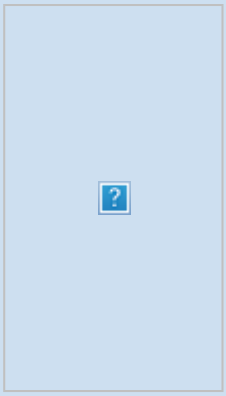
January 2009

Cancer: Molecular Structure Illustrates Form and Function

Recent progress in structural biology at OCI has yielded interesting findings that will leave their mark on future targeted cancer therapies. The team, led by UHN's Dr. Cheryl Arrowsmith, has discovered the molecular structure of the cancer protein Pirh2 and the mechanics behind how it contributes to a cancer promoting environment.



"Pirh2, originally discovered at UHN by Dr. Sam Benchimol, is a member of a unique group of proteins that bind to the cancer fighting protein p53, preventing it from stopping dangerous cancer cell growth," explains Dr. Arrowsmith.

Using an arsenal of structural biology techniques, the team has discovered the 3-dimensional shape of Pirh2 and the areas within this protein that bind to the p53 protein thereby tagging the latter as 'cellular waste'.

Notes Dr. Arrowsmith, "The family of proteins that Pirh2 belongs to has garnered a lot of attention in cancer research recently because of the important role it plays in cancer development and growth, and its involvement in many types of cancers. Continued research will aim to develop therapies that target the removal of these proteins to promote p53 activity and control of dangerous cancer cell growth."

Nat Struct Mol Biol. 2008 Dec;15(12):1334-42. Epub 2008 Nov 30. [Pubmed abstract]. *Research was supported by the Canadian Cancer Society through the National Cancer Institute of Canada, the US National Institutes of Health, the Canada Research Chairs Program, and the Leukemia and Lymphoma Research Society of Canada.*

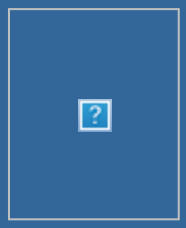
Cancer: Studying the Benefits of Outpatient Palliative Care Intervention

An OCI research initiative led by Dr. Camilla Zimmermann is one step closer to understanding how outpatient palliative care clinic (OPCC) consultations can improve patient symptom control and satisfaction. This is important in the growing interest of palliative care not only in the inpatient and home setting, but also in the outpatient setting.

The prospective study, conducted at the Princess Margaret Hospital, evaluated consultation feedback from 123 patients and found that one week after the initial palliative care consultation, patients experienced a 10% change on the scale of overall symptom control which was sustained at one month. Specifically, patients

OCI Investigator Wins Rawls Prize

UHN congratulates OCI's Dr. Geoffrey Liu for receiving the 2008 William E. Rawls Prize sponsored by the Canadian Cancer Society.



The award--presented to a young investigator--recognizes Dr. Liu's research contributions in pharmaco-genetic epidemiology and medical oncology which have led to important advances in cancer control within the past decade.

Welcome to Dr. Muthuswamy

UHN Research is pleased to welcome Dr. Senthil Muthuswamy, Senior Scientist and Lee K. and Margaret Lau Chair in Breast Cancer to the Ontario Cancer Institute.

Dr. Muthuswamy's laboratory explores alternative strategies for treatment of breast cancer. His research is focused on preventing the growth of precancerous lesions before they become malignant tumours.

Dr. Muthuswamy's laboratory will be located on the 9th floor of the Princess Margaret Hospital.

experienced significant improvement in symptom control for anxiety, insomnia, dyspnea, depression and pain.

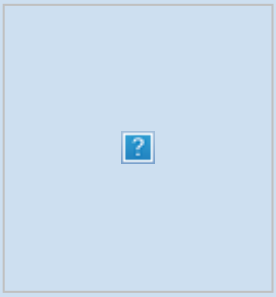
Patient satisfaction also improved for a number of criteria, such as "Information given about how to manage pain," "Doctor's attention to symptoms," "Pain relief," "How thoroughly the doctor assesses symptoms," and "Speed with which symptoms are treated."

"Our study has been able to show that the OPCC is efficacious for the improvement of symptom control and helps increase patient satisfaction with care at a very critical period," comments Dr. Zimmermann. "It is also the first study to show feasibility of recruitment of patients attending a palliative care clinic. Our future studies are continuing to expand our knowledge on this important area of research by investigating the effect of early palliative care intervention."

J Clin Oncol. 2008 Dec 8. [Epub ahead of print]. [Pubmed abstract]. *Research was supported by the National Cancer Institute of Canada and the Canadian Cancer Society.*

Parkinson's Disease: Characterizing the Impact on Brain Cell Connections

A missing piece in the Parkinson's Disease (PD) puzzle has been the knowledge of how synaptic plasticity—the ability of connections between brain cells to change—affects the development of disease in the absence of dopamine. Recent work by a TWRI team has brought new evidence to light regarding this missing puzzle piece.



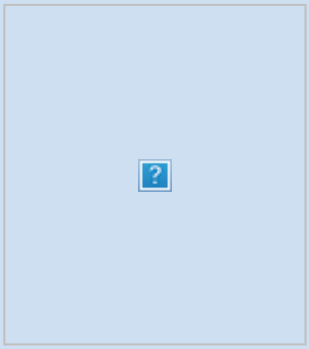
Led by Dr. William Hutchison and his doctoral student Ian Prescott and colleagues Drs. Jonathan Dostrovsky, Elena Moro, and Andres Lozano, the team characterized the synaptic plasticity of a specific region of the brain in 18 PD patients undergoing deep brain stimulation. Their findings show that when comparing patients 'on' or 'off' dopamine medication, the drug (or absence of it) clearly impacts brain signals and regulates synaptic plasticity in an activity-dependent manner.

"This is very interesting for PD patients because we've been able to show that levodopa acts to control synaptic plasticity in a region of the brain that was not known before. The close correlation of patients' symptoms to activity in this region suggests that it may play an important role in the development and progression of PD symptoms,"says Dr. Hutchison. "By better understanding the mechanics behind this disease, we can come closer to more targeted treatment therapies used in symptom management."

Brain. 2008 Dec 2. [Epub ahead of print]. [Pubmed abstract]. *Research was supported by the Parkinson's Society Canada.*

Lupus: Monitoring the Advantages of Methotrexate

Researchers at TWRI with collaborators across Canada recently revealed advantages in using methotrexate to treat patients with moderately active lupus.



Methotrexate is a commonly prescribed drug for the treatment of rheumatoid arthritis that increases the body's production of anti-inflammatory and immunosuppressive effects. Findings from the UHN double-blind, randomized, placebo-controlled study of patients with moderate systemic lupus erythematosus (SLE), led by Dr. Paul Fortin, show that in comparison to study participants on placebo, patients prescribed methotrexate experienced decreasing disease activity and lowered daily prednisone dose.

"Methotrexate was not only significant in reducing time-average prednisone use but patients also scored significantly better on the mental health component of the quality of life scale," says Dr. Fortin. "As with any medication, there are some common side effects which patients should discuss with their physicians but our findings show that methotrexate use is beneficial for patients with moderately active lupus, especially in patients without damage."

Arthritis Rheum. 2008 Dec 15;59(12):1796-804. [Pubmed abstract]. *Research was supported by the Arthritis Society of Canada and Mayne Pharma Inc.*

Thyroid Cancer: Stopping Cancer Growth Where it Starts

Investigations by TGRI researcher Dr. Mingyao Liu and doctoral student Monika Lodyga, together with their colleagues from the Universita Federico Il di Napoli in Italy, have uncovered an important onco-protein in the growth and survival of thyroid cancer cells.

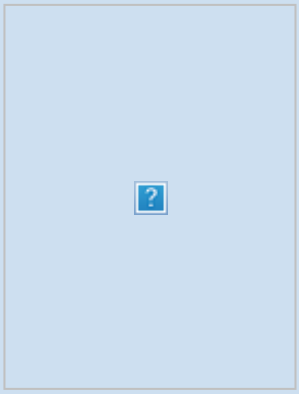
Using thyroid cell lines from humans, Dr. Liu and his team were able to successfully show that the XB130 protein contains a region in its structure that is targeted by RET/PTC kinase—a protein pathway responsible for promoting thyroid cancer.

"When XB130 is phosphorylated by RET/PTC, it prefers to associate with PI 3-kinase. This association acts as a bridge to link the two pathways, so that they are activated to specifically promote thyroid cell growth and survival," says Dr. Liu. "Knowing where the thyroid cancer growth process begins will allow us to develop novel therapies that stop the disease in its tracks."

Oncogene. 2008 Dec 8. [Epub ahead of print]. [Pubmed abstract]. *Research was supported by the Canadian Institutes of Health Research, the Italian Association for Cancer Research, MIUR, Alleanza contro iL Cancro and the European Union Contract FP6-36495 (GENRISK-T).*

Virology: Understanding the Mechanisms of Infection

A new finding from TGRI adds important knowledge to our understanding of how infection, especially poxviruses, spreads throughout the human system and where the spread may potentially be stopped.



The immune system contains chemokines, or proteins responsible for relaying messages that ignite T cells into action launching an immune response. During an immune response, a chemokine receptor, CCR5, plays a pivotal role in how the immune system responds.

"When we conducted a CCR5 bone marrow transplant into mice without CCR5, virus infection occured as evidenced by lung and spleen infection," says study lead Dr. Eleanor Fish.

The team showed that CCR5 plays a role in spreading vaccinia virus (VACV), a poxvirus that led to the global eradication of smallpox. When mice deficient for CCR5 were infected with VACV, viral loads were diminished in the spleen and brain in comparison to mice with CCR5.

"This is the first evidence showing that CCR5 is important for the migration of T cells out of affected lungs following intranasal VACV infection," comments Dr. Fish. "We show that CCR5 expression in T cells contributes to the spreading of VACV beyond lung tissue, which suggests CCR5 may in fact be required for whole body poxvirus infection."

J Virol. 2008 Dec 10. [Epub ahead of print]. [Pubmed abstract]. *Research was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC), the Canadian Institutes of Health Research and the Canada Research Chairs Program.*