



Cancer: Deciphering Important Gene Patterns

Tumor stage is currently the best predictor of patient survival in non-small cell lung cancer (NSCLC), but new evidence from a team of OCI investigators may provide important prognostic information—independent of tumor stage—that may affect treatment strategies.

Explains Dr. [Igor Jurisica](#), "Many useful molecular markers have been identified for several cancers, including NSCLC. However, for many technical reasons these small predictive sets of genes usually have poor overlap across studies. Our recent study provides another explanation for this lack of overlap, and is the first comprehensive study of predictive signatures."

Dr. Jurisica and his graduate student Paul Boutros, along with team members Drs. [Frances Shepherd](#), [Ming-Sound Tsao](#) and [Linda Penn](#) (Paul's co-supervisor), developed an algorithm and used it to analyze data from four previous lung cancer studies—a follow-up study to one led by Dr. Tsao (2007). The team found that the algorithm could accurately predict patient survival outcomes, a result validated in four external datasets, and the largest pooled data set from eight separate NSCLC studies comprising 589 patient samples.

"Based on our calculations, we've found another half million different six-gene signatures—gene activity between six genes—that could predict NSCLC," comments study author Paul Boutros. "The six-gene signatures we've found have a potential to help us understand the biology of NSCLC, and provide alternative markers for identifying patients with poor prognosis."

Boutros PC, Lau SK, Pintilie M, Liu N, Shepherd FA, Der SD, Tsao MS, Penn LZ, Jurisica I. Proc Natl Acad Sci USA. 2009 Feb 24;106(8):2824-8. [Pubmed abstract]. Research supported by the National Cancer Institute of Canada, Natural Sciences and Engineering Research Council, the Princess Margaret Hospital Foundation, Genome Canada, IBM, the PreCarn Foundation, and the Canadian Institutes of Health Research.



Three Canada Research Chairs Renewed

UHN congratulates the following awardees on the recent renewal of their Canada Research Chairs (CRC) totaling approximately \$3.5M in research dollars over the next seven years.

Chair awardees are: Dr. Kevin Kain, Tier I Canada Research Chair in Molecular Parasitology; Dr. Alejandro Jadad, Tier I Canada Research Chair in eHealth Innovation; and Dr. Peter Cheung, Tier II Canada Research Chair in Chromatin Regulation.

UHN Welcomes Dr. Shannon Dunn

UHN welcomes Dr. Shannon Dunn to the Toronto General Research Institute, Division of Cellular and Molecular Biology. Shannon joins UHN from California where she spent a number of years at Stanford University researching Multiple Sclerosis (MS) in Dr. Lawrence Steinman's lab.

Her research with TGRI will focus on sex differences in autoimmune diseases. Her studies will expand upon her discovery that Peroxisome Proliferator-Activated Receptor alpha (PPARalpha) is expressed at higher levels in male vs. female T cells. Her work has revealed that the expression of this protein is sensitive to the levels of male sex hormones and that PPARalpha has an inhibitory effect on the development of EAE, a mouse model of MS.

Mark Your Calendars: TWRI Research Day 2009



Lung Cancer: A New Three-Sided Approach to Therapy

Findings from a recent UHN investigation are shedding light on a new course of therapy that may be available to patients with malignant pleural mesothelioma (MPM)—cancer of the lining of the chest or abdomen—to overcome current challenges relating to diagnosis and treatment.

Led by TGRI's Dr. Marc de Perrot and colleagues, 60 patients with MPM from Princess Margaret Hospital were administered a 'three-sided' treatment approach which consisted of cisplatin-based chemotherapy, surgery and high-dose radiation. Results showed that half of the patients were able to successfully complete the study and that up to a 5-year disease-free survival rate was observed in 53% of patients.

"These results are very encouraging for patients with tumors that can be surgically removed and can complete each stage of treatment," comments Dr. de Perrot. "For some patients, disease stage remains a strong predictor of outcome and additional clinical studies are needed to help manage treatment strategy for these patients."

de Perrot M, Feld R, Cho BC, Bezjak A, Anraku M, Burkes R, Roberts H, Tsao MS, Leighl N, Keshavjee S, Johnston MR. J Clin Oncol. 2009 Feb 17. [Epub ahead of print]. [[Pubmed abstract](#)]. Research supported by the Mesothelioma Research Foundation at Princess Margaret Hospital.

Neurology: New Tools Investigating Development

TWRI researcher Dr. [Philippe Monnier](#) and colleagues have developed a tool that will allow investigators to study protein function in a new manner. It has also enabled the discovery of the importance of two protein regions involved in axon (brain cell connector) outgrowth in the pathway responsible for vision.

Using a variety of molecular tools, the team engineered several specific antibodies (scFvs) and found that they were capable of maintaining regions of proteins in an orientation that allowed the proteins to be studied over a two week period. The antibodies also specifically recognized the target protein RGMa, the protein responsible for regulating proper axon pathfinding during development.

Says Dr. Monnier, "scFvs antibodies are capable of holding regions of proteins 'motionless', making possible new functional studies. This new tool has been significant to our work because we have been able to provide the first evidence that both regions of the RGMa protein are important for properly directing cells involved in vision during the development of the central nervous system in the chick. These new tools will be used in future studies to help us better understand vision and where treatment strategies for vision loss can be used one day."

Tassew NG, Charish J, Chestopalova L, Monnier PP. J Neurosci. January 28, 2009. 29(4):1126-31. [[Pubmed abstract](#)]. Research supported by the Krembil Foundation and the Canadian Institutes of Health Research.

Mark your calendars for TWRI's annual Research Day to be held on Wednesday May 13, 2009 at 89 Chestnut Street.



The event is celebrating its 9th anniversary of featuring TWRI research and is open to TWRI investigators, trainees and staff and TWH clinical researchers.



Major Depressive Disorder: Tracking Multiple Drug Treatments

TWRI researchers have determined that young children and adolescents with major depressive disorders (MDD) are receiving broad regimens of pharmacotherapy that are within FDA approved and unapproved standards for the management of mood syndromes.

Comments study lead Dr. [Roger McIntyre](#), "In the past twenty years, the occurrence of mood and behavioral disorders among children and adolescents has increased significantly and we wanted to understand what was being done to help treat this group of patients."

Examining pharmacotherapy patterns for 1544 children and adolescents diagnosed with MDD, the TWRI team has shown that polypharmacy has significantly increased over the years, especially between 1997 and 2003. In particular, individuals with ADHD, bipolar disorder and psychotic disorders, especially in males and non-Africans, were more likely to be prescribed multiple medications.

"What we've found here is that the pattern of antipsychotic drug use in children and adolescents has increased and changed in accordance with FDA warnings and regulations," says Dr. McIntyre. "Future studies should continue to evaluate the therapeutic benefits of drug combinations for mood and related disorders and in particular, the efficacy and safety of newer medications in these patients."

McIntyre RS and Jerrell JM. J Clin Psychiatry. 2009 Jan 27. [[PubMed abstract](#)]. Research supported by the Substance Abuse and Mental Health Services Administration.

HIV: Evaluating the Value of New Treatment Options

TGRI's Dr. [Sharon Walmsley](#) and an international team of colleagues have confirmed that use of the boosted protease inhibitor saquinavir/ritonavir (SQV/r) in HIV-1-infected patients is as effective as existing treatments when used as part of combination HIV therapy.

Currently, the most effective initial treatment for patients with the HIV-1 virus is a combination of drugs aimed at preventing the virus from multiplying rapidly.

"This Gemini study, unlike other research initiatives, followed patients, who had never been treated for HIV-1 infection, for 48-weeks to determine if SQV/r is as effective as the currently widely prescribed lopinavir/rionavir (LPV/r) treatment strategy when used in combination with Truvada," notes Dr. Walmsley.

In fact, the study findings show that SQV/r was as effective as LPV/r in keeping HIV-1 virus counts low in patients. Surprisingly, unlike LPV/r,



patients prescribed SQV/r treatment experienced smaller increases in triglyceride levels, an important finding as HIV-1 patients are at an increased chance of experiencing metabolic syndrome, and in some cases, coronary artery disease.

"This is very important in terms of future treatment strategies because SQV/r works as effectively as current practices but without as severe risks to the heart," says Dr. Walmsley. "These findings add additional support to current treatment guidelines and reinforce their use as a viable component for first-line therapy of HIV-1-infected patients."

Walmsley S, Avihingsanon A, Slim J, Ward DJ, Ruxrungtham K, Brunetta J, Bredeek UF, Jayaweera D, Guittari CJ, Larson P, Schutz M, Raffi F. J Acquir Immune Defic Syndr. 2009 Feb 12. [Epub ahead of print]. [[Pubmed abstract](#)]. Research supported by Roche Pharmaceuticals.



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