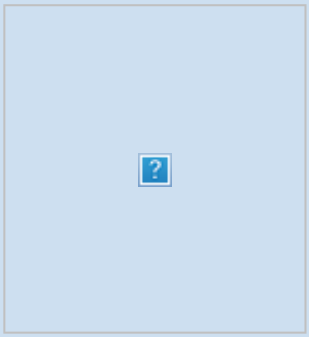
May 2009

Cancer: Boosting the Body's Immune System

An international team of investigators led by OCI's Drs. Pamela Ohashi and Tak Mak, have devised a method that can boost the body's immune system and direct it to specifically target cancer cells. Currently, it is clear that a patient's immune system can destroy tumor cells however, the majority of current approaches to enhance this action are not optimal.



"The promise of using the body's own defenses to fight cancer is enormous," comments study co-lead Dr. Mak. "The day is coming when immunotherapy may help spare cancer patients the toxic side effects of traditional therapies and greatly improve their quality of life while treating the disease."

Using an animal model, the team combined a viral vaccine with interleukin-7 (IL-7)—an important protein of the immune system necessary for proper immune development—to show that the combination was able to significantly improve the ability of key immune cells to attack tumors.

Comments study lead Dr. Ohashi, "We are extremely excited because our research has revealed the unexpected ways IL-7 works to break down barriers that naturally block the immune responses to tumors. This is important because current vaccine approaches for immune therapy induce a response in just 2-5% of patients."

Future studies of IL-7 therapy will help determine the ways it can most effectively be used, including extending the length of therapy, combining IL-7 with other strategies or using alternative repeated vaccination protocols.

Pellegrini M, Calzascia T, Elford AR, Shahinian A, Lin AE, Dissanayake D, Dhanji S, Nguyen LT, Gronski MA, Morre M, Assouline B, Lahl K, Sparwasser T, Ohashi PS, and TW Mak. Nature Medicine E Pub ahead. [Pubmed abstract]. *Research supported by the Canadian Institutes of Health Research, the Ontario Institute for Cancer Research, the Terry Fox Foundation, the National Cancer Institute of Canada, the Boninchi Foundation, and the Irvington Institute with the Cancer Research Institute.*

UHN Salutes OCI Investigator

UHN congratulates Dr. Brenda Gallie on being recognized by the Scientific Selection Committee of the Alcon Research Institute (ARI) for her outstanding research in the study of vision.

The award provides $200,000 in unrestricted grant money for Dr. Gallie to continue her research into the underlying causes of retinoblastoma. Dr. Gallie will present her research at the 2011 ARI symposium. The ARI supports global advancements in eye health by honouring those who make outstanding research contributions to the vision sciences.

Congratulations Dr. Gallie!

CFI Leaders Opportunity Fund Awardees Announced

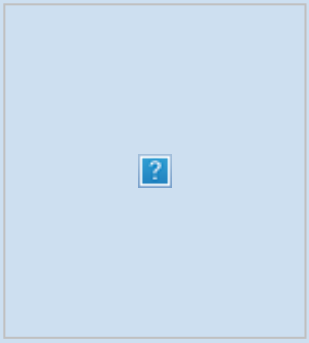
The Canada Foundation for Innovation (CFI) announced its most recent application round awardees, which includes OCI's Dr. Senthil Muthuswamy who was awarded funds from the Leaders Opportunity Fund (LOF) to help establish the Laboratory for the Study of Polarity Proteins in Breast Cancer.

In total, the CFI-LOF program announced $26M in support for 117 projects across 29 Canadian research institutions. Since its creation in 1997, CFI has committed almost $4.5B in support of more than 6,000 projects at 129 research institutions in 64 municipalities across Canada.

Canadian Cancer Society Supports UHN Research

Breast Cancer: Assessing Risk Early On

OCI investigators have conducted a unique mother-daughter study that provides further understanding of breast density, an inheritable characteristic known to be a strong risk factor for breast cancer, and suggests that risk assessment and prevention of breast cancer might start early in life.



Led by Dr. Norman Boyd, the team recruited 400 pairs of mothers and daughters and used Magnetic Resonance Imaging (MRI) to examine breast tissue in daughters, aged 15-30 years, as well as a random sample of 100 of the mothers. Mothers underwent mammography and a random sample of 100 also consented to have a breast MRI. Results showed that percent breast water variation was higher in 15-19 year olds than in 20-30 year olds, and that this variation decreases with age.

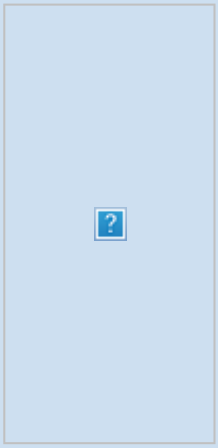
Height and weight, the mothers' breast tissue characteristics, and higher blood growth hormone concentrations were also linked to higher percent breast water. The team found that every additional 5 cm in the daughters' heights was associated with a 3% increase in percent breast water, which suggests a mechanism by which growth might affect the risk of cancer.

"Our findings suggest that differences in breast tissue composition in early life may be a potential mechanism for this increased susceptibility to the effects of carcinogens at early ages," comments Dr. Boyd. "By identifying the environmental and genetic factors that influence breast tissue composition early in life, we may be able to develop safe and effective methods of prevention."

Boyd N, Martin L, Chavez S, Gunasekara A, Salleh A, Melnichouk O, Yaffe M, Friedenreich C, Minkin S, Bronskill M. [Pubmed abstract]. *Research supported by the Canadian Breast Cancer Research Alliance, the Lau Chair in Breast Cancer Research.*

Malaria: Focusing Treatment Efforts During Pregnancy

TGRI researchers have discovered how a specific protein of the immune system contributes to the development of placental malaria (PM). PM—the accumulation of malaria parasites in the placenta during pregnancy—is a leading cause of maternal and infant mortality and this recent discovery will help in the development of future treatment options for patients with PM.



"There is significant activity in the immune system during pregnancy and we wanted to determine what factors are involved in the development of PM as it is currently poorly understood," comments study lead Dr. Kevin Kain.

With TGRI's Dr. W. Conrad Liles and colleagues from the US and Kenya, the team conducted a series of molecular investigations on plasma and placental blood samples taken from Kenyan women with and without PM at the time of birth. Their studies revealed that infected blood cells activated the immune protein C5 (a potent inflammatory protein and essential component of the immune

UHN congratulates recent Canadian Cancer Society (CCS) Research Grant awardees on their successful proposals totaling approximately $4.1M in new research dollars over the next six years. CCS awardees include Drs. Jan Jongstra, Murray Krahn, Ben Neel, Linda Penn, Ming-Sound Tsao, Li Zhang and Camilla Zimmermann.

Out of 350 grant applications, the CCS approved 60 projects across Canada, including five projects as a direct result of the CCS (Ontario Division) special call for lung cancer research applications.

Congratulations to all!

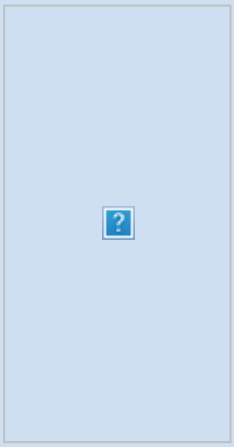
response), which in turn amplified the inflammatory response to malaria—particularly with immune proteins known to be associated with adverse pregnancy outcomes such as premature delivery and intrauterine growth restriction.

"Of particular importance, C5a levels were significantly elevated in women with PM," says Dr. Kain. "We were able to show that blocking C5a and its receptor responsible for mediating its inflammatory effects caused significant decreases in immune activity. With continued investigations, the team plans to confirm that C5a is a clinically useful biomarker of PM and that disrupting C5a and/or its receptor could be a novel therapeutic approach to improve outcomes in placental malaria."

Conroy A, Serghides L, Finney C, Owino SO, Kumar S, Gowda DC, Liles WC, Moore JM, Kain KC. PLoS ONE. 2009;4(3):e4953. Epub 2009 Mar 24. [Pubmed abstract]. *Research supported by the Canadian Institutes of Health Research, Genome Canada through the Ontario Genomics Institute, the National Institutes of Health.*

Noonan Syndrome: Understanding the Mechanics of Disease

Findings from the lab of OCI Director Dr. Benjamin Neel highlight how exactly mutations participate in the development of Noonan syndrome (NS)—the most common single-gene cause of congenital heart disease.



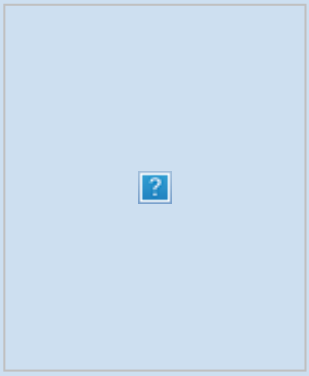
With co-author Dr. Toshiyuki Araki and colleagues, the team used a mouse model to show that cardiac defects typically found in patients with NS—due to mutations in the gene PTPN11—are the result of the incorrect activation of Shp2 in the endocardium (the lining of the interior surface of heart chambers) of the developing heart. The team was also able to show that cardiac defects in NS are a result of signaling pathways extending a specific period of development.

Comments Dr. Neel, "For the first time we've been able to provide detailed 'mechanics' behind cardiac defects seen in this disorder. Mutations in same locus are the likelihood of leukemia. Future studies in this area will work towards understanding the signaling dynamics to determine the best course for therapeutic intervention."

Araki T, Chan G, Newbigging S, Morikawa L, Bronson RT, Neel BG. Proc Natl Acad Sci U S A. 2009 Mar 24;10 (12):4736-41. Epub 2009 Feb 27. [Pubmed abstract]. *Research supported by the National Institutes of Health and the Leukemia and Lymphoma Society.*

Parkinson's Disease: Defining Patterns of Communication

Recent findings from a TWRI investigation have found strong evidence outlining differences in dopamine binding and release in the brain that may act as markers of vulnerability to addiction, associated with pathological gambling in a number of patients with Parkinson's disease (PD). PD is characterized by reduced levels of the neurotransmitter dopamine in the brain. The current treatments of choice for PD include medications that help to increase dopamine levels in the brain.



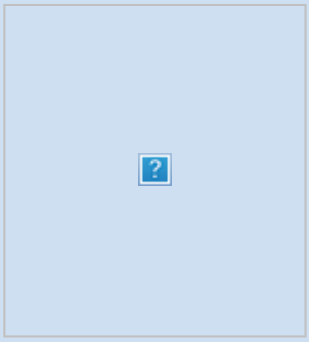
The team used positron emission tomography (PET imaging) to compare dopaminergic function during gambling in patients with PD. Interestingly, patients with pathological gambling showed greater decreases in binding dopamine in specific regions of the brain than those patients that do not exhibit pathological gambling.

Comments study lead Dr. Antonio Strafella, "For the first time we've been able to show that in two important regions of the brain, there is a significant difference in dopamine release for PD patients with pathological gambling. This suggests that there are abnormalities in dopamine binding and release that may be markers of disease vulnerability. With future studies, PD patients may provide a model to better understand the development of this disorder."

Steeves TD, Miyasaki J, Zurowski M, Lang AE, Pellecchia G, Van Eimeren T, Rusjan P, Houle S, Strafella AP. Brain. 2009 Apr 3. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Ontario Problem Gambling Research Centre and the Canadian Institutes of Health Research.*

ADHD: Identifying the Interplay of Genetics

Findings from a recent UHN investigation studying children with reading disabilities (RD) and attention-deficit/hyperactivity disorder (ADHD) have revealed the possible contribution of shared genetic factors to these disorders.



Led by TWRI's Dr. Cathy Barr, the team studied over 200 families to conduct a series of genetic tests in specific regions of chromosome 6—a region known to hold a risk gene for RD—to show that one particular gene region (VMP/DCDC2) is strongly associated with ADHD and inattention and hyperactivity symptoms in children with ADHD. This suggests that, in addition to RD, this region on chromosome 6 may contribute to ADHD.

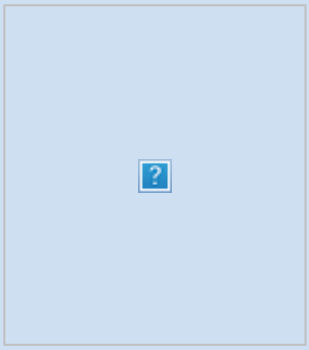
"We've been able to narrow the search area suggesting that genes associated with ADHD might be found in this area of chromosome 6," says Dr. Barr. "This provides us with a better understanding of the genetics behind these disorders and highlights this area as being potentially involved in inattention and hyperactivity. Future studies will be conducted to conclusively show if and how this region is responsible for these two different effects."

Couto JM, Gomez L, Wigg K, Ickowicz A, Pathare T, Malone M, Kennedy JL, Schachar R, Barr CL. Biol Psychiatry. 2009 Apr 10. [Epub ahead of print].

[Pubmed abstract]. *Research supported by the Canadian Institutes of Health Research.*

Nephrology: Identifying Pathways Promoting Growth in Cystic Kidney Disease

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disorder that accounts for 5% of end stage renal disease in Canada. Findings from a TGRI-led study associated with the gene activity of this disease is leading investigators closer to understanding where future targeted therapies for the disease may exist.



"For most patients with ADPKD, end stage renal disease occurs by late middle age due to massive enlargement and distortion of normal kidney architecture," explains study lead Dr. York Pei. "It is important to understand how these cysts grow so that we can develop novel treatments targeting this aspect of the disease that leads to kidney failure and other serious complications."

The team conducted a global analysis of gene activity on 13 renal cysts of different sizes, 5 minimally cystic tissue samples, and 3 normal renal samples and found significant activation and 'cross-talk' of pathways responsible for cell growth in renal cysts. Furthermore, in comparison to normal renal samples, cysts had lost proper programming of the signals that allow cells to develop into normal kidney cells.

"Being able to detect which signaling pathways have increased their activity, in particular those pathways responsible for promoting cell growth and proliferation, provides us with an initial point of focus for future studies," says Dr. Pei. "This knowledge is of critical importance as we work towards developing treatments to reduce cyst enlargement to delay progression to kidney failure."

Song X, Di Giovanni V, He N, Wang K, Ingram A, Rosenblum ND, Pei Y. Hum Mol Genet. 2009 Apr 3. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Kidney Foundation of Canada and the Canadian Institutes of Health Research.*