October 2010

Cancer: Identifying the Cells that Cause Cancer

Tumour initiating cells (TICs) are a specific type of cell with the properties of stem cells—they have the ability to give rise to more specific cell types and replicate indefinitely—and are thought to be a main cause of tumours. TICs are identified by their ability to form tumours in mice and were believed to be rare in many cancers; however, a recent study suggested that the type of mouse model used to identify TICs could affect how researchers determine the number of these cells present in a tumour. Therefore, it is possible that the number of TICs has been underestimated in many human tumours.

In a recent issue of *Cell Stem Cell*, a team of UHN scientists including Drs. Ben Neel, Laurie Ailles, Ming Tsao, Nadeem Moghal and Thomas Waddell, along with colleagues at Johns Hopkins (William Matsui), investigated this possibility and determined that TICs are indeed rare in several types of lung, head and neck cancers and pancreatic cancer, regardless of the type of mouse model used to identify them. However, it is important to use specific methods when growing TICs in order to accurately determine their frequency in a tumour.

As Dr. Neel explains "The presence of TICs may make a tumour difficult to effectively treat because, if even one TIC survives, it can give rise to a tumour. This study shows that it is important to study the TICs for each specific type of cancer in order to accurately determine their number."

Ishizawa K, Rasheed ZA, Karisch R, Wang Q, Kowalski J, Susky E, Pereira K, Karamboulas C, Moghal N, Rajeshkumar NV, Hidalgo M, Tsao M, Ailles L, Waddell TK, Maitra A, Neel BG, Matsui W. Cell Stem Cell. 2010 Sep 3;7(3):279-82. [Pubmed abstract]. *Research supported by the National Institutes of Health, the Pancreatic Cancer Action Network, the Ontario Institute for Cancer Research, the Waxman Foundation, the Ontario Ministry of Health and Long Term Care, the Canada Research Chairs program, and the Canadian Institutes of Health Research.*

Lung Cancer: Gene Signature Helps Predict Benefits of Chemotherapy

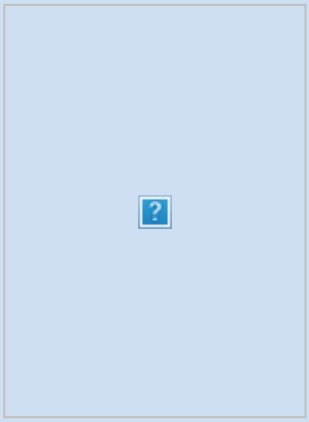
McEwen Director Named 'Transformational Canadian'

UHN congratulates Dr. Gordon Keller—Director of the McEwen Centre for Regenerative Medicine and OCI Senior Scientist—for being named one of the Top 25 Transformational Canadians in a poll conducted by the Globe and Mail. Cutting across six different fields—business, science and technology, the environment, education, health care and the community—these Canadians are being recognized for having made a difference by immeasurably improving the lives of others.

In the Science and Technology category, Dr. Keller is being recognized for having shown innovation and leadership through the advancement of technology that is transforming our world through his pioneering regenerative medicine research program.

For complete coverage of the Globe and Mail's interview with Dr. Keller, as well as the other 24 awardees, visit the Globe's 25 Transformative Canadians.

Recent findings out of OCI provide healthcare teams with important new information that may help guide the appropriate post-operative treatment for patients with early-stage non-small-cell lung cancer (NSCLC). The team conducted an in-depth analysis of gene expression from over 130 frozen tumour samples to determine if this signature or 'pattern' of gene activity could help identify patients as high- or low-risk for disease recurrence.



As explained by study lead Dr. Ming Tsao, "Not all patients benefit from chemotherapy after surgery and our findings here will help identify those patients with less aggressive cancer who may be spared from the potentially debilitating side effects of this treatment."

Working with collaborators at the NCIC Clinical Trials Group (CTG) at Queen's University in Kingston and supported by funding from the Canadian Cancer Society, the team performed genomic analysis of lung tumour samples collected from patients across Canada participating in the NCIC CTG BR.10 study. From that, the team identified a genetic signature for patients with significantly different survival outcomes.

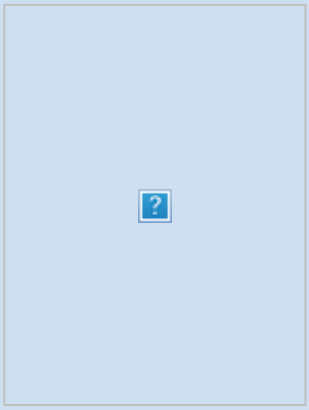
The team identified a set of 15 genes that, in 62 patients who did not receive chemotherapy after surgery, predicted which patients had aggressive cancers with high risk of recurrence and death (31 patients), and which had less aggressive disease and low risk of recurrence (31 patients). The signature was then applied to another 356 patients (with either stage IB or II NSCLC) without treatment and predicted improved survival after therapy.

"We're quite excited by our findings because this 15 gene signature was capable of predicting patients with aggressive cancer and showed that these patients also experienced the greatest benefit from chemotherapy with a 67% reduction in the risk of death," explains Dr. Tsao. "This study also shows that the 15 gene signature may identify patients with both stage I and II cancer who may benefit from post-operative therapy, and help other patients avoid potentially harmful treatment. Importantly, these findings help us move one step closer to personalized medicine for patients."

Zhu CQ, Ding K, Strumpf D, Weir BA, Meyerson M, Pennell N, Thomas RK, Naoki K, Ladd-Acosta C, Liu N, Pintilie M, Der S, Seymour L, Jurisica I, Shepherd FA, Tsao MS. J Clin Oncol. 10 Oct 10;28(29):4417-24. Epub 2010 Sep 7. [Pubmed abstract]. *Research supported by the Canadian Cancer Society, the US National Cancer Institute, the Canada Foundation for Innovation, the Canada Research Chairs Program, the Ontario Ministry of Health and Long Term Care, and GlaxoSmithKline for supporting the establishment of the JBR.10 frozen tumor bank.*

Neuroscience: The Cellular Basis of Neural Impulse Transmission

Information coded as impulses is transferred from one neuron to its target at synapses. At these close neuron-neuron contacts the impulse opens voltage sensitive calcium channels allowing the influx of calcium ions (Ca2+) and this ion then acts as a 'second messenger' to trigger the release of neurotransmitters by the fusion of a secretory vesicle with the surface membrane. Thanks to TWRI's Dr. Elise Stanley, it is now established that the relationship between the calcium channel and the secretory vesicle is very intimate, so much so that the fusion of a secretory vesicle can be triggered by the plume of Ca2+ entering through a very closely situated single calcium channel.



There was, however, one major mystery. Since the ability of the single channel to trigger transmitter release is directly proportional to the amount of Ca2+ that enters, the largest calcium channel species—the L type (a member of the CaV1 family)—would be predicted to serve this role for transmitter release. Yet this function is almost always served by the intermediate sized, CaV2 (N type), family channels. Since calcium channel families were originally characterized under highly non-physiological conditions, Dr. Stanley and her team set out to test if these channels exhibit different properties under physiological ion conditions.

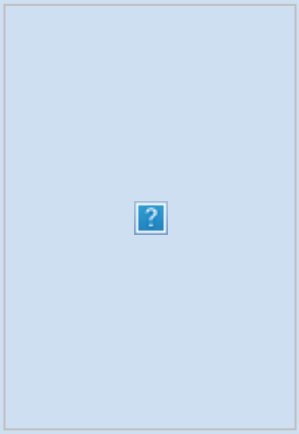
A detailed analysis of Ca2+ entry rates for all three calcium channel families with physiological Ca2+ demonstrated that the CaV2 family representative exhibits the largest conductance, explaining its selection at the presynaptic terminal. In collaboration with Victor Matveev (New Jersey Institute for Technology), mathematical modeling showed that Ca2+ influx through a single member of this family is sufficient to trigger the fusion of a secretory vesicle located 25 nm from the channel.

Explains Dr. Stanley, "These findings may help to explain why nature evolved this new family of channels, permitting an efficient transmitter release mechanism with a modular molecular organization. Our next objective will be to determine how this exquisitely organized 'molecular machine' plays a role in synaptic modulation which is critical for memory and behaviour modification." Since transmitter release is involved in virtually every aspect of nervous system function these results have a very broad impact for the understanding of normal brain processing and, in turn, a variety of central and peripheral nervous system disorders.

Weber AM, Wong FK, Tufford AR, Schlichter LC, Matveev V, Stanley EF. Nature Neuroscience [Epub ahead]. [Pubmed abstract]. *Research supported by the Canadian institutes for Health Research, the Canada Research Chairs Program, the Ontario Graduate Scholarship and National Science Foundation.*

Heart Disease: Preventing Injury Following Transplantation

In a key finding published in this month's issue of *Circulation*, TGRI researcher Dr. Vivek Rao and colleagues identified that the Epidermal growth factor-like domain 7 (Egfl7) protein protects cells against inflammation that typically follows a period of low oxygen, which occurs during a heart transplant.



The team determined that Egfl7 levels are increased in coronary endothelial cells—cells lining the cavities and surface of the heart—following exposure to low oxygen conditions. When cells were treated with Egfl7, the levels and activity of proteins causing immune cells to stick to endothelial cells were lower. Importantly, Egfl7 restricted the activity of a key regulatory protein (NF-kB), suggesting that altering the activity of this protein is an important step in the ability of Egfl7 to protect cells.

"Events that promote inflammation in the body can occur after heart transplant, and can lead to the development of atherosclerosis where arteries in the heart narrow due to fat build-up, blood vessel narrowing and/or blood vessel destruction due to increased inflammation following transplant," explains Dr. Rao. "Learning exactly how and when to increase the activity of Egfl7 may be an important new therapeutic strategy to regulate inflammation and injury in patients".

Badiwala MV, Tumiati LC, Joseph JM, Sheshgiri R, Ross HJ, Delgado DH, Rao V. Circulation. 2010 Sep 14;122(11 Suppl):S156-61. [Pubmed abstract]. *Research supported by the Heart and Stroke Foundation of Ontario.*

Diabetes: Detecting Sugar Sensing Pathways in the Brain

TGRI researcher Dr. Tony Lam and colleagues have uncovered the brain's circuitry involving the forebrain and hindbrain that is necessary for the processing and 'sensing' of sugar in the blood. The findings lend important new knowledge to our understanding of how the brain processes signals from the blood to account for, and deal with, the proper processing of sugar.

As explained by Dr. Lam, "Scientists have known that a region in the brain called the hypothalamus is responsible for sensing and regulating sugar production by the liver; however, until now the exact circuits within the brain required to do this were largely unknown."

With colleagues from the Imperial College in South Kensington London, Dr. Lam blocked the activity of a neurotransmitter receptor, N-methyl-D-aspartate (NMDA) receptor, specifically in the hindbrain region of the brain known as the dorsal vagal complex (DVC). When the team analyzed the data in conscious and unrestrained rodents, they found strong evidence showing that blocking NMDA receptors in the DVC prevented sugar sensing mechanisms in the body necessary to lower sugar production in the liver.

"We have sound evidence showing that the DVC NMDA receptor is necessary for the hypothalamus to detect blood sugar to lower the production of glucose," says Dr. Lam. "Specifically, we show that nutrient sensing activates, or turns on, a forebrain-hindbrain (front-back), cross-talk in the brain so that the necessary communication between different regions can cooperate to lower glucose production in vivo. Future studies will help determine if, or how, other known brain circuits may also be

involved in this communication pathway. New drugs could eventually be developed targeting signaling molecules in selective region(s) of the brain that would potently lower blood sugar levels in diabetes."

Lam CK, Chari M, Rutter GA, Lam TK. Diabetes. 2010 Sep 24. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Canadian Institutes of Health Research, the Banting and Best Diabetes Centre, the Wellcome Trust, the Medical Research Council (UK), the European Union (FP7 "IMIDIA"), the Canada Research Chairs Program and the John Kitson McIvor Endowed Chair in Diabetes Research.*

Virology: Developing New Methods to Fight off SARS

Recent findings out of TGRI suggest new methods for harnessing the power of the immune system to respond to viral infections, such as those seen in the 2002-2003 outbreaks of Severe Acute Respiratory Syndrome (SARS), which is caused by infection with the SARS coronavirus. These findings could provide significant help towards the development of novel treatments for coronavirus infections.

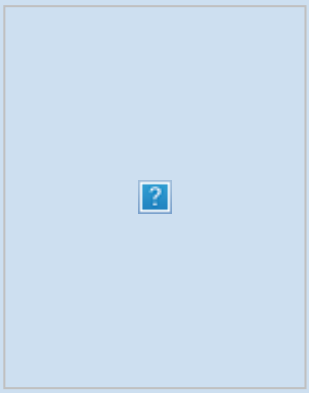
Led by Dr. Ian McGilvray and colleagues Drs. Gary Levy and Aled Edwards, the team replicated SARS infection in mice to examine how ubiquitination—the process that marks proteins as cell 'waste' and triggers their removal—was involved in regulating the immune system. Findings show that treating mice infected with SARS-like pneumonitis with one of three different agents designed to block the ubiquitination process (PTCD, MC132 and PS-341) resulted in a 40% increase in survival and improvement in lung histology. Lung virus replication, as well as the number of proteins in the lung association with inflammation and disease, was also reduced.

"Specifically, we have been able to show that blocking the cellular proteosome attenuates pneumonitis and the expression of genes responsible for producing inflammation by decreasing virus replication and the resulting inflammation response," says Dr. McGilvray. "By blocking the proteosome, we have been able to decrease viral load and, ultimately, infection. Future studies will further examine how blocking this machinery may be an effective new treatment for severe coronavirus infection in order to help uncover remedies that protect the general population in the event of a re-emergent outbreak."

Ma XZ, Bartczak A, Zhang J, Khattar R, Chen L, Liu MF, Edwards A, Levy G, McGilvray ID. J Virol. 2010 Sep 22. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Canadian Institutes of Health Research and the University of Toronto Training Program in Regenerative Medicine.*

Parkinson's Disease: Learning the Benefits of Combined Therapy

For patients with advanced Parkinson's disease (PD), long-term use of levodopa (L-Dopa)—a compound designed to increase levels of dopamine in the brain—can lead to serious reductions in the drug's ability to reduce PD symptoms and can contribute to the development of uncontrollable body movements known as dyskinesia. A recent TWRI study has found strong evidence pointing towards the use of combination therapies to help increase the effects of L-dopa and decrease the likelihood of developing diskinesia.



Led by TWRI's Dr. Jonathan Brotchie, the team used L-dopa in combination with fipamezole, a compound designed to block

specific receptors in the brain responsible for relaying information from one brain cell to another. Findings show that, when used in combination with L-dopa, fipamezole was able to increase the anti-PD effects and duration of L-dopa action by up to 98%. In addition, the study went on to show that the proportion of time without dyskinesia was significantly greater at 79% when fipamezole was used in combination with L-dopa, than was experienced with high doses of L-dopa alone (45%).

"This is exciting because, for the first time, we have been able to show that fipamezole in combination with L-dopa helps to significantly increase the duration of time L-dopa works to reduce PD effects," explains Dr. Brotchie. "We have also shown that this increased duration and quality of L-dopa action may represent therapeutically valuable actions of fipamezole and this particular class of drugs. Future studies will work towards better understanding this relationship so that researchers can develop new therapeutic strategies for motor complications in patients with PD."

Johnston TH, Fox SH, Piggott MJ, Savola JM, Brotchie JM. Mov Disord. 2010 Oct 15;25(13):2084-93. [Pubmed abstract]. *Research supported by the Krembil Neurosciences Fund and Cure Parkinson's Trust.*