November 2009

Lung Transplantation: Gene Therapy Repairs Injured Lungs

In a world first, a TGRI team led by Dr. Shaf Keshavjee has successfully used gene therapy to repair previously unsuitable donor lungs for transplantation. The eloquent series of investigations, conducted outside the body, were used to probe inflammation and organ rejection, two main complications after transplant surgery.

Explains first author Dr. Marcelo Cypel, "Anything we can do to prevent lung injury, especially in the first 72 critical hours after surgery, would have a significant impact on survival and quality of life after transplantation."

Studies were conducted in large animal and human models of end-stage lung disease. Using an innovative procedure that was developed by the team, donor lungs were maintained at normal body temperature and administered IL-10 gene therapy. IL-10 was the chosen gene therapy candidate specifically for its anti-inflammatory capabilities.

Findings showed that lungs treated with IL-10 gene therapy had significantly improved blood flow throughout the organ and were considerably better at taking in fresh oxygen and removing carbon dioxide. In fact, the effect was so significant it lasted up to 30 days post-surgery.

"We are very excited," says Dr. Keshavjee. "It is as if gene therapy 'turbocharges' each individual cell to manufacture many more proteins in its own IL-10 factory. This protein decreases the inflammatory potential of cells injured before and during the transplant process. It also has the capacity to turn down the recipient's immune system, which rejects the transplanted organ."

Cypel, M., Liu, M., Rubacha, M., Yeung, J.C., Hirayama, S., Anraku, M., Sato, M., Medin, J., Davidson, B., de Perrot, M., Waddell, T.K., Slutsky, A.S., and Keshavjee, S. Sci Transl Med 28 October 2009: Vol. 1, Issue 4, p. 4ra9. [Pubmed abstract]. *Research supported by the Canadian Institutes of Health Research, and the Center for Gene Therapy National Institutes of Health.*

Head & Neck Cancer: Clarifying Trial Terminology

New California Partnership Spurs Stem Cell Research

Two multidisciplinary cancer stem cell projects co-led by UHN researchers Drs. John Dick, Tak Mak and investigators in California, have been awarded funding through the Collaborative Partnership Program with The California Institute for Regenerative Medicine (CIRM). The two Canada-California collaborative projects on cancer stem cells were selected from 31 applications that targeted a broad range of diseases and injury.

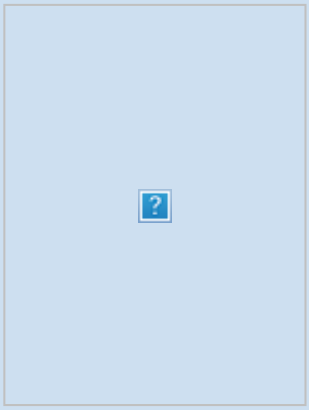
Led by Dr. Dick and the University of California, San Diego's Dr. Dennis Carson, the team will focus research efforts on the development of novel drugs to treat leukemia. This project will directly address the urgent need for new therapeutic interventions as half of adults diagnosed with leukemia die of the disease.

Dr. Mak and Dr. Dennis Slamon at UCLA will use a pipeline strategy to develop novel drugs targeting cancer-initiating cells in solid tumour cancers. Reviewers of the application determined that the proposed drugs would provide a significant clinical benefit to cancer patients and recognized the unique capabilities of the assembled team to successfully identify and develop new drugs.

Each Canadian team has requested close to $20M over four years, with their Californian partners requesting similar levels of funding from CIRM. Funding for the Canadian scientists is being provided by the Canadian Institutes of Health Research and Genome Canada.

PMH Pioneer Honoured by Canadian Medical Hall of Fame

An OCI-led investigation into the challenges of reporting relevant end-points in clinical trials for head and neck cancers is providing important evidence in support of the need to standardize the selection, definition and reporting of time-to-event end-points in clinical trials of locally advanced squamous cell carcinomas of the head and neck (SCCHN), or head and neck cancer.



Notes study lead Dr. Lillian Siu, "For reasons such as complex anatomy and management, SCCHN represents a challenging disease for the reporting of end-points and tracking end-points in clinical trials. We wanted to understand why this might be so."

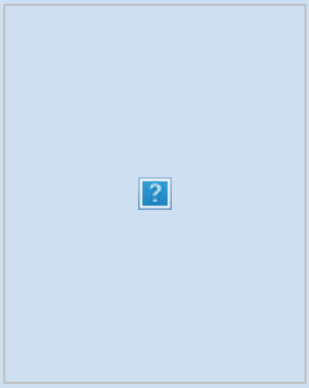
Along with research counterparts at the Institut Gustave Roussy in France, the team reviewed all English published randomized trials that began on or after 1978 and enrolled previously untreated patients with nonmetastatic SCCHN that had also received primary radiotherapy with or without any concomitant anticancer agent. Surprisingly, the team discovered a total of 17 different types of end-points with locoregional control and overall survival accounting for 70% of primary trial end points. However, among 72 end-points tracking locoregional data, 29% of studies did not define the term at all.

Dr. Siu further explained that key information was omitted in many reports including variations in scheduled timing. Methods to track failures were also frequently missing in published reports. These findings provide strong evidence towards standardizing definitions similar to those used in the Radiation Therapy Oncology Group 0522 Trial and reporting beyond the first failure to capture the full pattern of disease evolution in patients with SCCHN.

Le Tourneau C, Michiels S, Gan HK, Siu LL. J Clin Oncol. 2009 Oct 5. [Epub ahead of print]. [Pubmed abstract]. *Research supported in part by the Fondation de France.*

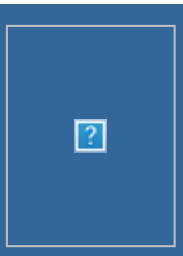
Parkinson's Disease: 'Stimulating' Ways to Prevent Falls

Deep-brain stimulation (DBS) of the pedunculopontine nucleus (PPN)—a region of the brain involved in posture and gait control—may be effective in preventing falls in patients with advanced Parkinson's Disease (PD) as outlined in a recent study from investigators at TWRI. Currently, gait and postural instability are some of the main burdens of disease in patients with PD and their pathophysiology remains unknown —perhaps until now. Specifically, for patients with PD, falls and walking difficulty are a major source of disability.



Led by Dr. Andres Lozano and colleagues Drs. Elena Moro, Jonathan Dostrovsky and William Hutchison, the team conducted a double-blind study of the effects of DBS of the PPN in six advanced PD patients with significant gait and posture abnormalities. Patients having undergone surgery to implant the electrodes for DBS in the PPN reported a significant reduction in the number of falls two years post-

We are proud to announce that Dr. Vera Peters (1911-1993) will be inducted into the Canadian Medical Hall of Fame, recognizing her efforts in changing the management of Hodgkin's disease and breast cancer.



Dr. Peters' is renowned for her 1950 seminal discovery that Hodgkin's disease could be cured with radiation. Her approach became known as the "Toronto approach" which had treatment tailored to the individual disease characteristics effectively minimizing treatment exposure—a process which took 30 years to be accepted. She was also an early advocate of breast-conserving surgery (lumpectomy) followed by radiation, which is as effective as radical masectomy.

She has been recognized throughout her career with many accolades including being appointed a Member of the Order of Canada (1975), and an Officer of the Order of Canada (1977); she was awarded a Medal from Centre Antoine Beclere (Paris) and was the first R.M. Taylor Medal and Award recipient (1979) from the Canadian Cancer Society. Also in 1979, Dr. Peters received the Gold Medal Award from the American Society for Therapeutic Radiology and Oncology which is bestowed on revered members who have made outstanding contributions to the field of radiation oncology.

Heart Experts Needed

The Training Program in Regenerative Medicine (TPRM) is looking for UHN heart experts to donate their time between the hours of 12pm and 4pm for a minimum of two consecutive hours of participation at the Ontario Science Centre's Body Worlds and the Story of the Heart exhibition.

Volunteer scientists, researchers and health experts sre needed to staff an area inside the Body Worlds exhibition called "Heart to Heart – Ask the Expert" daily at specific times to create an opportunity for dialogue with visitors. The purpose of the dialogue is to discuss current research projects, news items, and specific topics all tied to monthly themes which include:

- Diabetes Month (November)
- Anti-Stress Month (December)
- Non-Smoking Month (January)
- Heart Month (February)

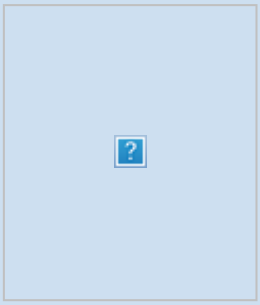
Experts are needed for all months listed above and participants will receive a certificate for their contribution of time to this event.

surgery. Significant improvements were also noted in walking and other non-motor features such as rapid eye movement sleep in comparison to pre-surgery. The UHN team is pioneering the use of PPN DBS surgery in patients with PD.

"Our study lends further support to the important role PPN plays in regulating or coordinating brain events responsible for falls in PD patients," says Dr. Lozano. "Larger scale studies are needed to determine future therapy targets, as well as the full benefits and potential side effects of PPN DBS for patients with gait and posture disturbances who are disabled by falls."

Moro E, Hamani C, Poon YY, Al-Khairallah T, Dostrovsky JO, Hutchison WD, Lozano AM. Brain. 2009 Oct 21. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the National Parkinson's Alliance.*

Diabetes: Focusing on Early Diabetes Complications



More emphasis should be placed on mechanisms that initiate early decline in renal function that eventually progress to advanced kidney failure—which can require hemodialysis or kidney transplantation—in some patients with Type I Diabetes (T1D), according to TGRI study findings reported in this month's Kidney International. Currently, it is believed that the development of advanced kidney failure only occurs after proteinuria (the finding of a large amount of protein in the urine indicating kidney damage) has been present for months or years.

Led by UHN's Dr. Bruce Perkins, the team tracked 79 patients with T1D for an average of 12 years after the onset of microalbuminuria—the first early sign of damage that occurs years before proteinuria—to follow changes in their renal function and urine proteins. Surprisingly, as many as one-third of patients with T1D developed advanced kidney failure only 12 years after the onset of microalbuminuria. Few patients who progressed to advanced chronic kidney disease developed proteinuria—which did not precede, but accompanied the progression to advanced-stage kidney disease.

"Our findings are surprising because we've been able to show for the first time that the process of renal function loss begins very early, at a stage when we would usually regard a patient with T1D as fairly healthy," explains Dr. Perkins. "There is strong evidence here that microalbuminuria is not a sufficiently robust marker for the development of advanced-stage kidney disease in T1D patients. We need to direct research towards discovering markers of damage that could identify those at risk of advanced-stage kidney disease 5 to 10 years before its development, when the potential to prevent progression still exists."

Perkins BA, Ficociello LH, Roshan B, Warram JH, Krolewski AS. Kidney Int. 2009 Oct 21. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the National Institutes of Health, the Joslin Diabetes Center, and the Banting and Best Diabetes Centre.*

Brain Injury: Determining What Contributes to Damage

Hypoxia or ischemia—a shortage of oxygen and blood supply—can cause

For more information about the program and how to get involved, please contact TPRM master educator Cheryl Bodnar or TPRM program coordinator Anna Kushnir.

Honourable Mention for OCI Research

UHN congratulates Dr. Igor Jurisica and colleague Michael McGuffin whose paper "Interaction Techniques for Selecting and Manipulating Subgraphs in Network Visualizations" has been selected as 1 of 4 for InfoVis' 2009 "Honourable Mention Paper Awards".

NAViGaTOR is currently the fastest, most scalable, and flexible tool for visualizing protein-protein interaction networks. For more information and to access the tool visit ophid.utoronto.ca/navigator

serious injury in the central nervous system. A TWRI team has discovered a previously unknown mechanism in signaling that may contribute to long term injury.

Comments study lead Dr. Peter Carlen, "There are two types of synaptic release mechanisms that contribute to the accumulation of glutamate, a neurotransmitter in the brain that, in higher concentrations, can contribute to neural injury. What our investigations have done is take a closer look at one of the mechanisms to determine how it contributes to injury and if we can understand how to stop this from happening."

With Dr. Hui Ye, the researcher driving this study, the team investigated the mechanics of the action potential (AP)-dependent and independent pathways under normal and hypoxic/ischemic conditions in brain tissue to understand if or how these pathways may contribute to the release of glutamate. Findings show that the AP-dependent pathway remarkably contributes to 74% of the overall glutamate release—which poses a serious disturbance to brain networks and their normal functioning.

"The kind of AP-dependent release we observed in our studies could occur almost immediately in an animal after a critical decrease in oxygenated blood supply," explains Dr. Carlen. "An outpouring such as this could play a significant role in later irreversible damaging changes in the brain. Our future studies will look to see how we can prevent something like this from happening."

Ye H, Jalini S, Zhang L, Charlton M, Carlen PL. J Cereb Blood Flow Metab. 2009 Oct 21. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Canadian Institutes of Health Research, Heart and Stroke Foundation of Canada, Alzheimer Society of Canada, and Pfizer Canada.*

Breast Cancer: Understanding the Relationship between Treatment and Menopause

Findings from a recent OCI-led study into the relationship between adjuvant chemotherapy and the early onset of menopause are providing important information for young women to consider over the course of their treatment regarding symptom severity and the probability of early menopause.

With colleagues from Australia and France, UHN lead author Dr. Ian Tannock recruited 41 women who had undergone menopause as a result of chemotherapy and 57 healthy women who had undergone recent natural menopause to complete two questionnaires evaluating symptom severity, quality of life, and fatigue following two annual clinic visits. The group found that patients who underwent menopause as a result of chemotherapy reported worse menopausal symptoms (and in particular, worse hot flashes) than women who had undergone natural menopause.

"Our findings provide strong evidence towards the notion that women undergoing chemotherapy-induced menopause may experience worse symptoms than women undergoing natural menopause," reports Dr. Tannock. "A large percentage of women will experience early menopause as a result of chemotherapy. These findings will assist patients in making an informed decision about adjuvant chemotherapy for breast cancer that will now include knowledge of the risk of premature menopause and the

frequency and severity of the associated symptoms."

Mar Fan HG, Houédé-Tchen N, Chemerynsky I, Yi QL, Xu W, Harvey B, Tannock IF. Ann Oncol. 2009 Oct 14. [Epub ahead of print]. [Pubmed abstract].

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