Special Issue: Regenerative Medicine

On October 25, UHN will mark the launch of the McEwen Centre for Regenerative Medicine, a transformative centre that aims to accelerate the development of better, more effective treatments for life-threatening conditions through regenerative medicine.

Regenerative medicine harnesses the body's own healing power by replacing damaged cells, tissues, or organs via transplantation, gene therapy, and cell therapy, among others.

In this special issue, we spotlight some of UHN's contributions to this fast-moving field in 2006.

New Research Breakthroughs at UHN

Cancer: Targeting CD44 Halts Leukemic Stem Cells

AML cells

Dr. John Dick, scientific associate Liqing Jin and graduate student Kristin Hope have discovered that a monoclonal antibody directed to the adhesion molecule CD44 could be a novel treatment for acute myeloid leukemia (AML). New strategies for treating AML are critical, since existing therapies only offer a 30% long-term survival rate.

Antibody treatment decreased leukemic stem cells (LSCs) in AML mouse models generated by transplanting human LSCs into non-obese diabetic/severe combined immune-deficient or 'NOD/SCID' mice. The antibody blocked trafficking of LSCs to supportive microenvironments, induced differentiation, and reduced certain stem cell properties such as repopulation.

"In a broad sense, our findings demonstrate that it's possible to target LSCs by disrupting their microenvironment, rather than their proliferation," explains Dr. Dick. "Our study may open up new strategies for targeting solid tumours by interfering with their interactions with their environments."

Nat Med. 2006 Sep 24; [Epub ahead of print] [Pubmed abstract]
Research supported by Canadian Institutes of Health Research, Leukemia and Lymphoma Society, Fondation de France, Association pour la Recherche sur le Cancer, National Cancer Institute of Canada, Canadian Cancer Society, Terry Fox Foundation, Ontario Cancer Research Network, Genome Canada, MAT Biopharma and the Canada Research Chair Program.

Spinal Cord Injury: Adult Stem Cells Offer Growing Hope

The discovery that transplantation of adult brain stem cells into the sites of

spinal cord injuries (SCI) in rats helps restore mobility could lead to improved treatment for SCI in humans. SCI can affect the body's ability to send signals to and from the brain, leading to paralysis.

In a study led by UHN's Dr. Michael Fehlings and postdoctoral fellow Soheila Karimi, the adult brain stem cells were able to multiply and replace missing spinal cord cells as well as partially regrow the missing myelin sheath—a coating around nerve cells that permits them to carry signals to and from the brain.

"The treatment actually improved movement and coordination in rats with SCI. Although further research is needed, our work confirms that adult brain stem cells show strong potential for treating SCI," says Dr. Fehlings.

J Neurosci. 2006 Mar 29;26(13):3377-89. [Pubmed abstract] *Research supported by Canadian Institutes of Health Research, Stem Cell Network, Ontario Neurotrauma Foundation, Christopher Reeve Paralysis Foundation and Sam Schmidt Paralysis Foundation.*

Fabry Disease: Making Progress in Gene Therapy

Dr. Jeffrey Medin and his research group have shown that cells engineered to express, or produce, the enzyme alpha galactosidase (alpha-gal) can correct characteristics associated with Fabry disease in an animal model of the disease.

Normally, alpha-gal is present in the lysosome—the digestive system of the cell—and it is responsible for breaking down fat and other molecules. Lack of alpha-gal causes the build up of these molecules, and can lead to strokes, heart attacks, and kidney damage in people with Fabry disease.

Mouse models for Fabry disease were transplanted with blood, or hematopoietic, stem cells engineered for gene therapy using a new viral system to produce alpha-gal and monitored over 24 weeks. The presence of alpha-gal was observed in the relevant organs and the accumulation of harmful molecules was reduced. Similar outcomes were also observed in secondary transplanted mice.

"Taking it one step closer to a clinical setting, we cultured cells from a person with Fabry disease and added the gene to them, which gave us results similar to the mice," explains Dr. Medin. "These techniques may represent a future therapeutic option for adult Fabry patients."

Gene Ther. 2006 Aug 24; [Epub ahead of print] [Pubmed abstract] *Research supported by National Institutes of Health (US) and National Organization of Rare Diseases.*

Transplantation: Anti-Rejection Drug mTOR-ments Blood Vessel Cells

UHN researchers Dr. Thomas Waddell, Heather Ross, and Vivek Rao have provided evidence that an anti-rejection drug given to patients after transplant is harmful to blood vessel cells.

Line up

“Our study shows that this drug is targeting a certain type of cell—endothelial progenitor cells—specifically, and causing cell death by inhibiting mTOR, a protein involved in cell growth, survival and differentiation,” explains Dr. Waddell.

Anti-rejection drugs, or immunosuppressants, are toxic to the cells lining the inner layers of blood vessels and have substantial side effects. Endothelial progenitor cells are involved in regulating the repair and replacement of these damaged cells.

The finding also suggests that inhibiting these cells with rapamycin may attenuate transplant vasculopathy—severe damage to the blood vessel wall that is the most common cause of death after heart transplantation—normally attributed to cell overgrowth.

Am J Transplant. 2006 Sep;6(9):2069-79. [Pubmed abstract] *Research supported by Wyeth Canada.*

Heart Attack: Bone Marrow Molecule Signals Repair “Troops”

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.

Better Liver Transplants: Answer's in the Genes

The recent anonymous living liver transplant at TGH—and the thousands of other liver transplants that occur annually around the world—may be improved by the recent identification at UHN of a set of genes involved in acute liver injury.

A donated liver undergoes many stresses during transplantation and if it

becomes injured, the likelihood increases of the transplanted organ failing or being rejected.

UHN researchers, led by Dr. Ian McGilvray, used microarrays to compare liver gene activity during and after transplantation with gene activity in chronic liver conditions—such as hepatitis B or C infections.

“We identified 25 genes that were uniquely active in acute liver stress—such as during transplantation—but not active in chronic liver diseases,” says Dr. McGilvray. “Many of these genes have never before been linked to acute liver injury. These results could aid researchers in understanding the molecular processes behind acute liver damage and lead to better outcomes for liver transplants.”

Am J Transplant. 2006 Apr;6(4):806-24. [PubMed Abstract] *Research supported by Fujisawa Canada and Physicians' Services Incorporated Foundation.*

Upcoming Events

Symposium to Celebrate Launch of McEwen Centre for Regenerative Medicine at UHN

Mark your calendar for the opening of the McEwen Centre for Regenerative Medicine taking place on October 25 from 1pm-5pm at the MaRS Centre.

Co-chaired by Dr. Gordon Keller, Director, McEwen Centre for Regenerative Medicine and Dr. John Dick and organized by the Toronto General & Western Hospital Foundation, the symposium will feature keynote speaker Dr. George Daley, from Harvard Medical School, who will be talking about stem cells in disease and regenerative medicine.

Local leaders of the field will also be addressing topics from stem cell development and cancer stem cells to the regenerative capacity of organs like the heart and spinal cord.

The McEwen Centre for Regenerative Medicine was established at UHN in 2003 with a generous donation from Robert and Cheryl McEwen. Its mission is to be a catalyst for regenerative medicine research by facilitating collaborations and promoting research and awareness in the field.

For more information see the McEwen Centre Symposium website.

Research News

UHN Researchers' Work Published as 'Milestones'

UHN researchers Drs. James Till, Ernest McCulloch and John Dick have been featured in "Milestones in Cancer", a publication by the editors of the prestigious journal *Nature* on pioneering cancer discoveries over the last 100 years. Read about them in Milestone 6 - Cancer Stem Cells.

A Message From Your Editors

Many thanks to those of you who participated in our survey. There was a 38% increase in responses compared to our last survey.

According to the results, 81% of recipients read *Net Results EXPRESS* most months or every month. Multiple respondents indicated that the e-newsletter is a valued medium for keeping up-to-date on UHN Research.

Watch for stories over the next year in new areas as highlighted by our respondents.

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