

# SRI

## MAGAZINE

Inventing the Future of Health Care

Sunnybrook Research Institute / 2009

### Just What Is Regenerative Medicine, Anyway?

The definitive guide on how to build a better body. Or not.

### Forward-Looking

Original thinking begets a little device with big promise to change how complex heart conditions are diagnosed and treated

### Smarter, Faster, Better

Tomorrow's cancer care is being invented right here, right now

### Critical Care

At full tilt: Sunnybrook researchers race to explain the H1N1 virus and be prepared to treat its most vulnerable victims

### Into Africa

Going global to help build sustainable care in developing countries



# NOVEMBER

**Inventing the Future of  
Health Care**  
Sunnybrook Research Institute  
2009

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To read more about research at SRI,  
visit [www.sunnybrook.ca/research](http://www.sunnybrook.ca/research)

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Pictured opposite is a fluorescent image of stromal cells from the thymus. The thymus is the main organ of the body in which T cells—the building blocks of the immune system—grow. Stromal cells provide structure to the thymus and support the growth of T cells. In red are actin filaments, which give the cell its internal structure and help transport proteins. In blue are the cell's nuclei, which hold its DNA. Scientists at SRI are studying stromal cells to understand better how they support the growth of T cells. This knowledge will help them make better T cells in the lab, and more efficiently, and could ultimately lead to the design of “customized” cells for patients.

IMAGE: KOROSH KIANIZAD

## 16 CRITICAL CARE

As anxiety about the H1N1 influenza pandemic unfurled across the globe, a Sunnybrook research team led the first studies to detail what the virus looks like, with the shocking conclusion that it hits the young and healthy the hardest—and that hospitals better be prepared

## 20 FORWARD-LOOKING

The heart is a powerful and much-studied organ. The ability to visualize the workings of its chambers and vessels remains a challenge, however, a serious obstacle given that most of what goes wrong with the heart—including cardiovascular disease, the primary cause of death globally—happens there. Needed is a better way to see what goes on in these innermost places. One Sunnybrook trainee may have found it

## 24 JUST WHAT IS REGENERATIVE MEDICINE, ANYWAY?

Unpacking one of the hottest phrases in medical science to understand how researchers at Sunnybrook are engineering tissue and delivering therapy to repair and restore the human body

## 30 SMARTER, FASTER, BETTER: ON-THE- HORIZON INNOVATIONS IN CANCER CARE

Researchers here are developing new methods and technologies to hasten detection, dramatically improve diagnosis and make treatment more targeted, innovations that are close to making—or in some cases already making—patients' lives better

## 36 INTO AFRICA

Sunnybrook scientists travel to Africa, intent on making a difference by translating research know-how into clinical results

# Message From the President and CEO, and the Chair of the Board

Sunnybrook Health Sciences Centre



DAVID A. LESLIE AND DR. BARRY A. MCLELLAN

Sunnybrook is proud of the many accomplishments our researchers have made this past year and, more importantly, we are inspired by what will come next. Our vision is to invent the future of health care and while our scientists have made a host of breakthroughs that are improving patient care today, we are encouraged that they are not content to rest on their laurels.

Our faculty, staff and students are inspired by a challenge. Their relentless pursuit of Sunnybrook's ambitious vision ensures that some of the most insurmountable health care issues of our time become manageable. The impossible becomes possible and the ability to find a cure is limited only by the ability of our staff to be motivated by an idea to change the way something has always been done.

In this past year, our staff members have made significant advances that have saved lives in areas where others have abandoned hope. They have helped hearts beat strong again, found and eliminated tumours where there were thought to be none, and have helped patients spend less time in hospital and more time doing what is important to them.

This past year, Sunnybrook made a substantial commitment to our future in research and established the world's first Centre for Research in Image-Guided Therapeutics. With the help of the Canada Foundation for Innovation's Research Hospital Fund and the support of our community, the construction of this

new Centre, now underway, will provide a home for some of the most innovative research in the world. In this new Centre, research will be conducted on new methods of removing difficult to treat cancers, without ever performing surgery. Regenerative medicine will be pioneered to repair the damaged brain tissue of stroke and Alzheimer's patients and our scientists will lead discoveries that will restore the immune systems of critically ill patients.

In the pages of this magazine you will see results of the more than \$100 million in research that Sunnybrook conducts each year. Each of these stories is an example of how the future is being invented every day at Sunnybrook. Much has been accomplished and there is much more on the horizon. We invite you to visit [www.sunnybrook.ca](http://www.sunnybrook.ca) to learn more about the exciting work of the Sunnybrook Research Institute and how you can support our continuing efforts to achieve our vision and invest in your future.

David A. Leslie  
Chair, Board of Directors

Barry A. McLellan  
President and CEO

## Message From the Vice-President, Research

Sunnybrook Health Sciences Centre

The cranes are gone! In the wake of the construction blitz leading up to and throughout 2009, an expanse of empty new space devoted to Sunnybrook Research Institute (SRI) is now before us.

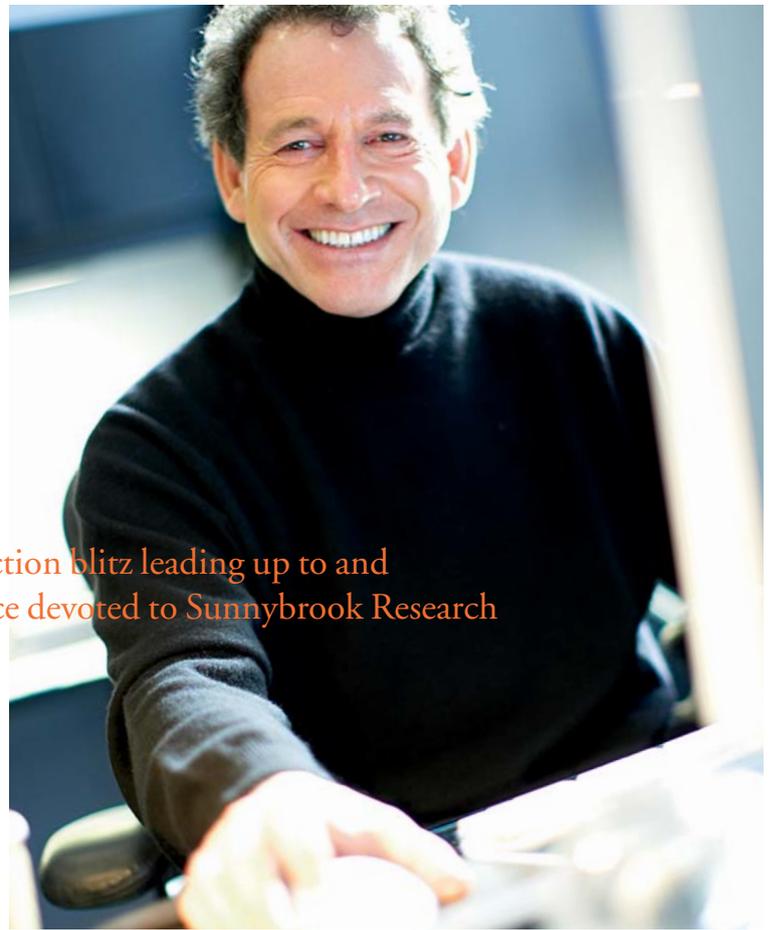
This space, on M6 and M7 of Sunnybrook's Bayview campus, will be home to the world's first Centre for Research in Image-Guided Therapeutics.

Following the successes our faculty shepherded over 2008/2009, with more than \$175 million accrued in support of our vision *to invent the future of health care*, we are poised to execute the next phase—to fill in the empty shell with the labs, offices and facilities that will comprise the centre. Leading up to this phase, thousands of hours involving our faculty, supported by architects and construction experts, have been devoted to designing every square foot. We are eagerly anticipating occupancy in 2011.

We are all proud of being able to point to just shy of one-half million square feet of space devoted to our research enterprise across all of Sunnybrook, but it's how we make it big that matters. Those that gravitate toward hospital-based research are of a palpably distinct complexion; our faculty are dedicated not only to discovery for discovery's sake, but also to its application. Why? The answer is simple, and I think epitomizes the posture of our faculty: because they can do!

The importance of discovery research, wherein scientists at SRI work to unravel the complexities of health at the molecular and cellular levels need be underscored. Without a molecular "catalogue" that characterizes "health" we cannot know how to intervene in a disease. We cannot know how to make it better or stop it from ever happening. Our work does not stop at a catalogue, however; ever-vigilant, our faculty are dedicated to applying their discoveries toward creating new and better ways of preventing, detecting and treating disease.

We already do this with aplomb. With the realization of the Centre for Research in Image-Guided Therapeutics we will do it even better. This unique infrastructure will support an integrated approach to discovery research and its clinical application. It will foster even greater collaboration among scientists and practitioners. It will enable learning, clinician to researcher, and researcher to clinician, toward creating better ways of doing business better for our patients and their families.



DR. MICHAEL JULIUS

Sunnybrook "owns" its research enterprise, an obvious, but I think essential, concept that would not bear fruit were it not for the tenacious support of Sunnybrook's senior leadership team, led by Dr. Barry McLellan, and its Board of Directors, led by David Leslie. Research is not an activity happening "beside" our mandate to deliver the best health care; rather, it is the platform from which we ensure that we are at the vanguard of the ever-unachievable goal of inventing its future.

It all starts here!

**Michael Julius**  
Vice-President, Research

Professor, Departments of Immunology  
and Medical Biophysics  
Faculty of Medicine, University of Toronto

# Ovation

We spotlight some especially notable achievements of scientists at Sunnybrook Research Institute (SRI) in 2008 to 2009.

## National Awards

The government of Canada recognized two SRI scientists by renewing their Tier 1 Canada Research Chairs, the most prestigious research award granted by the federal government. **Bob Kerbel** holds the Canada Research Chair in Tumour Biology, Angiogenesis and Anti-Angiogenic Therapy. **Donald Redelmeier** holds the Canada Research Chair in Medical Decision Sciences. **Kaveh Shojanja** was awarded a Tier 2 Canada Research Chair in Patient Safety and Quality Improvement. Nine scientists at SRI now hold Canada Research Chairs.

The Canadian Institutes of Health Research (CIHR) awarded **Susan Bronskill**, **Dennis Ko** and **Damon Scales** each a New Investigator Award, designed to support outstanding researchers in their work. **Nick Daneman** received a CIHR Clinician Scientist Award, which provides highly skilled clinician-scientists with an opportunity to develop further their research programs. To **Michael Schull**, CIHR awarded an Applied Chair in Health Services and Policy Research, an honour designed to recruit and retain the world's highest quality health services researchers.

The Royal College of Physicians and Surgeons of Canada presented **Redelmeier** with the Wightman Professor Award for research and clinical excellence.

## Provincial Awards

From the Ministry of Research and Innovation, **James Carlyle** and **Gregory Czarnota** each received an Early Researcher Award, a highly competitive prize that supports researchers who show great promise in their early careers in building a research team.

**Czarnota** was also named a Research Chair in Experimental Therapeutics by Cancer Care Ontario. The Cancer Care Ontario Research Chairs program aims to attract leading new researchers to Ontario and to support scientists already working in the province.

**Amy Cheung** received a Career Scientist Award from the Ministry of Health and Long-Term Care. This salary award is given to enable promising researchers to devote at least 75% of their time to their research, to help ensure that they have the skills, training and experience they need to become influential health services researchers in Ontario.

From the Heart and Stroke Foundation of Ontario, **Alexander Dick**, **Rob Fowler**, **David Gladstone** and **Ko** each received a Clinician Scientist Award.

The College of Physicians and Surgeons of Ontario recognized **Richard Wells** with a Council Award, which honours outstanding Ontario physicians.

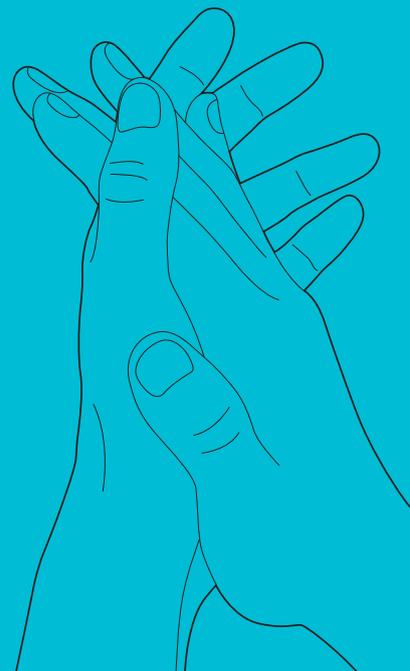
## Fellowships and Other Honours

**Daneman** was awarded a 2008 CIHR Bisby fellowship, which provides additional funding for participation in national and international workshops, conferences and meetings related to the recipient's research.

**Schull** was awarded a Detweiler Travelling Fellowship from the Royal College of Physicians and Surgeons of Canada. The fellowship is intended to improve the quality of medical and surgical practice in Canada.

In other honours, the European Institute of Oncology awarded **Kerbel** the 2008 Breast Cancer Award, **Kathleen Pritchard** was awarded the Cosbie lectureship, which is sponsored by the Canadian Cancer Society and the Canadian Oncology Society; and **David Cole** was invited by the University of Milan to be a visiting professor in Milan and San Giovanni Rotondo.

For more on awards to researchers at SRI, visit the awards section under "about us" on the web site: [www.sunnybrook.ca/research](http://www.sunnybrook.ca/research).



# Abstracts

## Make Mine a Single

If giving one course of corticosteroids to a pregnant woman at risk of delivering her baby too soon reduces the risk of respiratory distress syndrome, bleeding into the brain and death in a preterm infant, then might giving more be better? That's the question that scientists at Sunnybrook's Centre for Mother, Infant and Child Research, including **Dr. Elizabeth Asztalos**, a neonatologist and researcher in the **women and babies research program**, set out to answer in a study led by Mount Sinai researcher Dr. Kellie Murphy. They conducted a clinical trial of 1,858 women at high risk of giving birth too early who hadn't delivered their babies 14 to 21 days after a first course of corticosteroids. The trial spanned 20 countries. Women were assigned to one of two groups: those who received steroids every 14 days until they gave birth, and those who did not (the placebo group). The authors found that giving multiple courses of corticosteroids does not reduce the risk of infant death or complications, compared with only one course. It does, however, make it more likely that newborns will weigh less, be shorter and have smaller heads. The authors concluded that it's safest to stick to a single course.

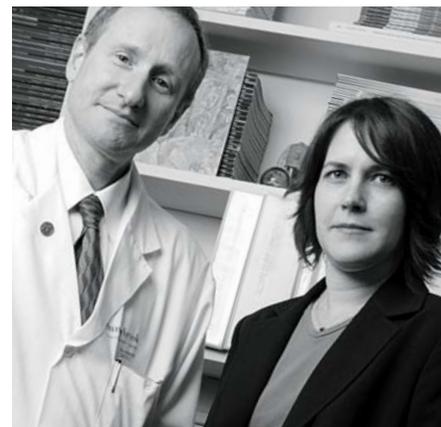
## Guiding Aid for People With Dementia and Their Caregivers

About 34 million people are projected to be diagnosed with Alzheimer's disease (AD) by 2025. Challenging at all stages, severe AD presents correspondingly severe challenges for patients, and for clinicians and family caregivers. **Dr. Nathan Herrmann**, a psychiatrist in geriatrics and researcher in the **brain sciences research program** at Sunnybrook, working with a colleague at McGill University, published evidence-based guidelines in 2009 on how to manage severe AD, and improve quality of life for patients and caregivers. Recommendations (there were 17) for clinicians from the *Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia* include

monitoring and managing patients' cognition, and medical and nutritional status closely and often; assessing caregivers' health and safety; and first using drug-free approaches to improve behavioural and psychological symptoms, where feasible. Antipsychotic drug therapy may be used in cases where nondrug approaches don't work, but the higher risk of stroke and death must be considered. For severe depression, selective serotonin reuptake inhibitors may help. And, therapy with a cholinesterase inhibitor or memantine may slow cognitive decline.

## Preventing Potentially Fatal Drug-Drug Interactions

Guidelines for cardiologists recommend patients treated with ASA (Aspirin) after a heart attack also receive proton pump inhibitors, commonly prescribed to treat gastric-acid ailments like ulcers and heartburn. Many of these patients, however, will also be taking clopidogrel (brand name Plavix), an anti-clotting drug that when combined with ASA helps prevent future heart attacks. As **Dr. David Juurlink**, a physician and scientist in the **Schulich heart research program** at Sunnybrook found, however, the combination of certain proton pump inhibitors and clopidogrel is risky business. In a study of more than 13,000 patients aged 66 years and older, he found that the drug combination increases patients' risk of having a heart attack by 40% within 90 days of hospital discharge from the first one. These results have dramatic implications for public health, given the estimated millions of people worldwide affected. The study's authors noted that the effect was found with specific proton pump inhibitors; therefore, they advised that patients avoid these in favour of either pantoprazole, which was not linked to a higher rate of heart attacks, or another antacid, if needed, upon consulting with their cardiologist or family doctor.



TOP TO BOTTOM:  
DRS. SHARYN GIBBINS AND ELIZABETH ASZTALOS; DRs. NATHAN HERRMANN AND KRISTA LANCTÖT; DR. DAVID JUURLINK



TOP TO BOTTOM:  
DR. ROBERT KERBEL; DRS. JACK TU AND  
DENNIS KO; DR. PAUL MARKS

### Mixed Reviews for Anticancer Drugs

Dr. Robert Kerbel, a senior scientist in the Odette cancer research program at Sunnybrook Research Institute (SRI), and his lab have found that some antiangiogenic drugs, which have been shown to slow the growth of cancerous tumours in certain patients by blocking new blood-vessel growth, might have an opposite effect to that desired. Instead of curbing the spread of tumours, such therapies might accelerate it, notably in patients with metastatic cancer (where the disease has spread from the primary site). The important study, published in *Cancer Cell*, was done using preclinical models, but it could have clinical implications for patients. To wit, results indicate that use of antiangiogenic drug therapies in earlier-stage cancer should be closely monitored and evaluated; moreover, the findings reinforce the view that such drugs should not be used “off-label” in situations where they are not approved for use. Kerbel and his coauthors also noted that despite the study’s findings, the overall effect of these antiangiogenic drugs is still one of a net clinical benefit of prolonged survival for certain cancer patients.

### Drug-Coated Stents Safe: Study

When they hit the market, drug-eluting (coated) stents were heralded as a breakthrough to keep newly reopened blood vessels from closing again after cardiac surgery. The honeymoon was put on pause when research then suggested these stents weren’t as safe as their bare-metal counterparts. Enthusiasm returned when further study proved that, in fact, they were safe for patients using them for “on-label” indications, meaning

for uses approved by the Food and Drug Administration (FDA). Less clear, however, is if they are safe for “off-label” indications—for use in procedures that the FDA has not approved, a common occurrence. Drs. Dennis Ko and Jack Tu, clinician-scientists in the Schulich heart research program at Sunnybrook, addressed this gap by studying data of more than 14,000 patients who had either on- or off-label indications for drug-eluting stents. Their analysis showed that these stents were effective in reducing the need for target vessel revascularization, a surgical procedure to restore blood flow to blocked blood vessels, without increasing heart attack risk. More importantly, they found that patients who received a drug-coated stent for off-label indications had lower rates of death compared with patients who received bare metal stents. Tu and Ko noted that, while reassuring, the findings should be confirmed in randomized controlled trials.

### Using Imaging To Detect Graft Instability After Knee Repair

The anterior cruciate ligament (ACL) is one of four ligaments in the knee. Injuries to it are often sports-related. Treatment for athletes and others who rely on knee stability to perform well in their daily lives usually is surgical reconstruction. After ACL graft reconstruction, if symptoms persist, or instability recurs, then magnetic resonance (MR) imaging can be used to investigate. Responding to some reports of increased intrasubstance signal-intensity changes detectable at long-term follow-up, and the suggestion that this might indicate problems with the graft, like degeneration or partial tearing, Dr. Paul Marks, an orthopaedic surgeon and associate scientist in the Holland musculoskeletal research program at Sunnybrook, and colleagues did a study. They assessed the presence of increased intrasubstance signal intensity in ACL grafts, and if such signal-intensity changes are associated with clinical ratings of graft instability and patient function four to 12 years after ACL reconstruction. They found that small amounts of increased intrasubstance signal intensity within an ACL graft were visible at long-term MR follow-up, but that they are not directly related to instability or patient function.



### Colonoscopy Linked to Fewer Deaths in Left, Not Right, Colon

Colonoscopy, during which a narrow tube is inserted into the colon, which is then inspected, is the most effective screening method for colorectal cancer. It is also the costliest, and carries with it risks, like substantial miss rates. What is unknown is if it has any effect on death from colorectal cancer. Accordingly, **Dr. Linda Rabeneck**, a senior scientist in the **Odette cancer research program**, and colleagues did a study to determine if colonoscopy was related to fewer deaths from colorectal cancer. They analyzed the records of more than 10,000 people who had been diagnosed with colorectal cancer over five years, and who died, and compared these with “controls,” people who were similar but who did not die. They found that colonoscopy was associated with fewer deaths from colorectal cancer only when cancer was in the left colon. The chance of dying was the same for everyone who underwent colonoscopy if the cancer was in the right colon. The authors noted the study had some limitations, including no information on if people who had a colonoscopy did so for screening or diagnosis. Nonetheless, their findings support recommendations that colonoscopy be used to screen for colorectal cancer, notably in the left colon, though they also show that it is not a perfect test for reducing deaths from colorectal cancer.



TOP TO BOTTOM:  
DR. LINDA RABENECK; DR. DONALD  
REDELMEIER; DR. BRIAN WONG

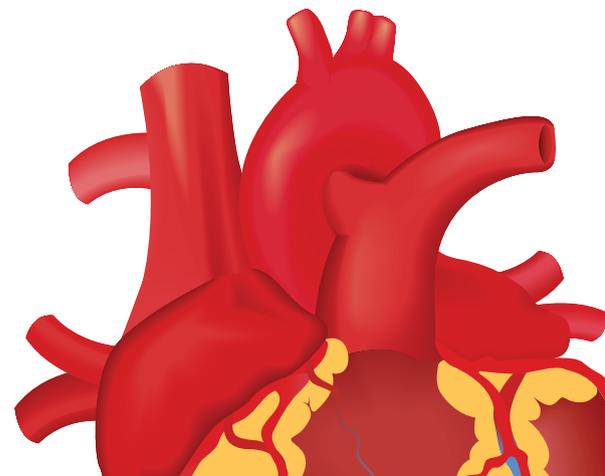
### Statins Linked to Delirium After Surgery

**Dr. Donald Redelmeier**, a senior scientist in the **trauma, emergency and critical care research program** at SRI, and colleagues have found that the use of statins, prescribed to lower cholesterol, is linked to a higher risk of delirium after elective surgery for elderly patients. Postoperative delirium can lead to more need for intensive care, a higher risk of hospital-acquired infections and a longer hospital stay. In some cases, it becomes permanent. Because studies show that postoperative delirium might be related to changes in blood flow in the brain, and the effect of statins is to alter blood flow, Redelmeier hypothesized that statins could promote delirium after surgery—and that’s what he found. The authors noted that the link between statin

use and postoperative delirium was more than coincidental, especially for patients who were given higher doses of statins and whose surgeries took longer and were not for a heart condition. While they noted that there might have been other variables that they did not study that could explain the link, they suggested that until clarifying research is done, it might make sense to stop taking statins temporarily before surgery, if necessary starting them again one or two days afterward, the period in which patients are most prone to heart attack.

### Paging Dr. Right

When effective communication among health care workers can tip the balance from life to death for patients, and hospital staff rely on pagers to communicate, then it’s critical the paging system works. As researchers from Sunnybrook and Toronto General Hospital discovered, however, sometimes it doesn’t. **Dr. Brian Wong**, an associate scientist in the **veterans and community research program** and physician at Sunnybrook, and colleagues scoured paging records for residents at both hospitals over two months to assess how many pages were sent to the wrong physician, namely, to a resident when he or she was scheduled to be off duty. They found 14% of pages were sent to the wrong doctor. Of these, pages were typically sent during the post-call period or off-duty evenings, or during scheduled academic half-days—in each case when the resident was out of hospital. Examining the pages, the researchers found that 47% were either an emergency—requiring immediate response—or urgent—calling for response within one hour. The authors noted that their findings extrapolate to more than 4,300 pages per year at each hospital, including about 2,000 emergency or urgent pages. Since the study’s publication, Wong has devised a centralized computerized paging system as a pilot program on a general medicine ward at Sunnybrook; its impact is being studied.





# Snapshot: Capital Expansion at Sunnybrook Research Institute

## The Centre for Research in Image-Guided Therapeutics By the Numbers

# 30

companies with which partnerships at SRI will be built or strengthened

# 35

new researchers who will be recruited to SRI

# 55

scientists and clinician-scientists from across Sunnybrook who will use the centre, even before new recruits

# 245

trainees and students who will be hired to work in the centre

# 150,000

square feet the centre will add for research at Sunnybrook

# \$14 million

amount the centre will attract in contributions from the private sector

# \$75 million

amount Canada is investing into the centre

# \$160 million

total project cost of the centre

Our most exciting building project is underway! The Centre for Research in Image-Guided Therapeutics—which will be unique in Canada—will add two new floors and almost double the space dedicated to discovery at Sunnybrook.

It will equip our research teams with everything they need to invent the medical imaging technologies and therapies of tomorrow. It will bring together scientists and research-minded clinicians, along with highly skilled lab staff and trainees, into one state-of-the-art space to work cheek by jowl on making new discoveries.

These discoveries will lead to new and better ways to detect, diagnose and treat some of the most pressing problems in health care, among them cancer, heart disease, musculoskeletal disorders, immune-system deficiencies, stroke and Alzheimer's disease.

The centre will dramatically boost our capacity to achieve our vision of inventing the future of health care. Here's a glimpse of what our research teams will be doing:

- Engineering complex medical devices, such as one that will allow a doctor to navigate through a blocked blood vessel in 3-D. These devices, which will be built in Canada's only hospital-based device development lab, will ultimately be commercialized.
- Creating high-intensity focused ultrasound devices paired with magnetic resonance imaging that will let doctors do "surgery" without cutting through skin, for example to destroy cancerous tumours of the breast, prostate, liver and kidney.
- Designing cell-based therapies in our new strictly controlled current good manufacturing practices lab to repair damaged heart tissue and blood vessels, or damage to the brain, and to rebuild devastated immune systems.
- Inventing noninvasive technology capable of disrupting the blood-brain barrier just long enough to be able to deliver targeted gene or drug therapy deep into previously inaccessible regions of the brain, for example to treat Alzheimer's disease.

Want to know more about this project and the benefits it will bring to Canadians? Visit [www.sunnybrook.ca/research](http://www.sunnybrook.ca/research).

The Centre for Research in Image-Guided Therapeutics is funded primarily by the Canada Foundation for Innovation through the Research Hospital Fund. Additional support comes from the Ontario government, Sunnybrook Health Sciences Centre, industry partners and donations from our partners and patrons in the community. If you would like to contribute to the Centre, visit [www.sunnybrook.ca/foundation](http://www.sunnybrook.ca/foundation).

We can carry with us organisms capable of causing serious disease and widespread global outbreaks.

## Cited!

Dr. Andrew Simor is director of clinical integrative biology at Sunnybrook Research Institute and head of the department of microbiology and the division of infectious diseases at Sunnybrook. He is also a professor in the departments of medicine, and laboratory medicine and pathobiology at the University of Toronto.

Soon after the first case of severe acute respiratory syndrome (SARS) was recognized in Canada in March 2003, Dr. Andrew Simor says he knew that the virus causing this illness was one that he and his colleagues who study infectious diseases had never seen.

“We knew that this was something different, and that we needed to communicate this experience to the broader medical community in as expeditious a manner as possible,” says Simor of the outbreak.

Though SARS originated in Southeast Asia and spread around the world, Toronto was second only to China in terms of the size of the outbreak. Simor and colleagues from Toronto’s Mount Sinai Hospital acted quickly to gather, cull and analyze pertinent data from each of the first 10 cases in Canada.

The researchers contacted editors at *The New England Journal of Medicine*, who wanted to disseminate information about the mysterious illness quickly. Their paper, “Identification of severe acute

respiratory syndrome in Canada,” was published online just two weeks after the World Health Organization issued a global alert about the disease. The paper was the first to describe in detail the clinical symptoms of SARS, and factors related to the incidence and spread of the disease in the early Canadian cases. It has been cited in peer-reviewed journals an impressive 1,205 times since its publication in 2003.\*

While the SARS virus and the H1N1 influenza virus are different, Simor says he believes the SARS experience has been very useful in H1N1 pandemic planning.

“We live in an environment that’s so different from that of 20 or 30 years ago in terms of the ease with which we can travel from one part of the world to another. We can carry with us organisms capable of causing serious disease and widespread global outbreaks. This is what happened with SARS, and what we’re currently experiencing with the [H1N1] pandemic,” he says. “Understanding the epidemiology of how infections can spread globally is important and directly relevant to pandemics.”—Alisa Kim

Current funding comes from the Canadian Institutes of Health Research, Public Health Agency of Canada, Pfizer Canada, BD and Bio-Rad Laboratories.

\*Google Scholar, December 7, 2009



DR. ANDREW SIMOR

## HANDLE WITH CARE

Extremely preterm infants are exquisitely sensitive to pain and stress. Even so, there is no reliable way to recognize this suffering. How, then, to know? Sunnybrook researchers are tackling this very question, with an eye to measuring and relieving discomfort in babies born much too soon

# It was her first job, and she never left it.

Dr. Sharyn Gibbins began caring for preterm infants as a nurse in the 1980s. Although she knew right away that she wanted to pursue training as a researcher, and eventually completed a PhD in 2001, she also knew what population she would end up studying.

“My heart has always belonged to the tiniest, most immature, fragile babies,” says Gibbins, now a neonatal nurse practitioner and associate scientist in the women and babies research program at Sunnybrook Health Sciences Centre. Extremely preterm infants are those born at 27 weeks or

earlier, and they typically weigh less than one kilogram. The smallest fit in an open hand and weigh little more than a can of pop.

These newborns require intensive care to survive, and are subjected to a host of medical interventions. At the same time, they are the babies least able to endure such procedures without feeling pain or suffering damage. Unfortunately, although there are over 40 measures of pain in full-term babies that provide effective guidance for doctors and caregivers, there are almost no reliable

pain measures for these extremely preterm infants.

In 2007, Gibbins set out to find some, in the first study of its kind. With Dr. Elizabeth Asztalos, director of Sunnybrook Research Institute’s Centre for Mother, Infant and Child Research, and colleagues at the Hospital for Sick Children in Toronto, Gibbins videoed and analyzed 50 of these infants undergoing a painful procedure (heel lance, used to draw blood) and a nonpainful procedure (diaper change). The researchers, who are also faculty members at the University of Toronto, looked for physiological, behavioural and biochemical changes.

Results were mixed. Salivary biochemical readings of the stress hormone cortisol, and physiological monitoring of heart rate and breathing showed no differences during the two procedures. But the researchers did determine that four facial actions—brow bulge, eye squeeze, nasolabial (nose-to-lip) furrow and vertical mouth stretch, all of which are established indicators of pain—were significantly present during the heel lance.

“They’re good signs for us to recognize, and then use to determine what else we should do to return that baby to a steady state,” says Asztalos. Gibbins was also pleased with the study. “I think it is important,” she says. “It is the first paper that has critically looked at this population.” But, she adds, “It highlights that facial expression is only part of the puzzle.”



MARIE BAGG AND DR. SHARYN GIBBINS



The other part of the puzzle, Gibbins expects, is body movements. She and Asztalos are therefore launching a larger study that will look at movements in the arms, legs, hands, feet and head, along with facial expressions, to see if they will provide additional information on what these infants feel.

A big challenge in measuring pain in these babies, explains Asztalos, is that how they respond to a painful or stressful maneuver is partly dependent on their developing central nervous systems. “An infant with a very immature central nervous system may not have the capacity to demonstrate some of the behaviour that you see in more mature babies,” she says. And that state of development varies greatly in infants with a gestational age of 24 weeks compared with those at 32 weeks, or even 28. “Technically, that ability to respond to pain is not required for a 24-weeker,” says Asztalos. “They shouldn’t be out there. They should be in the uterus, which cushions the baby so that they don’t have to feel pain.”

Twenty years ago, only about 40% of those very preterm babies were “out there” at all. Today, owing to research-driven changes in care and new technologies, about 65% of babies born at 24 weeks’ gestation survive; babies born at 26 weeks or later have a survival rate above 90%.

Improvements in ventilation techniques and medications, including antenatal steroids for pregnant women at risk for

delivering a preterm baby, have been critical. Nutritional practices have also changed: it is now standard to start feeding preterm infants the day after birth, while it was once common to start on day three, by which time many infants had already entered a state of metabolic breakdown. “The whole thinking process of how we approach these babies has evolved, so we’re much more proactive supporting them,” says Asztalos.

Also, the environment of the nursery has changed. Sunnybrook’s neonatal intensive care unit (NICU) is quieter than it once was, and each incubator is shielded from harsh lighting, which research has shown can dramatically enhance infant comfort. When the women and babies program moves into its new state-of-the-art home at Sunnybrook’s Bayview campus in 2010, the entire NICU will have controlled lighting, noise-reduction features and several other design elements intended to ease stress on its tiny patients.

“I think the overall appreciation of how vulnerable these babies are has changed,” says Gibbins. “And the whole movement of pain is being driven by so many professional groups that it’s no longer okay to deny anyone’s pain, including an infant’s. It’s just not okay.” Critically, research again has shown that when babies are in stress or pain, they are more susceptible to other medical problems; hence the importance of further research, including Gibbins and Asztalos’ new study, that will show more

definitively what hurts these preterm infants and what interventions alleviate their discomfort.

That research, however, is difficult to conduct. Not many of these babies are born, even in a city as large as Toronto, which has three NICUs. The size of the infants makes getting enough recording equipment into the incubators a technical challenge and a lot of work for research personnel. And, says Gibbins, “you’re asking parents to participate at a really horrible time in their lives. I’m a bit envious of people who study healthy populations of [full] term infants.”

For all these reasons, when Gibbins proposed a study on very early babies for her PhD, her thesis committee told her, “Don’t study them. You’re not going to finish, and the goal of a PhD is to learn research and move on.” Though it ran strongly against her emotional inclinations, says Gibbins, the advice was good. It also helps explain why researchers still don’t know enough about these babies—a gap Gibbins is determined to fill. “I finished my PhD in four years, published, and since then have worked on the population I’ve always wanted to study, without the constraints of school.”

— Jim Oldfield

The Hospital for Sick Children Foundation funded Gibbins and Asztalos’ research. The Canadian Institutes of Health Research is funding the new and larger study.

## BRAIN ATTACK COUNTERATTACK

Stroke, which strikes 50,000 Canadians each year, is the most prevalent cause of brain disability, but it's also preventable. That's why researchers, who have made great advances in treatment, are executing an earlier line of defence: prevention

"It was like a miracle."

That's how Richard Westwood describes what happened the evening of January 24, 2009.

Mr. Westwood was watching hockey on television when he called out to his wife Lois in the next room of their North York condominium. She didn't answer. He went to check on her and found she couldn't speak. Worried she might be having a stroke, he called 911, and within a few minutes the fire department arrived, followed by an ambulance.

The paramedics recognized it was a stroke—Mrs. Westwood's entire left side was paralyzed—and transported her directly to Sunnybrook's Regional Stroke Centre, bypassing the nearest hospital emergency departments. A computed tomography (CT) scan showed a clot had blocked blood flow to her brain. The Sunnybrook stroke team quickly administered a clot-busting drug called tissue plasminogen activator (tPA) that began

to dissolve the clot. Feeling returned to her foot, then limbs, about two hours later.

After a night of careful monitoring, Mrs. Westwood regained all movement in her left side, and another CT scan showed the clot was gone. A few days later she was home, fully recovered.

On the phone from her home nearly one year later, the month after her two great-granddaughters visited from California and a day after her twice-weekly carpet-bowling outing, Mrs. Westwood was upbeat.

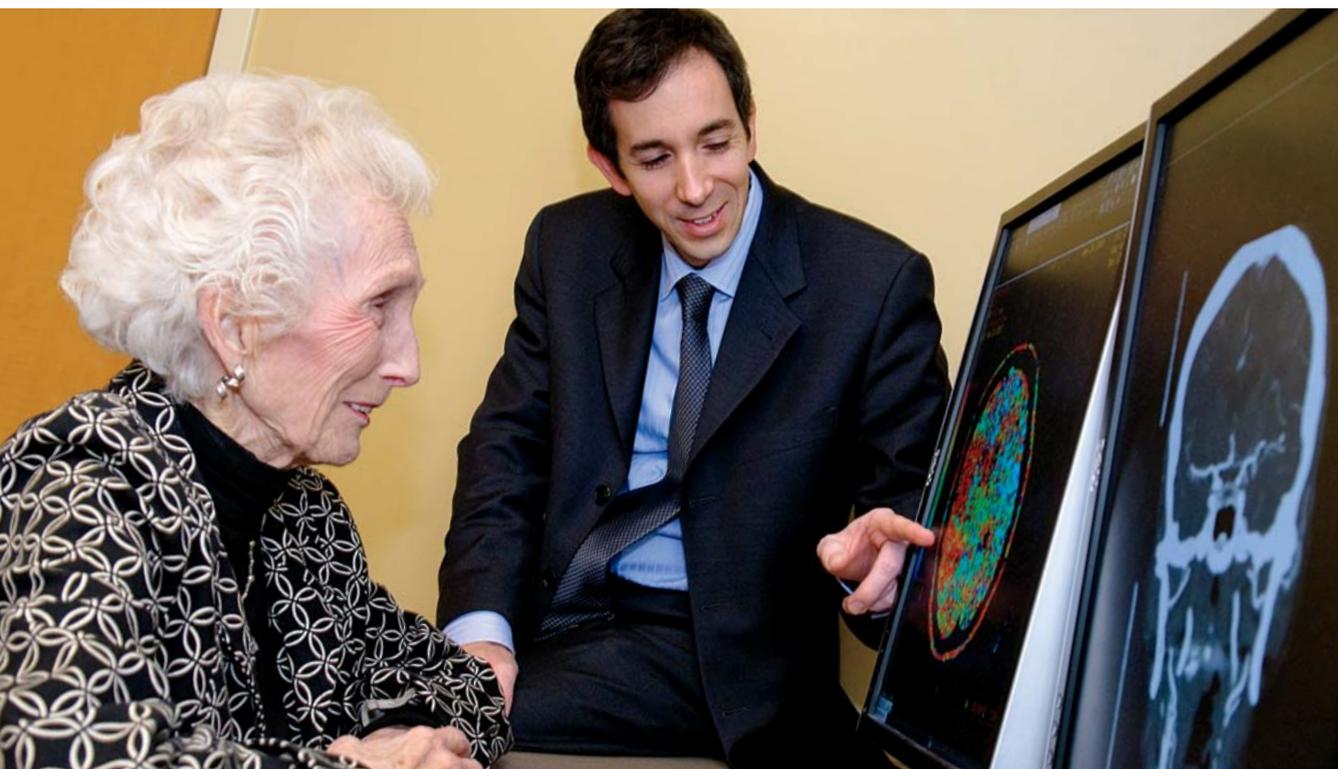
"I'm doing very well. I have pretty much everything I could want," she said.

Mrs. Westwood's treatment success was part of a Toronto-wide Code Stroke protocol, implemented by the Ontario government in 2005 to speed acute stroke patients to a Regional Stroke Centre for initial management. The protocol addressed the problem of limited accessibility to tPA, which at the time was not reaching many patients because not all hospitals offered this therapy, and there

has been a three-hour post-stroke time window in which it must be delivered.

"It's an important initiative," says Dr. David Gladstone, director of the regional stroke prevention clinic at Sunnybrook, who was called in to treat Mrs. Westwood in the emergency department the night of her stroke. "When it works well, tPA can reverse the signs and symptoms of a stroke within minutes. But timing is critical—the faster tPA can be administered, the greater the chance of a good outcome."

In 2009, Gladstone, a scientist at Sunnybrook Research Institute and assistant professor in the department of medicine at the University of Toronto, published a paper in the journal *Stroke* that examined the initial success of the Code Stroke protocol at Sunnybrook. Gladstone and his colleagues found that Sunnybrook treated four times as many patients with tPA immediately after the protocol was launched compared to the same time period the previous year,



LOIS WESTWOOD AND DR. DAVID GLADSTONE

# “Prevention is much better than a cure, especially when dealing with stroke,” he says.

thereby achieving one of the highest stroke treatment rates in North America. Delays between stroke onset and drug administration also decreased significantly.

Gladstone says he is hopeful that this type of stroke protocol can be sustained, but meanwhile he’s making strides in another area of stroke research: prevention. “Prevention is much better than a cure, especially when dealing with stroke,” he says.

Noting that stroke has reached “epidemic” proportions—it’s now the world’s second-leading cause of death and the most common cause of neurological disability among Canadian adults—Gladstone says that the societal burden of stroke will worsen in the coming years without a major shift toward optimizing prevention strategies.

Of particular concern for Gladstone is effecting that change is improving the diagnosis and treatment of atrial fibrillation, a common condition in which the heartbeat can become sporadically irregular, and which is one of the biggest risk factors for stroke. Up to one in three strokes is “cryptogenic,” meaning of unknown cause, but Gladstone believes many of these strokes are related to undetected, intermittent atrial fibrillation.

He is therefore leading a multicentre, cross-Canada, randomized controlled trial called EMBRACE that will investigate a new diagnostic strategy to detect atrial

fibrillation in patients who have had an unexplained stroke or mini-stroke. Patients will wear a heart-monitoring device attached to a soft belt, which will check for arrhythmias for 30 days continuously. Gladstone says he suspects it will be more effective than the standard one- or two-day monitoring approach now used. “If we can improve the early detection of atrial fibrillation in this high-risk population, then more patients will receive appropriate blood-thinning medication, and more strokes, deaths and disability will be prevented,” he says.

In 2009 Gladstone published another study in *Stroke* examining the use of anticoagulant medication in more than 500 patients known to have atrial fibrillation who were admitted to Ontario hospitals with a stroke. The data, based on the Registry of the Canadian Stroke Network, showed an alarming number of patients had not been prescribed anticoagulant medication, which works by preventing the blood from clotting. Among those who were taking warfarin—an anticoagulant proven to lower stroke risk by 64%—three-quarters were “subtherapeutic,” meaning levels of the drug in their system were insufficient. Overall, only one in 10 patients in the study were taking adequate anticoagulant therapy at the time of their stroke.

“Older studies from other countries had also demonstrated this problem of an

underuse of warfarin for patients who would benefit most from it,” says Gladstone. “We thought that by now the situation would have improved, but sadly it has not.”

There are many reasons why doctors don’t prescribe warfarin despite its proven benefits. It can lead to bleeding side effects, and even when a patient is a good candidate a physician’s single bad experience with someone who has hemorrhaged can create a powerful psychological deterrent. As well, warfarin is prone to food and drug interactions, and it requires frequent blood-level monitoring, a responsibility that not all doctors or patients want.

Gladstone is hopeful that a new class of blood-thinning drugs under development may be safer and easier to prescribe than warfarin for some patients. “If the newer drugs are proven safe and effective, they could help solve one of the biggest care gaps in stroke prevention.”

Meanwhile, Gladstone—whose grandmother suffered a stroke related to atrial fibrillation before warfarin or tPA were available—stresses the importance of anticoagulant management with patients and their health care practitioners. “Nearly every week in the hospital we see patients admitted with a disabling stroke related to atrial fibrillation that might have been avoided or lessened in severity if only they had been taking appropriate preventative medication. We must correct this practice gap,” he says.

That message got through to Mrs. Westwood, who has atrial fibrillation and who has now maintained preventive anticoagulation with warfarin since her stroke. “Dr. Gladstone told me to always take it, and never let anyone tell me not to take it unless there’s a really good reason,” she said of the medication, before driving to her physician’s office for a blood-level test.—Jim Oldfield

Gladstone’s work is funded by the following: Heart and Stroke Foundation of Ontario Centre for Stroke Recovery, Canadian Stroke Network, Sunnybrook department of medicine and University of Toronto department of medicine.

## THE NOT-SO COLD SHOULDER

New freezing technique for shoulder surgery relieves pain without compromising breathing, a common complication of anesthesia

With one hand Dr. Colin McCartney glides the ultrasound probe over the base of the patient's neck. As high-frequency sound waves emitted from the probe bounce off tissue in the patient's body, the corresponding images produced on the monitor in front of him allow McCartney to peer inside and identify the brachial plexus nerves, a bundle of fibres that run from the patient's neck down his arm. In McCartney's other hand is a needle containing a smaller-than-normal dose of local anesthetic, which he slowly injects into the groove between the muscles that house the roots of the visualized nerves, temporarily shutting off sensation from the patient's upper arm and shoulder to his spinal cord and brain.

This procedure—low-volume ultrasound-guided interscalene blockade (ISB)—is an innovation that provides effective pain relief while minimizing health risks linked to current anesthetic practice in shoulder surgery. McCartney, an anesthetist and researcher in the Holland musculoskeletal research program at Sunnybrook Health Sciences Centre, helped develop this technique to reduce the amount of anesthetic used in ISB, a freezing technique commonly used for pain control in shoulder surgery.

“The problem with the higher volume [local anesthetic] is that it causes a lot of other side effects,” says McCartney, who is also an associate professor in the department of anesthesia at the University of Toronto. “It blocks the phrenic nerve in 100% of cases, which can cause some patients discomfort. In a few patients it can cause respiratory distress and hypoxia [oxygen deprivation]. I wanted to develop a technique that would provide the advantage of pain relief and reduce the chances of getting these side effects.”

As McCartney notes, a major drawback of ISB is that it numbs the phrenic nerve on the side of surgery, a nerve in the neck that supplies movement to the diaphragm. The contraction and expansion of the diaphragm muscle allow us to breathe in and out; when the phrenic nerve is frozen, respiratory problems can follow, including temporary paralysis of the diaphragm. The use of ISB in patients with diminished lung capacity, such as those with lung disease, the morbidly obese and the elderly, is therefore restricted.

The standard volume used for this nerve block is 20 ml or more of local anesthetic. In a paper published last year in the *British Journal of Anaesthesia*, McCartney and his colleagues showed that using ultrasound to guide the administration of just 5 ml of the local anesthetic ropivacaine for ISB provides the same pain relief as the standard volume, but with less risk of respiratory problems. Their study was the first to show the benefits of this low-volume technique.

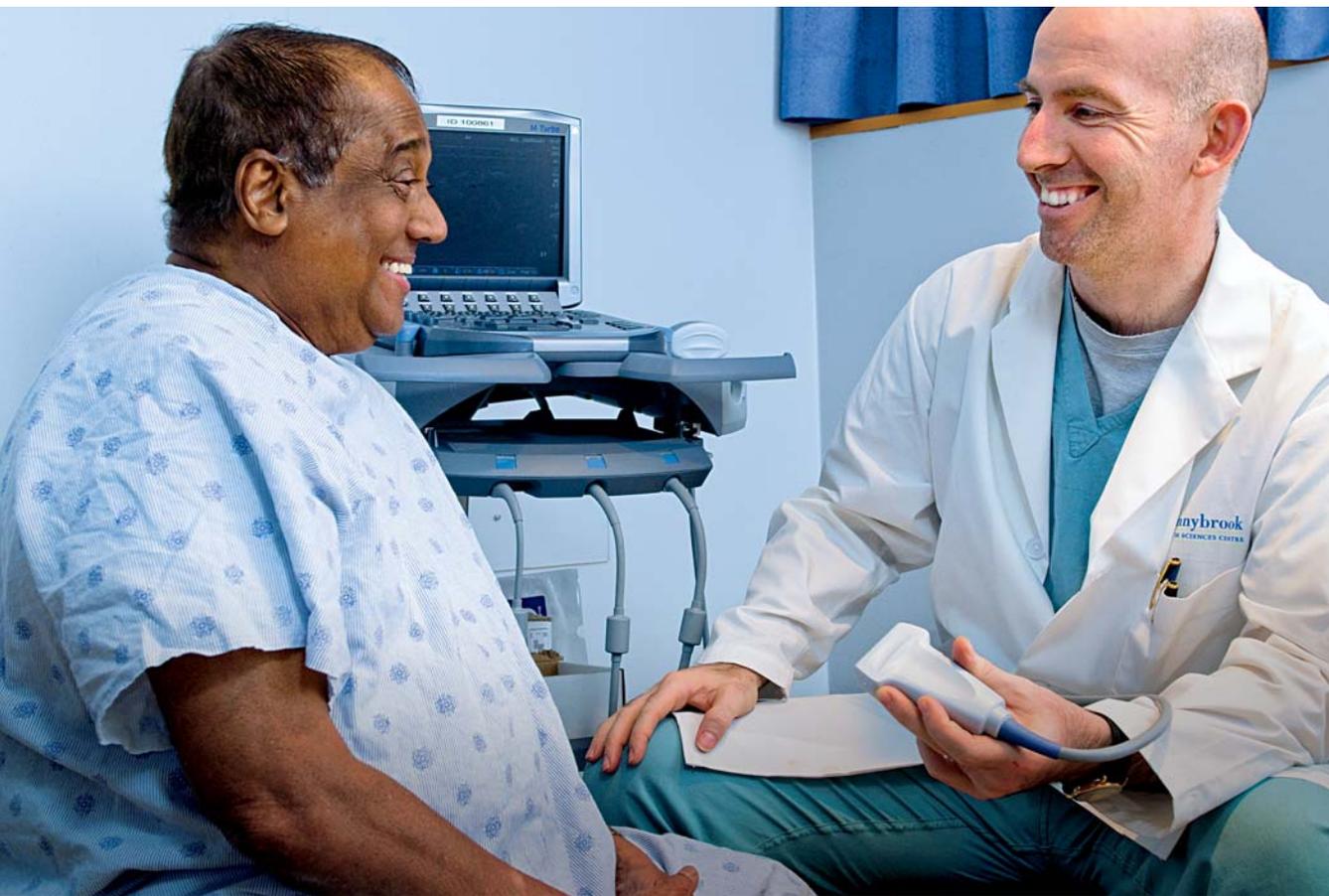
In the study, 40 patients scheduled to have shoulder surgery were randomly divided into two groups; one group received the low-volume block; the other, the standard 20 ml block. Neither the patients nor the researchers assessing the outcome knew which of the two blocks the patients received. The groups were similar in terms of age, gender and the kinds of surgical procedures that were done. Ultrasound imaging was used to perform ISB on both groups.

Pain scores measured after surgery and the amount of morphine used were similar for both groups. However, fewer people in the group that received the low-volume anesthetic experienced partial paralysis of the diaphragm, compared with those who received the standard-volume injection. Moreover, 40% of the patients who received the standard-volume block developed complications, including breathing problems, voice hoarseness, prolonged hiccups and Horner's syndrome, a temporary eye disorder caused by paralysis of the sympathetic nervous system. None of the patients who received the low-volume block experienced these adverse effects.

Although some of McCartney's colleagues remain skeptical about the benefits of the low-volume technique, he says he senses a shift in attitude toward the practice. “At the time we published the study people said to me, ‘There's no way you could use

“I have a low pain tolerance, but I felt pretty good,”

says Obeyeskere, who now enjoys greater range of motion and less pain in his shoulder.



JOHN OBEYESKERE AND DR. COLIN MCCARTNEY

5 ml. That's ridiculous. Why would you use such a low volume?' But people are realizing that a small amount of local anesthetic goes a long way if it's placed very precisely."

Case studies published last April by anesthesiologists from the Mayo Clinic suggest that McCartney's research is making an impact on clinical practice. The studies, which cite his paper, feature patients who would not normally be candidates for ISB due to pre-existing health conditions. The Mayo Clinic authors reported being able to provide safe and effective pain relief using low-volume ultrasound-guided ISB while avoiding respiratory complications.

"The importance of the [Mayo Clinic] series was that up until now, people would avoid doing ISB on patients with any respiratory disease or patients who were markedly obese because they're at much higher risk of having respiratory problems afterwards," says McCartney. "The problem with that is that even when an ISB is avoided in these patients, they

subsequently have to take larger amounts of pain-relieving narcotic drugs, which also impair their respiratory drive and cause other side effects such as nausea, vomiting and dizziness. With a low-volume block [patients] can get better pain relief from the block, which doesn't cause respiratory impairment, and they need to take little, if any, narcotic drugs."

John Obeyeskere, a participant in one of McCartney's research studies, benefitted from the low-volume technique. A 71-year-old man with asthma, Obeyeskere would normally be contraindicated for the standard-volume block due to the risk of impaired breathing. Last July, McCartney performed low-volume ultrasound-guided ISB to anesthetize Obeyeskere's left shoulder during surgery.

"I have a low pain tolerance, but I felt pretty good," says Obeyeskere, who now enjoys greater range of motion and less pain in his shoulder. Not only was his recovery fast, but he also says he did not feel the need to take the prescribed painkilling drugs in the days after the surgery.

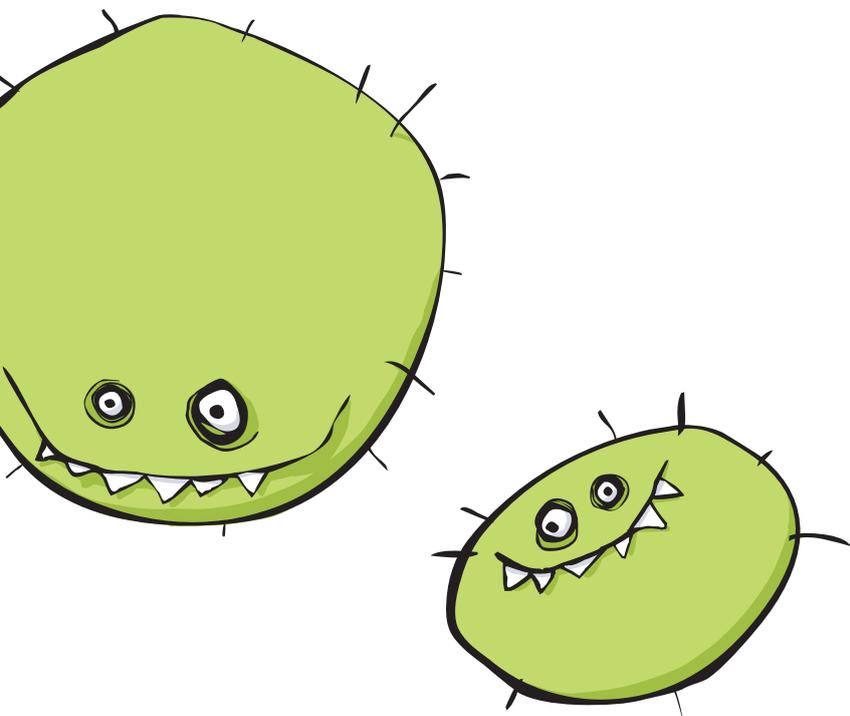
Despite these successes, McCartney says he believes that influencing clinical practice widely will be a "slow process." While publishing research and teaching are important aspects of shaping health care, he also thinks that educating the public about new findings can help change medical practice.

"When a patient says to a physician, 'I've heard about this research, I'll show you the article,' it puts the physician under some pressure to say, 'I'm going to evaluate this as a new method and see whether I can introduce this into my practice.' I think the key driver of patient care is sometimes the patients themselves."

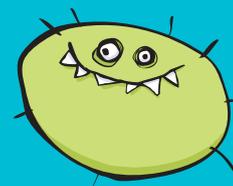
—Alisa Kim

McCartney's research was funded by the Physicians' Services Incorporated Foundation.

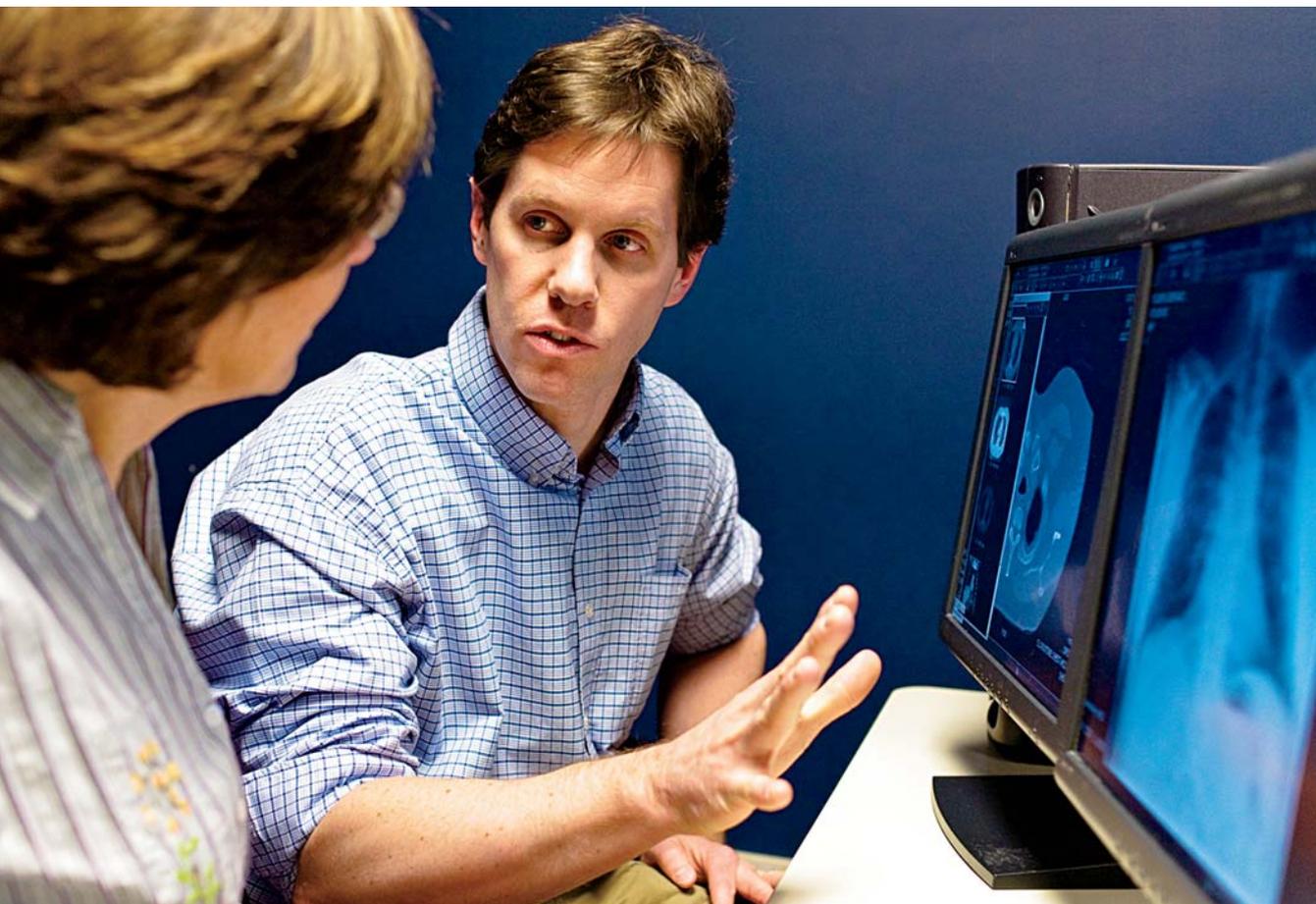
# Critical



# Care



As anxiety about the H1N1 influenza pandemic unfurled across the globe, a Sunnybrook research team led the first studies to detail what the virus looks like, with the shocking conclusion that it hits the young and healthy the hardest—and that hospitals better be prepared *By Jim Oldfield*



DR. ROBERT FOWLER

Surprise, followed by skepticism. That was Dr. Stephen Lapinsky's reaction, in the spring of 2009, to the first data by Dr. Robert Fowler from Sunnybrook Health Sciences Centre showing just how sick H1N1 patients in Mexico were getting. "It didn't make sense because these were young patients who basically couldn't physically be ventilated," says Lapinsky, the site director of the intensive care unit (ICU) at Mount Sinai Hospital in Toronto. "It was a very unusual situation."

Lapinsky soon lost his skepticism. He contacted his research colleagues at Sunnybrook and in Mexico, and they verified that many of the H1N1 patients were indeed requiring intensive lung support to breathe, and that several were young—unlike those who typically fall critically ill with influenza. Moreover, a lot of these patients had no underlying medical problems that might explain the severity of their illness, and a significant number had died. Within a few weeks, results from a similar study of Canadian patients confirmed several of the findings from Mexico.

Fowler, an associate scientist at Sunnybrook Research Institute and critical care doctor at Sunnybrook, was the senior researcher on both studies, which were collaborative projects involving members of the Canadian Critical Care Trials Group (CCCTG), including Lapinsky, and the researchers in Mexico. "The implications for resources within hospitals were substantial, knowing that these were patients who would need uncommon forms of lung and life support, not just for a day or two, but for many weeks," says Fowler, who is also an assistant professor at the University of Toronto.

The *Journal of the American Medical Association* published the two studies online in October 2009, noting in an editorial that they were done with "remarkable" speed and that they were two of the first in the world to address the "paucity of data" surrounding H1N1. But months earlier, through the summer and fall of 2009, the unpublished findings changed pandemic planning for this new strain of influenza across Canada and around the world.

### Critical Planning

Previously, H1N1 planners didn't consider ventilators a major issue. "Our pandemic plan at Mount Sinai was to use transport ventilators, or anesthesia-type ventilators, but with the research data we soon realized this would be inadequate," says Lapinsky. By the summer of 2009, Mount Sinai staff had made plans to acquire more sophisticated ventilation equipment, including high-frequency oscillators and extracorporeal membrane oxygenation machines, in advance of the winter flu season.

At Sunnybrook, the ICU already had a range of ventilation devices, but staff collaborated with the Ministry of Health and Long-Term Care to ensure access to more, and developed a plan to accommodate a surge of H1N1 cases that included caring for patients in areas of the hospital other than the ICU.

At the same time, Fowler and his CCCTG colleagues, with the Public Health Agency of Canada, began taking stock of all Canadian intensive care beds, ventilation equipment and staffing capacity—a task that proved surprisingly difficult. "Remarkably, although we had a sense of ICU beds [in Toronto], nobody really had a good idea of numbers at a national level," says Fowler.

Typical Canadian ICUs are between 90% and 100% occupied at any given time, so there's rarely much room for a surge in patients. Recognizing the importance of a comprehensive ICU inventory, the Public Health Agency freed up a data collector, and the group completed the bulk of the work by the time the studies were published in October. Meanwhile, several Canadian provinces bolstered their central supplies of ventilation equipment to handle potential demand in those ICUs found to have limited resources.

### Critical Collaboration

While the two studies altered ICU resource planning in Canada, their standardized case-reporting forms enabled researchers

in Canada and Mexico to determine which patients were getting critically ill and not surviving. “We really wanted to get a handle on, of the people who were dying, what they were dying of,” says Fowler. “Did they have other medical conditions, or was this flu actually killing them?”

To develop the case-reporting form for Mexico, Fowler consulted with members of the CCCTG, and with Sunnybrook’s president and CEO Dr. Barry McLellan, whose background in the Ontario coroner’s office helped Fowler draft a framework to attribute cause of death. Sunnybrook’s research ethics board fast-tracked approval of the draft, and the result was a form—ready just four days after the Mexicans requested it—that enabled them to describe accurately the course of H1N1 in specific types of patients.

The investigators in Mexico had contacted Toronto researchers early in 2009, in part because they wanted the benefit of Canada’s experience with SARS in 2003. Based on their SARS experience, Toronto researchers and critical care physicians conveyed infection prevention measures they thought would be useful, and stressed the importance of research; additionally, the form that Fowler and his colleagues produced, which enabled the Mexicans to determine that H1N1 was killing young, healthy patients, was crafted from a SARS case-report form.

But another important reason that Mexico came to Canada for help, according to Fowler, was the cooperative nature and research achievements of the CCCTG. “The Canadian critical care community has for many years been collaborative in their approach to academics and clinical care, and has to a degree ‘pollinated’ critical care groups around the world with the idea of collaborative research,” says Fowler. As well, he says, the Mexicans viewed the CCCTG as a trusted team that would not undermine their work by claiming it as their own.

### Critical Message

The CCCTG is a model of collaborative success. Since its founding in Hamilton in 1989, the group has published over 75 peer-reviewed papers, 10 in the high-impact *New England Journal of Medicine*, and inspired similar groups in about a dozen other countries. Fowler calls his participation in the CCCTG “the richest education I’ve ever undertaken,” and was thrilled when critical care groups in Australia, the U.K., Europe and the U.S. asked the CCCTG to help them roll out the H1N1 reporting structure in their own countries, which they did through the summer and fall of 2009.

This global proliferation in turn laid the foundation for the International Forum for Acute Care Trialists (InFACT) H1N1

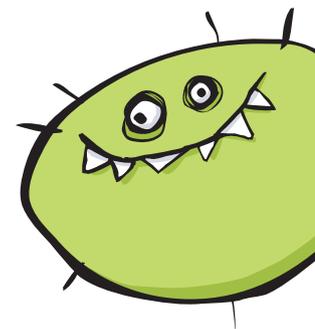
Collaboration, which is being led by Dr. John Marshall, chair of the CCCTG and a scientist at St. Michael’s Hospital in Toronto. The InFACT initiative, in which Fowler is participating, will see researchers in several countries sharing data to develop common metrics to improve critical care for H1N1 patients over the coming months—or years, depending on the severity of the pandemic. Marshall says the data sharing will be easier owing to the standardized case-reporting form and Fowler’s interaction with other critical care groups. “Rob has done a heroic job of bringing people together and melding this into a very global response to the pandemic,” says Marshall. “And I think it’s his incredible willingness to pass credit around that has really driven the success of the process so far.”

One of the findings that came from a comparison of the Mexican and Canadian studies—the sort that should emerge as the InFACT effort progresses—was that 40% of patients who became critically ill with H1N1 in the Mexican study died, versus 20% in Canada. Many of the Mexican patients came into the hospital much sicker, and later, than those in Canada, and they didn’t have access to the same life-supporting technology and care. “The message,” says Fowler, “was that it may be important for young, otherwise healthy people to present for aggressive care early rather than later in their illness.”

Critical care researchers and pandemic planners around the world clearly took that message seriously. The studies were cited by other peer-reviewed research more than a dozen times within six weeks of publishing, and media outlets across the world devoted coverage to the findings. In Canada, knowledge of the severity of H1N1, and of which patients were most at risk, likely limited the impact of the virus in 2009.

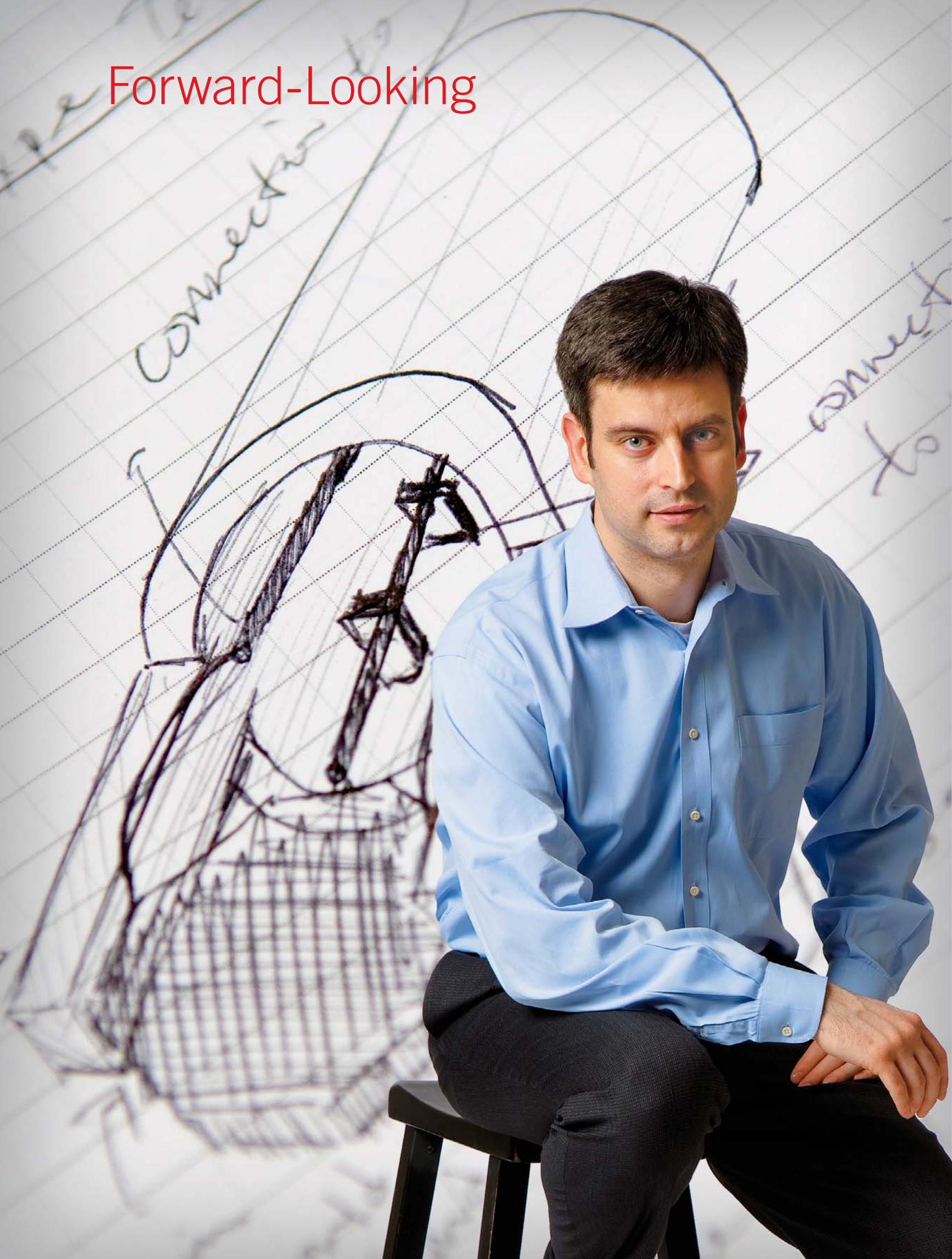
Despite some tragic and highly publicized deaths, and considerable difficulty getting rapid funding for H1N1 research—the latter a problem the CCCTG is lobbying hard to fix—Marshall says he’s reasonably happy with how Canada has dealt with the virus to date. “There’s understandably a huge amount of anxiety about H1N1 that has led to hyperbole on both sides, either understating or overstating the seriousness of the problem,” says Marshall. “But I think what’s necessary is to be somewhat sanguine about the fact that we’re learning as we go, and as long as people are maximally engaged and committed to that process, then we will make it through pretty well.”

Fowler’s research was funded by the Canadian Institutes of Health Research, Public Health Agency of Canada, Ontario Ministry of Health and Long-term Care, and Heart and Stroke Foundation of Canada.



“The message,” says Fowler, “was that it may be important for young, otherwise healthy people to present for aggressive care early rather than later in their illness.”

# Forward-Looking



# The heart

is a powerful and much-studied organ. The ability to visualize the workings of its chambers and vessels remains a challenge, however, a serious obstacle given that most of what goes wrong with the heart—including cardiovascular disease, the primary cause of death globally—happens there. Needed is a better way to see what goes on in these innermost places. One Sunnybrook trainee may have found it

By Stephanie Roberts

On cinema screens across North America, 3-D is hotter than ever. The fantastical concepts of *Avatar* and *Up* exist, however, in the realm of the imaginary. Not so the ideas of one enterprising clinician-researcher at Sunnybrook Health Sciences Centre, who has also harnessed the power of 3-D, but in the sphere of the real. Dr. Brian Courtney has built a device that can see inside the heart's chambers in three dimensions—no geeky plastic glasses required.

His invention takes aim at some of the stickiest challenges facing 21st-century cardiology. “When we’re talking about complicated procedures like burning or ablating structures in the heart to get rid of a heart rhythm problem, or putting in new devices, like a replacement valve, then it becomes a three-dimensional problem, and there aren’t very good techniques to guide these 3-D procedures at this point,” says Courtney.

Rather, there weren’t.

Courtney’s device builds on a technique called intravascular ultrasound imaging, IVUS for short, which is done in about 15% of patients in North America who have a coronary angioplasty or stenting procedure to open blocked blood vessels. The technique is used to ensure stents have been placed correctly, or to identify things that a coronary angiogram, a type of X-ray that is the workhorse of the cardiac cath lab, cannot see.

During IVUS, a catheter, a thin tube, is threaded from an artery in the leg or arm into a blood vessel in the heart. At the catheter’s

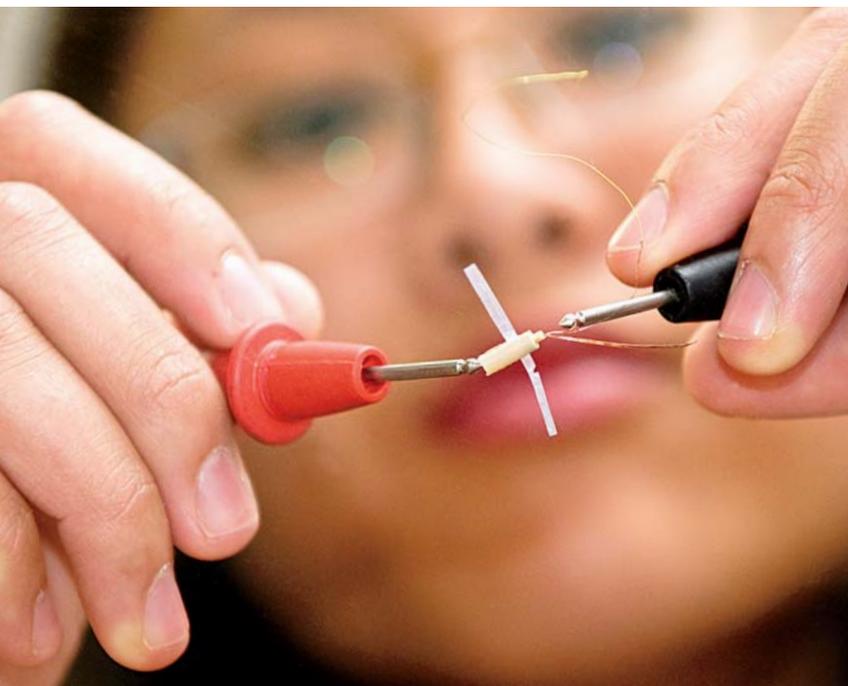
tip is an ultrasound transducer, or probe, which looks off to the side. It sends the information it captures back to an ultrasound machine for viewing. In this way, clinicians can see inside a blood vessel and be confident in doing procedures like angioplasty that the stent they’ve chosen is the right size and properly positioned.

While IVUS catheters take pictures of vessels, a larger version, called an intracardiac echocardiography (ICE) catheter, takes pictures of bigger structures and chambers. Both types of catheters, IVUS and ICE, however, are limited to 2-D imaging. Moreover, as cardiovascular procedures become more complex, patients are exposed to a lot of radiation or kidney-damaging dye.

Courtney’s coolly named 3-D forward-looking ICE catheter solves these problems by displaying images in high-resolution 3-D in real-time. And, it offers another inventive twist: the capacity to look ahead of its tip, instead of only to the side. “When I explained it to my mother, she said, ‘Oh, so current catheters are like driving but looking out the side window, and forward-looking catheters are like looking out the windshield, so you can actually see where the car is going,’” says the 36-year-old, smiling. “I’ve used the analogy ever since.”

## A PROGRESSIVE SPIN

With these capabilities, clinicians can get the catheter closer to the tissue of interest. It also can reduce the need for X-rays and helps with navigation, says Courtney: “If you have a forward-looking



device, then you can see ahead of the device, and you can see where you are moving the catheter toward.”

The innovation is a feat others have tried to own. “People have been working on this for 20 years—to come up with a catheter that is forward-looking using ultrasound imaging,” says Courtney. “They’ve struggled with it because these catheters have to be disposable, therefore they have to be somewhat inexpensive, they have to be reliable and they have to produce good images.”

Where others have failed, Courtney and his team at Sunnybrook Research Institute (SRI) are succeeding: they’ve shrunk it to be the same size as a 2-D ICE catheter, and the images they’ve made with the prototype were very good: “better than we were expecting,” he says.

Price-wise, he estimates his 3-D forward-looking ICE catheter will ring in at less than one-half of the \$3,500 it costs in Canada for the 2-D version. New technologies, especially advanced ones, aren’t known to come in cheaper at the outset, so how is this possible?

To understand how, one need take a step back, to learn a bit about how ultrasound catheters work. At the tip of a catheter is a transducer, an electrical device that converts one form of energy to another, in this case, sound waves to electrical signals. Inside the catheter is a torque cable that is attached to a motor. Images are produced when the cable is rotated, typically at about 30 rotations per second, causing the probe to look out, spin around and capture information. This information is received by the ultrasound machine, which processes the signals to produce an image on a monitor. Advanced 2-D catheters have probes composed of many electronic elements, which helps with resolution but makes the technology much more expensive.

Courtney’s approach is different: “What we do is take a single element or a single transducer, and just change the direction of the rotation using a mechanical concept.

“We mount the catheter on a pivot point and change the speed of rotation. When we go at slow speeds our catheter looks off to the side; but when we really spin the torque cable, the transducer, which is at the far end of that cable, is mounted in such a way that centrifugal force causes it to tilt. So at very high speeds it looks forward.” Relying on mechanics rather than electronics makes it cheaper to build and thus to buy.

### **AN ENTERPRISING MIND**

So, the 3-D forward-looking ICE catheter hits the mark on novelty, image quality and cost-effectiveness. Results from the

ultimate test, however—impact on patient care and by extension the health care system—won’t be seen until the device is in doctors’ hands, some years away.

To get there faster, Courtney has founded a company to commercialize the technology. Colibri, Latin for hummingbird (“They are fast, efficient and beautiful,” he explains), was incorporated in November 2007. Courtney is its president and CEO. He and six co-founders wrote the original patents.

The initial focus of Colibri is the described 3-D image-guidance technology, a broad-based imaging platform with many potential applications. Courtney is also building a device that could have even bigger impact: a catheter that can detect a heart-attack-in-the-making.

At the core is “vulnerable plaque,” a type of fatty buildup that forms in the wall of an artery. This lipid-rich plaque stays hidden in the wall, sheathed by a thin coating, until something causes it to rupture—high blood pressure or inflammation, say. When it bursts, the plaque leaks into the artery and causes a clot to form. The clot strangles blood flow, which brings on a heart attack or stroke, and not infrequently, sudden, shocking death.

Often, victims of a detonated vulnerable plaque have no idea they’re in peril until they’re stricken. Most pressing, then, is a means to identify these plaque before it’s too late. Current technology doesn’t have the power to do this.

Courtney’s might, though. It would be able to detect if the cap covering a fat-filled plaque has thinned, one sign of a lurking vulnerable plaque and often a precursor to a heart attack. It could also identify plaque with a lipid-rich centre, another indicator. To do this, Courtney has coupled ultrasound and optical imaging, creating an innovative tool that is greater than the sum of its parts.

### **WEDDED BLISS**

Ultrasound is good at seeing through blood and relatively far through tissue, two tasks that defeat optical imaging. Where optical imaging triumphs, however, is in its high resolution and contrast, capabilities ultrasound lacks and that give doctors the sensitivity and specificity they need to distinguish a nonthreatening from a potentially fatal plaque.

“If you were to look at a plaque that was filled with scar [tissue] but that doesn’t have a lot of lipids in it, then that’s a plaque that’s probably less dangerous than one that has a lot of cholesterol deposits and a thin fibrous cap over it. Optical coherence tomography is able to identify whether there is a lipid- or cholesterol-rich core to a plaque. It’s also able to identify a thrombus [clot] in a blood vessel better than ultrasound or angiography.”

Courtney’s catheter is the first to marry the two technologies to produce an all-in-one imaging capability. “We built it in such a way that the ultrasound and optical imaging are precisely coregistered with each other, so when you take an ultrasound image and you take an optical image, you know that you’ve taken each of the exact same place in the blood vessel, and you can map the two information sources on top of each other, so you can take advantage of each of them,” he says.

As a third-year resident in the department of cardiology at the University of Toronto (his research and much of his clinical training are at Sunnybrook), Courtney has been able to gain

# Courtney is also building a device that could have even bigger impact: a catheter that can detect a heart-attack-in-the-making.

insight into patients' needs, as well as those of his physician peers. "The clinical community has been very supportive. I get to talk to a lot of doctors that do procedures that would potentially benefit from this kind of technology."

Indeed, at every step of the way, the trainee has garnered the interest of colleagues in medicine and research. "We've probably shown our idea to people who together have hundreds of person-years of experience in the field, and everyone has said, 'That's very interesting. I've never seen anything like that before.'"

## SPLIT PERSONALITY

Courtney's multi-branched focus is atypical. Rare is a doctor who is a researcher who is an entrepreneur.

Colibri is his third start-up company, the last two being in the U.S. while he was attending medical school at Stanford University. This is the one with which he has been most involved, he says. The benefits to patients are clear, and there is a bona fide business opportunity. "We can help a lot of people. It makes it easy to tell the same story to the clinicians as you tell to the business people," he says.

His dual focus on medicine and research seems a natural fit. He says he is motivated to do science because he wants to do better medicine. "I enjoy looking after patients and the complexities of day-to-day clinical medicine," he says. "But there are situations

that we see routinely that are limited by the tools we have available, where patients suffer or we spend way too much money. I think there are many ways of doing things better."

Being on the frontline of care is as crucial, he says: "If I were to be a researcher or entrepreneur all the time, I'd be frustrated because I wouldn't get the day-to-day joy, the sense of doing things for patients and seeing the result, and I'd be farther removed from the context of why I'm doing the development."

He credits the milieu at SRI as instrumental in deciding where to do his residency. "Here, we're able to build not only ultrasound systems from the ground up, but optical systems from the ground up. There is technical expertise here that enables us to be very flexible in our design, well beyond what most other imaging research centres in the world can do."

There are the top-tier facilities at SRI; there is also the highly rated imaging research team. He cites in particular the mentorship of senior imaging scientists Drs. Stuart Foster and Graham Wright, both world-renowned in their respective fields. He's working with Wright and Dr. Brad Strauss, a clinician-scientist in the Schulich heart research program, on using his 3-D ICE catheter to provide image guidance during a range of cardiovascular procedures.

Longer-term, Courtney says the focus may turn to therapy. "Once we build a catheter that can do the imaging to help guide procedures, it might be worthwhile to combine some therapeutic capabilities onto these catheters. Then we would be able to build things that would combine therapy and 3-D image guidance on the same catheter," he says.

That'd be another first.

Today, though, the focus is on technology development—refining, validating and testing the device, which includes securing more funding to accelerate activity. Rarely easy, the economic climate has made it even more challenging, though Courtney notes there has been an "up" side. "It meant that we really had to focus and be efficient. The best ideas that come out of a time where funding is this difficult to get means that only the best ideas will survive. I am hopeful that we have a very good chance of being one of the success stories."

Courtney's research has received funding from the following: BioDiscovery Toronto, Canadian Institutes of Health Research, Ontario Ministry of Research and Innovation, Ontario Centres of Excellence, Sunnybrook Research Institute and The Health Technology Exchange. The Canada Foundation for Innovation provided infrastructure support.



BRIAN LI, DR. BRIAN COURTNEY, ANNIE LEUNG AND ALAN SOONG



JUST WHAT IS  
REGENERATIVE MEDICINE,  
ANYWAY?

UNPACKING ONE OF  
THE HOTTEST PHRASES IN  
MEDICAL SCIENCE  
TO UNDERSTAND HOW  
RESEARCHERS  
AT SUNNYBROOK ARE  
ENGINEERING TISSUE  
AND DELIVERING  
THERAPY TO REPAIR  
AND RESTORE  
THE HUMAN BODY

BY JIM OLDFIELD

# IN

2006, the National Institutes of Health (NIH), the largest funding body for medical science in the U.S., issued a state-of-the-field report on regenerative medicine. The report's cover boasted an image of the Greek deity Prometheus, chained to a rock and under siege by an eagle. According to myth, Zeus sent an eagle to eat Prometheus's liver as punishment, but Prometheus was able to regenerate the organ, and survived despite daily attacks by the eagle.

The NIH report claims that Prometheus is a fitting symbol for regenerative medicine, a field that, broadly defined, means restoring health by growing organs and engineering tissue. And, the field has seen spectacular success. In 2006, Dr. Anthony Atala of Wake Forest University announced that his team had implanted lab-grown bladders in seven patients, and that all seven had been doing well—some for up to six years.

But after 30-plus years of research, such breakthroughs are rare, and the field is more complex. Where scientists once thought the right type of cells, properly placed next to the right scaffold, would on their own become a tissue or organ, they now know that's often not enough. Replicating the intricate signals exchanged among cells and how those cells interact with their environment is increasingly important. For Dr. Graham Wright, whose team has spent years using imaging to visualize experimental regenerative techniques, one word comes to mind on hearing regenerative medicine: "caution."

"Regenerative medicine is one of those fields that can be oversold easily," says Wright, director of the Schulich heart research program at Sunnybrook Research Institute (SRI) and a professor at the University of Toronto. "It's enticing to say, 'I'm going to grow a heart and put it in.' But I think the field has recognized that this is a complex challenge, and that we have to understand the processes associated with tissue *response* and *repair* to advance this goal."

One approach, Wright says, is to focus on damage caused by disease, and then work to limit and repair it. Doing so, he says, first requires understanding how the body—especially the vascular and immune systems—interacts with tissues. One

problem in this regard has been ensuring the survival of cells and tissue meant to repair damage once injected or implanted. A considerable challenge in small animals, the issue is even more complex in larger systems, like humans, where cells take longer to reach their destination and require significant vasculature (blood supply) and nutrients to function. "It's not simply a matter of growing and implanting tissue," says Wright. "We also have to think about the system from a molecular and cellular point of view, and work with the system to repair damage."

To that end, researchers at SRI are working on clinically relevant problems in tissue engineering and therapy delivery. They have made advances that could shape patient care within a few years for those with diabetes, degenerative disc disease, heart disease and cancer. At the same time, they are extending the foundational knowledge of regenerative medicine that may yet allow scientists to fulfil the field's Promethean promise.

## Healing Wounds, Healing People

One advance that may prove a boon for diabetics is Vasculotide, a compound developed at SRI that can be applied as a cream to help wounds heal better and faster. Many people with diabetes have poor circulation, and this leaves them prone to injuries that don't heal. Up to 15% of these people will develop ghastly, painful sores, usually on the feet or lower legs. There are few effective treatments, and as many as one in five patients with these wounds will require limb amputation.

Vasculotide speeds up wound healing in diabetic mice by 30% to 40%. Co-invented by Dr. Dan Dumont, director of molecular and cellular biology at SRI and a scientist in SRI's Advanced Regenerative Tissue Engineering Centre (ARTEC), and his research associate Dr. Paul Van Slyke, the fully synthetic compound mimics the properties of the protein growth factor Angiopoietin (Ang) 1. This is desirable, explains Van Slyke, because Ang 1 is a "master regulator" of blood-vessel growth, development and stability—useful, therefore, in closing wounds. While Ang 1 is difficult to purify on a large scale, unstable and potentially unsafe, Vasculotide has none of these problems. Moreover, it can be made cheaply.

# “REGENERATIVE MEDICINE

is one of those fields that  
can be oversold  
easily,” says Wright.



TOP TO BOTTOM:  
DR. JUAN CARLOS ZÚÑIGA-PFLÜCKER; DR. GRAHAM WRIGHT;  
DRS. CARI WHYNE AND ALBERT YEE

Critically, Vasculotide also improves the quality of the wound closure. In Dumont’s lab, Van Slyke picks up an image series of purple, pink and white cross-sections showing three wounds—each treated differently—and their underlying tissue. The first two reveal tissue layers beneath typical diabetic wounds. “You can see [the tissue] is spongy, fatty and lacking support,” says Van Slyke, pointing out several large white clumps just below the skin. The third image shows a wound treated with Vasculotide. Several layers of purple and pink fibres, or “granulation” tissue, are packed between a small layer of fat and the wound surface. “This is all connective tissue and blood vessels feeding the wound,” says Van Slyke. “Its thickness would provide resistance to the wound reopening. And that’s a major issue in diabetic wound healing—patients get up to walk around, and the wound just blows back open.”

Vasculotide is so promising that the NIH selected the compound for its Type 1 Diabetes Preclinical Testing Program, a precursor to its “rapid access” program, which fast-tracks therapies from the bench to the clinic. The program will fund four San Diego-based trials of Vasculotide in increasingly large animals over the next year. Dumont, who also holds the Canada Research Chair in Angiogenic and Lymphangiogenic Signalling, and is a professor at U of T, has formed a spin-off company to commercialize his technology.

While Vasculotide has implications for diabetes, Dumont and Van Slyke have evidence, which they continue to collect, that it may be useful in other conditions where improving blood supply can improve treatment, including age-related macular degeneration (loss of vision), stroke and heart disease. It may also help solve the key question facing regenerative medicine researchers: how do you provide blood supply and nourishment for cells, tissue and organs grown in the lab?

## A Matter of Environment

In 2002, Dr. Juan Carlos Zúñiga-Pflücker, a scientist at SRI, found a way to grow T cells from stem cells in a Petri dish. T cells are virus- and infection-fighting white blood cells, which many scientists believe will one day be able to be harnessed to restore

# YEE, WHYNE AND WOODHOUSE

are working to develop a treatment  
that would slow disc degeneration at a much  
earlier stage, before expensive,  
invasive and variably effective surgery  
is the only option.

immunity in patients with severe immune deficiencies. The breakthrough transformed the field of immunology by allowing immunologists to observe and manipulate T cell development in unprecedented detail.

Since then, Zúñiga-Pflücker has been searching for a means to maintain these lab-grown T cells over time. One of his ideas was to build an artificial thymus, the main organ in which T cells grow in the body. This led to talks with Dumont. “If we ever have this 3-D [thymic] structure to implant, it would have to be vascularized [provided with a blood supply],” says Zúñiga-Pflücker, who holds the Canada Research Chair in Developmental Immunology and is the director of ARTEC. “So what Dan’s lab is doing will be applicable to a lot of regenerative medicine approaches where achieving vascularization is important for any tissue you’re growing.”

From those talks, the two developed a method, which they’re refining, to improve the generation of the blood stem cells Zúñiga-Pflücker’s lab uses to grow T cells.

At the same time, Zúñiga-Pflücker and his postdoctoral fellow Dr. Mahmood Mohtashami discovered a way to support T cells that doesn’t require an entire organ-like structure. “It turns out we didn’t need to be as sophisticated as we thought, so we scaled down the idea of a fully 3-D thymus to something simpler,” says Zúñiga-Pflücker.

Their method combines a select mix of molecules in a 2-D environment, and increases T cell numbers with cells harvested from the same animal that could receive them as therapy, opening a door to more “personalized” T cell regeneration.

The trouble is, this approach produces only a small number of T cells. Hence, says Zúñiga-Pflücker, it’s still possible that some type of 3-D structure that reproduces the thymic environment might work better. To that end, he continues to collaborate with Dumont and with Dr. Kimberly Woodhouse, associate director of ARTEC, who specializes in chemically engineered scaffolds that can support vasculature and 3-D tissue growth.

Woodhouse is dean of the faculty of applied science at Queen’s University and a professor at U of T, who maintains an appointment as scientist at SRI. She works with ARTEC

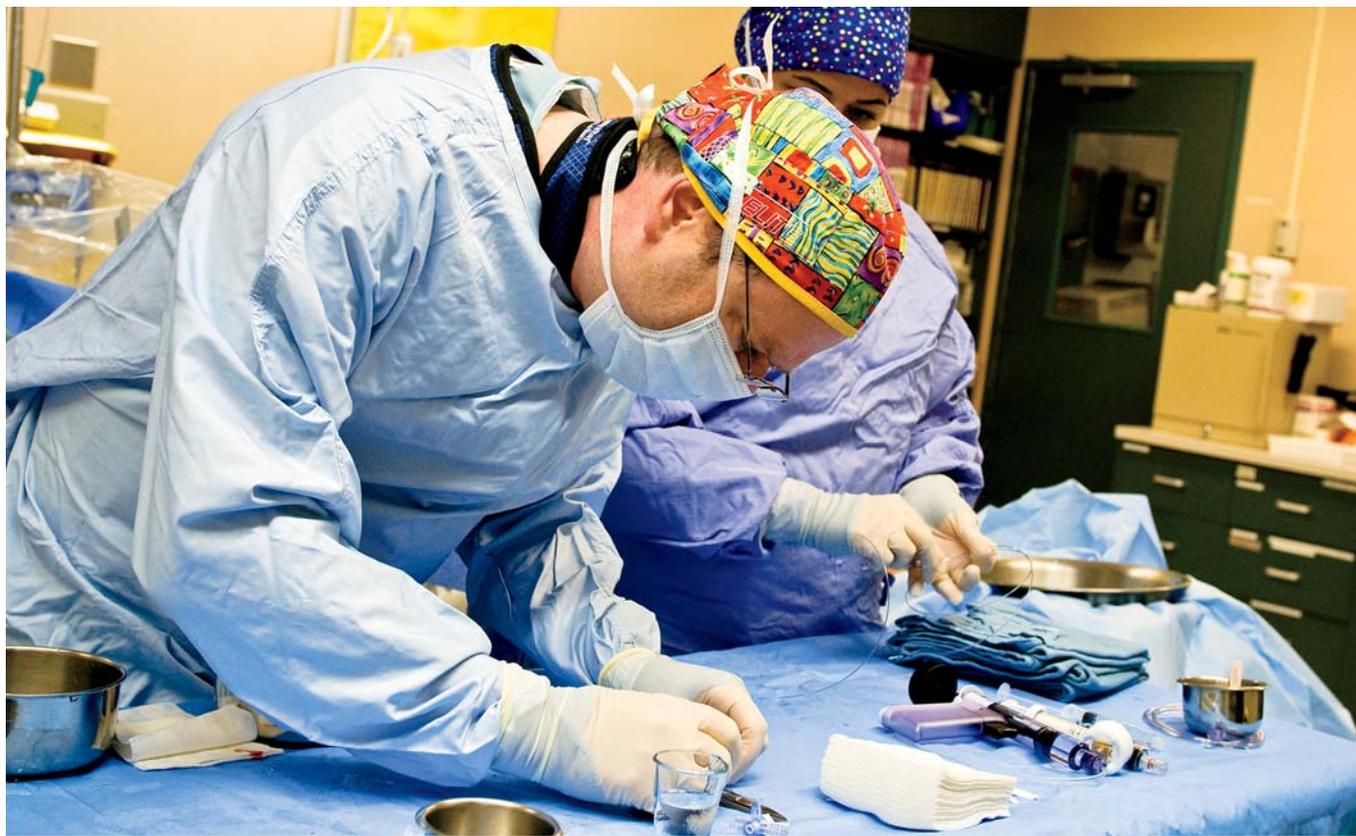
scientists Drs. Cari Whyne and Albert Yee on regenerative approaches to degenerative disc disease.

While some disc degeneration with aging is normal, as much as 85% of the population will have chronic (lasting three months or more) back pain. For those who require invasive treatment, options are limited. “Right now, a lot of surgical therapies are directed toward the end stages of the condition,” says Yee, a researcher at SRI, who is also a surgeon at Sunnybrook Health Sciences Centre and an associate professor at U of T. “If you have a worn-out disc and you’re symptomatic with a concordant constellation of symptoms, then we either fuse the disc or give an artificial disc replacement—but both have varied results.”

Yee, Whyne and Woodhouse are working to develop a treatment that would slow disc degeneration at a much earlier stage, before expensive, invasive and variably effective surgery is the only option. They have had some success with a liquid hydrogel that solidifies once injected, providing a structural support that is flexible but can withstand repetitive spinal load-bearing. They will



DRS. DAN DUMONT AND JENNIFER ALAMI



DR. BRADLEY STRAUSS

publish those results this year, and are moving on to the next stage: how the implant interacts with the environment of the spine at the molecular and cellular level. “We want to reinstate the mechanical environment, but we may need to include additional cells or growth factors to help the cells get back on track, otherwise they’ll just go off down the wrong path again,” says Whyne, who is director of the Holland musculoskeletal research program at SRI and an associate professor at U of T.

### Imaging for Cell-Based Therapies

A key aspect of translating this musculoskeletal and other regenerative medicine research to patients is imaging—particularly magnetic resonance (MR). Imaging enables disease diagnosis, but it is also increasingly essential to monitor the delivery of regenerative therapies and the body’s response to those therapies. Wright is partnering with other scientists in SRI’s Centre for Molecular and Cellular Response and Repair (CMCRR) and the Imaging Research Centre for Cardiac Intervention to develop novel imaging techniques for cell-based regenerative therapies.

One such therapy is for chronic total occlusions (CTOs), which are coronary or peripheral arterial blockages lasting more than six weeks. Peripheral CTOs can result in leg pain with walking and, in severe cases, amputation; coronary CTOs produce chest pain and lower life expectancy.

Pioneered by Dr. Bradley Strauss, a scientist in molecular and cellular biology at SRI, cardiologist at Sunnybrook and professor of medicine at U of T, the treatment uses an enzyme called collagenase to help restore blood flow in the blocked areas, or lesions. Strauss found that injecting collagenase softens the blockages enough to enable minimally invasive percutaneous (through the skin) intervention, where a surgeon draws a guide-wire over the blockage before doing angioplasty—a preferable alternative to bypass surgery and drugs, the current standards.

By tagging capsules and molecules with iron or gadolinium, each of which alters the MR signal to create a local positive contrast around the agent, Wright and Dr. Charles Cunningham, an imaging scientist at SRI and assistant professor at U of T, are working to monitor the delivery of Strauss’s therapy and its

effect on microvasculature. “Collagenase is an exciting new development, but one of the questions around it is how far you can get the collagenase into the lesion; it likely relies on a microvascular network to penetrate beyond the lesion’s surface,” says Wright.

They’ve validated the techniques in preclinical models, and expect it will provide the quantitative feedback to take the therapy, which Strauss is now testing in a clinical trial at Sunnybrook, to a new level of efficacy.

Wright’s overriding goal is to improve the ability of researchers and clinicians to track, in a way that can be measured over time, the physiological changes with disease and repair. Traditionally, imaging has provided mostly anatomical information, but long-term studies of regenerative interventions require measurements of blood volume and flow, local oxygen consumption, inflammation, and their effects on tissue. These measurements will be essential in tracking disease evolution and patients’ response to emerging treatments.

Wright looks forward to locating his lab alongside the labs of Dumont, Zúñiga-Pflücker, Strauss, Cunningham and about 100 other SRI staff in the CMCRR’s new home, now being built on the seventh floor of the hospital’s M wing. “We’ve got basic biology, imaging physics, molecular targeting and clinical expertise. Having that group together will be valuable in moving this whole area ahead.”

As with Strauss’s work, says Wright, success in regenerative medicine will be incremental. “But I think we’ll see quicker translation to the clinic with this approach,” he adds. “These will perhaps be smaller steps than some people originally pictured, but through those small steps we will get closer to the long-term goal of providing solutions for people.”

Funding this research into regenerative medicine are the following: BioDiscovery Toronto, Canadian Cancer Society Research Institute, Canadian Institutes of Health Research, Krembil Foundation, MaRS Innovation, McLaughlin Centre for Molecular Medicine, Ontario HIV Treatment Network, and Ontario Ministry of Research and Innovation. Providing infrastructure support are the Canada Foundation for Innovation and Ontario Innovation Trust.



**SMARTERFAS**



## On-the-Horizon Innovations in Cancer Care

Researchers here are developing new methods and technologies to hasten detection, dramatically improve diagnosis and make treatment more targeted, innovations that are close to making—or in some cases already making—patients' lives better

By Alisa Kim

**STER BETTER**

# THE ADVANTAGE: CLEARER PICTURES THAT MAY HELP DOCTORS DIAGNOSE BREAST CANCER MORE ACCURATELY AND REDUCE THE INCIDENCE OF MISSED CANCERS AND FALSE ALARMS.

“It was more like a spider web, not a lump.”

That was what Joanne Nevison learned about the mass in her breast when she was diagnosed with breast cancer in March 2007. Within a week of getting the diagnosis from her family doctor, Nevison, aged 50 years, was at Sunnybrook’s Odette Cancer Centre, where she was told that because it was so large, the 7-cm tumour had to be reduced with chemotherapy before surgeons could remove it.

Her oncologist, Dr. Greg Czarnota, who is also a scientist at Sunnybrook Research Institute (SRI), asked whether she would like to be part of a clinical study to evaluate a new imaging system to monitor the effectiveness of chemotherapy.

She was game: “I wanted to help with the research, to help other people,” she says.

Research and education are critical to understanding and preventing disease, and improving patient care. Scientists at SRI are inventing innovative technologies to detect cancer sooner and with greater precision. They are also identifying new ways of evaluating therapies to enable patients to receive more effective, personalized care, and discovering ways to improve existing treatments by reducing harmful side effects.

The technology Czarnota was studying revealed that the drugs Nevison was taking were shrinking the tumour. Surgeons successfully removed it in July of that year. Her treatment concluded with a final round of chemotherapy. The self-employed businesswoman now checks in every six months for follow-up care.

## SMARTER

From his office on the sixth floor of Sunnybrook’s S wing, SRI imaging physicist Dr. Martin Yaffe has his eye on a number of promising directions in cancer research. His focus is on the early detection of cancer, when tumours are one millimetre, the size of a head of a pin. Today, tumours are normally spotted when they are bigger than one centimetre, comprising over 200 million cancer cells.

“Imaging in cancer has been looking for masses, physical changes as the cancer begins to grow. To get to that point, the cancer has to have been there for quite a while, so that approach is never going to be highly sensitive,” says Yaffe, who holds the Tory Family Chair in Oncology Research. “We’re really looking for fingerprints of the cancer, and we’re trying to develop sensitive tools to do that.”

The subtle clues for which Yaffe and his colleagues are sleuthing are functional, or physiological, changes in cellular metabolism and blood flow that betray the presence of otherwise imperceptible malignant cells. As the co-leader of the Ontario Institute for Cancer Research’s (OICR’s) One Millimetre Cancer Challenge, Yaffe oversees projects at SRI and across the province that are using sophisticated technologies to track molecular and functional changes in the body that are associated with cancer—“smarter imaging,” as he puts it.

The research behind the program adapts existing imaging systems such as X-ray, magnetic resonance imaging (MRI), positron emission tomography

and ultrasound, by adding probes to detect early-stage cancers. To this end, Yaffe, who is also a professor in the department of medical biophysics at the University of Toronto, has assembled a team of experts—physicists, chemists, biologists and clinicians—to develop and test advanced imaging and screening techniques.

“Cancer is a complex problem, and the solutions require bringing together talents from different areas,” says Yaffe, of the multidisciplinary approach. “The OICR program has let us ask what we think are the important questions related to imaging and cancer, and find the people we think can contribute to answering them. My job is to pull it together.”

One project harnessing the program’s varied scientific expertise involves the use of microbubbles to track cancer growth. Microbubbles are tiny pockets of gas that are smaller than a red blood cell and can pass harmlessly through the microcirculation. Exploiting these properties, SRI scientist Dr. Peter Burns developed a method that uses bubbles as a contrast agent for ultrasound to visualize blood flow. Injected into blood vessels and excited by high-frequency ultrasound waves, the microbubbles vibrate, displaying areas of angiogenesis (the formation of new blood vessels from pre-existing ones) that may be linked to spreading cancer.

Burns, who is the chair of the department of medical biophysics at U of T, and his SRI colleagues are also using microbubbles to detect cancer by attaching a molecule to the bubbles; the molecule works as a “magnet” to attract other tumour-specific



DR. GEORG BJARNASON

molecules. Finally, they are developing a way to add microbubbles to treat cancer. By loading the bubbles with an anticancer drug and using ultrasound to aim and burst them at the disease site, patients can receive locally targeted therapy.

Burns's work is at the preclinical stage. Yaffe anticipates that research on the use of these methods in humans will begin within one year.

An innovation that is now being studied for clinical use is digital breast tomosynthesis. Like 3-D digital mammography, tomosynthesis uses X-rays to produce an image of the breast, which can be stored or sent electronically. Tomosynthesis takes X-ray photos of the breast snapped at different angles, which are then processed using computer software to construct a 3-D image. The advantage: clearer pictures that may help doctors diagnose breast cancer more accurately and reduce the incidence of missed cancers and false alarms.

The detailed images are also useful in treating breast cancer. "[Digital tomosyn-

thesis] gives the surgeons or whoever performs therapy on the breast cancer a much better idea of what they're dealing with so that they can get a 3-D picture of the disease, and can plan the therapy in a way that's going to be most appropriate," says Yaffe. Sunnybrook Research Institute is part of a multi-institutional study evaluating this technology, the results of which Yaffe expects to have next year.

"We don't have all our eggs in one basket," he says of the various activities comprising the One Millimetre Cancer Challenge. "It's a diversified investment portfolio in research where there's multiple possibilities for solutions to a problem. One of them will likely emerge more quickly or as a better approach, and we'll then follow that more energetically."

### **FASTER**

At the bustling Odette Cancer Centre, Yaffe's colleague Czarnota is fighting cancer on two fronts: in the lab and in the clinic. Czarnota is using his passion for medicine

and science to find ways of improving care for Nevison and other women who have breast cancer.

Czarnota, who is also an assistant professor at U of T and was recently named a Cancer Care Ontario Research Chair in Experimental Therapeutics and Imaging, is using ultrasound imaging to study tumour death to develop better cancer treatments. His lab is also designing ways to evaluate treatments more quickly using ultrasound and optical imaging technologies.

He has performed a clinical study monitoring the effectiveness of chemotherapy in women with locally advanced breast cancer—characterized by large, aggressive tumours confined to the breast area—using SoftScan, an optical imaging system created by Advanced Research Technologies Inc. The SoftScan system characterizes delicate but important physiological changes in breast tissue, including blood flow and blood oxygen content, that reveal the status of a tumour. Lasers probe the patient's breasts at four wavelengths of light; a detector then measures how much light the breast absorbs. This information is used to calculate blood proteins, water content and light scattering power, all of which can tell physicians how the tumour is responding to therapy. The process is noninvasive and safe.

Czarnota used the SoftScan system to learn how Nevison and the other women in the study responded to neoadjuvant chemotherapy, drugs used to shrink large tumours before they are surgically removed. Each patient received five scans—one before the therapy began; after they

# TIME IS PRECIOUS TO A CANCER PATIENT.

began taking the drugs, at weeks one, four and eight; and prior to surgery.

He began to see results after the patients' third scan.

"What we found is that using this method, we can see changes in breast tumours very early on," says Czarnota, amid an array of computers in his quiet office. "This provides oncologists a measure by which they can objectively change therapies from ones that are ineffective to ones that can be effective. That might mean switching from one [type of] chemotherapy to another; it might mean switching from chemo

to radiation. I think for these women with aggressive breast tumours, it has the potential to improve survival."

The five-year survival rate for women with locally advanced breast cancer ranges from 20% to 40%, versus 87% for women with early-stage breast cancer. Time is precious to a cancer patient; to wait for several months to determine whether chemotherapy is working—especially when drugs are not reducing tumours—can be fatal. "For someone to have six months of a type of chemo or hormone therapy that's not effective is a loss of time for that patient, as well as health care dollars.

Rather than having someone undergo an expensive course of antiangiogenic drugs that can cost tens or hundreds of thousands of dollars, this may allow one to determine quickly whether that drug is useful or not for this type of patient," says Czarnota.

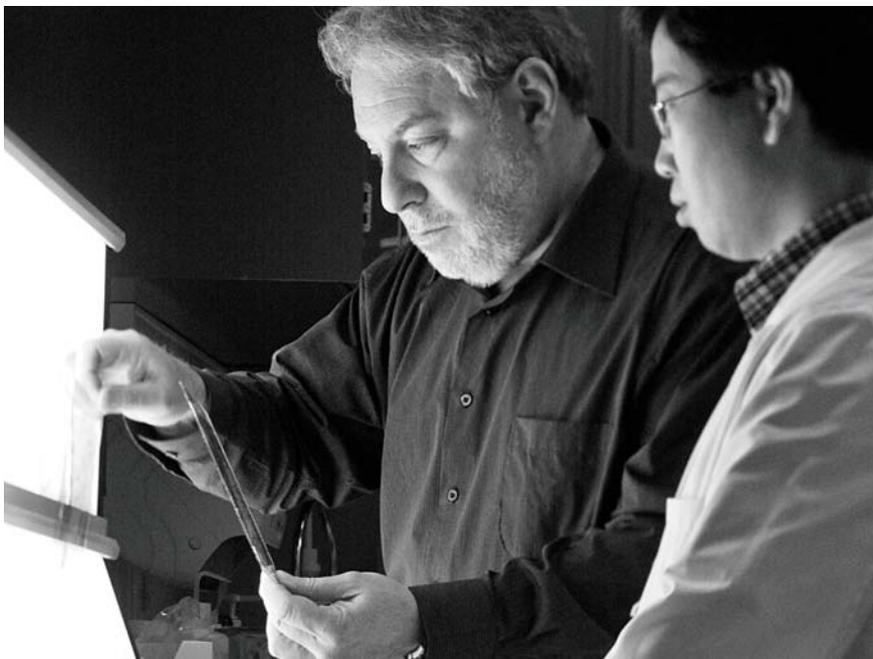
His findings have important implications for changing clinical practice. Typically, breast cancer patients receive an MRI scan before therapy and just prior to surgery, with no imaging test ordered in-between. This research suggests that optical imaging may be a viable means of filling the gap. "Oncologists will see patients on a week-to-week basis and feel patients' tumours. That's a very subjective measure of response. This [technology] could be developed as a standard method to assess tumour response."

## BETTER

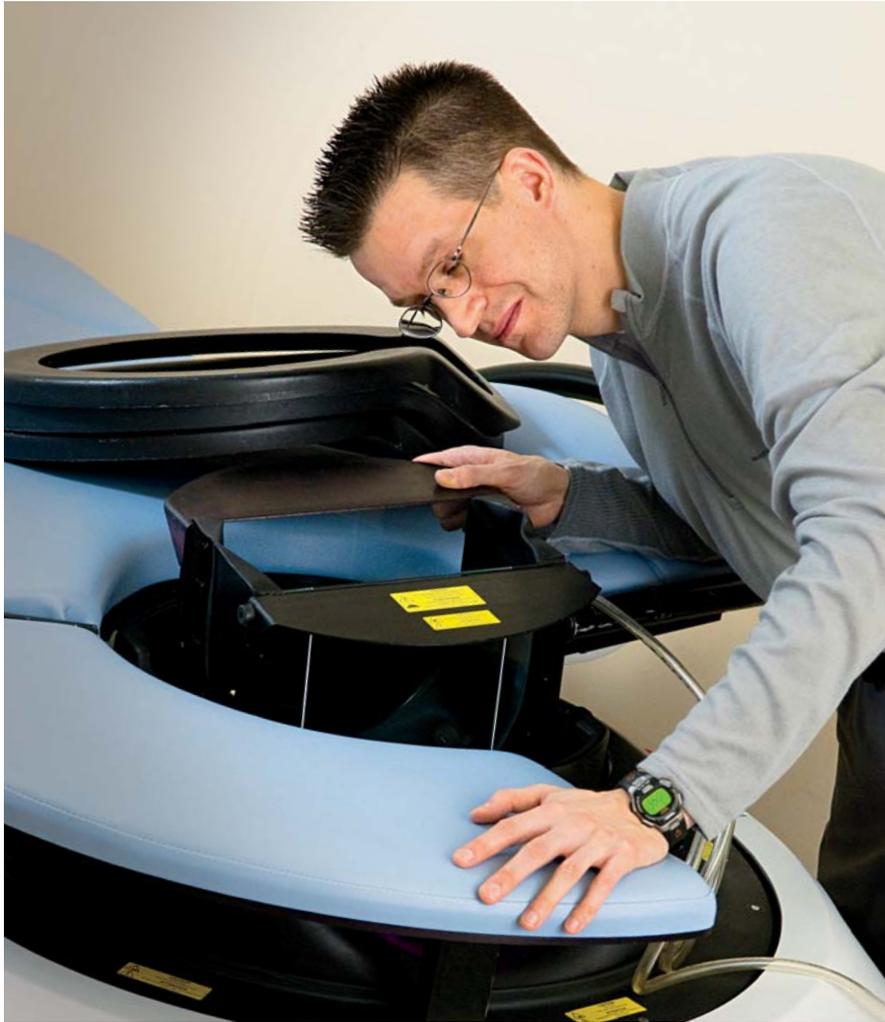
Down the hall, on the second floor of the Odette Cancer Centre, Dr. Georg Bjarnason is watching the clock.

An oncologist and senior scientist in clinical integrative biology at SRI, Bjarnason is studying chronobiology—how biological processes are linked to the body's circadian rhythm. The only researcher in Canada studying the effects of chemotherapy and radiation on people at different times of the day, Bjarnason aims to determine the optimal time for treatment, to maximize efficacy and minimize side effects.

In a paper published last year in the *International Journal of Radiation Oncology, Biology and Physics*, Bjarnason,



DRS. MARTIN YAFFE AND LAIBO SUN



DR. GREG CZARNOTA

who is also an associate professor in the department of medicine at U of T, showed the results of a proof-of-principle study comparing the effects of radiation given in the morning versus the afternoon. In it, Bjarnason and colleagues across Canada studied the incidence and severity of oral mucositis (inflammation of the mouth lining) in over 200 patients with head and neck cancer receiving radiotherapy either between 8 and 10 a.m., or between 4 and 6 p.m.

Oral mucositis is a side effect of radiation that plagues head and neck cancer patients, often forcing doctors to stop treatment prematurely. Its symptoms include pain, dryness of the mouth, changes in saliva and taste, and difficulty swallowing. Severity of mucositis ranges from mild discomfort to extensive damage such that patients cannot eat on their own and require feeding through a tube connected to their stomachs. In the study, researchers scored the patients' mucositis based on visible damage to the mouth.

Having determined from his prior research that the cells lining the mouth go

through the phases of the cell division cycle over 24 hours, and that healthy cells are in a phase that is less sensitive to radiation early in the day, Bjarnason surmised that giving radiation in the morning could reduce oral mucositis. "If we wanted to get a theoretical answer, we would have treated people at 3 a.m. but that wouldn't have any impact, because you're not going to do that in clinical practice," he says, wearing his physician's hat. "So we said, realistically, people can have treatment early in the day or at the end of the day. Are these times going to have a clinically significant impact?"

It appears they do.

Bjarnason found that, compared with the afternoon group, there were fewer patients in the morning group who had severe oral mucositis. What he found most compelling was that weight loss—caused by difficulty eating due to mucositis—among patients in the morning group stabilized five months after treatment, whereas patients in the afternoon group continued to lose weight for much longer. "I think that is the strongest evidence, because when looking

at the mucositis grade, there's inter-observer variability. But when the patient steps on the scale, that's pretty objective," says Bjarnason.

The benefits of morning radiotherapy were even more striking in a subset of 100 patients who, due to their inoperable tumours, required higher doses of radiation. Within this subset, 44% of patients in the morning group developed severe mucositis, compared to 67% in the afternoon group. Moreover, it took longer to reach this level of damage in the morning group. "The clinical scales to measure mucositis are imperfect because they're so subjective. When we took the people who got the highest dose, this reduction [of mucositis] became statistically significant, and the time until they developed this was prolonged," he says.

Determining whether this innovation can improve the survival rate of head and neck cancer patients will require a larger clinical trial, says Bjarnason. But, he notes, "I've received calls from people who do this kind of therapy in the States and elsewhere saying 'I've seen your paper. We now try to do the treatment early in the day.'" As to when this research will more widely change the way in which therapy is delivered to these patients, it may be just a matter of time.

Funding this research into cancer are the following: American Association for Cancer Research, Canadian Cancer Society, Canadian Institutes of Health Research, Cancer Care Ontario, Ontario Institute for Cancer Research, Ontario Ministry of Research and Innovation, Pfizer Canada and Wyeth-Ayerst. The Canada Foundation for Innovation and Ontario Innovation Trust provided infrastructure support.



ARGELIA

LIBIA

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ANGOLA

ZAMBIA

NAMIBIA

BOTSWANA

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DORSAL DE GUINEA

CORRIENTE DE BENGUELA

CUENCA DE ANGOLA

C. St. Mar

# He who learns, teaches.—African proverb

By Alisa Kim

## INTO AFRICA

From a picturesque campus nestled in an affluent neighbourhood in Toronto, Canada, a pair of Sunnybrook Research Institute (SRI) scientists is helping to improve the health care, body and mind, of people thousands of miles away. Though their academic interests are different—Dr. Peter Burns in medical imaging and Dr. Anthony Feinstein in psychiatry—their research and expertise are making a difference in communities in Africa that lack health care resources and infrastructure.

“We do medical research only because we want to improve the medical care of people,” says Burns, an imaging scientist at SRI and chair of the department of medical biophysics at the University of Toronto. “I think all of us at Sunnybrook want and expect the impact of our work to be global.”

The global reach of their work—Burns in expanding the use of ultrasound in Malawi, and Feinstein in developing the first mental illness rating scale in Botswana—is being felt by African medical practitioners, in whose hands are now new diagnostic tools.

### TAKING CARE OF VULNERABLE MINDS

It would take three flights and over 24 hours for Feinstein to reach his destination. The lengthy trip from Toronto to Gaborone, Botswana is one the brain sciences researcher from SRI has made repeatedly to help build the country’s mental health care system. In two years he made four trips—self-funded—to help develop the Setswana version of the 28-item General Health Questionnaire (GHQ), a self-report screening tool used to indicate overall mental health. Setswana is the language spoken by nearly 80% of Botswana’s population. Created by British psychiatrists in 1979,

the self-administered GHQ, which has been translated into several languages and is used worldwide, measures the presence and severity of psychiatric disorder.

“Now the country has a rating scale for mental illness, which it never had before,” says Feinstein, who also helped develop the GHQ for use in Namibia. “The advantage with respect to Botswana is that it can be widely used because of the uniformity of the language spoken throughout the country.”

While in Botswana, Feinstein trained researchers to do a structured clinical interview of a sample of participants who filled out the GHQ. This involved teaching researchers how to make clinical judgements based on the interview, in order to compare their ratings with the participants’ self appraisals of their mental health. Feinstein found that the interviewers’ assessments satisfactorily matched the participants’ self-reported evaluations, thereby validating the responses to the translated questionnaire.

The rating scale can be used in clinics and hospitals to identify those who are psychologically distressed so that medical practitioners can prioritize care, an important benefit given the scarcity of mental health resources in Botswana. Feinstein’s hope is that the tool will also be used to support people with human immunodeficiency virus (HIV), who represent one-quarter of Botswana’s population. “It’s like a triage,” he says. “Not everyone who is HIV-positive is going to have psychological difficulties. If you have limited resources, you have to focus them on those most in need. With the GHQ you can determine who that is.”

Feinstein also gave talks at the department of psychology at the University of Botswana, and visited the country’s psychiatric hospital, where he consulted on a variety of cases during his

The rating scale can be used in clinics and hospitals to identify those who are psychologically distressed so that medical practitioners can prioritize care, an important benefit given the scarcity of mental health resources in Botswana.

short but intense visits. “It wasn’t just the development of the rating scale; there was the broader aim of lecturing and getting people familiar with psychiatry, mental health and my specialty, neuropsychiatry,” he says.

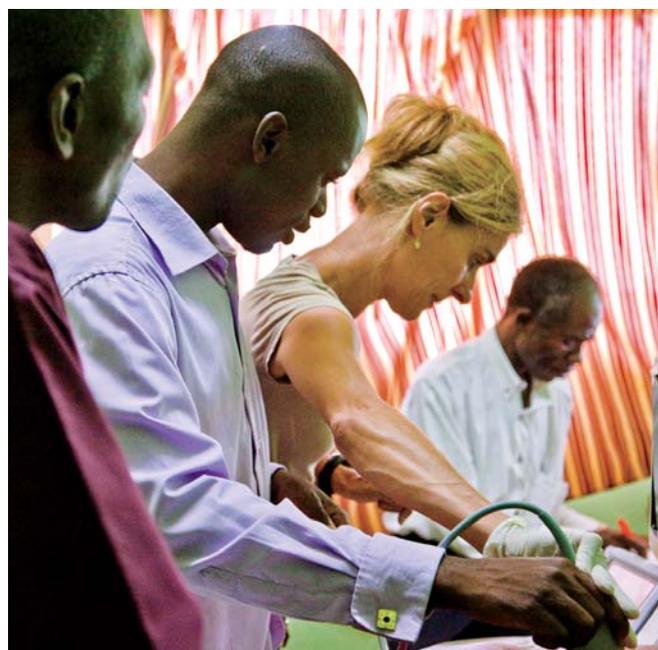
Through other research studies, he is also raising awareness about mental illness in people whose distress has hitherto been ignored: war journalists and contractors working in combat zones. A pioneer in this field, Feinstein is studying the psychological trauma experienced by members of these professions, and educates industry leaders on how to provide support to employees working in places of conflict. Last spring, he published the results of a study in the *Journal of Traumatic Stress* that was the first to show that many contractors working in war zones are experiencing psychological problems and not receiving therapy. Feinstein thinks one reason for contractors’ reluctance to discuss their emotional problems is the fear that doing so will be perceived as weakness.

“If people [working in war zones] are aware of what the potential problems are, then they might be more open to receiving help,” he says. “I think the biggest benefit from research like this is education: helping professions that are not psychologically savvy understand what can go wrong emotionally and how important it is not to ignore this.”

### DELIVERING EXPERTISE AND TECHNOLOGY TO DISTANT LANDS

When his Sunnybrook colleagues Drs. Michael Schull and Josée Sarrazin told him that they were taking their three children to Malawi on a one-year sabbatical, Burns saw an opportunity. Convinced of the viability of ultrasound imaging in developing countries, he proposed a pilot project whereby Sarrazin, a radiologist, would bring with her a portable ultrasound system to improve access to the technology in Malawi.

“Ultrasound is one of the most flexible and cost-effective medical imaging modalities in the world. Many places that don’t have the money or the infrastructure to support even an X-ray machine are able to support the use of ultrasound,” says Burns, who, no stranger to outreach work, also sits on the advisory board



TOP PHOTO: DR. ANTHONY FEINSTEIN

BOTTOM PHOTO: DR. JOSÉE SARRAZIN AND ULTRASOUND TRAINEES IN MALAWI



ALYSSA HOSEMAN AND DR. PETER BURNS

of SAFER (Social Aid for the Elimination of Rape). Founded by SRI graduate students, SAFER is a grassroots organization that helps victims of sexual violence in the Democratic Republic of the Congo.

Schull and Sarrazin moved their family to Malawi in July 2009 as part of Schull's work with Dignitas, a medical humanitarian organization. An emergency physician at Sunnybrook and researcher at SRI, Schull is developing a community-based model for the prevention and treatment of HIV and acquired immune deficiency syndrome. Sarrazin is training doctors and technicians in Malawi to use ultrasound imaging to help pregnant women, and is building networks between doctors in Malawi and Canada. Her presence in the southern city of Zomba, home to the country's only university, doubles the number of radiologists in Malawi.

Burns's collaboration with Sarrazin is an experiment in teleradiology. Thanks to the donation of the compact engine within an ultrasound machine by Zonare Medical Systems, and the crackerjack computer skills of his lab members, Burns provided Sarrazin with a powerful, lightweight system. Consisting of a handheld ultrasound unit and a laptop computer, the system—which weighs just over five pounds—can run on batteries for one hour. It will be used to support newly trained Malawian medical professionals after Sarrazin returns to Toronto.

"Not only will Dr. Sarrazin be able to use [the system] to help pregnant women in Malawi now, but when she returns and is back at work at Sunnybrook, she'll be able to look at the work they're doing there, to continue teaching and give them the advantage of her expertise," says Burns.

Using free open-source software, Burns's lab members Kogee Leung, Athavan Sureshkumar and Ross Williams turned the scanning unit and laptop into a picture archival and teleradiology system. Whenever Sarrazin scans a patient, the image is automatically stored and sent, fully encrypted, to a Sunnybrook server for a radiologist to review.

Though their contact is sporadic (due to challenges in communication in Malawi), Sarrazin told Burns that she is "delighted" with the improvised system. "Our job is to put together the skills

of medical practitioners with portable, adaptable and low-cost technology that will do the job," he says. "The fact that we've done it in a small way here is very exciting because we can imagine ways of repeating this many times over, and giving people in distant countries whom we've never met the advantage of a combination of technology and access to expertise which we have in Canada."

Alyssa Hoseman, an undergraduate student at the University of Guelph, is coordinating the project by liaising with Sarrazin and members of the Burns lab. She became interested in the project after meeting Burns at an open house for the department of medical biophysics at U of T.

"I was just getting a feel for what goes on in terms of the logistics of Third-World aid," she says of her role in the project. "There's a lot of organization that needs to be done because the lines of communication are so broken and there are so many people involved. I was the middle person helping to bring things together."

Hoseman spent last summer working at Sunnybrook, and continues to work from Guelph with Sarrazin and Sureshkumar to "work out a few kinks" with the file transfer system. Like Burns, her desire is to see this work replicated in other developing countries. "We've established a system that will enable telemedicine in the Third World, which means doctors here [at Sunnybrook] can interpret the scan. Having the system as a pilot project and using it as a model for other projects which can be implemented all over the Third World is my vision," she says.

There have been some snags along the way, including Internet and power outages, as well as running out of ultrasound gel, but Burns is nevertheless cautiously optimistic. "The real challenge is doing something that's sustainable. This is the first step toward making a sustainable structure possible in Malawi. Although there are lots of challenges, it's an exciting thing to do."

Burns's research is funded by the Ontario Institute for Cancer Research and the Terry Fox Research Institute.

Feinstein's research on the development of the GHQ for use in Namibia was funded by the Guggenheim Foundation.

# TOPS IN THEIR

# CLASSES

Science educators say that offering in-the-field opportunities to students when they're young is critical to stoking passion for discovery and creating tomorrow's leaders in innovation.

Two researchers at SRI agree, and have done something about it

The career path of Dr. Rajiv Chopra does not betray a lack of direction.

While working as a graduate student at Sunnybrook Research Institute (SRI) in the lab of imaging scientist Dr. Michael Bronskill, Chopra helped develop a minimally invasive treatment for prostate cancer that uses focused ultrasound waves guided by magnetic resonance imaging (MRI) to kill cancer cells and spare healthy tissue—a promising alternative to surgical removal of the prostate. Now an imaging scientist himself at SRI, and an assistant professor of medical biophysics at the University of Toronto, Chopra has founded a spin-off company with Bronskill to bring the technology to market, and ultimately to patients.

But Chopra didn't work in research until he was a graduate student. Following a series of meaningless summer jobs in high school, he entered undergraduate studies at McMaster University not knowing the difference between a scientist and an engineer. "Guidance counsellors weren't useful, so having real research experience probably would have been influential," says Chopra of his time in high school. Having pondered that gap in his past for years, Chopra says he jumped when the chance to provide others with formative research experience arose.

Dr. Kullervo Hynynen's arrival in Toronto in 2006 was the catalyst for that opportunity. Hynynen is the director of imaging research at SRI and holder of the Canada Research Chair in Imaging Systems and Image-Guided Therapy. He pioneered the use of focused ultrasound to dissolve uterine fibroids—a noninvasive treatment now available clinically—and has adapted the technology for breast and brain cancer treatments, which are now in clinical testing. While at Harvard before coming to Toronto, Hynynen offered short, informal summer placements in his lab to a few high-school students. Based on that experience, he helped start a formal outreach program at the University of Kuopio, his alma mater in Finland.

As a high-school student, Hynynen, like Chopra, was not exposed to research. "I didn't know what research was like, and I would have appreciated an opportunity to work in a lab before I went to university, to better know what to study," says Hynynen.

In 2006, based on their mutual lack of early research experience, Hynynen and Chopra offered summer placements in their labs at SRI to two students from Toronto's Marc Garneau Collegiate Institute. The students, part of Garneau's Talented Offerings for Programs in the Sciences (TOPS), worked shoulder-to-shoulder with research technicians, engineers and graduate students for eight weeks.

Since then, enrollment has exploded. This past summer, the fourth for the program, saw 17 TOPS students and three from other Toronto-area high schools working on a spectrum of projects, from computer programming and simulation, to the electronics of MRI and mechanical ultrasound testing.

"The kids learn a tremendous amount, about what they want to do, or what they don't want to do," says Henri van Bommel, one of two TOPS teachers who coordinate the outreach program for Garneau. "What an awesome experience for an able kid in high school."

Beyond discovering the type of work they might like—"what blows their hair back," as van Bommel puts it—and learning the important distinctions among engineer, technician, scientist and other research positions, the students experience another critical component of a good education: challenge. "I'm so pleased to work with Sunnybrook because they don't mess around—they get these kids for real jobs and real tasks," says van Bommel. "It's a rich experience, not a-day-at-the-office-shredding-paper kind of nonsense."

Having disengaged somewhat from his own high-school studies, van Bommel is passionate in his belief that all students—the disadvantaged, the average, but also the best—need learning opportunities that test their abilities.

Growing up on a farm in Ontario, he was unaware of the jobs to which studies in science could lead, or of the extent of his own aptitude for math and physics. He spent 12 years as a butcher before attending university. Now a physics and astronomy teacher in Garneau's TOPS program, van Bommel has devoted himself to those students he believes most likely to be unchallenged: high achievers. Without courses that offer a degree of difficulty, he says, good students won't flourish. Moreover, they often grow to have a false sense of the work required for future success; this can lead to underperformance or a crisis when they enter university or the workforce, where expectations are higher.

With program director Michael McMaster and other Garneau teachers, van Bommel

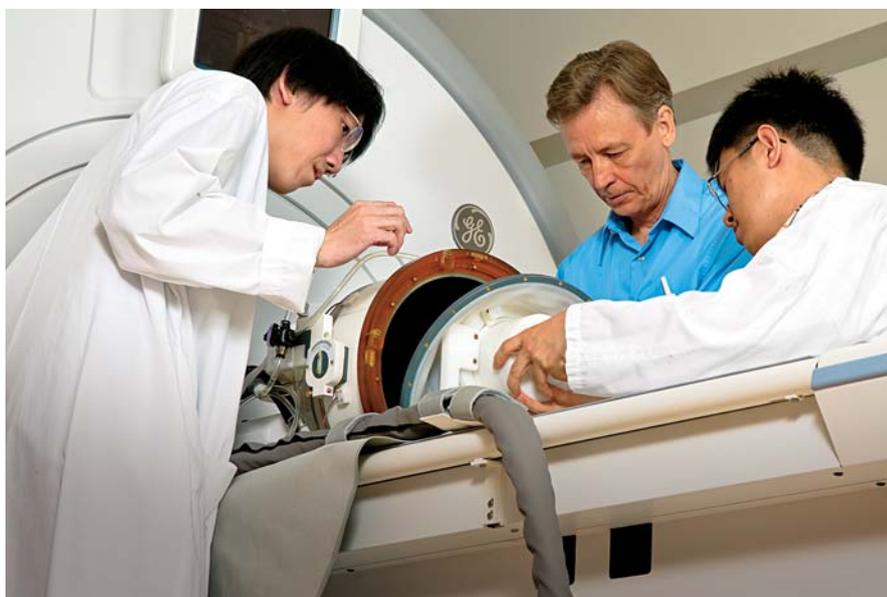
has helped make TOPS one of Canada's most successful programs for enriched learning in math and science. Based on merit, the program accepts about 60 students from across Ontario each year. Collectively, graduates of the program typically earn more than \$1 million in university scholarships annually.

The quality of the TOPS program attracted Hynynen and Chopra when they first sought a partner for their outreach initiative. Chopra discovered TOPS through a Google search, and he and Hynynen were impressed with the level of academic challenge the program offered. Their expectation going in was that even if the students didn't make a productive contribution to the research in their labs, it would still be worthwhile because they would be giving students that early

exposure to research they never got. "But that hasn't been our experience," says Chopra. "Most of them, with a few exceptions, have been super productive. They see this as an opportunity they would otherwise never get, and they don't let it slip by. They work really hard."

Galina Gheihman is a TOPS student whose poise, organization and passionate intellect defy her age. Just 17 years old, she plans to pursue medical science but is unsure whether to study physics, biology or another field at university. On the second-last day of her summer placement, Gheihman took a break in Sunnybrook's On-the-Go bistro to talk about her experience.

"One thing I learned is that I can't get away with not knowing programming if I move on in this field," says Gheihman



TOP PHOTO: STEFAN HADJIS, GALINA GHEIHMAN AND ROBERT STARUCH  
BOTTOM PHOTO: DRs. YUEXI HUANG, KULLERVO HYNYNEN AND JUNHO SONG



TOP PHOTO: ARVIN ARANI, FRANK ZHAO AND MANDY ZHANG  
 BOTTOM PHOTO: ROBERT STARUCH AND DR. RAJIV CHOPRA

“Some of my friends perceive research to be boring, but I think it’s fascinating,” says Zhao.

of medical biophysics, pulling out a lab book neatly composed with notes and PowerPoint slides to make her point. Both her projects this summer involved programming. In the first, she used a computer language to create video animations of cancer-killing ultrasound treatments. For the second, she ran over 100 simulations of how ultrasound heats tissue, to determine the optimal temperature at which a new generation of chemotherapy drugs will become active. The goal of this approach is to avoid the system-wide toxicity that is a byproduct of most chemotherapeutics, by heat-activating them only at the site of the cancer.

Perhaps the best measure of what Gheihman has learned about biophysics was her understanding of the research papers that her supervisor Robert Staruch, a doctoral student in Chopra’s lab, gave her to read. By summer’s end, she was assessing their strengths and weaknesses with the critical eye of a scientist, and incorporating their findings into her final PowerPoint presentation to the entire

ultrasound lab group—a requirement for all outreach students. At that, says Gheihman, “I was amazed and really proud.”

The technical facilities and resources at SRI are a further boon to the students’ summer experience. Gheihman was given space in the ultrasound lab and her own computer. She was also introduced to cardiac researchers working on preclinical models of human heart disease, an experience of particular interest given her enthusiasm for both physics and biology.

Gheihman’s fellow TOPS student Stefan Hadjis requested and was given materials to build MRI coils. Through reading research papers and employing the electronics knowledge he learned in van Bommel’s advanced placement physics C class, Hadjis found an alternative method for constructing coils, of which he eventually built 20, to image animals of various sizes.

Former TOPS student Frank Zhao also made good use of the facilities at SRI.

Now a second-year U of T student whom Chopra asked back this summer after an especially productive placement the year before, Zhao had access to two MRI scanners, which he used to measure a vibrating intracavity applicator’s shear-wave penetration of prostate-like gels. The goal of this research is to enable MRI elastography, as the technique is known, to screen for prostate tumours, which are stiffer than surrounding tissue.

Zhao’s experience at SRI spurred his interest in research as a career. “Some of my friends perceive research to be boring, but I think it’s fascinating,” says Zhao. “You get all these problems to solve, and nobody really knows the answers. You’re the first one to come up with a solution, the first to see something new. That’s really cool.”

That Zhao returned to SRI after a year at U of T highlights the mutually beneficial aspect of the outreach program. Students gain access to the institute’s facilities and exposure to medical research, and SRI receives the benefit of the students’ work and is better placed to recruit those students for undergraduate and graduate study. In this respect, says van Bommel, the arrangement has been “a nice marriage.”

Then there’s the less tangible matter of buzz. “The high-school students came in, and the entire lab energy went like this,” says Chopra, raising his hand above his head. “And it stayed there for eight weeks. I’d love for them to be here all the time.”

—Jim Oldfield

Sunnybrook Research Institute and the Ontario Ministry of Research and Innovation (MRI) provided funding for the summer outreach program. The Canada Foundation for Innovation and MRI provided infrastructure support.

## WHAT HAVE YOU LEARNED FROM A STUDENT?

Three researchers at Sunnybrook Research Institute offer insight on how mentoring the next generation of medical scientists has had an impact on their lives.

### Dr. Isabelle Aubert

Scientist

Brain Sciences Research Program

Assistant Professor, University of Toronto

Students are the driving force of research, transforming ideas into experimental realities and discoveries. It is fun, stimulating and rewarding to work with them. They are also among the best teachers, when we are open to listening to them. As a scientist and mentor, I want to provide a stimulating and positive environment so that the students can be in the “zone” and feel encouraged to bring their brilliant ideas forward and make them become reality. I often tell students this quote from Shunryu Suzuki: “In the beginner’s mind there are many possibilities, but in the expert’s mind there are few.” I’ve learned from students that we should all work on rediscovering (if we have lost it!) our beginner’s mind, so that we can see things anew, and see the many possibilities on our path to discovery. Hopefully, students are learning as much from me as I am learning from them. Each one of them is contributing to make me become a better scientist and a better mentor. Thanks to all!

### Dr. Robert Jankov

Neonatologist and Scientist

Women and Babies Research Program

Associate Professor, University of Toronto

I have been fortunate to have a number of wonderfully bright summer students come through my lab, each of whom has brought a unique set of skills and perspectives. Seeing the occasional “light bulb moment” when explaining a concept is incredibly satisfying; that said, oftentimes the students learn more from each other than from me. I’ve

learned how important it is to listen as well as explain; questions posed from a “naïve” viewpoint have led to interesting new experiments and directions in research that I had never considered. Finally, having derived great satisfaction and pride in watching students advance their own careers after leaving the lab, I’ve also learned how fulfilling it is to be a mentor and not just a supervisor.

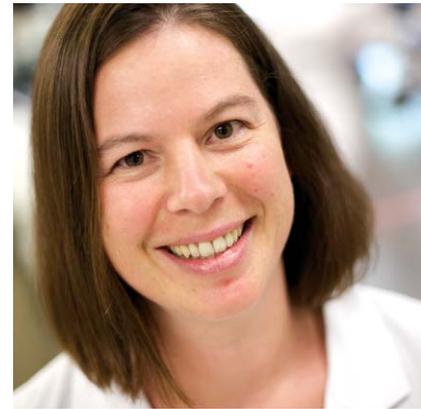
### Dr. Robert Nam

Urologist and Associate Scientist

Odette Cancer Research Program

Assistant Professor, University of Toronto

I have the privilege of supervising many students, from the undergraduate to postgraduate levels, at the patient’s bedside, in the operating room and in my lab. My most striking observation has been the extreme diversity in their backgrounds, including educational, cultural and personal learning abilities. The last has been the most challenging. The same approach in teaching one student does not necessarily apply to another. The patience and persistence I have acquired from these experiences have helped me develop more maturely as a person, husband and father. One of the most rewarding experiences has been to train and mentor students to the level of a fully licensed academic urologist—including how to teach someone not only to take out a prostate, but also to analyze its tumour DNA for posterity. These “high-engine” students challenge me in terms of offering state-of-the-art approaches and treatments for urologic diseases. They can also provide insights into research that I had not considered before. This quid pro quo makes teaching and mentoring a truly rewarding experience.



TOP TO BOTTOM:  
DR. ISABELLE AUBERT; DR. ROBERT JANKOV



DR. ROBERT NAM

## BUILDING A BRIGHTER FUTURE

“Whenever a family member has been sick, we have always chosen Sunnybrook to take care of them.”

“Family matters more to us than anything in the world,” says Douglas Mahaffy. Douglas and his wife, Adrienne, were both born and raised in Toronto and have always thought of Sunnybrook as the city’s premier hospital.

As Adrienne points out, “Whenever a family member has been sick, we have always chosen Sunnybrook to take care of them.”

It’s more than just Sunnybrook’s world-renowned medical care that has earned the trust of the Mahaffys. It’s

also the “wonderful staff, with such sunny dispositions and who work so well as a team,” adds Adrienne.

The Mahaffys, following earlier donations to arthritis, urology and colposcopy, recently made a donation to support Sunnybrook’s top research minds—support that will ensure we are able to attract and retain the people who will invent the future of health care. These brilliant Sunnybrook scientists are working in areas such as testing the use of ultrasound to obliterate brain tumours without ever

making an incision; growing new brain cells that can repair the physical destruction of the brain caused by Alzheimer’s disease; and, reproducing the fine hairs of the inner ear that are missing in people who can’t hear.

So why did the Mahaffys choose to support research? As Douglas explains, “Like us, everyone wants the very best for their family; to know they’re happy and healthy, and have access to a great hospital if their health and quality of life is jeopardized.

“By supporting the work of Sunnybrook’s scientists, we are making a very real investment in a healthier future for our children, their families and friends, and for people around the world who will benefit from the medical breakthroughs coming out of Sunnybrook.”

### HELP US ACHIEVE OUR \$64 MILLION SUNNYBROOK RESEARCH CAMPAIGN GOAL

Sunnybrook’s vision is to invent the future of health care. Research is the engine that powers this innovation. The \$470 million Campaign for Sunnybrook is investing \$64 million into new research facilities, researchers and specialized research equipment. To support our fundraising goal please visit [www.sunnybrook.ca](http://www.sunnybrook.ca) or contact Paul McIntyre Royston at [paul.mcintyre.royston@sunnybrook.ca](mailto:paul.mcintyre.royston@sunnybrook.ca) or call 416-357-0199.



DOUGLAS AND ADRIENNE MAHAFFY

# Q&A

## Dr. Kaveh Shojania

Dr. Kaveh Shojania is a scientist in the veterans and community research program at Sunnybrook Research Institute and a professor at the University of Toronto. He holds the Canada Research Chair in Patient Safety and Quality Improvement and is director of the U of T Centre for Patient Safety, a partnership among the university, Sunnybrook Health Sciences Centre and the Hospital for Sick Children.

### The Centre for Patient Safety launched in 2009. How's it going so far?

It's going well. A lot of the work has been just getting the centre up and running, but one exciting initiative already is a course we've been teaching. It's geared toward researchers and clinicians, most of whom come with a project they want to develop in their area. We introduce them to core topics in patient safety, like the epidemiology of adverse events, including common types of events and their causes, investigation techniques for critical incidents and human error factors—for instance, those related to equipment design.

### How have people responded?

Very positively. Several members asked for more process design and incident investigation material, so now we cover in more detail how to walk through a “root cause analysis,” say, for a major medication overdose, which is a bit like the accident investigation following a plane crash. You address categories of causes—equipment failure, fatigue, scheduling—then look at the order of events and contributing factors for a structured approach.

### How does that knowledge play out on the ground?

Many front-line clinicians face complex problems in patient safety and quality improvement. They may know experts with knowledge on certain facets of a problem, but often they won't know how best to tackle the whole problem. So bringing together a well-rounded cadre of people that can expose clinicians to various aspects of a problem, and ways of solving it, is a big plus.



DR. KAVEH SHOJANIA

### There's some tension around how much research should be done before implementing an intervention.

#### Has thinking shifted on that issue?

I'm part of a panel in the U.S. that is trying to develop some principles on that question. The issue is this: there are a lot of ideas out there about what might improve patient safety. For some ideas, say a pre-surgery checklist to minimize infections, it's not expensive, and the side effects of implementation are small, so it's not worth too much debate about evidence. But for others, like hospital-wide computerized order entry [of medications], there are big costs and potential for unintended consequences, like disrupted workflow. On evaluating examples of those larger interventions, you'll likely find success stories and failures, and in some cases the discrepancy is due to the evaluations being of unequal rigor. But in many cases—and that's what this panel is about—it's probably a result of contextual factors. Plus, many times, even the “ingredients” of the intervention aren't clear. For instance, was it just a checklist, or were there behind-the-scenes changes in teamwork and culture required to support the intervention?

### So deciding when to implement a potential improvement is becoming more complex?

Yes. Again, look at computerized order entry. There's a system in Boston that seems to work better than most. The system itself may be better, or perhaps the hospital is more invested in safety—maybe both are true. Also, it might matter how the electronic reminders sent to clinicians are designed or how quickly the hospital IT group provides support when problems arise. Even the personalities of the people who lead the program could be a factor. These are all relevant to why the intervention might have worked. The point is, widely recommended interventions can have variable effects in different hospitals. And that's where this debate is going—trying to understand those contextual factors.

Shojania's work is funded by the Canada Research Chairs Program. The Centre for Patient Safety is funded by the University of Toronto, Hospital for Sick Children and Sunnybrook Health Sciences Centre.

# GLOBAL REACH

Where in the world is SRI? Take a look at the map to see where researchers profiled in this year's magazine are working with clinical and research colleagues all over the world.





**Germany**  
Berlin  
Bonn  
Erfurt  
Hannover  
Homburg/Saar  
Leipzig  
Marburg  
Munich  
Nurnberg  
Regensburg  
Wiesbaden

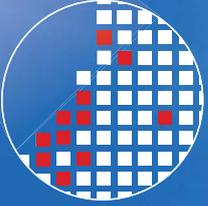
**Belgium**  
Brussels  
Liege

**Finland**  
Kuopio

**Switzerland**  
Basel  
Lausanne  
Zurich

**Russia**  
Ivanovo  
Moscow

**Poland**  
Gdansk  
Lodz  
Poznan



**Jordan**  
Amman

**Israel**  
Afula  
Beer Sheva  
Bnei Brak  
Haifa  
Holon  
Jerusalem  
Kfar-Saba  
Petach Tikva  
Ramat-Gan  
Tiberias

**China**  
Shanghai

**Japan**  
Tokyo

**Malawi**  
Zomba

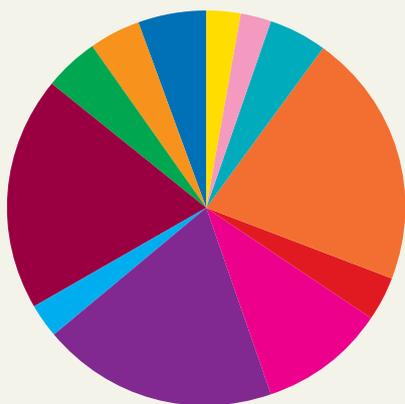
**Botswana**  
Gaborone

**South Africa**  
Pretoria

# QUICK STATISTICS

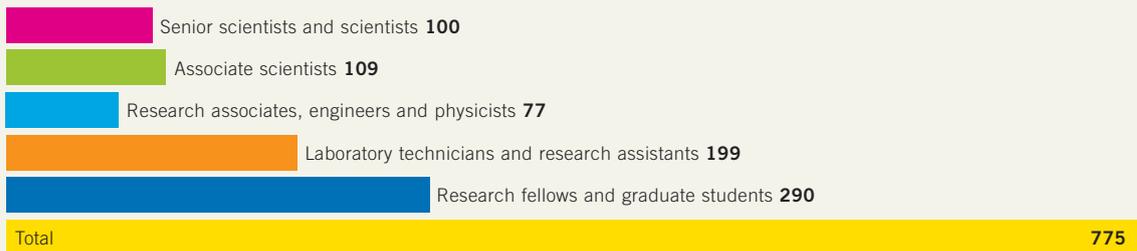
## Major sources of external funding

Sunnybrook Research Institute is grateful to the many sponsors who, with each dollar they give, help support research here.



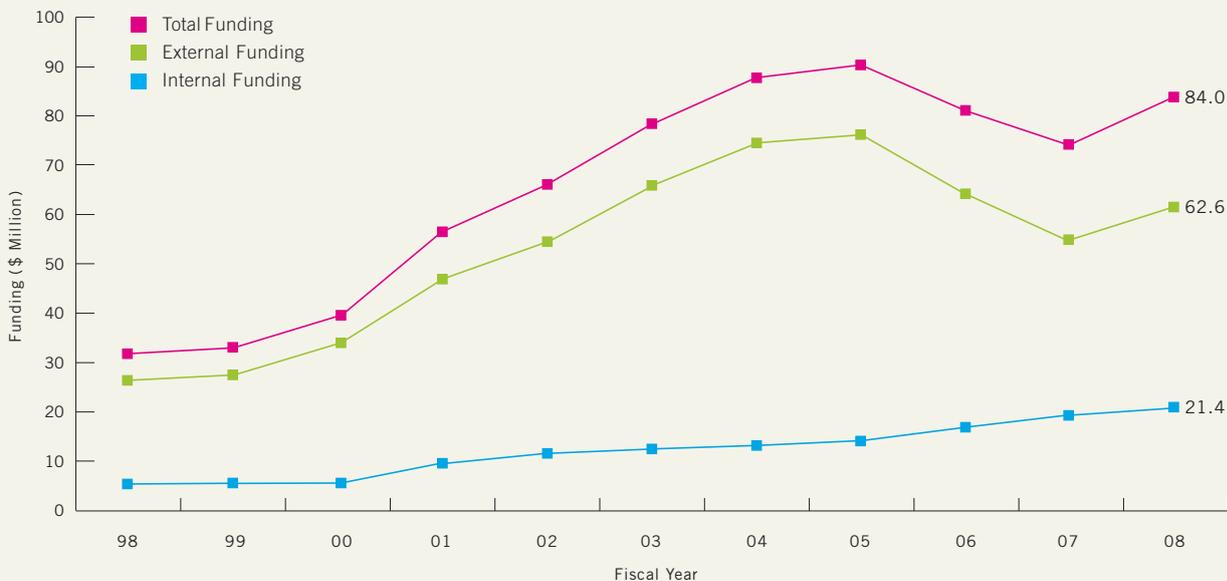
- \$62.6 MILLION (2008–2009)**
- Canada Foundation for Innovation 3%
  - Canada Research Chairs Program 3%
  - Canadian Cancer Society Research Institute 5%
  - Canadian Institutes of Health Research 21%
  - Donations and Trust Income 4%
  - Foundations 10%
  - Industry 19%
  - Ministry of Health and Long-Term Care 3%
  - Ministry of Research and Innovation 19%
  - Other Funding Sources 4%
  - Other Government Sources 4%
  - U.S. Sources 5%

## Research Staff



## History of Research

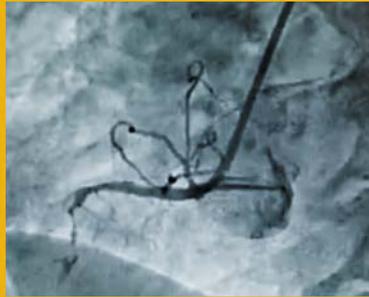
Expenditures at Sunnybrook Research Institute



THIS IS THE



HEART.



THIS IS THE  
BLOCKED ARTERY.

THIS IS THE ENZYME THAT  
SOFTENS THE BLOCKAGE IN  
THE ARTERY SO THE HEART  
PATIENT CAN SEE  
ANOTHER DAY.



THIS IS THE  
HEART PATIENT.

THIS IS THE DAY.



THAT'S WHY IT MATTERS.



INNOVATION WHEN IT MATTERS MOST.

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