES cells, Dr. Keller and his team showed that signals from the Notch pathway can direct hemangioblasts, precursors of blood and blood vessel cells, to grow into heart cells.

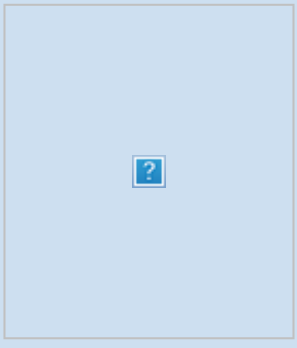
The study shows that this re-directed growth pathway occurs when the Notch signaling coordinates the activity of two other paths, the BMP and Wnt pathways, which are key in early stages of development.

"This re-direction occurs at a specific point in time and, by understanding the regulation during these developmental stages, we can start targeting certain time points to strategically and efficiently develop specific types of cells," says Dr. Keller. "This is an exciting time in regenerative medicine and continued research will help get us to more targeted therapies."

Nat Biotechnol. 2008 Oct;26(10):1169-78. Epub 2008 Sep 28. [Pubmed abstract]. *Research supported by the National Institutes of Health.*

Immunity: Stressing the Importance of Checkpoints

The immune system protein Fas—which is critical to maintaining homeostasis in the peripheral lymphoid organs—is an essential checkpoint governing T and memory B cell homeostasis, according to findings from a recent OCI study.



Checkpoint defects result in the overproduction of the B cells responsible for destructive immune cell organ invasion that are found in autoimmune syndromes, acute lymphoblastic leukemia, hairy cell leukemia and lymphomas.

The research team, led by Dr. Tak Mak and assistant scientist Dr. Zhenyue Hao, created a mouse model and used a series of genetic experiments to show that, in mice lacking the Fas gene in B cells, these B cells infiltrate the liver and lungs, causing multiple organ failure, altered lymphoid

All Things Research: 2008 Research Report Available Online

Available online, the 2008 Research Report features major events and achievements that collectively lead to inspiration, innovation and impact in research.

In addition to research statistics, also featured is the "Year in Review", prestigious investigator awards and new UHN partnerships. To view and download this year's report, visit www.uhnresearch.ca/news.

Stem Cell Network Supports UHN Research

A UHN project is one of 10 new awards announced recently by the national Stem Cell Network (SCN).

The large, multi-disciplinary initiative led by OCI's Dr. Gordon Keller will produce liver cells from human embryonic stem cells (hESC) and induced human pluripotent stem cells (ihPS) to test toxicity levels of drugs related to drug metabolism

Research will improve the drug discovery process and increase the potential for patient-specific therapy—a breakthrough that would mean less animal testing and results that are more applicable to human biology.

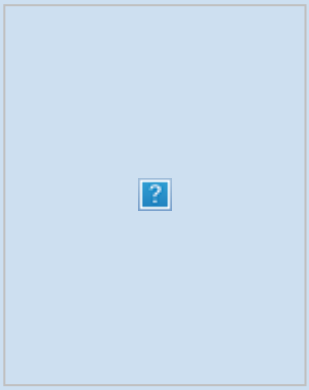
architecture, and dramatic changes in T cell signaling.

According to Dr. Hao, the Fas protein is imperative for maintaining the correct balance of T and B cells in the immune system. If this checkpoint is disrupted, damaging B cells will be overproduced, leading to significant immune system issues.

Immunity. 2008 Oct 1. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Terry Fox Foundation, the Canadian Institutes of Health Research, the Leukemia and Lymphoma Society, the Deutsche Forschungsgemeinschaft, and the National Institutes of Health.*

Cardiology: Preventing Risky Heart Cell Remodeling After Injury

Patients with acute or chronic ischemic injury who are also at a high risk of congestive heart failure may benefit in years to come from recent preclinical evidence out of TGRI showing that injected skeletal myoblasts—undifferentiated or 'young' muscle cells—improve cardiac function following injury.



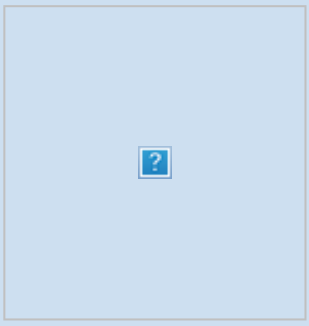
Led by Dr. Ren-Ke Li and colleagues Drs. Richard Weisel and Terrence Yau, the team injected myoblasts into infarct (damaged) or noninfarcted muscle tissue around the heart at 5 or 30 days following heart injury in a preclinical mouse model. Regardless of when they were injected, these cells improved global heart function and preserved heart wall thickness/elasticity in non-injured areas of the heart.

"It's exciting to see that these injected cells were so well able to improve ventricular and overall heart function," notes Dr. Li. "These findings provide strong evidence that structural remodeling of heart cells is important for improving outcomes in congestive heart failure."

Circulation. 2008 Sep 30;118(14 Suppl):S130-7. [Pubmed abstract]. *Research supported by the Heart and Stroke Foundation, the Canada Research Chairs Program, and the Canadian Institutes of Health Research.*

Cancer: A New Model Explores Cell Aging and Cancer Causing Genes

Investigation by OCI researcher Dr. Homayoun Vaziri and colleagues into how cancer cells bypass natural cell death and grow indefinitely is shedding light on how and where future cancer therapies could be targeted. This research focuses on telomerase—a protein responsible for maintaining chromosomal structures named telomeres. Telomerase is the only gene known that upon expression in normal cells makes telomeres long and makes the cells divide indefinitely.



"Sea urchins of Canada's west coast have very close ancestry with vertebrates such as humans and due to their short developmental period they provide the opportunity to look at developmental mechanisms and cell

aging. Sea urchin embryos are simpler but the wiring of their telomeres closely resembles that of humans," says Dr. Vaziri. "Their telomere lengths and sequence is identical to that of humans."

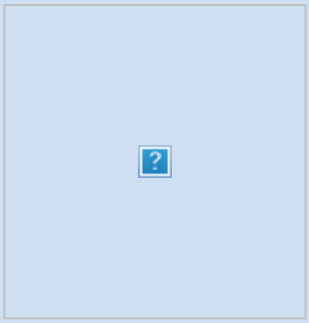
Using a series of molecular investigations, the team showed, for the first time, the existence of duplicated telomerase genes SpTERT-S and SpTERT-L in sea urchins. Changes in these specific genetic regions changed telomerase activity and, ultimately, bypassed cell death.

"What is fascinating about these two telomerase genes is that they—like genes in cancer cells—keep changing and mutating," says Dr. Vaziri. "Cancer cells continuously mutate their functional genes, allowing them to stay 'one step ahead' of the body's protective mechanisms as well as cancer drugs. Our sea urchin study represents the first example of a new mechanism which creates this type of genetic diversity. Understanding this mechanism may ultimately help us control cancer cell growth through controlling telomerase activity."

Mol Biol Cell. 2008 Oct 22. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Canada Foundation for Innovation and the Canada Research Chair Program.*

Psoriatic Arthritis: Where Fatigue Fits In

Recent findings by TWRI researcher Dr. Dafna Gladman and colleagues have shown that fatigue is a common symptom in psoriatic arthritis (PsA)—which is an inflammatory arthritis associated with psoriasis and affects both genders equally—and is associated with other factors, such as pain and psychological distress.



"It's important to acknowledge other disease factors so as to understand how they affect the way a patient copes with disease," notes Dr. Gladman.

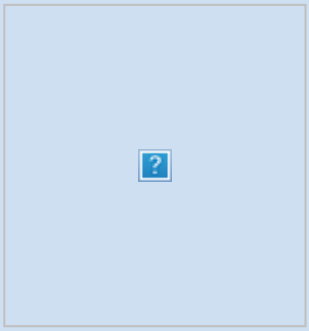
Using a questionnaire and statistical model, 499 patients from the University of Toronto PsA clinic were studied to investigate the relationship between disease-related and psychosocial variables and fatigue scores (mFSS). Results indicate that fatigue is associated with pain, female gender, physical function disability, and medication status. Fatigue provides information that does not overlap with other outcome measures.

"The results show how healthcare teams can work with patients to help improve how they deal with various disease symptoms. Future studies will need to look into the impact of other factors such as sleep quality, smoking status and body mass index to really appreciate how fatigue affects individual patients with PsA," she says.

Ann Rheum Dis. 2008 Oct 17. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Canadian Institutes of Health Research, the Krembil Foundation, and the Medical Research Council (UK).*

Anorexia: Factors Predicting Successful Weight Management

A recent National Institutes of Health funded study by UHN researchers Drs. Allan S. Kaplan, Marion Olmsted, Jacqueline Carter and Blake Woodside has shown that the best predictors of weight maintenance in anorexia nervosa (AN) patients over a one year follow up period following weight restoration are a higher weight or body mass index (BMI) reached and avoidance of rapid weight loss immediately following treatment.



In collaboration with colleagues at the New York State Psychiatric Institute, Columbia University, the TGRI team followed 93 AN patients over a period of 6 to 12 months (treated at TGH or New York) whose weight had been restored following intensive treatment. Patients were randomly assigned treatment with the drug fluoxetine or placebo along with cognitive behavioral therapy. After one year, they found that patients with a higher BMI prior to randomization and lower rate of weight loss after randomization had a greater likelihood of maintaining a normal BMI.

"Interestingly, compared to patients in New York, patients at the Toronto site were much better at maintaining their weight following initial weight restoration," says study lead Dr. Kaplan. "Our findings indicate that early weight loss is highly predictive of relapse long term in anorexia nervosa and suggest that stressing greater weight restoration during intensive treatment and aggressive weight maintenance strategies after discharge from intensive care will assist in preventing relapse and improving the long term outcome of patients with AN."

Psychol Med. 2008 Oct 10:1-9. [Epub ahead of print]. [Pubmed abstract].
Research supported by the National Institutes of Health, Eli Lilly and Co., Abbott Laboratories, Ortho McNeil Pharmaceuticals and GlaxoSmithKline.