July 2008

Malaria: Enzyme Deficiency Confers Protection in Humans

Surprising new findings from the lab of TGRI researcher Dr. Kevin Kain highlight the genetic advantages and molecular mechanisms that may confer a protective advantage against malaria in humans.

In partnership with colleagues from McGill University, study lead Dr. Kain discovered that individuals deficient for the enzyme pyruvate kinase (PK)—required for energy production in the body—have a two-tiered system of disease protection. These PK-deficient individuals show a reduction in the invasion of red blood cells by malaria parasites and an increased occurrence of phagocytosis of ring-stage-infected red blood cells.

"Our research shows that people who have this enzyme deficiency or those who carry the gene trait for this deficiency may be protected from severe and fatal malaria." Says Dr. Kain. "This work could lead us in the direction of novel therapies to treat and prevent this disease where it is endemic."

N Engl J Med. 2008 Apr 24;358(17):1805-10. Epub 2008 Apr 16. [Pubmed abstract]. *Research supported by the Canadian Institutes of Health Research and Genome Canada.*

Colorectal Cancer: Detailing Genetic Changes in Disease

Recent news out of OCI has important implications in screening patients with familial colorectal cancer. A recent collaboration with Mount Sinai Hospital and the University of Victoria, this research could pave the way for increased precision in the genetic screening of patients.

Led by UHN scientists Drs. Robert Bristow and Steven Gallinger, the team investigated the effects of mutations in the MUTHY gene, which has a role in the DNA repair process in thwarting the development of cancer. Data suggest that specific single and larger-scale mutations lead to defective proteins that can no longer repair DNA in an orderly manner—which ultimately produce colorectal cancer.

Campbell Family Establishes New Research Institute

A long-term gift given by the Campbell family in the amount of $37.5M will create the new Campbell Family Cancer Research Institute (CFCRI) housed at the Ontario Cancer Institute. This brings the total support provided by the Campbell Family to $67.5M, the largest cumulative private gift to cancer research in Canada.

Dr. Wouters Joins OCI

UHN Research welcomes Dr. Bradly Wouters, Senior Scientist and Director of the Hypoxia and Microenvironment Program at the Ontario Cancer Institute.

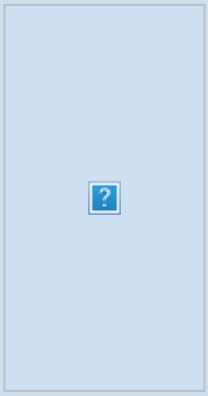
Dr. Wouters and his team are investigating the tumor microenvironment and are primarily interested in understanding the cellular and molecular responses to hypoxia and their influence on the biological behavior of tumors. His laboratory has discovered important stress response pathways that are activated in response to oxygen deprivation that act, in part, through regulation of mRNA translation.

Notes Dr. Bristow, "Our studies here add supporting evidence to the fact that genetic mutations in this repair gene, and ultimately DNA repair proteins, are associated clinically with increased cancer risk. Having identified these structural changes in proteins, this knowledge could assist in the development of more precise screening tools in the future for people at risk for this disease."

Gastroenterology. 2008 May 7. [Epub ahead of print]. [Pubmed abstract]. *Research supported by National Cancer Institutes of Canada and the Canadian Institutes for Health Research.*

Hepatitis B: Examining New Therapeutic Approaches

For chronic hepatitis B patients who are no longer responsive to lamivudine—the currently accepted treatment option—findings from a TGRI-led international study of the drug entecavir point to a new therapy option that lowers the levels of hepatitis B virus (HBV) DNA.



To determine the efficacy, safety and resistance of entecavir in non-responsive lamivudine patients, study lead Dr. Morris Sherman and colleagues recruited a total of 286 patients and assigned them to one of two treatment groups.

By the end of the first year of study, the proportion of patients in the entecavir group with clinically significant decreased levels of HBV DNA increased from 65% to 81% and remained consistent throughout the second year of the study.

"Second year findings show that patients continue to benefit from entecavir without any major safety concerns and that this treatment holds real promise for patients no longer responsive to lamivudine," says Dr. Sherman. "For patients with very high baseline levels of HBV DNA, treatment response with entecavir may be heightened by combining it with other antivirals."

Hepatology. 2008 Jun 8. [Epub ahead of print]. [Pubmed abstract]. *Research supported by Bristol-Squibb.*

Dr. Tak Mak Renews Prestigious Chair

UHN congratulates Dr. Tak Mak on the recent successful renewal of his Tier 1 Canada Research Chair in Inflammation Responses and Traumatic Injury—an award valued at $1.4M over the next 7 years.

The award will support his work in metabolic targeting as an anti-cancer strategy. In addition, Dr. Mak also received funding for a $1M related project from the Canada Foundation for Innovation.

Dr. Mak is one of 27 UHN researchers who hold Canada Research Chairs (CRC)—a program started by the federal government to attract and retain scientific excellence in Canada. To date, CFI has contributed over $34.8M to the University of Toronto and its affiliated hospitals for infrastructure related to the CRC program.

Recognizing a UHN Champion of Vision Research

Dr. Martin Steinbach has been recognized by the international Association for Research in Vision & Opthalmology (ARVO) as the 2009 Kupfer Awardee.

Dr. Steinbach is recognized for his distinguished public service on behalf of eye and vision research and will be presented with the award at the annual ARVO Annual meeting next May. The award is named in honor of Carl Kupfer, who served as Director of the National Eye Institute at NIH for 30 years.

Congratulations Dr. Steinbach!

Psoriatic Arthritis: Classifying the Role of Family

The relationship between the skin disease psoriasis and the chronic inflammatory joint disease, psoriatic arthritis (PsA) is a complicated one. Studies into PsA and uncomplicated psoriasis are providing key information about the role heredity may play in this type of arthritis which causes inflammation and pain in the joints as well as a scaly rash on the skin.

TWRI study lead Dr. Dafna Gladman and colleagues from the Psoriatic Arthritis Program, in the Centre for Prognosis Studies in the Rheumatic Diseases, recruited 100 PsA patients and all available first degree relatives to test for the presence of PsA using a screening questionnaire, clinical examination and laboratory tests.

"To really understand if genetics play a role in this disease, we need to first carefully look at close relatives of PsA patients, specifically full siblings, parents, and children," notes Dr. Gladman.

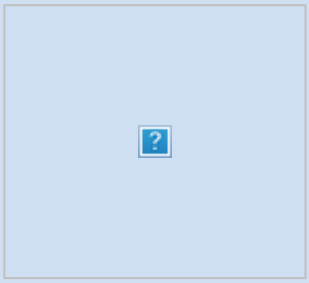
The group found a strong heritable or family risk for PsA: 7.6% and 15.2% prevalence of PsA and psoriasis in first degree relatives, increasing to 7.7% for PsA and 17.7% for psoriasis in siblings. These numbers translate into a risk ratio for PsA of 30 for any first degree relatives and siblings. The risk for psoriasis was 7.6 in family members and 8.8 in siblings.

Says Dr. Gladman, "Because we've used family members, we can't discount how environment affects disease development and future studies will need to take a hard look at this as well."

Ann Rheum Dis. 2008 Jun 4. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Krembil Foundation.*

Prostate Cancer: Evaluating the Impact of Hospital and Surgeon Volume

Radical prostatectomy (RP), a common treatment for localized cancer, has excellent long-term disease control. However, a UHN-led initiative is exploring how common short-term complications are affected by factors such as high hospital and surgeon volume, and how these can be modified to benefit patients.



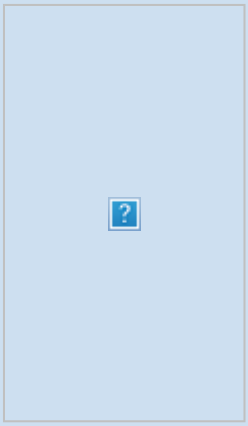
TGRI leads Drs. Shabbir Alibhai and George Tomlinson examined in-hospital mortality and complications across eight Canadian provinces between 1990 and 2001 in patients following RP representing more than 72% of the population. Through statistical modeling, it was found that lower rates of most in-hospital complications following RP are associated with higher hospital and surgeon volumes.

Notes Dr. Alibhai, "Our study also provides additional evidence to support the fact that increasing age and comorbidity are associated with higher mortality and complication following RP. Future studies will focus on relationships between surgical volumes and long-term complications as these also are very important to patients."

J Urol. 2008 May 14. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Canadian Institutes of Health Research, the Toronto*

Rehab Foundation and the Ontario Ministry of Health.

Parkinson's Disease: Targeting Stimulation for Movement Control



New findings from TWRI researchers have outlined changes in blood flow in response to deep brain stimulation (DBS) to the pedunculopontine nucleus (PPN)—a region of the brain involved in controlling posture and behavioral states such as wakefulness and rapid eye movement sleep—and its effect on patients with Parkinson's disease.

Using imaging technology to map the changes in blood flow to this region during and following DBS, UHN researchers Drs. Antonio Strafella, Andres Lozano, Anthony Lang, Elena Moro and Dr. Ballanger examined a patient with advanced Parkinson's disease and found that changes in cerebral blood flow to this movement centre caused significant positive changes in behavior, including a 20% improvement in motor function.

"This is the first time we've been able to show that stimulating the PPN with DBS may be able to change blood flow to the region, significantly improving symptoms," says study lead Dr. Strafella. "This is a significant finding for many patients because with continued studies, this may be applicable across many movement disorders."

Mov Disord. 2008 May 15;23(7):1051-4. [Pubmed abstract]. *Research supported by the Parkinson's Society of Canada and the Canadian Institutes of Health Research.*