

# Research Triumphs

JULY 2005

**HELPING PATIENTS  
MAKE INFORMED  
DECISIONS**

**PREGNANT WOMEN**  
Dr. Mark Walker and the  
OMNI Group study effects  
of twin and multiple fetal  
pregnancies on women's  
health

**ANTI-DEPRESSANTS**  
Dr. Dean Fergusson deter-  
mines increased risk of sui-  
cide attempt

Ottawa Health Research Institute

**OHRI**  **IRSO**  
Institut de recherche en santé d'Ottawa

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July 2005

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# Ensuring that the results of research impact on the patient

It is often said that basic science can be carried out anywhere - why do we need to do it in a hospital?

A fair question and one that I have been asked many times. Let me answer based on my own experience. In 1971, I went to the Hospital for Sick Children in Toronto as a young geneticist and began to study how genes were expressed in cells - pretty basic stuff. As a result of being in a hospital,



we had the opportunity to study a very special muscular dystrophy patient - whose DNA was key to our subsequent identification of the defective gene and the protein made by the gene and to our current understanding of the disease. This discovery resulted in a worldwide shift in research toward prevention and treatment based on that knowledge, and just as importantly, it brought an immediate halt to

millions of dollars in research that had been “barking up the wrong tree.”

Today, in this hospital, we have many basic scientists working on problems that depend heavily on the hospital setting: Dr. John Bell’s work on viruses that destroy cancer cells; Dr. Cathy Tsilfidis’ work on gene therapy to block retinal degeneration; Dr. Fraser Scott’s work on the role of wheat proteins in diabetes; and Dr. Rashmi Kothary’s work that stumbled on a gene defect that causes blindness. Two of these stories are featured in this issue.

Clinical epidemiology is less about discovery and more about the study of population health and health-care delivery. Our internationally recog-

nized “clin epi” group is among the best in the world, and collectively has had a substantial impact on the way patients are managed in this hospital and throughout the world. In this issue we feature three stories: Dr. Paul Hebert’s work on when to give (or not give) a blood transfusion to a critically ill patient; Dr. Mark Walker’s work on the maternal risk associated with twin, triplet and quadruplet pregnancies; and Dr. Dean Fergusson’s work on the risk of attempted suicide in people taking selective serotonin reuptake inhibitors. Each of these studies provides valuable information necessary for optimal patient care based on evidence.

Our clinical epidemiology program, under the guidance of Dr. Jeremy Grimshaw - a leading expert in knowledge translation - is steadily moving this hospital toward a leadership position in evidence-based practice. The hospital has recently declared its desire to embrace knowledge-based care as a cornerstone of the organization and the highly trained clinical epidemiologists will be key to that success. The recent appointment of Dr. Phil Wells as Director of Clinical Research will assist in achieving this goal.

As I reflect on some of our successes, it is clear that both basic science and clinical epidemiology have served us well, and led to important advances for the citizens of Ottawa and people around the world. Now our challenge is to go the next step and marry the two - creating a synergy that will propel us further along the path toward national recognition as the academic health science centre of choice.

A handwritten signature in dark ink, appearing to read "Paul Hebert". The signature is written in a cursive style and is positioned above a horizontal line.

# Working Together To Set Us Apart

Dr. Paul Hebert is a physician in the Intensive Care Unit of The Ottawa Hospital, a senior scientist at the OHRI and a Professor of Medicine and Epidemiology at the University of Ottawa. Having a hand in each organization has helped him extend his reach to thousands around the world.

**The long-standing** partnership between the OHRI, The Ottawa Hospital and the University of Ottawa has been a tremendous asset to all three well-respected organizations. And to Dr. Paul Hebert, it has “made all the difference in the world.”

When Dr. Hebert was approached by another, high profile university about three years ago with a very attractive package, the OHRI, The Ottawa Hospital and the University of Ottawa combined efforts and sprang to action. Recognizing the valuable contributions Dr. Hebert brought to the Intensive Care Unit and refusing to let him go, the three partners offered to realize one of Dr. Hebert’s biggest dreams: rather than save one life at a time, he could save thousands. He has never looked back.

By creating a Chair in Transfusion and Critical Care Research, Dr. Hebert could now delve into research and teaching -- two new prospects he knew would mutually

benefit each other, as well as his existing clinical practice. The new chair allowed him to increase his research practice from a modest team of one to a highly successful and productive group of 11. And the results of that research are touching thousands around the world.

“When you are involved in critical care practice, if you do a good job, you can save a life,” notes Dr. Hebert. “But when you do research, in transfusion for example, you have now told as many as 200,000 physicians how to treat probably hundreds of thousands of patients. You can guide the rest of the world in their care and you can do it over, and over again.”

The same sort of logic holds true for Dr. Hebert’s role as a professor at the University of Ottawa. He is able to guide the career of hundreds of

students - the future of our health-care in fact - with the important lessons he has learned both as a critical care physician and a researcher. The multi-hyphenate titles are equally attractive to students, who are lured to the university thanks to its impressive faculty.

And to complete the circle, Dr. Hebert can take the important strides made in research as well as those taken as a professor back to the bedside, where patients at The Ottawa Hospital can rest assured they are in very capable and highly productive hands. The innovations he brings forth continue to benefit all three well respected organizations daily. Dr. Hebert is certainly a great example of this ongoing collaboration but there are so many others.



# The implications of Twin and Multiple fetal pregnancies on Womens' Health



**M**ore women giving birth in their later years has given rise to fertility treatments which has in turn led to what can be described as an explosion in twin, triplets and quadruplet pregnancies. And while studies have been conducted to determine the impact on babies, mothers have so far been largely ignored.

## Filling a void

Struck by the lack of such vital information, Dr. Mark Walker, a scientist in Obstetrics and Maternal Investigations, set out to find the data on his own. His conclusions inspire some concern.

By extracting all records for obstetric deliveries in Canada (except Quebec) from 1984 to 2000 contained in the Discharge Abstract Database collected by the Canadian Institute of Health Information, Dr. Walker has determined that multi-fetal pregnancies

increase the risk of adverse outcomes for mothers. The report, which was published in BJOG: an International Journal of Obstetrics and Gynaecology, notes that heart



attacks are almost 4 times more common in women who have multi-fetal pregnancies, heart failure is almost 13 times more common and venous thrombosis - a blood clot disorder - is 2 ½ more common. All told, Dr. Walker noted that multiple gestation pregnancies are associated with an increased risk of morbidity for the

mother.

Such findings indicate that mothers need to be better informed to cope with the increased risk associated with twin or multiple gestation pregnancies, according to Dr. Walker. "Individuals involved in assisted reproductive techniques need to take this information into account," said Dr. Walker, who is also a practicing physician at The Ottawa Hospital and Assistant Professor at the University of Ottawa. "Patients also need to be better informed to be vigilant for complications."

"By including such a strong research component into the care of our patients, The Ottawa Hospital is ensuring that innovation in healthcare finds its way from the bench in our Research Institute to the patient's bedside in the Hospital," noted Hospital CEO, Dr. Jack Kitts. "We are grateful to Dr. Walker and the OHRI for these important revelations."

# SSRIs - Setting the Record Straight

## DR. DEAN FERGUSON RESOLVES A LONG STANDING DEBATE

Intrigued by a lengthy and well publicized debate questioning a link between anti-depressants and risk of suicide, Dr. Dean Fergusson quickly realized that given his extensive background in epidemiologic and analytic research, he could likely contribute to the answer.

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*“This provides the most comprehensive and conservative evidence to date on the association between SSRIs and suicide risk. It also highlights deficiencies in trial design and the reporting of rare but serious harms.”*

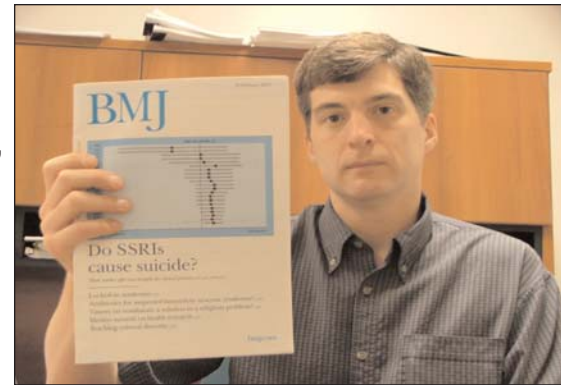
Dr. Dean Fergusson  
Clinical Epidemiologist  
OHRI

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Basing their conclusions on an exhaustive review of published randomized controlled trials of selective serotonin reuptake inhibitors (SSRIs), a group of investigators, led by Dr. Dean Fergusson has found that anti-depressants contribute to a two-fold increase in the risk of suicide attempts.

The study never questioned the value of these medications, but his findings, published in the *British Journal of Medicine*, inspire some concern and strongly encourage a closer monitoring of individuals who take these widely prescribed drugs. The research team reviewed randomized controlled trials comparing an SSRI with either placebo or an active, non-SSRI control. As a result, 702 trials were included in the study (representing 87, 650 patients with a wide range of clinical conditions) looking at both fatal and non-fatal suicide attempts.

Overall, the study noted a significant increase (more than twofold) in the odds of suicide attempts for patients receiving SSRIs compared with placebo or therapeutic inter

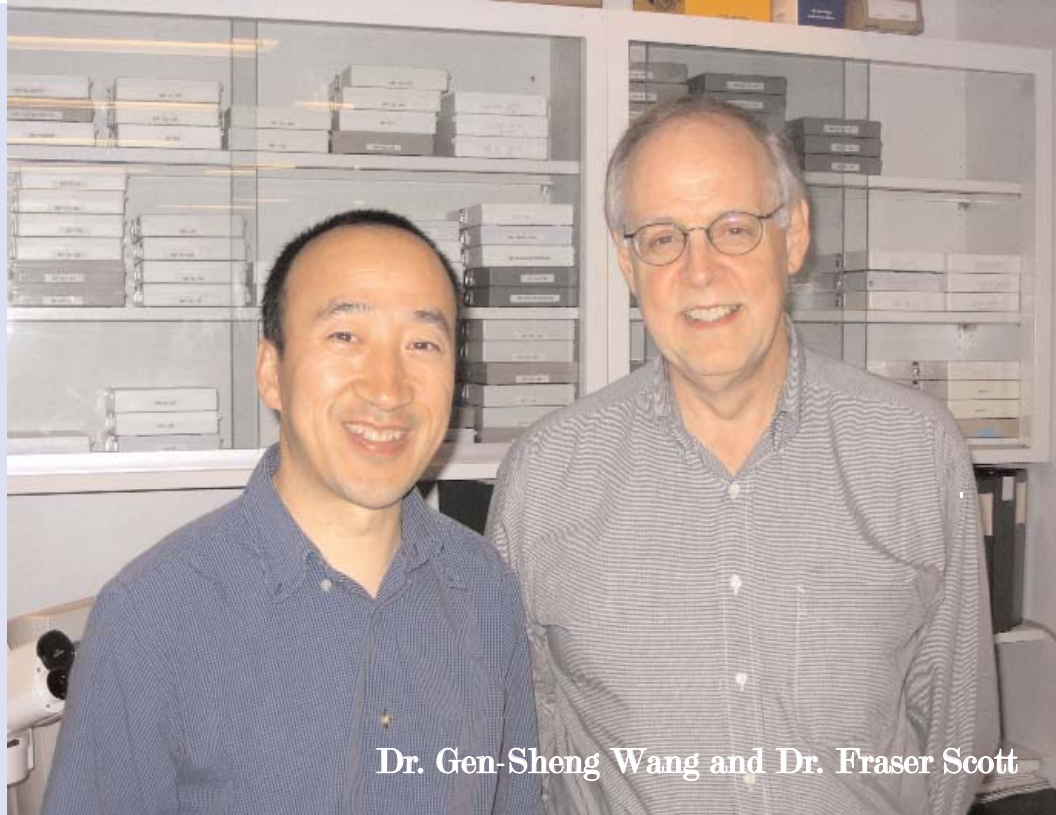


ventions other than tricyclic antidepressants - another class of drugs. Although it might appear small, the incremental risk remains a very important population issue because of the widespread use of SSRIs.

“This study is important for two reasons,” noted Dr. Fergusson. “First, it provides the most comprehensive and conservative evidence to date on the association between SSRIs and suicide risk. Second, it highlights deficiencies in trial design and the reporting of rare but serious harms.” Dr. Fergusson's study also observed several major methodological limitations in the published trials, prompting him to add that stronger and better reporting mechanisms might be in order.

It is important to note, however, that anyone taking these drugs, who may have concerns, should always consult a physician or pharmacist.

# Discovering a clue to reversing diabetes



Dr. Gen-Sheng Wang and Dr. Fraser Scott

**FOR SOME TIME**, scientists have known that a regenerative or repair process -- involving the development of specialized structures called tubular complexes -- is switched on during physical and chemical trauma to the pancreas (the gland that manufactures and secretes crucial insulin in the body). People therefore thought these structures were formed only in response to these types of injuries. In patients with type 1 diabetes, the pancreas is already damaged. The cells that produce insulin in the pancreas are destroyed by the person's own immune system, requiring them to take daily insulin injections to survive.

Thanks to research spearheaded by the Ottawa Health Research Institute (OHRI), we now know that this same repair process is actually present and is increased in the pancreas of adult diabetes-prone rats - whose diabetes closely resembles that of humans. This is the first indication that this repair or regenerative process is attempting to

reverse the damage - counteracting the loss of insulin-producing cells during the natural course of disease development in rodents that spontaneously develop diabetes. With this new information, scientists can now attempt to manipulate and further control the process, and hopefully, some day treat this incurable condition.

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**"The key message here is that there is a repair process that is present..."**

**Dr. Fraser Scott**  
Senior Scientist  
OHRI

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The findings were published in the May edition of *Laboratory Investigation*, a journal of the Nature Publishing Group.

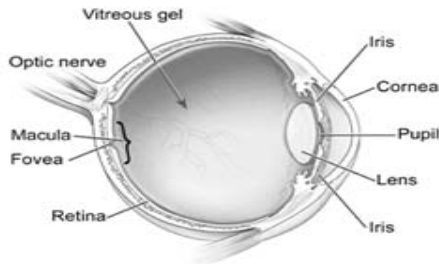
"The key message here is that there is a repair process that is present in

the pancreas of individuals during the destructive phase and this process is increased in an attempt to maintain insulin-producing cells," noted Dr. Fraser Scott, a senior scientist at the OHRI and a professor at the University of Ottawa, who led the study. "It was not known to be present before. This is new and important information in the fight against type 1 diabetes."

Diabetes is increasing in many developed countries. For example, the incidence of type 1 diabetes in the Avalon Peninsula of Newfoundland ranks among the highest in the world. Over 2 million Canadians have diabetes and approximately 10 per cent of people with diabetes have type 1 diabetes, the most severe form.

Dr. Wang, a research associate at the OHRI and lead author of the study, explains: "Further investigation is required to increase this compensatory process in order to restore insulin in people with type 1 diabetes."

# A VISIONARY DISCOVERY



From Left: Dr. Patrice Cote, Dr. Rashmy Kothary

**R**esearchers in the Molecular Medicine Program initially embarked on a study to better understand how a specific gene, known as *Scn8a*, controls electrical impulses in nerves. But scientists did not expect to find an entirely new function for this well-known gene.

The research, published in a recent edition of *Journal of Neuroscience*, is the first indication that the *Scn8a* gene has a role in the function and development of photoreceptors - the first cells in the eye to detect light in the retina of the eye and send signals to the brain (instrumental to vision.)

"The way this is happening is baffling," noted Dr. Patrice Côté, the lead author of the study and a senior postdoctoral fellow in the laboratory of Dr. Rashmi Kothary at the OHRI. "It just goes to show how complex and intricate the entire vision process is and how much we still need to explore to fully understand its entire functioning."

Researchers studied mice lacking

the *Scn8a* gene, using an electroretinogram (which could be likened to an electrocardiogram) and discovered that in addition to suffering from paralysis, the mice were also blind. By ruling out virtually all other possibilities, the scientists further determined that the deletion of the *Scn8a* gene was responsible for the blindness, although they could not definitively establish how one contributed to the other.

The discovery demonstrates that the gene, which is normally expressed in the brain, is clearly necessary for the function of the photoreceptors. The next step will be to determine exactly what role the gene plays in vision. That might be possible by exclusively removing the gene from the retina and seeing - when the mouse matures - if the retina is degenerating. Dr. Kothary, the senior author on the study who is also a professor at the University of Ottawa, stated: "we are quite excited by this finding. It represents a first step in uncovering a novel pathway in retinal development and should provide insight into the establishment of vision."

## Promoting Clinical Trial Registration

**D**r. Jeremy Grimshaw, Director of the OHRI Clinical Epidemiology Program, is co-author of the Ottawa Statement, which brings together international experts in a bid to renew calls for registration of clinical trials. The statement is currently being used as a guide by the World Health Organization.

The group of 100 international experts is calling for the public registration of all clinical trials. The Ottawa Statement, the result of an open meeting hosted by the Canadian Institutes of Health Research (CIHR) in October 2004, was published in April in the *British Medical Journal* (BMJ).

### Sharing knowledge

"Publicly registering clinical trials will lead to the sharing of new knowledge that will accelerate the development of safer, more effective treatments," said Alan Bernstein, President of CIHR. "Consensus that public disclosure is a necessary ingredient of ethical clinical research is growing and CIHR's decision last summer to register the randomized controlled trials it funds is contributing to this momentum."

To learn more and/or to register, log onto:  
<http://ottawagroup.ohri.ca/>



# Centre for Stem Cell and Gene Therapy breaks ground

New floor



Stem cell research is inspiring tremendous hope thanks to its vast potential. With the completion of the new Centre for Stem Cell and Gene Therapy, expected in July 2006, the OHRI will be at the forefront of this promising research

**S**tem Cells carry untapped possibilities that scientists at the OHRI are anxious to explore. Already, bone marrow stem cells have been found to have highly successful applications in the fight against Leukemia. New research indicates that stem cells found in other areas of the body or in an embryo could prove equally, if not more, valuable for tissue repair and regeneration following disease or injury. The labs at the stem cell centre will be built to further understand and define stem cell usage.

OHRI scientists have already made great strides with stem cells to advance our understanding and eventually, perhaps even find a cure for various diseases. We already have a few success stories, including: Dr. Michael Rudnicki has discovered a protein that directs adult stem cells to develop into muscle. The discovery

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could have important implications in the fight against such debilitating conditions as muscular dystrophy. Dr. Lynn Megeney is one of only two scientists in the world to discover stem cells in the heart. This inspires hope that we can reverse the damages incurred by heart disease. The new centre will allow this work to expand and will become home to an additional six research groups all dedicated to making stem cell therapy a reality. The new floor will house laboratories for stem cell research, cell production facilities and a conference centre.

The Ottawa Hospital Foundation has been crucial to this endeavour, raising money in the community for its eventual completion. For their efforts and for the tremendous support we continue to receive from the community, we offer a heartfelt thank you. We are confident that generosity will yield important results.

[www.ohri.ca](http://www.ohri.ca)

The battle against  
some of the deadliest  
diseases is being  
fought brilliantly right  
here in Ottawa



Research • Education • Innovation

Recherche • Enseignement • Innovation

## OHRI Scientists Are **Leading the Charge**

### IN PARTNERSHIP WITH

- The Ottawa Hospital
- The University of Ottawa

EXTERNAL RESEARCH  
FUNDING OF \$62M IN 2004

### MAJOR RESEARCH PROGRAMS IN:

- Blindness
- Blood Disorders
- Cancer
- Diabetes
- Muscle Disease
- Obesity
- Parkinson's Disease
- Reproduction
- Stroke

With 300 Scientists and Clinical Investigators, 300 trainees and a total staff of more than 1100, the OHRI is bringing innovative solutions to health care problems right here in Ottawa. Examples include:

-Cancer therapeutics, including viruses that kill cancer cells and leave healthy cells untouched.

-Stem Cell Research, which could well hold the key to tissue repair and regeneration for diseases such as diabetes, muscular dystrophy, Parkinson's disease and stroke.

-Knowledge translation in which scientists are leading the nation in their efforts to ensure that results from the laboratory reach the patient's bedside.

-Clinical trials to measure the effectiveness of new drugs and to evaluate existing therapeutic options for a broad range of diseases.

To those who have supported our efforts we offer a heartfelt thank you.

With continued community support, our research staff will continue to win key battles in the fight against some of the most debilitating diseases.

To learn more about the institute, visit [www.ohri.ca](http://www.ohri.ca)