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New Research Breakthroughs at UHN

Neurology: Using Imaging to Predict Response to Therapy

The first randomized controlled trial to examine differences between brain activity in people with depression being treated with drugs or with psychotherapy may help researchers understand how these different treatments work—and which treatment may be the best choice for a specific individual—according to authors of the study Drs. Sidney Kennedy and Roger McIntyre and Mr. Jakob Konarski.

The UHN-led study followed 24 patients in a major depressive episode who received only one type of therapy. Patients' glucose metabolism was monitored over 16 weeks with PET scans. Using this imaging technique, researchers were able to visualize similarities and differences in the brain function of people who responded to treatment—and to see the patterns that identified “non-responders”, or people who did not benefit from treatment. The study demonstrated conclusively that "talk therapy", like medication therapy, changes brain activity.

Says lead author Dr. Kennedy, “This study makes important strides towards pinpointing neuroimaging predictors of treatment response in unipolar depression, an emerging area of research. Developing baseline responses prior to treatment may help understand which treatment patients respond to best.”

Am J Psychiatry. 2007 May;164(5):778-88. [Pubmed abstract] *Research was supported by the Canadian Institutes of Health Research and Wyeth Pharmaceuticals.*

Brain Cancer: Suppressing Growth is Key

Patients with glioblastoma multiforme (GBM)—the most common and malignant of all human brain tumours—have new hope today, as Krembil researchers have discovered a new gene that suppresses tumour growth in the brain and could be a potential target for future therapies.

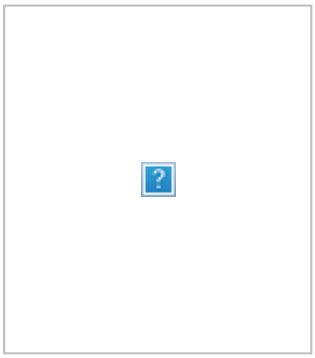
Using a combination of molecular techniques, UHN researcher Dr. Abhijit Guha and colleagues utilized a mouse brain tumor model they have created and discovered a novel genetic alteration in human brain tumour samples. They showed that the Gata6 gene is a direct target for mutations and loss of whose normal expression leads to progression of low-grade human brain tumors to malignant ones. Restoration of Gata6 decreased malignant brain tumor growth, leading to current studies aimed at defining what are the additional genes whose normal regulation is disrupted by loss of Gata6 and thereby contributing to malignant

progression of brain tumors.

“GBM is a very difficult type of cancer to control and understanding how this gene and the genes regulated by it, contributes to GBM formation and growth, adds to our arsenal of future therapeutic and diagnostic tools,” say Dr. Guha. “Ultimately we may be able to create a treatment that can use the suppression power of Gata6 to manage brain cancer.” The team is based at the Hospital for Sick Children and Toronto Western Hospital.

Proc Natl Acad Sci U S A. 2007 May 8;104(19):8053-8. Epub 2007 Apr 26. [Pubmed abstract] *Research was supported by Restracomp, the National Sciences and Engineering Research Council of Canada, the Canadian Institutes of Health Research, the National Cancer Institute of Canada, the Cleveland Foundation, and the National Institutes of Health.*

Cancer Survivors: Understanding Cognitive Impairment



A new approach to designing psychological tests used to assess post-chemotherapy cognitive impairment is advocated by a recent study from OCI researcher Dr. Ian Tannock and clinical research fellow Dr. Janette Vardy.

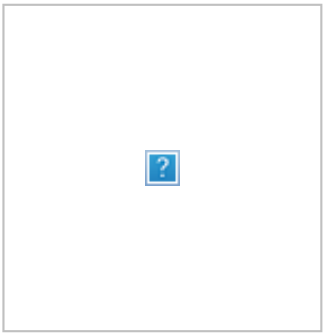
Cognitive impairment in cancer survivors occurs intermittently and can be difficult to assess. UHN researchers reviewed current literature and determined that there is a lack of consistency in defining cognitive impairment in survivors.

To better help cancer survivors, researchers suggest developing clear criteria for impairment and developing comprehensive but brief tests which are easier to administer and more suitable to repeat administrations.

"Our work has shown the need for more user-friendly and more sensitive tools to gauge and understand how chemotherapy affects cancer survivors," says Dr. Tannock. "In this respect cancer researchers can learn from colleagues in other specialties who have met similar needs for different patient groups."

J Clin Oncol. 2007 May 7; [Epub ahead of print]. [Pubmed abstract] *Research was supported by the National Cancer Institute of Canada and the Susan G. Komen Foundation.*

Pancreatic Cancer: Combination Therapy Offers Promises



A new combination therapy has been demonstrated to prolong survival time in people with advanced pancreatic cancer, according to UHN researchers Dr. Malcolm Moore and Steven Gallinger. The new approach uses the compound erlotinib to target specific pathways overproduced in pancreatic cancer.

The two-year UHN-led National Cancer Institute of Canada Clinical Trials Group study followed 569 patients treated with either gemcitabine—the current treatment standard—alone or in combination with

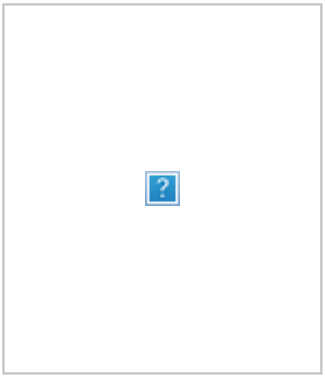
erlotinib. Patients who received the combination treatment experienced a significantly prolonged survival time and stabilization of disease.

“This combination therapy of gemcitabine plus erlotinib is the first advance in the treatment of pancreatic cancer in the past decade" says Dr. Moore. Erlotinib has been approved by the FDA and the European Medicines Evaluation Agency for the treatment of pancreatic cancer on the basis of this study and is under review by Health Canada

J Clin Oncol. 2007 May 20;25(15):1960-6. Epub 2007 Apr 23. [Pubmed abstract] *Research was supported by OSI Pharmaceuticals.*

ALS: Antibody Development has Diagnostic and Therapeutic Potential

A new antibody developed at OCI that recognizes a misfolded form of a protein involved in amyotrophic lateral sclerosis (ALS) —informally known as Lou Gehrig's disease— may make it easier to diagnose and monitor this motor neuron disease.



ALS is caused by mutations in a gene called Cu/Zn-superoxide dismutase (SOD1) that cause the SOD1 protein to misfold, resulting in a change in SOD1 activity which leads to the development of ALS symptoms.

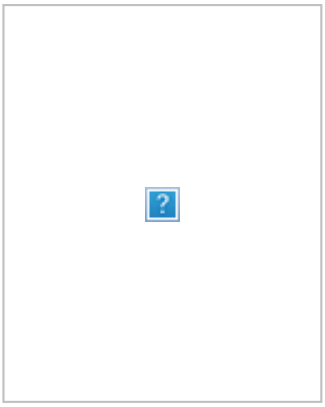
"The new antibody recognizes only the misfolded SOD1 and not the normal version, making it very specific to ALS. The antibody has potential to diagnose and ultimately treat the disease, since we may be able to manipulate the antibody to bind and neutralize the toxic effects of the misfolded form," says Dr. Chakrabartty.

This antibody also has utility in drug discovery efforts for identifying chemical chaperones that prevent or reduce misfolding of SOD1 in ALS. It has recently been licensed to Amorfix Life Sciences Ltd. for development of new treatments.

Nat Med. 2007 May 7; [Epub ahead of print] [Pubmed abstract] *Research was supported by the Neuromuscular Research Partnership--the Canadian Institutes of Health Research, the ALS Society (Canada), the Muscular Dystrophy Association (Canada), the ALS Association (US), the MND Association (UK) and the Temerety Family Trust.*

Brain Trauma: Identifying Rebuilding Blocks

A recent study by UHN's Dr. James Eubanks has identified a new gene, LCHN, important in our understanding of how the brain deals with ischemia-localized tissue damage and cell death due to lack of oxygen.



Using a rat model, the Krembil-led team discovered unusually high levels of LCHN in the brain following localized ischemia. Of particular interest is the fact this gene resides in specific growth spots in brain cells, suggesting that the gene plays a role in brain cell recovery and/or restructuring in the brain following ischemia.

"Specifically LCHN is involved with the growth of cell extensions that allow brain cells to communicate with each other," says Dr. Eubanks. "Our hope is that future research of this gene could identify an unrecognized pathway involved in the process of recovery. Having a greater understanding of these processes will allow us to target our therapies on specific genes and develop novel treatments sooner than expected."

J Neurochem. 2007 Apr;101(1):263-73. [Pubmed abstract] *Research was supported by the Heart and Stroke Foundation of Ontario.*

Breaking News from UHN Research

UHN Welcomes Three New Canada Research Chairs

UHN congratulates three of its researchers who were recently awarded Tier I Canada Research Chairs totaling approximately $4.2M in research dollars over the next 7 years.

The chair awardees include: Dr. Eleanor Fish , Canada Research Chair in Women's Health and Immunobiology (joint with UT); Dr. Linda Penn , Canada Research Chair in Cancer Genomics and Proteomics; and Dr. Benjamin Neel , Canada Research Chair in Signal Transduction and Human Disease. Dr. Neel also received funding for research infrastructure through the Canada Foundation for Innovation.
