Research Triumphs

December 2005

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Clue to a cause of miscarriage

Catching kidney disease early
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On the cover: Jesse Craig, a PhD candidate (with NSERC-CGS) in Dr. Benjamin Tsang’s group.
For more information about the OHRI and the research described in this publication, please visit www.ohri.ca.
Photo credit: Brain picture page 7 courtesy of Wally Welker (University of Wisconsin-Madison) from http://www.brainmuseum.org, supported by the US National Science Foundation Division of Integrative Biology and Neuroscience.
A New Era for Health Research in Ontario

The Ottawa Hospital is one of about 20 "research hospitals" in Ontario. About half of these conduct research through an affiliated research institute; others treat research as a hospital department or division. About five years ago the 20 research directors formed CORD, the Council of Ontario Research Directors, to further development of hospital-based research in Ontario. I have had the privilege of serving as co-director of CORD with Chris Paige from the University Health Network Research Institute, and this year CORD joined CAHO (Council of Academic Hospitals of Ontario) as its research arm. CORD is now positioned well to work with government on the provincial health research agenda.

On the government side there are major changes taking place, all of which bode well for the future. Most importantly, a new Ministry of Research and Innovation (MRI) has been formed and the Premier himself has elected to be the Minister. A search is underway to identify a prominent scientist as the Deputy Minister. MRI takes over the research budget of MEDT (Ministry of Economic Development and Trade) as well as a portion of the research budgets of several other ministries. The former Ontario Innovation Trust and Ontario R & D Challenge Fund as well as the indirect cost fund are now rolled into a new single fund called the Ontario Research Fund, under the control of MRI. I have been asked to serve on the Board of the Fund.

MRI has also developed a draft strategic plan called the Ontario Research and Commercialization Strategy. Earlier this year I took on the job of preparing CORD's response to the “Strategy” and submitted it to MEDT and MRI. In it I pointed out that Ontario's research hospitals conduct over 75% of the health research in the Universities, and have a work force in excess of 10,000 researchers and a budget in excess of $750 million - a powerful force for change in the health sector. The CORD document has been well received in government and I had an opportunity to present it at the annual CAHO meeting in October, on a platform with Tim McTiernan, the Acting Deputy Minister in MRI.

Why am I telling you all this? Because there is an excitement development at Queen's Park about a new approach to research - one that actually involves the scientific community in developing a plan. The Premier / Minister will soon be announcing the creation of the Ontario Research and Innovation Council to provide advice and to further develop the strategy. All this is a sea change from a year ago when scientists despaired that there was no research plan and no opportunity to influence government's thinking about research. The McGuinty Government has set us on a different course that for the first time involves scientists in government planning and that has to be good for research. Stay tuned. The next year could be very exciting.

Dr. Ronald Worton, CEO and Scientific Director
Ottawa Health Research Institute
Vaccines protect us against viruses and bacteria, but no vaccine works 100 per cent of the time. It is well known, for example, that the vaccine against the hepatitis B virus fails in 10 to 15 per cent of people - and those are healthy people. If a patient's immune system is damaged by chemotherapy, AIDS or other conditions, vaccines are far more likely to fail.

But a new clinical trial involving The Ottawa Hospital, the Ottawa Health Research Institute and spinoff biotech company Coley Pharmaceutical Group, has shown that a short strand of DNA containing a special signature can dramatically improve the efficacy of the hepatitis B vaccine in HIV-positive patients. The work is important for HIV patients, who are at high risk of contracting hepatitis B, but it has far reaching implications for vaccine research in general.

The breakthrough has roots in work done at the Loeb Health Research Institute, the predecessor of the OHRI at The Ottawa Hospital Civic campus. In the late 1990's, Loeb researcher Dr. Heather Davis co-founded a biotech company (now called Coley Pharmaceutical Group) to commercialize her work with researchers from the University of Iowa. Together, they developed a DNA molecule, called CPG 7909, which had great power to stimulate the immune system and potential in treating a wide variety of disorders such as cancer, chronic viral infections and asthma. That DNA molecule contains 24 bases, represented by the letters shown at the top of this page.

The key is in the letters “CG”. In human DNA, this CG combination is almost always modified with a "methyl" group on the cytosine (C), but in bacteria and viruses (and CPG 7909), the cytosines are not methyled. Because this is different than what naturally occurs in the human body, human immune cells recognize the pattern as a danger signal and "thinking" that the body is under attack by a pathogen, become activated. Adding this DNA sequence to a vaccine makes the immune response to the vaccine stronger, and therefore makes protection against the virus stronger.

Dr. Curtis Cooper, an Infectious Diseases specialist at The Ottawa Hospital, developed a clinical trial to see if CPG 7909 could improve the hepatitis B vaccine in HIV infected patients. Hepatitis B can cause serious liver damage and eventual liver failure.

"The results are quite dramatic," says Dr. Cooper, who is also a Clinical Investigator at the OHRI and an Assistant Professor of Medicine at the University of Ottawa. "Patients given CPG 7909 produced more than four times as many antibodies to the hepatitis B vaccine as patients who had the plain vaccine." Antibodies are one of the main attack molecules of the immune system. The study, recently published in the journal AIDS, shows that other parts of the immune system were similarly activated. "We have continued to follow many of these patients for several years and we found that the effect continues," adds Dr. Cooper. OHRI HIV researchers Dr. Bill Cameron and Dr. Jonathan Angel also collaborated on the study.

Dr. Davis is now the Managing Director of Coley Pharmaceutical Canada. She is also impressed with the results, and grateful for the Loeb's contribution, especially from former Chief Operating Officer (COO) Robert Hanlon (now COO of the OHRI).

"The Loeb, and especially Robert Hanlon, were very supportive of Coley in the early days by providing us with laboratory and office space and helping us with administration," she says. "Without that help, I'm not sure if Coley would be here in Ottawa in the same form that it is today."
In her research, Dr. Andrée Gruslin encountered many pregnant women who could not carry their unborn children to term because the placenta was too small to support fetal growth. In one case, she followed a woman who had had eight consecutive miscarriages due to this condition. Thanks to her latest discovery, Dr. Gruslin is closer to understanding why, and this insight may one day lead to a treatment.

Fetal growth restriction is an important cause of miscarriage in the developed world and is the second leading cause of infant mortality during or shortly after birth. About three per cent of pregnant women are diagnosed with the condition. Up until now, doctors understood that fetal growth restriction was often the result of abnormally small placentas but they had no more information to go on.

Through years of research, Dr. Gruslin, in collaboration with Drs. Qing Qiu, Benjamin Tsang, Ajoy Basak and Majambu Mbikay - all from the OHRI - have finally determined that a specific enzyme, known as pro-protein convertase 4 (PC4) may be responsible for the problem. The discovery was recently published in *Proceedings of the National Academy of Sciences*.

"What we have discovered is the enzyme that is responsible for activating the most important growth factor for the placenta," explains Dr. Gruslin, an Associate Scientist at the OHRI. Dr. Gruslin is also a Maternal and Fetal Medicine specialist at The Ottawa Hospital and an Associate Professor of Medicine at the University of Ottawa.

"The PC4 enzyme is like a pair of scissors that activates this growth factor by cutting it," she says. "In cases where there is fetal growth restriction, the growth factor is much less active because PC4 is not working enough." The growth factor is called IGF-II.

With this knowledge, doctors may soon be able to screen women for the condition early in pregnancy and monitor them more closely. Currently, women may lose a baby several times before doctors become aware of a potential problem. In time, this discovery could also lead to a new therapy for the condition, likely targeted to the gene that provides instructions for making the enzyme.

Fetal growth restriction currently exacts a huge financial burden on the health care system, with surviving babies often being treated in neonatal intensive care units for lengthy periods. The condition can also lead to complications in adulthood such as heart disease and diabetes. It obviously also takes a heavy emotional toll on the mother and family.

"I am delighted that we are able to collaborate in this exciting project where basic science research helps to unravel the mysteries of human reproductive diseases," says Dr. Benjamin Tsang, a Senior Scientist at the OHRI and a Professor of Medicine at the University of Ottawa.

**What we have discovered is the enzyme that is responsible for activating the most important growth factor for the placenta.**

**Blood samples from pregnant women with Fetal Growth Restriction (FGR) have a higher ratio of inactive to active growth factor (uncut to cut) compared with control pregnant women.**
From penicillin to X-rays and the first anti-malaria drug, many of the greatest medical discoveries have happened by accident. So hopes are high for the serendipitous discovery of a gene that controls fat by an OHRI group well known for muscle and stem cell research.

The story began almost a decade ago when Dr. Michael Rudnicki, then at McMaster University, was studying the role of a gene called p107 in muscle development. He engineered a special strain of mice that lacked the p107 gene (referred to as p107 knockout mice) to investigate the role p107 plays in forming muscle.

Although the mice had completely normal muscle, Dr. Rudnicki brought them to Ottawa anyway when he joined the OHRI (Dr. Rudnicki is now Director of the Molecular Medicine Program at the OHRI and a Professor of Medicine at the University of Ottawa). It was Dr. Anthony Scimè, a postdoctoral fellow in Dr. Rudnicki’s group, who eventually noticed that as the mice aged they remained leaner than other strains of mice.

“When we looked more closely, we found that the knockout mice had about 40 per cent less fat than normal mice and there was a 25 per cent difference in body weight,” says Dr. Scimè. “But even more surprising was the fact that almost all of their white fat was replaced by brown fat.”

White fat cells store fat, but brown fat cells use fat to generate heat. Humans are born with about five per cent brown fat by body weight, but with a comfortable lifestyle, most of this is lost shortly after birth. People and animals that are regularly exposed to cold retain brown fat deposits throughout life, and this type of fat is especially important as a heat source for hibernating animals.

“The p107 knockout mice eat as much as regular mice, but they burn fat more readily and have a higher metabolic rate,” says Dr. Scimè. With further research, the group found that p107 was working with another gene in the same family, called pRb, to stimulate fat precursor cells to produce white fat. Without p107, these precursor cells failed to mature or made brown fat instead. The study is published in the journal *Cell Metabolism*.

“This work was all done in mice, but humans also have genes for p107 and pRb,” says Dr. Rudnicki. If further research shows that these genes are involved in human fat development, Dr. Rudnicki suggests it could lead to new ways to treat obesity.

“We would certainly be better off if we made more brown fat and less white fat,” he says. “And a drug targeted against p107 might be able to tip this balance.” Obesity affects more than five million Canadians and is a major cause of diabetes and heart disease.

The Rudnicki group is not about to drop their work on muscle cells to begin developing fat drugs, but they will do more research to understand this pathway.

Dr. Mary-Ellen Harper, an Associate Professor of Medicine at the University of Ottawa, has studied brown fat for many years and collaborated on the current study. “These findings are exciting,” she says. “They provide yet another example of the value of interdisciplinary collaboration in medical research.”

White fat in normal mice (A) is replaced by brown fat in p107 knockout mice (B). Brown fat cells have smaller droplets of fat, more fat-burning factories (mitochondria), and they are embedded in a rich blood supply.
“Does it help patients?”

Cystic fibrosis doctor asks obvious question but gets surprising answer for expensive antibiotic test

Antibiotic-resistance is a universal cause for concern, but that concern is far more urgent for cystic fibrosis (CF) patients, who are plagued by chronic lung infections. CF-associated bacteria often don’t respond to any antibiotic individually, but they do sometimes respond to combinations - the trick is finding the right combination. So when a group of Canadian doctors developed a rapid test that did just this, it was widely acclaimed and adopted around the world. For just $300, patient bacteria samples were tested against dozens of antibiotic combinations to find the mixture that worked best.

Usually that would be the end of the story, but 15 years later, Dr. Shawn Aaron, one of the researchers who helped develop the test, has added a crucial new chapter: the test does not actually help patients.

Dr. Aaron and his colleagues recently published these results in The Lancet, a prominent British medical journal. They compared the new combination test with an older single-antibiotic test (which is about a tenth as expensive). In 251 CF patients at 12 centres, they found that administering antibiotics based on the new test results did not improve patient health by any measure. It might help a small subset of those patients, but further testing would be required to prove that.

Dr. Aaron, a Senior Scientist at the OHRI, says the study highlights how different the process is for adopting a new diagnostic test compared to a new drug. “New drugs go through years of testing in thousands of patients to prove that they are safe and effective before being approved,” says Dr. Aaron, who is also a Respirology specialist at The Ottawa Hospital and an Associate Professor of Medicine at the University of Ottawa. “But new diagnostic tests just have to be proven accurate. You don't actually have to show that they improve patient health. We weren't satisfied with this.”

“I was surprised and certainly disappointed by the results,” he adds. “But I'd rather we know than not know. Now we can focus our resources on improving the test or finding new ways to help cystic fibrosis patients.”

The Kidney Equation

Clinical trial shows simple equation and doctor education can increase detection of chronic kidney disease four-fold

Personalized medicine can be as simple as accounting for a patient’s age and sex, but the results can be dramatic. Such is the case with a study of chronic kidney disease detection led by Dr. Ayub Akbari, a Nephrology specialist at The Ottawa Hospital. Dr. Akbari is also a Clinical Investigator at the OHRI and an Assistant Professor of Medicine at the University of Ottawa.

Traditionally, family physicians have diagnosed kidney disease based on the level of a compound called creatinine in the blood. However, creatinine levels vary with muscle mass, so groups that tend to have less muscle (including women and the elderly) are often diagnosed later in disease progression.

But Dr. Akbari and his colleagues showed that adjusting creatinine levels using a simple equation that accounts for variables such as age and sex can fix the problem. The results, published in Archives of Internal Medicine, show that providing family physicians with an adjusted creatinine value (called eGFR) allowed them to detect four times more cases of chronic kidney disease than before. “If I had chronic kidney disease, I would want to know,” says Dr. Akbari. “Diet, exercise and medications can delay the progression of this disease. This may help some patients avoid treatments such as dialysis and transplantation.”

Mr. Paul Gould, CEO of the Ontario Association of Medical Laboratories (OAML) agrees. “This one small change can make a huge difference in disease detection, in chronic kidney disease management and in the quality of life for so many,” he says. In early 2006, Ontario's community-based medical laboratories (members of the OAML) will begin routinely reporting eGFR values to family physicians who order creatinine tests.
The greatest discoveries are often made at the interface between two disciplines and today one of the hottest interfaces is between computer science and molecular biology. The sequence of the code letters in the human genome, for example, could never have been assembled without sophisticated computers programmed to find overlapping DNA sequences.

This combination of computer science and molecular biology is called bioinformatics, and Dr. Miguel Andrade’s group is now applying it to stem cells. Dr. Andrade is a Scientist at the OHRI and an Assistant Professor of Medicine at the University of Ottawa.

Stem cells are cells that can divide to reproduce themselves, but also differentiate into many different types of tissues. OHRI researchers are working to develop stem cell-based treatments for diseases of the muscle, heart, brain and other organs.

The power of stem cells comes from the fact that they can turn into so many different cell types, but that same characteristic also makes them difficult to control. And complete control is necessary before discoveries in the lab can be brought into patients. For example, stimulating stem cells in the brain may one day help treat Parkinson’s disease, but researchers need to know how to coax those stem cells to become neurons and not muscle fibres.

Dr. Andrade’s group designed an online database called StemBase to help molecular biologists figure this out by looking at how different types of stem cells use different parts of their genome (express different genes). Launched in February 2005, StemBase catalogues data from researchers across the country. These researchers are united by Canada’s Stem Cell Network, led by Dr. Michael Rudnicki who is also at the OHRI.

“Twenty-nine investigators have submitted experiments so far,” says Dr. Andrade. “That includes more than 500 gene chips. Each gene chip measures the expression of tens of thousands of genes, so really, we have catalogued data from millions of experiments.”

By mining this data, researchers have already learned how certain genes control what type of cell a stem cell will become. And that information is helping them design ways to control the process.

StemBase is accessible at http://www.scgp.ca:8080/StemBase with free registration. So far, more than 300 academic investigators have signed up to access the data. StemBase also recently signed its first commercial licensing agreement with a pharmaceutical company. Any funds generated will go back into more research at the OHRI.
Cell death in the ovary and the brain

Two tales of excellence at the OHRI

Each year, the Ottawa Health Research Institute honours two top scientists at the The Ottawa Hospital Foundation Gala for Research. This year, both awards went to researchers who have made major advances in the study of cell death. Dr. Benjamin Tsang won the Dr. J. David Grimes Research Career Achievement Award for his work on cell death in the ovary (left), while Dr. David Park won the Researcher of the Year Award for his work on cell death in the brain (right).

Dr. Benjamin Tsang
Dr. J. David Grimes Research Career Achievement Award

The intense competition that sperm face to fertilize an egg is well known, but the struggle of the egg itself is rarely recognized. In fact, less than one percent of a woman’s eggs make it to ovulation, while the rest degenerate and die. Dr. Benjamin Tsang has worked tirelessly for more than thirty years to understand this process.

Dr. Tsang has made key discoveries about the factors that control whether ovarian cells live or die and he has found that these factors play a role in infertility and in determining the responsiveness of ovarian cancer to anticancer agents. He is currently studying ways to develop drugs or techniques to overcome chemoresistance, a major therapeutic problem for ovarian cancer patients.

Ottawa is a hub of reproductive biology largely because of Dr. Tsang’s leadership. He is the Director of the Reproductive Biology Unit in the Department of Obstetrics and Gynecology at the University of Ottawa, and a Senior Scientist in the Hormones, Growth and Development Program at the OHRI. Since his appointment 25 years ago, Dr. Tsang has organized the annual Ottawa Reproductive Biology Workshop, an important meeting place for reproductive biologists across North America. He is also the President of the Canadian Fertility and Andrology Society. In addition to being an outstanding scientist and leader, Dr. Tsang is a generous mentor and an ambassador for his Institute. He has been instrumental in establishing several high-level international collaborations and he is an Honorary Professor at the Chinese Academy of Sciences.

Dr. David Park
Researcher of the Year Award

The brain is one of those organs that just doesn’t follow the rules. Dr. David Park realized this in his groundbreaking work on a group of proteins called cyclin dependent kinases.

In dividing cells, cyclin-dependent kinases have traditionally been associated with regulating the cell cycle. But Dr. Park found that in neurons, which don’t divide, some of these proteins are associated with cell death. In deciphering this pathway, Dr. Park has found that drugs that inhibit cyclin dependent kinases can prevent brain cell death in some experimental models.

Dr. Park is a Senior Scientist in the Neuroscience Program at the OHRI. In 2003, he co-founded the Parkinson’s Research Consortium, a unique collaboration among 11 Ottawa scientists with diverse expertise. Dr. Park is also a member of the Canadian Stroke Network.

In 2003, Dr. Park received the University of Ottawa Young Researcher Award and, the year before, he was awarded the Young Investigator Award from the Faculty of Medicine, where he is an Associate Professor.

Dr. Park has received many other awards, including the Ontario Government’s Premier’s Research Excellence Award, the Dr. Michael Smith Promising Scientist Award from the Ottawa Life Sciences Council and the GlaxoWellcome Award.
Thank you for your support

As the research arm of The Ottawa Hospital, the OHRI is supported in part by the generous individuals and organizations who give to The Ottawa Hospital Foundation. Your donations have helped to support the research described in this publication, from advances in the detection of chronic kidney disease, to discovering a possible cause of miscarriages, to making vaccines work better in patients with weak immune systems.

We have also highlighted researchers who are tackling obesity, cystic fibrosis, ovarian cancer, Parkinson’s disease and stroke, but even that list doesn’t do justice to the breadth of health research conducted at the OHRI. With 300 scientists and clinical investigators, 300 graduate students and research fellows and 500 support staff, we are making progress against virtually all of the major diseases and health conditions that affect Canadians.

We would like to thank our donors in Ottawa and around the world for making this research possible.

Fundraising update

The Legacy Campaign
The Ottawa Hospital Foundation’s Legacy Campaign seeks to raise $100 million for The Ottawa Hospital and the OHRI. With the generous support of the people of Ottawa and beyond the Foundation has already raised $73 million. Forty per cent of the funds raised will support the OHRI.

The Kresge Challenge
We have been issued an exciting challenge: to raise the remaining $2 million required for the new Centre for Stem Cell and Gene Therapy by November 2006. If we can reach this goal, the OHRI will receive $800,000 from the Kresge Foundation, a private American-based foundation that issues challenge grants to charitable organizations around the world.

Construction update

Construction of the OHRI’s Centre for Stem Cell and Gene Therapy and Centre for the Prevention of Age-Related Blindness at the Eye Institute began in late 2004. Each Centre is a floor (approximately 30,000 square feet) on top of the University of Ottawa Eye Institute and adjacent to The Ottawa Hospital’s new Critical Care Wing at the General campus. Each floor will eventually hold more than 100 researchers and we expect to start moving them in by the summer of 2006.

The Centre for Stem Cell and Gene Therapy will allow OHRI scientists to further their research into the use of stem cell transplants, or stimulation of stem cells within our own bodies, to treat disorders such as muscular dystrophy, heart disease and diabetes.

The Centre for the Prevention of Age-Related Blindness at the Eye Institute will allow OHRI scientists to expand their research in areas such as artificial corneas, laser eye surgery, eye regeneration and gene-based treatments for various eye diseases.