

SRI

MAGAZINE

Inventing the Future of Health Care

Sunnybrook Research Institute / 2010

IN FOCUS

A probing look at how a new technology is redefining surgery as scalpel-free and opening up access to parts previously impassable

When Drugs Collide

Medications taken in combination can be toxic, sometimes fatally—but how to know which ones, and in what combination?

Hot Tickets

Double bill: two SRI spinoffs journey from innovation to acquisition

ALSO IN THIS ISSUE

[Battling Antibiotic Resistance](#)

[Stroke Research Takes Centre Stage](#)

NOVEMBER

Inventing the Future of Health Care
Sunnybrook Research Institute
2010

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To read more about research at SRI,
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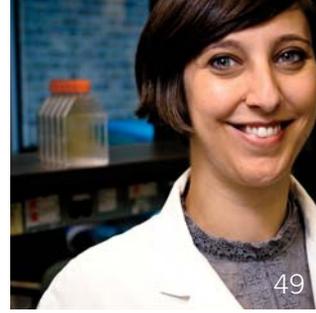
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Pictured opposite: Alzheimer's disease has devastating effects on more than 500,000 Canadians and their families. Focused ultrasound technologies are introducing new possibilities for the treatment of Alzheimer's disease. In this image, the stylized spheres represent microbubbles. Together, the bubbles and focused ultrasound temporarily disrupt the blood-brain barrier, enabling the delivery of therapeutics precisely and safely into the brain. Treated neurons are shown in green, untreated neurons in blue. Astrocytes, another kind of brain cell, are in red. Physicists and biologists at Sunnybrook Research Institute have joined forces to develop this treatment for Alzheimer's disease. For more, see story on focused ultrasound on page 20.

IMAGE: TAKEN WITH A ZEISS LSM 510 CONFOCAL IMAGING SYSTEM ON AN AXIOVERT 100 IN SUNNYBROOK RESEARCH INSTITUTE'S CENTRE FOR FLOW CYTOMETRY AND MICROSCOPY. DR. EMMANUEL THÉVENOT, A POSTDOCTORAL FELLOW IN THE LAB OF DR. ISABELLE AUBERT, COMPOSED THE IMAGES.

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Researchers at Sunnybrook are leading studies in how best to prevent stroke and optimize healing after it

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Image-guided sound waves will change medicine; here's how

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WHEN DRUGS COLLIDE

Drug-drug interactions have serious—and sometimes deadly—consequences for patients. They also put additional economic stress on an already strained health care system. A clinician-scientist at SRI is bringing these pharmacological faults into focus and highlighting alternatives

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HOT TICKETS

Inventing a medical device is a rare accomplishment. Rarer still is getting that invention into the global medical marketplace. Here's how two Sunnybrook Research Institute start-ups did just that, and became in-demand multinational acquisitions

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WONDER DRUGS NO MORE

It's a trend with sticking power: more and more, patients are contracting severe and even fatal infections against which antibiotics are impotent. Lest you think this is hyperbole, think again: we should be very, very concerned, says one SRI scientist who is leading the crusade against 21st-century superbugs

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

Sunnybrook Health Sciences Centre



DAVID A. LESLIE AND DR. BARRY A. MCLELLAN

“Every great advance in science has issued from a new audacity of the imagination.”

John Dewey

At Sunnybrook Health Sciences Centre, one conduit for our imagination is Sunnybrook Research Institute (SRI), through which we are boldly inventing the future of health care.

Our research institute is one of the largest in Canada and will soon occupy almost 500,000 square feet in the hospital. Every year our organization reaches new milestones that enable our researchers to advance medical science. Every year our scientists make advances that improve and transform patient care.

Last year was no exception.

In 2010, in partnership with Thunder Bay Regional Health Sciences Centre, we founded a unique dual-site centre for focused ultrasound therapy, in which teams of clinicians and researchers will perform incisionless surgery using ultrasound to destroy tumours and modify tissue in the brain and previously inaccessible areas of the body.

We continued construction of the Centre for Research in Image-Guided Therapeutics, set to open in late 2011. This \$160-million centre will provide better resources for all of our researchers, including the physicists who pioneered imaging technologies like focused ultrasound surgery for which Sunnybrook is known around the world.

The centre will also house regenerative medicine researchers who are testing stem cell therapies, and vascular biologists who are manipulating blood vessel growth to develop novel treatments for cancer, stroke and heart disease.

In partnership with MaRS Innovation, we steered new discoveries toward the clinic through commercialization, including a discovery called vasculotide, a compound that shows great potential to heal wounds, an especially important consideration for patients with diabetes. The research is in very early stages, but looks promising.

Epidemiologists at SRI found that women taking tamoxifen for estrogen-positive breast cancer had a much higher risk of dying if they were taking a common antidepressant. They also showed that other antidepressants from the same class don't carry the same risk—a finding that has changed treatment for tens of thousands of breast cancer patients.

These success stories embody the real-world outcome of our vision to invent the future of health care. In this magazine you can read these stories and more.

We hope you enjoy them. If you would like to learn more about research at Sunnybrook and what you can do to help us make health care better, please visit www.sunnybrook.ca/research.

David A. Leslie
Chair, Board of Directors

Barry A. McLellan
President and CEO

Message From the Vice-President, Research

Sunnybrook Health Sciences Centre

As one of the youngest of Toronto's hospital-based research institutes, Sunnybrook Research Institute (SRI) has enjoyed remarkable growth over the last 20 years.

We have evolved from 50 faculty doing \$2 million of research in 70,000 square feet in 1991, to 800 researchers doing more than \$100 million of research in 500,000 square feet today.

Sunnybrook Research Institute and Sunnybrook Health Sciences Centre have arrived. We're at the vanguard of integrating medical discovery into clinical care; indeed, we are inventing the future of this care. This includes creating a sustainable business plan in support of this remit, one rooted in extracting economic value from the knowledge we create.

Function follows form. Fostering collaboration among scientists and practitioners requires leading-edge space and equipment. The unique infrastructure that will house the world's only Centre for Research in Image-Guided Therapeutics will support a unified approach to discovery research and its clinical application. It will enable clinicians and researchers to learn from each other and to work together toward creating better ways of doing business better for our patients and their families.

Two related and long-planned developments executed this year have accelerated change at SRI: we have incorporated and MaRS Innovation is open for business!

While remaining owned and governed by Sunnybrook, the sovereign status of SRI enables us to integrate more fully with our academic physicians, while attracting contributions in support of our research, because we are now a preapproved Scientific Research and Experimental Development tax credit organization. This brings the Sunnybrook family closer together and increases the sustainability of our research enterprise.

Inventing the future of health care is supported by technological advances that enable disease prevention and its earlier detection, and the development of novel treatments. Over the last decade in Canada, discovery research and ensuing technology development



DR. MICHAEL JULIUS

have benefitted from more than \$100 billion of investment from provincial and federal governments.

Two related drivers have changed the way we do business over the last year. Governments supporting research are now supporting initiatives that enable them to extract economic benefit from these investments; and our discoveries must go through the rigours of commercialization before they can be offered to patients.

MaRS Innovation is helping SRI advance activities in both of these domains. For more on how SRI and MaRS Innovation are partnering to accelerate the development and commercialization of our discoveries, read the story on page 50.

Our progress in this, as in every, year is predicated by the stalwart support of Sunnybrook's senior leadership team, led by Dr. Barry McLellan, and Sunnybrook's Board of Directors, led by David Leslie. Advances this year, more than in any preceding year, have provided SRI with the stable foundation that will ensure that inventing the future of health care is our legacy. We hope you enjoy the stories in this issue of SRI's research magazine that show you how we are doing just that.

Michael Julius
Vice-President, Research

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

Building Great Science: the Centre for Research in Image-Guided Therapeutics at Sunnybrook Research Institute

Sunnybrook is building the Centre for Research in Image-Guided Therapeutics (CeRIGT), in which scientists will make discoveries and invent technologies that will redefine health care. The \$160-million CeRIGT—the only one of its kind in the world—was established with a \$75-million investment from the Canada Foundation for Innovation in August 2008. Here, we count down to the official opening of CeRIGT in November 2011. By Stephanie Roberts



1. Thinking big

Working in CeRIGT will be 55 scientists and clinician-scientists, and hundreds more research staff across 150,000 square feet. The expansion includes a dramatic two-floor addition to M wing. This hub of innovation will attract more than 35 new scientists, and 250 students and postdoctoral fellows for opportunities available nowhere else. Research in CeRIGT applies to many clinical areas, including cancer, and brain, heart and musculoskeletal conditions. Shown here, the hospital before construction.

2. Construction gets going

By June 2009, the shell was up and interior spaces were beginning to take shape. Dr. Juan Carlos Zúñiga-Pflücker, interim director of molecular and cellular biology at SRI, shown here looking at the floor plans with SRI staff and the construction managers, checked out the seventh floor of M wing, where cell therapy labs, chemistry labs, a good manufacturing practices facility and a massive device development lab will co-exist.

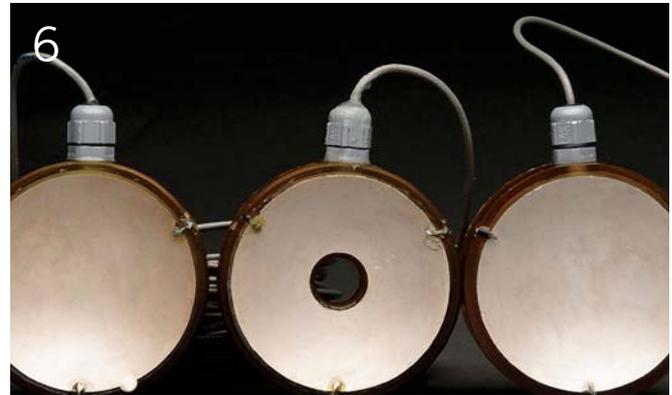


3. Pathology lab? Check!

2010 was an exciting year for CeRIGT; several facilities were finished, including the imaging research pathology lab headed by SRI imaging scientist Dr. Martin Yaffe. As Yaffe and research associate Dr. Gina Clarke explained to Dr. Morag Park (centre) of the Canadian Institutes of Health Research, scientists will devise new 3-D pathology techniques toward demystifying the nature of disease. These techniques will help doctors plan and deliver minimally invasive therapy.

4. An imaging hub unlike any other

A jewel of CeRIGT is an expanded imaging suite that has two 3T research magnetic resonance imaging (MRI) systems; two focused ultrasound brain devices—the only place in the world that does; a leading-edge computed tomography scanner; a hyperpolarizer and a 7T MRI system. Renovation wrapped up in October 2010. In November, SRI gave Premier Dalton McGuinty a tour of the facility during his visit to announce the creation of the Ontario Brain Institute. Dr. Sandra Black, director of the Brain Sciences Research Program, explained the promise of focused ultrasound to treat stroke and dementia.



5. Scalpel-free surgery suite opens

Also in November, SRI opened a dual-site MRI-guided focused ultrasound surgery research facility in partnership with Thunder Bay Regional Research Institute. At the launch, Dr. Kullervo Hynynen (far right), project lead of CeRIGT and pioneer of the technology, demonstrated how it works to Ontario Minister of Health and Long-Term Care Deb Matthews, Minister of Transportation and MPP for Don Valley West Kathleen Wynne, and MPP for Thunder Bay-Atikokan Bill Mauro. Hundreds of clinical trials will be run in this facility.

6. Scientists' workshop

In the 6,500 square-foot device development lab scientists and engineers will make complex medical devices like these ones—transducers for focused ultrasound systems—under highly controlled conditions. These devices ultimately will be commercialized, a necessary process to ensure lab-made innovations get to patients.

7. Regeneration central

On the top floor of M wing 20,000 square feet is for research in regenerative medicine. Scientists will design stem-cell-based therapies to repair damaged heart tissue and rebuild failed immune systems; and will develop imaging methods to be able to see these processes as they happen inside the body. These gleaming facilities, shown here with just final polishing needed, have also received investment from the Ontario Innovation Trust.

8. The future looks right

Mere months remain before all of CeRIGT is open and ready for the business of scientific discovery, set for the end of 2011. Core facilities will be available not only to everyone at SRI, but also to external researchers. Here, an architect's rendering gives a glimpse of what the future looks like—but for the real deal, stay tuned!

To learn more about CeRIGT, visit sunnybrook.ca/research/cerigt.
To donate to CeRIGT, visit sunnybrook.ca/foundation.

OVATION

We spotlight some especially notable achievements of scientists at Sunnybrook Research Institute (SRI) from 2009 to 2010.

National and International Awards

The Government of Canada awarded SRI senior scientist **Dr. Graham Wright** a Tier 1 Canada Research Chair in Imaging for Cardiovascular Therapeutics, the most prestigious research award granted by the federal government. With this appointment, 10 scientists at SRI now hold Canada Research Chairs.

The Canadian Institutes of Health Research (CIHR) awarded **Dr. Bojana Stefanovic** and **Dr. Jill Tinmouth** each a New Investigator Award, designed to support outstanding researchers early in their careers. The agency also recognized **Dr. Jack Tu** with an Institute of Health Services and Policy Research Article of the Year Award, which recognizes published research that has significantly advanced health services and policy research in Canada.

Dr. Richard Swartz received a Focus on Stroke Research Scholarship from the Heart and Stroke Foundation of Canada, CIHR and the Canadian Stroke Network. This salary award supports research in stroke medicine to prepare the health care system for the coming age-driven increase in stroke patients.

Dr. William Geerts received the Sol Sherry Lectureship award from the International Society on Thrombosis and Haemostasis. The award is given to individuals who are recognized internationally for their longstanding research into the prevention and treatment of thromboembolic and hemostatic disorders.

The Canadian Society of Internal Medicine presented **Dr. Donald Redelmeier** with the 2009 Dr. David Sackett Senior Investigator Award, which recognizes an individual for excellence in research.

From the American Psychiatric Institute for Research and Education, **Dr. Benjamin Goldstein** received the AstraZeneca Young Minds Award, a program that encourages promising young psychiatrists to select a career path in research.

The Canadian Association of Radiologists recognized **Dr. Richard Aviv** with a Young Investigator of the Year Award, granted to medical imaging researchers in the early stages of their careers.

From Prostate Cancer Canada, **Dr. Urban Emmenegger** received a Clinician Scientist Award. This award recognizes outstanding researchers and supports their work in the prevention and treatment of prostate cancer.

Provincial Awards

The Ministry of Research and Innovation gave Profound Medical Inc. a Premier's Catalyst Award, naming it the start-up company with the best innovation. The award recognizes excellence and leadership in innovations that are commercially successful. Profound Medical Inc. was spun-out of research conducted by **Drs. Michael Bronskill** and **Rajiv Chopra**, imaging scientists at SRI.

Dr. Rob Fowler and **Dr. Andrea Gershon** each received a Career Scientist Award from the Ministry of Health and Long-Term Care. This salary award enables promising researchers to devote at least 75% of their time to research, to help ensure they have the training and experience required to become influential health services researchers in Ontario.

Additionally, the Heart and Stroke Foundation of Ontario recognized **Tu** with a Career Investigator Award, granted to independent researchers in the field of cardiovascular or cerebrovascular disease.

Fellowships and Other Honours

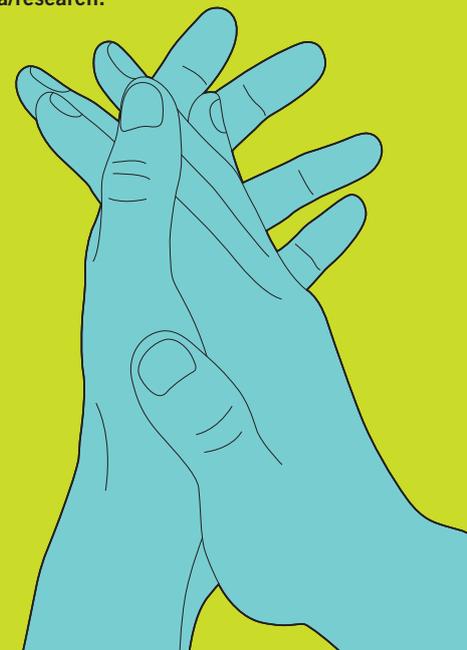
The Commonwealth Fund appointed **Dr. Michael Schull** a Harkness Fellow in Health Care Policy and Practice. This fellowship provides individuals with an opportunity to conduct a policy-oriented study while working with leading U.S. health policy experts.

The International Psychogeriatric Association recognized **Dr. Nathan Herrmann** with a 2009 Distinguished Service Award for outstanding service and contributions to geriatric mental health.

The American College of Physicians recognized **Dr. Andrew Simor** as part of the top 10% of all reviewers in *Annals of Internal Medicine* in 2009.

In other honours, the Acoustical Society of America appointed **Dr. Kullervo Hynynen** a Fellow in Biomedical Acoustics.

For more on awards given to researchers at SRI, visit the awards section under About SRI on the website: www.sunnybrook.ca/research.



ABSTRACTS

Designing Better Immunity

T cells are white blood cells that fight disease, bacteria and infection. They are essential to immunity. Bone-marrow transplants, AIDS and some anticancer treatments deplete T cells, leaving the body vulnerable.

Dr. Juan Carlos Zúñiga-Pflücker, a senior scientist in the Odette Cancer Research Program at Sunnybrook Research Institute, discovered a method to direct unspecified human stem cells into progenitor T cells in the lab. These early-stage cells, in turn, became mature, functional T cells when implanted in mice. The journal *Blood* published the important discovery.

Progenitor T cells are rare; as we age, our bodies produce fewer of them, and they lose their effectiveness. This discovery moves researchers closer to being able to design regenerative medicine treatments that could boost T cells in immune-compromised patients.

Do Hospital Report Cards Make the Grade?

In a 2010 study, Dr. Jack Tu, a physician and senior scientist in the Schulich Heart Research Program at Sunnybrook, found that publicly released report cards on hospital performance did not significantly improve the quality of cardiac care in Ontario.

Tu and colleagues studied delivery of care and outcomes for patients with acute myocardial infarction and congestive heart failure in 89 hospitals that were divided into two groups. One group received performance feedback starting in January 2004; the other starting in September 2005. The researchers then analyzed the staggered patient outcomes at both sets of hospitals.

The study showed a slight improvement in outcomes in the early feedback group. The researchers suggested that hospital-specific modifications in delivery of care might have been responsible for that progress. They also detailed challenges they encountered; policy-makers and clinicians, they suggested, might find those challenges instructive in future assessments of public report cards aimed at improving hospital performance.

A Spoonful of Sugar: Diabetes and Driving

Patients with diabetes face scrutiny when applying for a driver's license in Canada. In consultation with a patient's doctor, licensing agencies evaluate an applicant's fitness to drive and can deny a license based on that evaluation. They can also revoke a license after an accident or a doctor's report that cites a worsening of the patient's condition.

Research by Dr. Donald Redelmeier, a physician and senior scientist in the Trauma, Emergency & Critical Care Research Program at Sunnybrook, questions the rationale for these regulations. He and his colleagues found that a 1% reduction in glycosylated hemoglobin level—a measure of blood sugar in which lower numbers indicate better-managed disease—was associated with a 26% increase in crash risk in 795 diabetics in Ontario during the two-year study period.

Noting their results were counterintuitive, the researchers wrote that glycosylated hemoglobin is “neither necessary nor sufficient for determining fitness-to-drive,” even though licensing agencies use it as a metric. One possible explanation is that low glycosylated hemoglobin levels may correlate with hypoglycemia, in which low blood sugar can trigger dizziness, confusion and blurred vision.



TOP TO BOTTOM:
DR. JUAN CARLOS ZÚÑIGA-PFLÜCKER AND
PATRYCJA THOMPSON; DR. PAUL MARKS;
DR. ROBERT JANKOV



DR. DAVID HOULDEN

On Pins and Knees

Injury to the anterior cruciate ligament (ACL) of the knee can be painful and require reconstruction of the ligament. Among procedures, a femoral graft-fixation technique with bioabsorbable cross pins (which later dissolve and are absorbed by the body) has been shown in biomechanical testing to be a reliable method of repair. Sometimes, however, these cross pins break after implantation.

Dr. Paul Marks, an orthopaedic surgeon and associate scientist in the Holland Musculoskeletal Research Program at Sunnybrook, and colleagues did a study to assess the frequency of magnetic resonance (MR) imaging findings and complications related to bioabsorbable femoral cross pins during postoperative MR imaging follow-up care. They also compared MR images with clinical evaluations.

Results showed fractured cross pins and breaching of the posterior femoral cortex were seen relatively frequently in follow-up images after ACL reconstruction. Researchers also found that the position of the pin was related to the presence of a fracture, indicating pins oriented too far posteriorly might be fracture-prone. There was no link, however, between abnormal imaging findings related to cross pins and clinical results of joint instability or pain.

Mind and Body Linked: Study

Major depression affects up to 20% of people. Researchers have known for years that this debilitating condition is associated with dysfunction of the immune system and inflammation-inducing proteins called cytokines, a component of the immune system.

Dr. Krista Lanctôt, a senior scientist in the Brain Sciences Research Program at Sunnybrook Research Institute, and colleagues did a meta-analysis of studies that measured cytokine levels in patients with major depression. Their survey found significantly higher levels of two cytokines across studies, findings that strengthen the scientific link between depression and activation of the inflammatory response system.

The researchers noted that presence of the two cytokines has yet to be identified as a cause or consequence of major depression, but they outlined several biological mechanisms through which these proteins might alter mood.

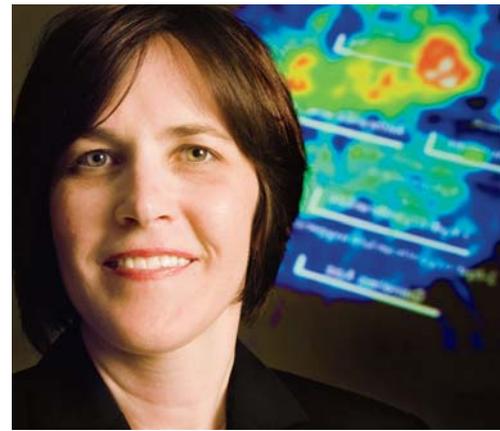
Worth the Wait

Prostate cancer affected an estimated 24,600 Canadians in 2010, making it the most common cancer in the country among men. If caught early, the disease is curable. Screening has therefore increased over the last two decades, likely contributing to a drop in mortality.

For every death avoided through screening, however, clinicians treat dozens of men, most of whom would die of causes other than prostate cancer. That treatment often produces adverse effects, including pain, incontinence and impotence.

Dr. Lawrence Klotz, chief of urology and an associate scientist in the Odette Cancer Research Program at Sunnybrook, and colleagues recently published updated results of an earlier clinical trial on watchful waiting, an approach in which physicians monitor individual patients closely and treat only if the cancer is progressing.

They affirmed a conclusion from the initial trial that watchful waiting, also called active surveillance, is safe for low-risk men. They also found it safe for men with intermediate risk aged 70 years and older, even over 10 to 15 years. Together, treated and nontreated patients were 18.6 times more likely to die of causes other than prostate cancer.



TOP TO BOTTOM:
DR. KRISTA LANCTÔT; DR. STEPHEN FREMES;
DR. GEORGE CHRISTAKIS

A Lungful

A common and effective treatment for neonatal respiratory illness is permissive hypercapnia, in which clinicians elevate carbon dioxide to reduce hypertension in the lung vasculature (the circulation between the heart and lungs). Hypercapnia is associated, however, with neonatal hemorrhage causing brain injury and with chronic lung disease in adults.

Better treatments for lung illness therefore depend on finding the biological mechanisms underlying hypercapnia's respiratory effects. In a 2009 study, **Dr. Robert Jankov**, a senior scientist in the Women & Babies Research Program at Sunnybrook Research Institute, found the first evidence that during induced hypercapnia, downregulation of an enzyme called arginase increases nitric oxide generation, which in turn results in one type of vasorelaxation, or reduced hypertension.

The study, which Jankov and colleagues conducted in preclinical models of respiratory illness, provides a potential explanation for the clinical benefits of permissive hypercapnia. It also opens a new line of biological investigation into the effects of carbon dioxide on respiratory function.

Predicting Outcome After Brain Trauma

Families of patients who are comatose due to traumatic brain injury want rapid and accurate prognoses. To address this need, **Dr. David Houlden**, an associate scientist in the Brain Sciences Research Program at Sunnybrook Research Institute, developed a test in the 1980s that correlated the brain's response (or lack of it) to electrical stimulation with patient outcome six months later.

Known as somatosensory evoked potentials (SSEPs), the grading system was adopted by clinicians and refined by more research. Houlden and colleagues recently honed the test further, publishing evidence in 2010 that SSEP grading on the third day after injury gives the strongest correlation with functional and cognitive outcome after one year.

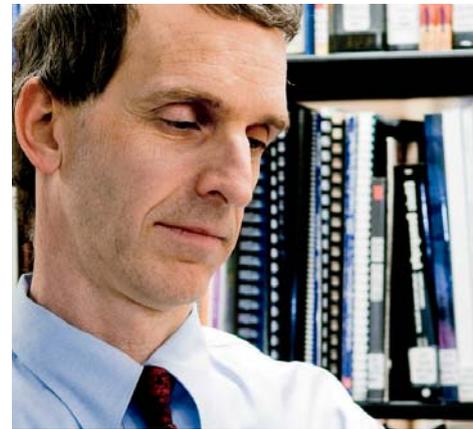
The study could provide a framework for more precise prognoses based on SSEP grades, and a way to analyze the effectiveness of new interventions by comparing predicted with actual outcomes.

Get a GRIIP

Schulich Heart Program researchers and cardiac surgeons **Drs. George Christakis** and **Stephen Frenes** led the first contemporary randomized clinical trial—Graft Imaging to Improve Patency (GRIIP)—to assess if a strategy of intraoperative graft assessment with criteria for graft revision during coronary artery bypass graft (CABG) surgery can decrease the rate of graft blockages, narrowed arteries or major adverse clinical events one year after surgery.

The trial enrolled 156 patients undergoing CABG surgery, and randomly assigned them either to the experimental imaging group or to the control (no imaging) group.

The scientists found that routine intraoperative graft assessment is safe and feasible. They found no difference in graft patency and clinical outcomes between groups one year after surgery. These results suggest that graft patency assessment need not be used regularly, but only when clinical suspicion of graft failure exists. Researchers also found that the incidence of saphenous vein failure (this vein is commonly used to create the bypass in CABG surgery) remains high despite modern practice and routine intraoperative graft surveillance.



TOP TO BOTTOM:
DR. JACK TU; DR. DONALD REIDELMEIER;
DR. LAWRENCE KLOTZ

ALL IN THE GENES

Cell biologist at SRI develops method that could chart a new course for treating cancer and other diseases at their source

Leaning forward in his office chair, hands clasped, Dr. Burton Yang is smiling.

A senior scientist in molecular and cellular biology at Sunnybrook Research Institute (SRI), Yang has reason to smile. In the last 10 years he has published more than 40 peer-reviewed papers, many in high-impact journals. Grant money is rolling in, and his lab group numbers six, including two postdoctoral fellows and a visiting scientist. Researchers in other countries invite him to speak about his work—on this day he has just returned from Iowa City—and in 2009 *Nature Cell Biology* published a discovery he calls “the most important” of his career.

That discovery is a method for expressing single microRNAs, and it has the potential to advance significantly microRNA research throughout the field of molecular biology, particularly in gene therapy to treat cancer and other diseases.

MicroRNAs are a type of ribonucleic acid (RNA), and they are very small—relative to a cell, they are like dust in a house. The sole job of RNA, scientists believed until recently, was as “messenger” in cell development: copying the genetic instructions contained in deoxyribonucleic acid (DNA) in an intricate series of

interactions called transcription. Some RNAs, in turn, are translated into proteins that, dependent upon their DNA and the genetic environment in which they were transcribed, become the hundreds of cell types—and trillions of cells—that comprise the human body.

In the early 1990s, the notion of RNA as mere messenger in this orchestral process was shattered when scientists discovered small-interfering RNA and microRNA, and showed they could regulate gene expression—the move from DNA to RNA to protein—which had dominated molecular biology for five decades. Researchers quickly discovered other classes of RNA, and the number of RNA categories soon exceeded 20.

The multiple roles of these RNAs have attracted keen attention from scientists, but interest in microRNA has been particularly intense. As Yang noted in his Iowa City presentation, the number of articles with the word “microRNA” grew from two in 2002 to more than 2,600 in 2010 in a sample of the world’s top journals. This interest has been driven by a growing understanding of the ability of microRNA to regulate the expression of other genes and, in some cases, to encourage gene expression.

Dr. Michael Julius, vice-president of research at Sunnybrook Health Sciences Centre and a professor of immunology and medical biophysics at the University of Toronto, says the impact of microRNA on molecular biology has been revolutionary. “The description of microRNA and its

capacity to alter gene expression has been fundamental to our recent understanding of cell development,” says Julius. “It’s actually been nicknamed the ‘micromanager’ of the genome.”

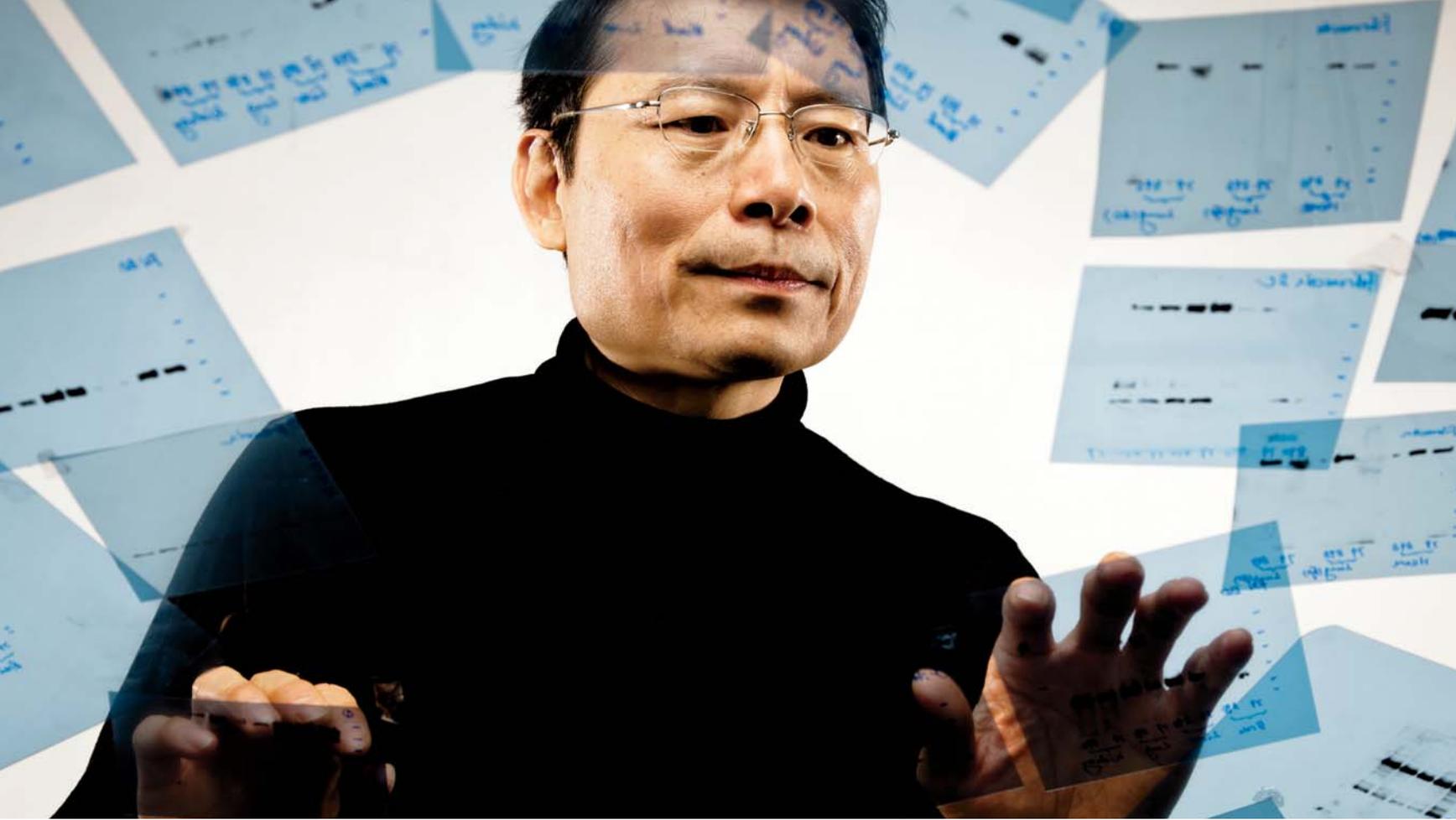
Before 1993, says Julius, scientists thought the next 50 years of molecular biology would be about understanding protein-DNA interaction, through proteins like transcription factors, for example, that tell DNA to turn on or off. “That notion has now been turned on its head, and we’re looking at RNA-DNA interactions,” he says.

A further level of complexity, says Julius, lies in the ability of microRNAs to change their chemical sequence. This feature enables them to interact with new varieties of genes and play a direct role in disease development and the delicate genomic balance that is good health. The importance of understanding microRNA has thus become paramount.

Enter Yang’s single-microRNA expression method.

A big problem in the study of microRNAs is that they frequently “express” as clusters. Researchers have been able to test and measure the function of particular clusters, but not the specific microRNAs, and thus their specific roles, within those clusters. One of the most-studied clusters, made up of seven microRNAs, is called

...a discovery he calls
“the most important”
 of his career.



DR. BURTON YANG

miR-17-92. Researchers have strongly linked overexpression of this cluster with numerous cancers, showing it both encourages cancerous cell proliferation and regulates genes that would otherwise keep malignant cell growth in check.

In the early 2000s, Yang and his lab were studying a type of protein called versican that plays a role in blood vessel and tumour growth. Looking at this protein and small-interfering RNAs, they had an idea for how they might express a single, mature microRNA to study its particular role, but their experiments testing this idea failed.

From that failure, however, they had an idea about why their new construct wasn't working. "Mature microRNAs are short, only about 20 nucleotides [the molecules that comprise RNA and DNA], so the enzymes that process them into mature microRNAs were unable to recognize them," says Yang, who is also a professor in laboratory medicine and pathobiology at U of T.

The solution, they discovered, was to use something called precursor microRNAs. Precursor microRNAs are 70 to 100 nucleotides long, and are therefore more recognizable to the enzymes that bind, slice and process them into a mature state.

Moreover, the lab expressed a single microRNA—miR-17, of the miR-17-92 cluster—in a Petri dish and in mice—

a first in the field. "Using cells only, we don't have a true physiological condition," says Yang. "But in the body of the animal, we're able to do it the right way. The body will not, for example, produce an unrealistic amount of microRNAs as might happen in a Petri dish, so you get quality control."

With the resulting transgenic mice, Yang and his lab precisely mapped several functions of miR-17. They found that when miR-17 was overexpressed, the mice developed much smaller bodies and organs, and fewer types of blood cells. They also found miR-17 produced those effects by acting on specific proteins called fibronectin and FNDC3A—a finding that matched results from other researchers showing a link between those proteins and miR-17. Yang and his group are now tweaking miR-17 expression to gauge its effect on blood and cancer cells. They hope this work will lead to new therapies to regenerate damaged blood vessels in patients with heart disease, and to shrink or halt tumours in those with cancer.

Building on Yang's breakthrough, other labs have begun using the single-microRNA expression method for their own studies in several clinical areas. Those labs have yet to publish results, but Dr. Wei-Yang Lu, a former colleague of Yang's at SRI, now an associate professor in physiology and pharmacology at the University of Western

Ontario, is using the method to study the role of miR-17 in the regulation of brain functions. Lu's preliminary data has shown that neurons in the brain of miR-17 transgenic mice are fragile when blood flow is restricted, suggesting that greater expression of miR-17 may increase the severity of stroke-induced brain damage. These results, he says, are "very exciting."

Yang, however, is quick to qualify the impact of his findings: "MicroRNAs are very complicated. One can regulate expression of many things, and that expression can be regulated by other microRNAs, so there may be something going on [that] we did not see."

That said, scientists have discovered over 1,000 microRNAs that influence interactions in more than 60% of the human genome, with profound effects on health. Given these findings, a method that promises better understanding of individual microRNA function should keep cell biologists busy—and Yang smiling—for some time to come.

— Jim Oldfield

Yang's work was supported by the Canada Foundation for Innovation; the Canadian Institutes of Health Research, including a China-Canada Joint Health Research Grant with the National Natural Science Foundation of China; the Heart and Stroke Foundation of Ontario; and the Ministry of Research and Innovation.

A BRILLIANT COMBINATION

Musculoskeletal researchers are pairing light and drugs to effect a more powerful way to kill cancer that has migrated to bone



DRS. MARGARETE AKENS AND CARI WHYNE

Imagine that your body could be healed by light.

That's what scientists at Sunnybrook Research Institute (SRI) are investigating using therapeutic photosensitizers—light-sensitive drugs—to treat patients with cancer that has spread to their spine.

Photodynamic therapy, also known as PDT, is a minimally invasive, safe and effective procedure that has been used around the world since the 1980s. It has been used to treat cancer of the skin, brain, breast and lung, and other diseases (for example, age-related macular degeneration, a disease of the eye that can lead to vision loss).

Photodynamic therapy combines a light-sensitive drug that selectively accumulates in cancer cells with locally applied light at a specific wavelength delivered via a laser. Together, the photosensitizer and light produce a reactive form of oxygen that destroys the cancer cells and shrinks the tumour.

About 75% of women with metastatic breast cancer have metastases in the bone, most commonly in the spine. This can lead to severe pain, fracture, structural

instability of the spine and even spinal cord injury resulting in paralysis. A PDT approach adds to and complements available treatments such as bisphosphonates (drugs used to treat bone loss and prevent fractures) and radiation therapy, which are not effective in all patients.

In 2010, Drs. Margarete Akens, Cari Whyne and Albert Yee from the Holland Musculoskeletal Research Program at SRI, and colleagues published the results of a preclinical study on the use of PDT for spinal metastases in the journal *Breast Cancer Research and Treatment*.

The study examined which drug and light dose would best destroy tumours within the spine while protecting sensitive tissues nearby, such as the spinal cord and nerve roots.

Akens, a junior scientist in the labs of Yee and Whyne, conducted the study on a preclinical model using human breast cancer cells. After the presence of tumour cells within the spine was confirmed with bioluminescence imaging (labelling the cancer cells so that they will emit light), Akens performed PDT using different concentrations of a light-sensitive drug and

altering how long a wavelength-specific light was delivered to the tumours. The best combination of drug and light dose resulted in cancer cell death and smaller tumours 80% of the time, while protecting the critical elements surrounding the spine.

"I was impressed to see the tumours destroyed and to have such a significant success rate each time I repeated the experiment," says Akens.

"In addition to killing tumour cells, we needed to protect and preserve the neural elements of the spine. We also needed to optimize our understanding of how PDT affects the bony elements of spine," says Yee, who is also a staff spine surgeon and orthopaedic coordinator for the bone metastasis clinic at Sunnybrook's Odette Cancer Centre, and co-director of the University of Toronto's department of surgery spine program.

While there is research and clinical evidence suggesting that PDT is an effective cancer therapy, little is known about how PDT affects bones.

In 2010, Akens, Whyne, Yee and collaborators published another study, this

“In addition to killing tumour cells, we needed to protect and preserve the neural elements of the spine.”

Dr. Albert Yee

one in the journal *Spine*, “Effects of Photodynamic Therapy on the Structural Integrity of Vertebral Bone.”

In the lab of Whyne, who is the director of the Holland Musculoskeletal Research Program at SRI and an associate professor in surgery at U of T, the triad conducted biomechanical testing and structural image analysis on healthy rats to see how bone would react when treated with PDT.

“We were very surprised to see that the bone became stronger, and that there was significant improvement in bone formation and mechanical stability after the treatment,” says Akens.

In yet another study published the same year, the researchers observed that there might be an additive or synergistic effect to bony stability when PDT is combined with bisphosphonates. This is important because many cancer patients with bony metastasis are routinely treated with bisphosphonates.

As a result of the researchers’ successful preclinical work, the team has received funding for a phase I clinical trial to evaluate the safety of PDT for the treatment of spinal metastases. Yee says he expects

the trial to begin early in 2011 with patients at Sunnybrook.

Researchers will give the light-sensitive drug intravenously. They will insert an optical laser fibre via a needle into the tumour within the spine, and turn on the light to destroy the tumour and potentially strengthen the remaining bone. This will be performed as an adjunct procedure for patients who are receiving vertebroplasty therapy to strengthen their diseased bony spine.

As the team prepares for the clinical trial, they say they are confident that PDT has the potential to change the way patients with cancer that has spread to the spine are treated. “It’s a way to kill tumour cells locally and improve the stability biologically of the surrounding bone,” says Whyne.

— Eleni Kanavas

Supporting this research are the Canadian Breast Cancer Foundation, Ontario chapter; Canadian Breast Cancer Research Alliance; Canadian Institutes of Health Research and Ontario Institute for Cancer Research. The Canada Foundation for Innovation and Ontario Ministry of Research and Innovation provided infrastructure support.



DRS. CARI WHYNE AND ALBERT YEE

HANDING OVER THE REINS

Researchers are studying how to ease the discomfort of childbirth by tailoring the experience to give women more control over it. They're also working to ensure women have equal access to pain relief services, no matter where they live

Coping with labour pain is something many mothers around the world know all too well.

Although clinicians have used various systemic comfort measures for many years, a limited amount of research has been conducted on developing better therapies for quality pain relief in obstetrics.

Now, scientists in obstetrical anesthesia at Sunnybrook Research Institute (SRI) are gathering evidence on the use of local anesthesia as an effective method for pain management and how it can enhance a woman's experience during childbirth.

Dr. Pamela Angle, director of the obstetrical anesthesia research unit (OARU) at SRI, and Dr. Stephen Halpern, a member of OARU and the head of obstetrical anesthesia in the Women & Babies Program at Sunnybrook Health Sciences Centre, seek to optimize pain relief in labour and postcaesarean care, particularly through epidural analgesia during labour—whereby a local anesthetic is injected into the lumbar area of the spine and freezes the nerves that transmit pain from the uterus.

Andrea Van Wieringen, a mother of two, chose to have a caesarean section and epidural for both of her deliveries because she “couldn't imagine being ‘asleep’ for the birth.”

“I strolled into the operating room where I got my spinal tap and waited for my C-section to begin,” says Van Wieringen, who delivered her second child in September at Sunnybrook's new birthing unit. “It was a great and calming experience to be able to ask my doctor questions while the operation was happening, and to watch everything from the glossy mirror effect on the ceiling in the delivery room.”

By keeping patient safety issues always in mind, especially important for the high-risk patients with whom they work, Angle is developing new health measurement tools for use in obstetric anesthesia to improve the quality of pain relief afforded by epidurals.



DR. PAMELA ANGLE

“Everything we do is driven from a woman's perspective,” says Angle, who is also an associate professor of anesthesia at the University of Toronto. “One challenge is that we measure labour pain by severity, but pain is multidimensional; it affects one's ability to think, along with one's emotional and physical well-being.”

In 2009, Halpern published a review in *Anesthesia and Analgesia* about patient-controlled epidural analgesia, whereby women in labour could adjust how much drug they needed through an electronically controlled infusion pump that delivered a prescribed amount of anesthesia intravenously. The review showed a trend toward improved maternal satisfaction when patients controlled their analgesia.

Clinicians introduced this technique in 1988, and it has been proven to be safe and effective. Two advantages of using patient-controlled epidural pain management are that it allows women to be

awake when they are giving birth, and it reduces the temporary sensation of paralysis in the lower body.

“The idea behind the study is that pain relief itself is not enough, because women want a birthing experience in their own way, which means they want to have more control of their lower body in order to feel what is happening,” says Halpern, who is also a professor of anesthesia, obstetrics and gynecology at U of T. “With patient-controlled epidural analgesia, women can feel less drugged by the anesthetic, and we can provide a more natural environment for them.”

While this type of pain management may increase the satisfaction of women in labour, the researchers say what remains to be seen is how best to deliver patient-controlled analgesia.

“One challenge is that we measure labour pain by severity, but pain is multidimensional.”

Dr. Pamela Angle

In another study published in the *British Journal of Anaesthesia*, Angle and Halpern studied 501 patients who had epidural labour analgesia and delivered their babies by caesarean section with local anesthesia.

Following guidelines from the Royal College of Anaesthetists in the U.K. on best practices in anesthesia care, the study aimed to determine how successful doctors were in using an epidural already in place for anesthesia for caesarean section. Results showed that clinicians were successful 96% of the time, which was within the guidelines.

“We actually use the epidural as a risk management strategy during labour to help women with diabetes and pre-eclampsia, and to prevent stroke and myocardial infarction,” says Angle about the increased risks caused by an aging population and rise in obesity rates.

In the event of an emergency caesarean delivery, an anesthesiologist can administer surgical anesthesia through the epidural for rapid and effective pain relief.

Research also shows more women are choosing to undergo caesarean section with an epidural or spinal because of the many advantages. Compared with general

anesthesia, these include superior postoperative pain relief, positive influence on breastfeeding and psychological advantages of being awake during the delivery.

Twelve hours after the surgery, Van Wieringen was walking around. She spent three days in postoperative care at Sunnybrook and says she felt very little pain, which was treated with medication during her stay in hospital.

While Van Wieringen had a positive birthing experience that empowered her, not all women may have access to the same pain relief measures, according to a recent study by Angle. Many rurally located hospitals are facing challenges associated with unequal access to obstetrical anesthesia care.

In 2009, Angle published a report in the *Canadian Journal of Anesthesia* that looked at the provision of anesthesia services, including epidurals, to pregnant women across Ontario. She found that in rural areas these services are often delayed or unavailable, giving rise to a two-tier maternity system in the province.

The study also explored the issues and barriers faced by physicians providing maternity anesthesia services in smaller community hospitals, and potential solutions to these barriers. Issues included too-few anesthesia staff, the need for ongoing mentorship and resources found in academic centres, and access to protocols to help physicians take up best practices in obstetrical anesthesia.

Vital anesthetic services that are part of the maternal newborn safety net within

the Canadian health care system include access to pre-labour and pre-caesarean medical consultations, use of epidurals for labour, management of post-caesarean pain and anesthetic risk management for critical cases during childbirth.

Angle says more than 50% of beds in high-risk maternal units in urban Ontario hospitals are occupied by women with low-risk pregnancies. Some of these women come for labour epidural pain relief that is often delayed or unavailable in rural hospitals.

Discussions with community physicians also identified a need for mentorship and continuing medical education in obstetrical anesthesia that is relevant to the needs of community practitioners. Angle has suggested linking university-based specialists from large urban hospitals with staff in rural hospitals through a knowledge transfer network that would provide support and help build education strategies.

“Even though this is a provincial study, it has national health implications,” she says. “If we can provide a minimum standard of care for women across the province, this could serve as a model for the country.” — Eleni Kanavas

Angle's work on rural community hospitals was funded by Ontario Women's Health Council, Sunnybrook Health Sciences Centre, the University of Toronto and Women's College Hospital.



HOPE HAPPENS HERE:

THE CENTRE FOR STROKE RECOVERY

RESEARCHERS AT SUNNYBROOK ARE
LEADING STUDIES IN HOW BEST
TO PREVENT STROKE AND OPTIMIZE
HEALING AFTER IT

BY ELENI KANAVAS

In January 2010 while watching TV in his Toronto home, Vincenzo Cirillo noticed the images on the screen started to blur. He adjusted his eyeglasses, to no avail. The problem persisted, leaving him unable to see clearly from his right eye.

That's when his wife, Stella Cirillo, scheduled an appointment with their optometrist. "I knew something was wrong because he took an awfully long time at the eye doctor's office," says Mrs. Cirillo. "When he came home, I didn't believe what he told me."

At age 67, Mr. Cirillo had suffered a "mini-stroke" caused by a blood clot in the back of his right eye. An estimated 10% to 20% of patients who have such a "warning stroke" or transient ischemic attack (TIA) will experience a major stroke within 90 days; one-half of these will experience a major stroke within 48 hours.

The next morning, Mr. Cirillo met with his family physician, who had reviewed the optometrist's report. The physician did an ultrasound scan of his neck. Results showed Mr. Cirillo had carotid artery disease, which is caused when plaque builds up in the carotid arteries, the arteries that are the main blood supply to the brain. When plaque forms here, it can block blood flow to the brain and eye, and lead to a massive stroke.

Within two days of his diagnosis, Mr. Cirillo had a referral to see Dr. David Gladstone and a team of experts at the Regional Stroke Prevention Clinic and Dr. Thomas and Harriet Black Acute TIA Unit at Sunnybrook Health Sciences Centre. One week later, a surgical team at Sunnybrook performed a carotid endarterectomy—also referred to as "stroke prevention surgery"—and removed the built-up plaque, restoring blood flow and dramatically reducing Mr. Cirillo's risk of a major stroke.

"Stroke is a massive public health problem in Canada and worldwide, and we are constantly striving to provide the best care, and discover newer and better treatments and prevention strategies," says Gladstone, director of Sunnybrook's Regional Stroke Prevention Clinic and a scientist in the Brain Sciences Research Program at Sunnybrook Research Institute (SRI).

In Canada, a stroke occurs every 10 minutes. It is the second-leading cause of death worldwide in people aged over 60 years, the most common cause of adult neurological disability in the country, and a main cause of physical and cognitive disability.

Sunnybrook is leading Canada's effort to address the national and global problem of stroke. In addition to the stroke prevention clinic and TIA unit, Sunnybrook houses

a Regional Stroke Centre and—critically for the future of research-driven stroke care—the Heart and Stroke Foundation Centre for Stroke Recovery. In this world-class centre, researchers and clinicians are working together to invent new standards of care and best practices in the treatment and prevention of stroke.

The Heart and Stroke Foundation of Ontario funded the establishment of the Centre for Stroke Recovery in 2002 as a virtual organization that combines the expertise, space and technology of three health care centres and their research institutes: Sunnybrook and SRI, the University of Ottawa and the Ottawa Hospital Research Institute, and Baycrest's Rotman Research Institute with the Kunin-Lunenfeld Applied Research Unit.

Dr. Sandra Black is the centre's site director at Sunnybrook, director of the Brain Sciences Research Program at SRI and a professor in neurology at the University of Toronto. She is leading a team of scientists and clinical researchers in neurology, imaging, neurophysiology,

neuropsychology and rehabilitation. They are investigating interventional methods using advanced imaging technologies, developing physical and cognitive assessments to assist in stroke recovery, and designing and testing new drug therapies.

The need for advances in stroke research—and their translation into care—is urgent. “We are seeing an increase in stroke patients because of an aging population, and there is a lot more we still need to understand about how we can help the brain make the maximum recovery and rehabilitate people after a stroke,” says Black.

RISKY BUSINESS: PREVENTING STROKE

In 2009, Gladstone published a study in *Stroke* that evaluated wait times for carotid artery surgery in Ontario as a key measure of quality of care in stroke prevention.

Wait times for this surgery are important because patients like Mr. Cirillo who have a warning stroke caused by carotid artery disease have a high risk of having another stroke. The benefit of this surgery for preventing strokes is best if the procedure is performed within two weeks after a warning stroke.

“Carotid artery disease is a major treatable risk factor for stroke,” says Gladstone, who is also an assistant professor of medicine at U of T. “At Sunnybrook, we are working hard to lead the way in providing rapid and accurate diagnosis and treatment planning for those in need, including expediting surgical treatment for the highest-risk patients.”

Using data from the Registry of the Canadian Stroke Network based at the Institute for Clinical Evaluative Sciences, Gladstone's study revealed that only one-third of Ontario patients who underwent carotid artery surgery did so within the recommended two weeks. One-half waited more than a month, and in 25% of cases surgery was delayed more than three months. “That's far too long to wait,” says Gladstone.

The study is now drawing attention to the importance of minimizing delays to diagnosis and stroke prevention surgery for patients with high-risk TIAs. Gladstone says he hopes the study will lead to better hospital protocols aimed at expediting care for these patients.

MAKING HEADWAY WITH INNOVATIVE IMAGING TECHNIQUES

A main focus of the centre's research is imaging, something for which scientists at SRI are renowned. For example, functional magnetic resonance imaging (fMRI), which shows the brain “in action,” and computed tomography perfusion imaging (another type of functional imaging that measures blood flow) are helping researchers understand what happens during stroke and quantify the amount of brain tissue loss caused by stroke.

PHOTO THIS PAGE & PREVIOUS: TIM FRASER

DRS. DAVID GLADSTONE AND RICHARD AVIV



THE CENTRE FOR STROKE RECOVERY IS A WORLD-CLASS CENTRE OF EXCELLENCE WHERE RESEARCHERS AND CLINICIANS ARE WORKING TOGETHER TO INVENT NEW STANDARDS OF CARE AND BEST PRACTICES IN THE TREATMENT AND PREVENTION OF STROKE.

Much of Black's research uses imaging to study brain-behaviour relationships and disorders that arise when these relationships go wrong. One example is the loss of language called aphasia, a disorder caused by damage to the left hemisphere of the brain. She is studying the use of structural and functional imaging in the diagnosis and monitoring of mild cognitive impairment, and in Alzheimer's disease and other dementias, in which language loss is prominent in some patients.

Studies show about 25% of stroke patients have dementia and 65% have some cognitive impairment; both greatly affect recovery. There is a relationship between stroke and Alzheimer's disease, emphasized by research that shows this disease can be unmasked by a stroke.

"Alzheimer's disease can cause a hemorrhagic stroke because amyloid deposits in the brain cause the vessels to become weak and bleed," Black says. "We've spent years developing imaging pipelines that allow us to look at the way atrophy and stroke disease are related."

Dr. Richard Swartz also uses imaging technology. Swartz is an imaging scientist at SRI, director of the stroke research unit at Sunnybrook and director of the stroke program at U of T. Through a "scanner-to-bedside" approach to stroke and cognition, he is exploring ways to improve the care of patients with problems affecting blood vessels in the brain, including atherosclerosis (plaque build-up in blood vessels), vasculitis (blood vessel inflammation) and — surprisingly — pre-eclampsia.

"Most people think of pre-eclampsia as an obstetrical disease, but it's what I call

a neurovascular disease. It's driven by pregnancy, but the most dangerous symptoms are from blood vessels in the brain," Swartz says. Pre-eclampsia may even be a "stress test" for vascular problems in later life — an idea Swartz is investigating with collaborators in obstetrical medicine. Imaging can help distinguish between pre-eclampsia and stroke, conditions that share symptoms of confusion and seizures, thereby improving physicians' treatment decisions.

The centre's imaging-focused researchers and Dr. Alan Moody, radiologist-in-chief of medical imaging at Sunnybrook and associate scientist at SRI, are pioneering the use of MRI for early diagnosis and intervention strategies to prevent strokes and heart attacks by identifying high-risk patients with carotid artery plaque.

The journal *Neuroradiology* published a study in 2009 by Moody and Gladstone that studied the association between carotid artery stenosis, narrowing of the carotid arteries, in men without any symptoms, and the risk of future strokes through an MRI examination of plaque characteristics. Results showed a positive link between intraplaque hemorrhage as

detected by MRI and future stroke events; this suggests using MRI to screen for intraplaque hemorrhage may be a useful means by which to classify the risk of future strokes in patients who don't have any symptoms, but who have some narrowing of the carotid arteries.

Researchers and clinicians at Sunnybrook will continue to find new ways to treat stroke and enhance patient recovery, Swartz says. "The connections between our research with Dr. Gladstone, Dr. Black and our partners in the Centre for Stroke Recovery has the potential years from now to change the way we diagnose and treat stroke patients."

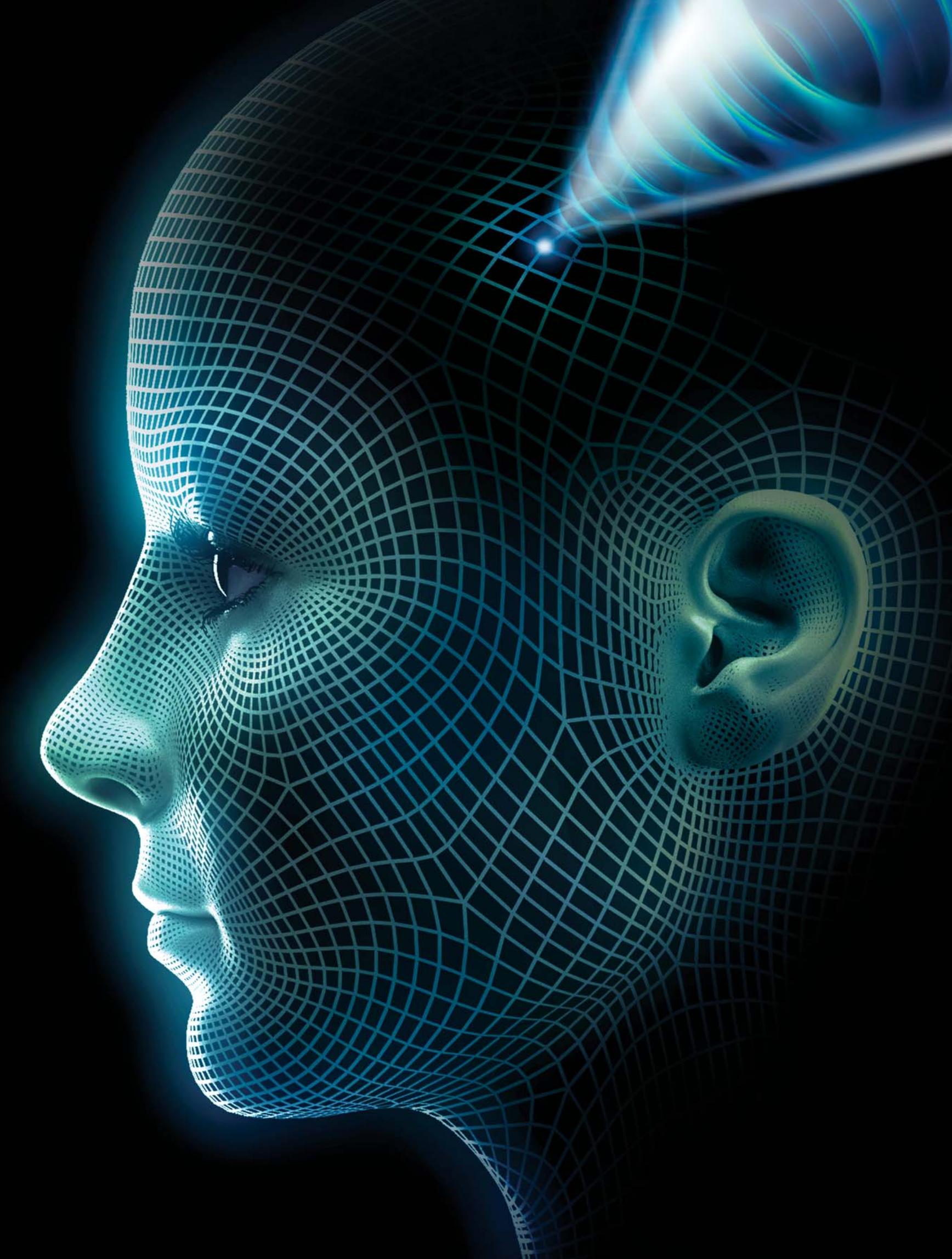
Days after Mr. Cirillo's carotid artery surgery, life returned to normal for his family. "I stayed in the hospital overnight, and when I got home the next day I was up and walking," he says. "I didn't feel much pain, and I was not going to sit around and do nothing."

Since then, Mr. Cirillo has continued to craft his homemade Italian wine and enjoy time with his family. He recently celebrated his 40-year wedding anniversary.

Black's research is funded by the Alzheimer Society of Canada, Canada Foundation for Innovation, Canadian Institutes of Health Research, Canadian Stroke Network, Government of Canada, Heart and Stroke Foundation of Ontario, National Institutes of Health, and Ontario Ministry of Research and Innovation.

Gladstone's research is funded by the Canadian Institutes of Health Research; Canadian Stroke Network; Departments of Medicine, Sunnybrook and University of Toronto; Heart and Stroke Foundation of Ontario; Ontario Ministry of Health and Long-Term Care; and Ontario Ministry of Research and Innovation.

Swartz's research is supported by a Canadian Institutes of Health Research/Canadian Stroke Network/Heart and Stroke Foundation of Canada award.



BY STEPHANIE ROBERTS

IN
FOCUS

IMAGE-GUIDED

SOUND

WAVES WILL

CHANGE MEDICINE;

HERE'S HOW

THE LATIN OF THE
poet Virgil dignifies
the medals
awarded to that rare
creature, the
Nobel Laureate.

In four of the prize's five categories, the inscription reads *Inventas vitam juvat excoluisse per artes*. It means, "And they who bettered life on earth by their newly found mastery;" or, more literally, "Inventions enhance life which is beautified through art." There is a less well-known phrase of Virgil's, however, one that as easily could have been chosen to express what marks those who achieve greatness in discovery: *Possunt, quia posse videntur*—"They can because they think they can."

Dr. Kullervo Hynynen heads imaging research at Sunnybrook Research Institute (SRI) and is a professor at the University of Toronto. He wanted only to be a scientist. "I never really thought about anything else," he says. "I always did experiments." Some time after he retired his Meccano kit what he did think about was how to invent a technology that renders the impenetrable penetrable and redefines surgery as scalpel-less.

Most of us will be familiar with ultrasound as a tool used either for diagnosis or, during pregnancy, to see inside the uterus. Ultrasound works by producing sound waves, the echoes of which are translated into "pictures" of internal structures. In this way, a doctor can see

if blood is flowing through an artery or measure the size of a fetus.

Therapeutic focused ultrasound is grounded in the same physics principles, but works differently: it harnesses sonic energy to effect a change in biological tissue. High-intensity focused ultrasound, or HIFU (pronounced hi-foo), generates heat to ablate, or destroy, tissue, like a tumour, inside the body. Lower-intensity focused ultrasound, which (so far) doesn't have a catchy acronym, is used in the brain, where high temperatures are not feasible. In addition, focused ultrasound is being explored as a way to deliver drugs and other biological agents into the brain.

The history of using ultrasound to destroy tissue goes back a long way—the first study to show that ultrasound could alter tissue biologically was in 1926, and a 1942 article established that it could be focused—but the path has not been smooth, even up to recently. Some of the glazier issues pertain to control: achieving the precision needed to heat only the target and not the healthy tissue surrounding it; knowing when the right temperature for ablation has been reached, and for the right length of time; and, in the case of the brain, training ultrasound through



LEFT TO RIGHT: DRs. GREG CZARNOTA, YUExI HUANG AND KULLERVO HYNyNEN

the skull without the beam scattering or becoming distorted.

Hynynen says he first saw the therapeutic promise of ultrasound as a doctoral student in Aberdeen, U.K., where he landed after completing a master's in physics in Finland, his birth country. He was exploring the use of microwaves to heat and destroy tumours. One day he attended a meeting at which he was assigned to review the literature on ultrasound. He did the review and switched gears. "From that, it was obvious ultrasound would be better," he says. Obvious, because ultrasound can penetrate deep and be focused, whereas microwaves can do one or the other singly, but not both at the same time. Less clear, however, was how to achieve the control needed to exploit the full potential of ultrasound as a therapy. After some work (simplifying the plot somewhat), he deduced that bringing magnetic resonance (MR)—with its superb capacity to display high-quality images of internal structures in real time—into the equation might be just the ticket, and in 1991 invented an MR-guided focused ultrasound system. Eight years later, GE Healthcare, then GE Medical Systems, formed a company to commercialize the system. That company, InSightec, has since worked with Hynynen to refine and develop further the system.

Twelve years on, punctuated by study after study establishing feasibility, safety and even clinical effectiveness, it does, indeed, appear to be just the ticket. If you haven't heard of it yet, you soon will. Focused ultrasound surgery, as it is also called, is an approved therapy for select conditions in the U.S., Europe and Canada. Many more applications are in clinical trials, edging closer to approval and promising to provide options where none exist, as in inoperable brain cancer, or where the best alternative—"traditional" surgery—is de facto highly invasive, not to mention risky and expensive.

Focused ultrasound surgery, which relegates the scalpel to the bottom of the surgeon's tool kit, is ushering in a paradigm shift in

medicine, says Hynynen. "It's disruptive technology. It's going to change the way people think," he says.

How does it work? Let's take uterine fibroids as an example. In 2003, Hynynen was part of a clinical team at Harvard's Brigham and Women's Hospital, where he was then located, that was the first to show using MR-guided HIFU to treat symptomatic fibroids is safe and feasible. These benign lesions affect up to 25% of women of childbearing age. Symptoms include heavy bleeding and pain. Many treatments are invasive; the most common one, hysterectomy, removal of the uterus, renders a woman infertile.

During the procedure, the woman lies prone on a table that has ultrasound transducers built into a cradle at the pelvic level, and that can be rolled into an MR scanner. First, doctors plan the treatment. They use MR to verify the location and size of the fibroids, position the transducer robotically, and map the starting temperature of and around the lesions, displaying these data in 3-D on monitors. Treatment then begins. The transducer focuses sound waves onto a fibroid in 15-second pulses. The energy from these sonications causes the targeted tissue—and only that tissue—to heat up and coagulate, or solidify. This is repeated until all targeted fibroids have been treated. Throughout, doctors use MR to guide the sonications and map the temperature changes, which tell them when the tissue has attained sufficiently destructive heat.

Treatment takes two to three hours. No anesthesia is needed. Tylenol may be given to reduce discomfort. Adverse effects are infrequent and rarely serious—skin burn, perhaps. After the procedure, the woman rests for an hour or two, and then goes home; usually she can return to work the next day. Success is measured by symptom reduction, which Hynynen says is "almost right away." The uterus is spared.

“IT’S DISRUPTIVE
technology.
It’s going to change
the way
people think,”
he says.

Making temperature maps inside the body is called thermometry. “MR is the only imaging modality that can do thermometry quantitatively over the range of temperatures that we need to do for these treatments,” says Dr. Rajiv Chopra, an imaging scientist at SRI and assistant professor at U of T. “With focused ultrasound, you can control the heating, plus you can measure temperature in the body with imaging and do better targeting.”

Therein lies the power of the technology: its precision and immediacy. With brain cancer, for example, Chopra notes standard protocol goes something like this: diagnosis with MR, then treatment with radiation or chemotherapy, followed by another MR scan eight weeks later to see if the treatment is working. He contrasts this to focused ultrasound surgery: “Within minutes after the treatment you can see if you’ve coagulated the tissue or not. It’s a very different paradigm—you have measurements that tell you with certainty [if] the tissues are dead or alive, and what’s been spared.”

The treatment for uterine fibroids is approved for specific indications in more than 20 countries, including in Canada; study on it continues, for example, to treat large fibroids or to test new systems. Sunnybrook Research Institute is conducting trials in this area, led by interventional radiologist Dr. Elizabeth David. In 2010, SRI opened an MR-guided HIFU research facility in the Odette Cancer Centre, part of a collaboration with Thunder Bay Regional Research Institute, which also has a focused ultrasound surgery suite. At SRI, the facility is part of the Centre for Research in Image-Guided Therapeutics.

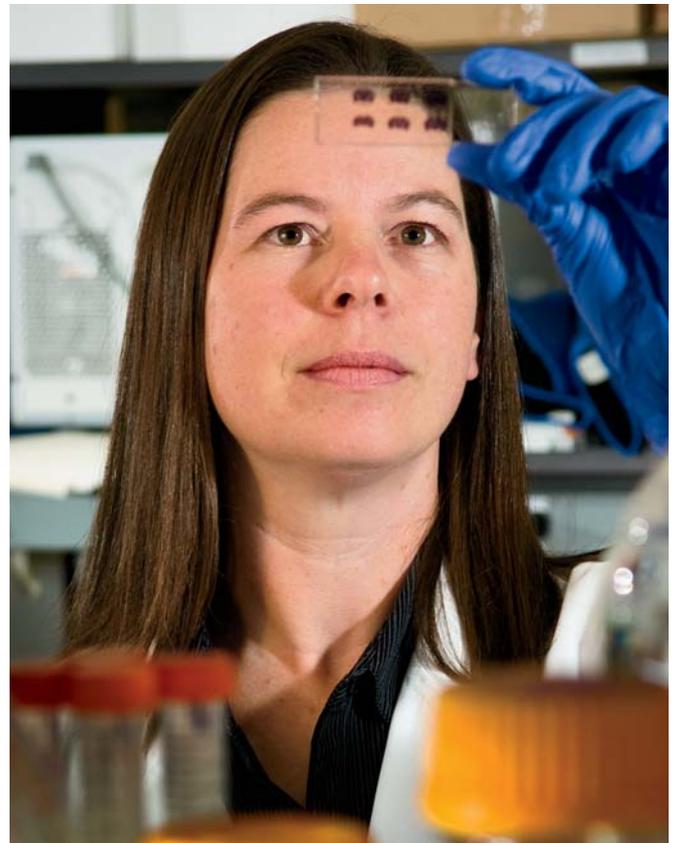
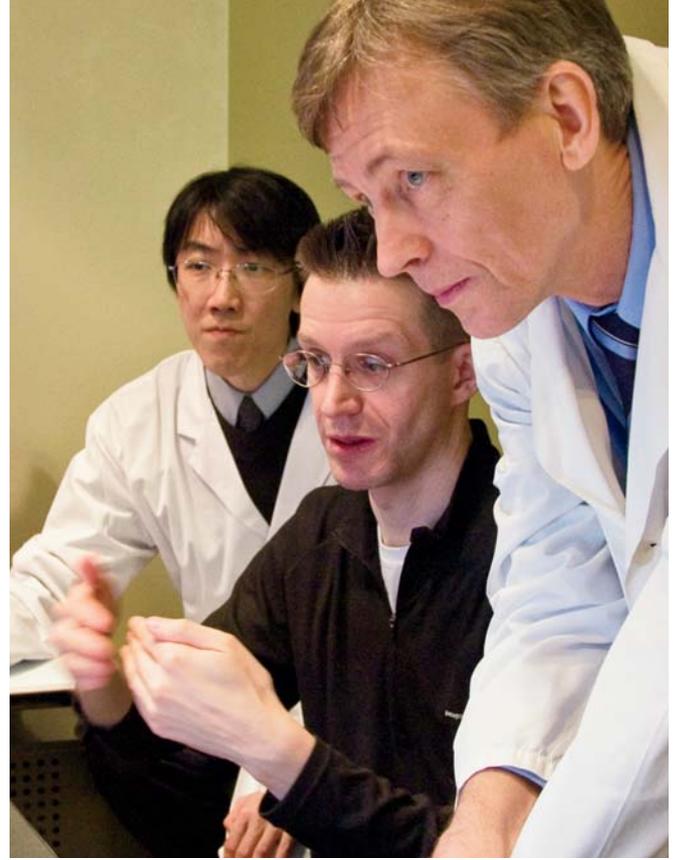
Focused ultrasound surgery for uterine fibroids is compelling as an example of this therapy’s power, but its potential in other areas is more gripping still. Of these, conditions that imperil the brain surely rank at the top: cancer, dementia, stroke—these shatter countless lives. The brain is devilishly difficult to treat,

encased as it is by the skull and further guarded by the blood-brain barrier, densely packed cells that bar entry to 95% of drugs, including most chemotherapeutics. Hynynen and his team, working with industry, developed a device that overcomes these obstacles. It enables even the most deeply nested lesions to be destroyed without opening the skull, and smuggles drugs past the blood-brain barrier to where they are needed.

The device resembles a clunky helmet. The transducer comprises more than 1,000 elements that are arrayed inside the device; roughly the size of dominoes, they look like black backsplash tiles, only uneven. In the case of lesions, the procedural principles are the same as for uterine fibroids—MR guides and monitors the focused ultrasound to heat and kill diseased tissue—with crucial differences to account for the challenges of the brain.

Bone gets hotter, and faster, than does soft tissue—not a good thing for delicate grey and white matter. In addition, individual skulls vary in shape and thickness, so while the helmet may be one-size-fits-all, treatment must be bespoke. Solving each of these problems was a technical masterwork by Hynynen and his team.

Spanning a years-long looping process of numerical modelling, computer simulation, prototype development and preclinical testing, they adjusted the frequency so that the device would generate a lower-frequency beam than that used for body tissue, and designed the multi-element transducer as a hemisphere, to distribute heating more widely. The half-circle shape and large number of transducer elements permit the therapy to be customized to individuals. This is done by using computed tomography imaging during treatment planning to take scans of the patient’s head. These scans provide data in 3-D on skull shape and density, which are then linked with transducer information and MR data on the structure of the targeted tissue. Altogether,



TOP TO BOTTOM: DRs. YUExI HUANG, GREG CZARNOtA AND KULLERVO HYNENEN;
DR. ISABELLE AUBERT

this provides a patient-specific “picture” that enables the neurosurgeon to calculate the beam path and make any corrections needed to ensure the beam does not scatter as it passes through the skull, but instead converges to focus with millimetre exactitude on the target. During the therapy MR maps the temperature changes, telling the surgeon when ablation has been achieved.

InSightec commercialized this device, too; research on it is advancing rapidly and has moved into patient trials. In 2010, Hynynen and a clinical team published the first evidence showing that ultrasound can be focused in the human brain noninvasively without cracking open the skull. Since then, groups in Boston and Switzerland have launched phase I clinical trials in brain conditions. At SRI, Hynynen will work with colleagues at the Odette Cancer Centre and other institutions to test the therapy in patients who have brain tumours or movement disorders.

Also exciting swelling interest is research into the nonthermal applications of the technology: manipulating it to transport drugs or other agents into the brain. About five years ago, Hynynen approached Dr. Isabelle Aubert, an SRI neuroscientist and assistant professor at U of T studying Alzheimer’s disease, to talk about it.

“When I first heard about it, I was, ‘Wow. Really? That will work?’” says Aubert, recalling the meeting that spawned their collaboration. She was instantly intrigued.

As Aubert explains, the use of antibodies to clear the brain plaques that feature in Alzheimer’s disease (these are large deposits of a protein called amyloid beta) is being studied in clinical trials. Therapy, however, is not being targeted to the brain, owing to the blood-brain barrier. Instead, researchers are injecting anti-amyloid antibodies into the bloodstream, hoping that they will pull the plaques from the brain and draw them to the blood, essentially neutralizing them.

“But Kullervo and I were thinking, the pathology is in the brain, so why not get in there? The clearance of the plaques by the current mechanism, just by the periphery, is really slow, and our thinking is that if you have Alzheimer’s disease, you don’t want to wait 12, 18 months before you see an effect,” she says.

Get in there is what they did, as published in the journal *PLoS One* in 2010. Aubert, Hynynen and graduate student Jessica Jordão used MR-guided focused ultrasound to deliver an anti-amyloid agent into the brains of mice with Alzheimer’s disease. Just days



TOP TO BOTTOM: DR. KULLERVO HYNYNEN; DR. RAJIV CHOPRA

later they found that plaque deposits had shrunk, effectively altering the disease's progression. "What was amazing is that within four days it reduced the plaque deposits; usually it takes at least a month to clear the plaques if you put it into the periphery," says Aubert.

How did they deliver the antibodies into the brain? Via the Ali Baba-esque power of microbubbles, harmless particles of gas that when injected into the bloodstream and paired with MR-guided focused ultrasound have an "open sesame" effect of disrupting the blood-brain barrier just long enough to let biological

agents slip in, before the barrier closes to resume its guard role. Guided by MR, ultrasound then conveys the drugs precisely to the target—the plaques, tumour or other tissue of interest.

Aubert and Hynynen are doing further study, including testing the effect of leaving the antibodies in longer and exploring gene therapy. The aim, says Aubert, is not only to clear the plaques, but also to repair damage and restore function. "The ultimate goal is to make people live better, longer," she says.

It's an aim that applies to all diseases for which therapeutic focused ultrasound shows promise, including stroke, which kills 14,000 Canadians a year and hobbles tens of thousands more. Hynynen and other researchers at SRI, including Dr. Sandra Black, director of the Brain Sciences Research Program, and Dr. David Goertz, an imaging scientist, are experimenting with MR-guided focused ultrasound to deliver and enhance the effect of clot-busting agents in the brain.

"Stroke will be a big application. I've got no doubt about it," says Hynynen. The main problem (apart from getting into the brain) is timing, he says. "With stroke, you have a window of opportunity of two to three hours where you have to get the treatment—everything has to be really quick—whereas with a brain tumour, you can plan it for days beforehand."

With so many applications for the technology, it's not surprising that some are closer than others to clinical translation (assuming regulatory approval, which is a whole other story). The technology for dementia and stroke has a way to go before it hits a hospital near you. For the disease that kills one in four Canadians, however, the timeline is shorter.

"Particularly in cancer, the technology is at the stage where it has gone out of the lab and into the hands of the medical manufacturer, and it's being deployed around the world in various

“WHEN I FIRST
heard about it, I was,
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says Aubert.

sites. That’s why it stands to have impact quickly,” says Dr. Greg Czarnota, director of the Odette Cancer Research Program at SRI. He and Hynynen are building a program that brings together scientists and clinicians to evaluate HIFU applications that Hynynen has developed. The role suits Czarnota, who alone at SRI is both an imaging scientist and a radiation oncologist. “You can call me the marriage broker,” he says.

He’s assembled about 10 clinicians and their staff into teams to evaluate the technology for brain tumours, bone metastases, recurrent breast cancer, liver metastases and rectal cancer. These trials will happen in the new focused ultrasound surgery facility. Many will be first-in-human trials, evaluating feasibility and safety. Czarnota, who is also an assistant professor at U of T, notes that for some cancers HIFU could become the brass ring of care.

“Think of it—if you can ablate a tumour completely, why have someone go for a month of radiation or chemotherapy that’s not necessarily going to work for a big tumour?” he asks.

He points to prostate cancer, specifically to a therapeutic device for this cancer that Chopra and Dr. Mike Bronskill, another SRI imaging scientist, invented. “It has the power to replace surgery and to replace radiation,” says Czarnota.

Chopra and Bronskill spent 10 years inventing the device. It fits inside the urethra and uses MR-guided HIFU to ablate tumours in the prostate gland in a 30-minute procedure. It aims to be as effective as surgery, with none of surgery’s harmful effects, like urinary dysfunction or impotence. The device has earned its stripes in preclinical studies, and was recently evaluated in a first-in-man study at Sunnybrook led clinically by Dr. Laurence Klotz, chief of urology. Chopra is encouraged by the results. “It confirmed that the technology worked as expected in humans, and that it could be an efficient, precise treatment for localized prostate cancer,” he says.

The next major step will be a phase I clinical trial. In parallel, the technology was commercialized in 2008 and spun-off into a company, Profound Medical Inc., which is developing a clinical system for transurethral ultrasound therapy for widespread use.

Time is especially relative in the world of science where delayed gratification is the norm, but each researcher interviewed for this story agreed that MR-guided focused ultrasound will shift the paradigm for patient care. For his part, Hynynen is not resting on his laurels. There is much more to do, he says, with help from a global research community. “The field is in expansion phase, and having more and more systems around the world, and more and more people working on it, the pace is accelerating. It has taken 20 years to get to this point, but the next, similar advances will be made in a much, much shorter time,” he says.

Standing on a path littered with progress, then, how far, really, is therapeutic focused ultrasound from changing medicine? Hynynen counsels patience: “It will take time.” With that qualification, however, he says he is confident in the technology’s capacity “to better life on earth,” as Virgil might have put it. “It will happen—50 years from now, there is no doubt that this will be the way to treat patients. Is it going to happen in the next five years? I don’t know. But it will happen—there is nothing else that can do this noninvasive surgery.”

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Dr. Hynynen holds the Canada Research Chair in Imaging Systems and Image-Guided Therapy.



WHEN

Drugs Collide

By Jim Oldfield

SOMETIMES, drugs meant to help cause harm.

While most medications are safe, dozens of regulatory withdrawals—and lawsuits—stretching back to thalidomide show that even when used alone and as directed, drugs can be unsafe. A much larger number, however, produce unwanted effects when they interact with dietary supplements, food, medical conditions—and other drugs.

Drug-drug interactions, in which one drug magnifies or reduces the effect of another, are particularly vexing for physicians, patients and researchers.

Although researchers screen new drugs for interactions via laboratory testing and clinical trials, they can't check for all interactions. Hundreds of prescription and over-the-counter medications are on the market. Potential two-drug combinations number in the tens of thousands, and figures for three-drug mixes are immense.

Moreover, studies that test for specific interactions don't replicate the diversity of patients who ultimately take them. This means drugs that appear not to interact with other drugs in the lab, or in healthy young volunteers, can produce different effects in the real world—where patients are typically older, have a higher burden of illness and take multiple medications.

While the process of drug testing is complex, the knot that binds drug-drug interactions to patient safety is Gordian in its difficulty to untangle.

Researchers have a weapon for that challenge: observational epidemiology. By applying statistical methods to databases of medications, patient care and outcomes—data that were not available just two decades ago—epidemiologists can identify and measure drug-induced harm in large populations. When premarketing drug testing fails to flag a safety problem, epidemiology offers a last line of defense.

Dr. David Juurlink is a scientist in clinical epidemiology at Sunnybrook Research Institute (SRI) and physician in internal medicine and pharmacology at Sunnybrook Health Sciences Centre. Through observational epidemiology, Juurlink, who is also an associate professor of medicine, pediatrics and health policy at the University of Toronto, has helped bring the scope of drug-drug interactions into focus, and has parsed the effects of specific drug combinations in patients with breast cancer, heart disease and other conditions. His findings have implications for millions

of patients and—critically—offer alternatives so that physicians can provide safer, more effective care.

The scale of the drug-drug interactions problem is difficult to gauge because such interactions are hard to detect; most, therefore, go unreported. But in 2003, in the *Journal of the American Medical Association (JAMA)*, Juurlink and colleagues published a study examining the clinical consequences of three dangerous and underappreciated, yet avoidable, drug interactions. They showed that over a six-year period in Ontario, hundreds of patients admitted to hospital with drug toxicity had been prescribed a drug known to interact with one they were already taking. Physicians had seen many of these patients shortly before the patients sought treatment for toxicity, suggesting they missed opportunities to avoid harm. This was the first study to characterize real-world consequences of drug-drug interactions.

In 2008, *JAMA* published a report noting that almost one in three American adults aged 57 to 85 years—about 18 million people—take five or more prescription medications. The same report found that 2.2 million may be at risk for drug-drug interactions. Other studies have found that adverse drug events, many of which are drug-drug interactions, account for up to 5% of hospital admissions, and that these hospitalizations cost, on average, \$16,000 (US). While these numbers



DR. DAVID JUURLINK

outline the scope of the problem, researchers agree that the actual number of interactions dwarfs those recorded.

Whatever the real number, it will continue to grow, primarily because aging populations are taking more medicines in combination. Addressing the problem at the level of practice is difficult, because physicians cannot keep pace with the growing list of interactions and often rely on pharmacists to flag dangerous combinations. Pharmacists watch for interactions, but they are prone to human error and their computer warning systems, though helpful, are imperfect. Biotech companies are developing laboratory tests that screen for drug-drug interactions, but those tests cover a limited range of drugs, and new medications bring new mechanisms. For these reasons, epidemiologists are essential for catching drug-drug interactions and highlighting alternatives.

In 2010, Juurlink and his colleagues in SRI's Odette Cancer Research Program did just that in a study that showed women taking tamoxifen for breast cancer faced a higher risk of dying of the disease

if they received a widely used antidepressant, as opposed to many other antidepressants from the same class.

Typically, women with "estrogen-positive" breast cancer take tamoxifen for five years after initial treatment. The drug reduces the risk of recurrence by about 50%; the risk of death by about 30%. One-third of women who take tamoxifen also take antidepressants called selective serotonin reuptake inhibitors (SSRIs), either for anxiety or depression, or to limit the hot flashes caused by tamoxifen—or both. Physicians have suspected for years, on the basis of surrogate outcomes and basic pharmacology, that some SSRIs might limit the effectiveness of tamoxifen, but research on the issue had been inconclusive.

Juurlink and his colleagues confirmed that the use of the SSRI paroxetine (brand name Paxil) was associated with an increased risk of breast cancer death among women taking tamoxifen, and that the risk was related to the degree of overlap between the two drugs. Women in their study took Paxil, on average, for less than one-half of their time on tamoxifen. The researchers estimated that one additional breast cancer death would result for every 20 women so treated; however, many women took the two drugs together for a longer period. "A woman who took Paxil for the duration of her tamoxifen therapy was effectively not taking tamoxifen," says Juurlink. "Paxil abolishes the benefits of an extremely important anticancer drug."

The study was the largest and most rigorous to date on the interaction between tamoxifen and paroxetine. The *British Medical Journal* published the work with an editorial that recommended physicians avoid co-prescribing the drugs, and that regulators require more warnings about the interaction on drug labels. The journal also suggested physicians consider gradually moving women already on the combination to another SSRI—a call they could make with certainty because Juurlink's study also found that several alternative SSRIs do not interfere with tamoxifen.

In turn, Juurlink and his colleagues had confidence in those alternatives, not only because the study was carefully designed, but also because as a clinical pharmacologist and former pharmacist, he knew the results were supported by insights from pharmacology. Tamoxifen works only after it is converted to an active metabolite called endoxifen, a process that occurs in the liver and is controlled by an enzyme called CYP2D6. In lab tests, paroxetine turns off this conversion process, whereas many other SSRIs do not. "The study's results reflect what basic pharmacology suggests. Venlafaxine and other antidepressants



DR. DAVID JUURLINK

don't cause this problem, but paroxetine and tamoxifen are simply a bad combination," says Juurlink.

Unexpectedly, the study found that another strong CYP2D6 inhibitor, fluoxetine (brand name Prozac), was not associated with an increased risk of death. That finding might have been due to the small number of those on fluoxetine, but it and other intricacies surrounding the biologic effect of tamoxifen suggest that some questions around this drug-drug interaction remain.

Without question, however, the study has changed care. Dr. Kathy Pritchard is a scientist at SRI, medical oncologist in the Odette Cancer Centre at Sunnybrook and co-chair of the National Cancer Institute of Canada's clinical trials breast cancer site group. In her practice, she avoids putting patients on paroxetine or other strong CYP2D6 inhibitors, and she has spoken with oncologists who have switched patients from paroxetine to antidepressants that aren't strong CYP2D6 inhibitors. She says Juurlink's

study, on which she and a fellow in her research group, Dr. Catherine Kelly, were co-authors, was a factor that has changed how she and other oncologists treat breast cancer patients.

The study's specificity was a particular strength, says Pritchard. It showed, for example, that another SSRI called venlafaxine does not interfere significantly with tamoxifen, and not simply because patients took it in lower doses—questions that, as Juurlink notes, would be impossible to examine through a clinical trial. "It's a nifty observational study," Pritchard says.

While Juurlink's breast cancer article tipped the balance on a question that researchers had already studied in patients, a paper he published in the *Canadian Medical Association Journal (CMAJ)* in 2009 alerted cardiologists to a drug-drug interaction that had only been shown in the lab—and of which many physicians were unaware.

Clopidogrel is an anti-platelet medication that reduces blood clotting in patients with heart disease or who have had a stroke.

Platelets help give blood an optimal consistency, but they can become sticky and block blood flow. This stickiness puts heart and stroke patients, in particular those who have had stents inserted (to prop open constricted vessels), at increased risk for cardiovascular problems.

Clopidogrel, known by the brand name Plavix, reduces the risk of additional cardiovascular problems significantly; in 2007 it was the second-best-selling drug in the world, with sales of \$7.3 billion (US). Because clopidogrel can cause unwanted bleeding, however, especially in the stomach, physicians often prescribe it with a proton pump inhibitor (PPI), a drug that protects the stomach. In several laboratory studies, researchers have shown that one of the most commonly used PPIs, omeprazole, interferes with the liver's conversion of clopidogrel into its active metabolite, resulting in stickier platelets.

In an observational study of 13,000 patients who had been discharged from hospital after a heart attack, Juurlink and his colleagues found that those on omeprazole and most other PPIs while taking clopidogrel were at risk of having another heart attack. Patients taking a PPI called pantoprazole, in contrast, were not at increased risk. This study was the first large-scale clinical evidence of a drug-drug interaction that lab science had shown was possible.

Its publication sparked controversy. An editorial in *CMAJ* called for physicians to reevaluate whether their patients on clopidogrel needed a PPI, and recommended that those who needed both medications

be put on pantoprazole or a similar drug. Other editorials were more cautious, calling for more research. In late 2009, spurred by another study published in *JAMA* six weeks after the Sunnybrook study, the U.S. Food and Drug Administration issued a public health advisory on the issue, and in March 2010 required that clopidogrel labels warn of the possible interaction. Other studies followed, using different methods and yielding different conclusions about this interaction, which remains contentious. Researchers on both sides of the issue have cited Juurlink's paper 271 times.*

While noting that reasonable people can reach different conclusions when presented with the same information, Juurlink maintains that PPIs are, as a class, overprescribed, and that co-prescription of the two drugs should be limited to patients with a valid indication. He also acknowledges there is evidence these drugs prevent intestinal bleeding in patients taking clopidogrel with aspirin. "When this study came out, we were concerned that the results might be misinterpreted. Our primary message to physicians and patients was that if you want to combine a PPI with clopidogrel, it makes sense to choose pantoprazole, because it will not interact with clopidogrel," he says.

Physicians worldwide have heeded that advice. Dr. Jack Tu is a scientist at SRI and cardiologist in the Schulich Heart Program at Sunnybrook who holds the Canada Research Chair in Health Services Research. "This is a very important study in the field of cardiology, and as a result of it many physicians—myself included—either stopped giving proton pump inhibitors to all patients or switched to pantoprazole," says Tu, who is also a professor at U of T. Calls from patients and pharmacists exposed to media coverage of the study helped drive that change, which Tu says was immediate and dramatic, the latter because millions of patients had been taking the two drugs together.

Some cardiologists have questioned whether the shift in practice was warranted. They point out that Juurlink's study was an observational study, not a clinical trial, and was therefore prone to "selection bias": patients who get Plavix and a PPI are often sicker than those who get only Plavix, so their poorer health could account for their worse outcomes.

Tu acknowledges that possibility, but notes Juurlink's study controlled for that bias. "Even those who haven't switched their prescribing patterns have become more cautious about prescribing the two drugs together," he says. "It's an issue that every cardiologist in the world now knows about."

Juurlink recognizes that some physicians are more convinced by clinical trials than by observational studies, but says the two are complementary: "Each gives us

information the other can't. A trial tells us how good a drug can be under ideal circumstances, but in real-world practice the story is often different. My interest is the latter, because what actually happens is sometimes very different than what could or should happen."

Juurlink says he found the science behind drug-drug interactions fascinating from the earliest stages of his training, and as a clinician he is keenly interested in whether a drug he is considering for a patient might interfere with one he or she is taking. More exciting, though, he says, is expanding knowledge of drug interactions and disseminating the new knowledge to clinicians. "If you can show that two drugs in combination can be dangerous, but also that another isn't, you give clinicians an alternative. That's gratifying, especially when doing so changes practice."

Juurlink's work is funded by the Canadian Institutes of Health Research, the Ontario Drug Innovation Fund, the Ontario Ministry of Health and Long-Term Care, and the University of Toronto.

*Google Scholar, January 17, 2011

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TICKETS

Inventing a medical device is a rare accomplishment. Rarer still is getting that invention into the global medical marketplace. Here's how two Sunnybrook Research Institute startups did just that, and became in-demand multinational acquisitions

By Jim Oldfield

Catch a Rising Star

On July 6, 2010, Cameron Piron, president of Sentinelle Medical, a Toronto-based developer of magnetic resonance imaging (MRI) equipment for the early detection of breast cancer, sold his company to U.S.-based women's health corporation Hologic for \$85 million.

The deal included an “earn out”—an additional sum equal to a multiple of Sentinelle’s revenue growth over the next two years—that will make it one of the biggest in the history of Canada’s medical device industry.

Though success was rapid—Piron founded Sentinelle just five years ago, based on research he did at Sunnybrook Research Institute (SRI) in the imaging lab of senior scientist Dr. Donald Plewes—it was not easy. Medical device startups in Canada must meet the rigorous demands of skilled and busy clinicians; navigate tight safety regulations and testing requirements; and deal with scarce venture capital and banks that don’t lend freely to startups.

Overcoming these and other challenges required a timely convergence of government funding for innovative research at SRI, economic opportunity and sound decision-making. Perhaps most critical to Sentinelle’s success, however, was a passion to make breast cancer screening for women better. “I can’t say enough about how Cameron and the others associated with Sunnybrook worked their hearts out,” says Plewes, who is also a professor of medical biophysics at the University of Toronto and a silent partner in Sentinelle. “This was more than an opportunity—it was a clarion call to participate in the breast cancer agenda, from a commercial perspective, and it was genuine.”

That clarion call was based on a pressing clinical need.

In the late 1990s, Plewes and colleagues at SRI had begun a clinical trial using MRI to screen women at high risk for breast cancer. As BRCA1 and BRCA2 gene carriers, these women had a lifetime risk of breast cancer approaching 85%, versus 11% for most women. Moreover, their cancers were aggressive and often fatal. The best that clinicians could offer these women were X-ray mammograms, which did not catch small tumours and produced false positives, leading to high rates of preventive mastectomy (breast removal).

Magnetic resonance imaging potentially offered increased detection and the confidence to avoid unnecessary mastectomies, but it had been developed to scan patients lying on their backs, which made breast imaging difficult. Plewes gave Piron, then a graduate student in his lab with a background in systems design engineering, the job of creating a better MRI system for breast imaging. Through several iterations, they honed a dramatically new prototype: patients lay face down on a detachable table, breasts neatly cupped in customized magnetic coils. Radiologists could gather high-resolution images with MRI, then quickly move patients to ultrasound, co-register the data in the system’s software and perform a biopsy if necessary. The process reduced patient time in the magnet by almost two-thirds, making MRI cost-competitive with mammography while providing more accurate results.



CAMERON PIRON

By 2003, radiologists and oncologists were so impressed with the prototype that they began asking Plewes and Piron how they could get one. Shortly thereafter, results from the Sunnybrook trial showed MRI could detect breast tumours with more than twice the sensitivity of other screening methods. The challenge then became how to commercialize and distribute the technology.

Though Piron had been exposed to business through his father, who was an entrepreneur, he had no training for starting a company. Plewes says that at that point, passion was again vital. “I think Cameron realized we were ahead of the curve—the clinical need—that we could see was going to spike. The passion to meet that need added enormously to the tenacity he and the others showed, in those days, to make it happen.”

The standard model for starting a company based on research innovation is to solicit venture capitalists, who invest expecting the company will generate short-term revenue with a single product that enables them to “exit”—get their money back quickly, with a profit.

Instead, Piron and his colleagues, with zero fundraising experience, raised the dollars privately by growing a network of donors among family, friends and radiologists excited about the technology. “There is a lot of private money out there,” says Piron. “People are uncertain where to put it, and they feel good about investing in a new technology for better detection of cancer.”

This approach proved crucial, says Piron, because it enabled the company to think long-term and invest in developing a rich

pipeline of products. By the time Sentinelle was ready for the acquisition by Hologic—largely because they needed a sales force of hundreds to meet demand, which Hologic could offer—their products were best in class.

Dr. Ken Brooks is the vice-president of new technology development at Hologic. He has evaluated about 200 potential acquisitions during his four years with the company, and was instrumental in the purchase of Sentinelle.

“Two things impressed me most about Sentinelle,” says Brooks. “The first was their ability to meet a clinical need for breast MRI that was unmet by the large vendors. This involved patient workflow, coil design, microdynamics, Monte Carlo modeling, etcetera—they just knocked that out of the park. Second, their software made the whole system integrated, which was very impressive.”

Brooks expects Hologic will eventually adapt Sentinelle’s software for most of their product areas, which cover mammography, women’s bone health, preterm birth care and gynecology. Near-term, Brooks and Piron say the hottest synergy will emerge in integrating Hologic’s interventional biopsy technology with Sentinelle’s software, for better breast cancer screening. “No company has owned development in those areas until now, so we’re well-positioned going forward,” says Piron.

Regarding hardware, Brooks says Hologic could use Sentinelle’s coil technology for imaging the female abdomen, head and neck, and they have long-term plans to apply that hardware to men’s health, for earlier detection of and treatment guidance in prostate cancer.

Piron credits his time in the lab of Plewes for shaping the mentality that enabled Sentinelle to produce a pragmatic line of products. “‘Apply what you think in practice or it’s no use.’ Don instilled that in everyone who worked with him,” says Piron. “It drove the technology development cycle in an incredibly rewarding way.” Clinicians now use Sentinelle’s system in over 200 North American sites, and the technology will soon be available around the world.

Concurrent with an applied focus and passion, a Canadian paradox may have shaped Sentinelle’s global competitiveness. The obstacles to starting a medical device company in Canada can spur a sink-or-swim approach that results in high-performing and cost-efficient products—unlike in the U.S., where easier access to capital can undermine efficient design and production. As the device market becomes more international, Canada is honing its production of increasingly saleable products. “It’s an interesting subtlety,” says Piron, “but a lot of Canadian companies are able to expand globally, because they have the right product to offer.”

No Borders

On September 9, 2009, Anil Amlani walked into the Bristol Lounge at the Four Seasons Hotel in Boston for a meeting he hoped would alter the future of his company.

Amlani, president and CEO of Toronto company VisualSonics, had secured a meeting with Kevin Goodwin, president and CEO of SonoSite, a Seattle-based firm with a global presence in hand-held clinical ultrasound.

Amlani was excited because he knew SonoSite was the ideal partner to adapt VisualSonics' preclinical high-frequency ultrasound imaging system—invented by physicists at Sunnybrook Research Institute (SRI)—for use in patients. Goodwin, however, had granted Amlani only 25 minutes between presentations at the investment and health care conference the two were attending to pitch VisualSonics as a potential acquisition.

Over coffee, Amlani outlined the clinical possibilities of the Vevo, VisualSonics' real-time device, which can image tissue microscopically up to three centimetres inside the body. Those potential applications included precise guidance for inserting intravenous lines in infants, a painful procedure that can require multiple needle jabs; early detection of rejection in skin grafts, enabling more effective alterations in treatments; better detection and characterization of skin cancer and diseases of the eye; and noninvasive imaging of blood flow in the hearts of newborns.

Goodwin, an ultrasound aficionado with 22 years in the business, was impressed. "After 15 minutes, he got it," recalls Amlani. Nine months later, SonoSite finalized a \$71-million deal to acquire VisualSonics, sealing one of the largest sales in the history of Ontario's medical imaging industry and putting micro-ultrasound on a fast track to transform radiology and improve care.

Behind the headlines of this success story is a lengthy and frequently unappreciated process of scientific discovery and commercialization known as the "research pipeline." The metaphor fits VisualSonics, whose origins can be traced back over 20 years to the lab of Dr. Stuart Foster, a senior scientist at SRI who holds the Canada Research Chair in Ultrasound Imaging.

In the late 1980s, with funding from the Terry Fox Foundation and other organizations with visionary mandates to support early-stage research, Foster, who is also a professor of medical biophysics at the University of Toronto, began tinkering with high-frequency ultrasound transducers. Just out of curiosity, Foster says, he and his lab were able to fashion the devices to perform reliably in imaging experiments; they discovered subsequently that the trans-

ducers could usefully image human anatomy, in particular the eye and skin. In the early 1990s, in collaboration with Toronto physician Dr. Chuck Pavlin, Foster and SRI licensed a system based on those curiosity-driven experiments to Carl Zeiss Inc., which made the technology available globally for diagnosis of eye conditions including cancer, glaucoma and corneal disease.

By the mid-1990s, it was clear the human genome project was progressing rapidly and that once the genome was mapped, questions of what genes do would proliferate. This piqued Foster's interest and altered his focus. There were no good ways of showing the results of adding or knocking out genes in experiments, a process known as phenotyping, but Foster thought imaging might help solve that problem. Experimenting with mice that lacked a gene called *Wnt-1*, Foster's lab noninvasively captured clear images showing that the brains of the mice had developed without a tiny part. "That was a definitive moment, in terms of understanding that high-frequency ultrasound allowed us to see a lot of interesting things that would have been impossible with any other technology," says Foster.

Because the equipment they used for the gene knockout experiment was mostly cobbled together, Foster and his lab regrouped and designed a completely new machine dedicated to mouse imaging. They considered the functions researchers might need, and what new technologies they should therefore incorporate. They produced a prototype, and with essential investment from Canadian venture capital firms VenGrowth Asset Management and Hargan Ventures, Foster formed VisualSonics to commercialize and distribute the technology.

Scientists in research organizations quickly expressed interest in the machine for studies of embryonic development, cardiovascular disease and cancer. Where early versions of the technology could image six frames per second, by 2004 the system was operating at 100 to 200 frames per second—viable for cardiology research. Over the next two years, VisualSonics grew to employ over 100 people and became the industry leader in high-frequency, real-time microultrasound, manufacturing more than 600 systems for research organizations around the world.

Spurred by new revenue, Foster and VisualSonics steered the technology through several more iterations.

The resulting linear array system, which VisualSonics released in December 2008, was a defining moment for the company and the history of ultrasound. Until that point, microultrasound systems were built around single-element transducers. The new system used 256 transducers in a linear array; by phasing the signals from each transducer, it produced a greater depth of field and enabled focusing at multiple points, which produced a better image. Because the transducers were fixed, there was no mechanical movement, which meant the system could achieve frame rates above 500 per second. Moreover, and critically, elimination of liquid from the machine's design made it safe for clinical use.

According to Amlani, four factors fomented the conditions for VisualSonics' scientific and commercial success: basic-science innovation at SRI; modest yet critical Canadian venture capital investment; funding from government and tax-incentive programs; and the availability of highly qualified engineers and application specialists from the university cluster in southern Ontario. "Those four things were essential and attractive, from a business perspective, and that's why [VisualSonics] is a great story for Canada," says Amlani.

For critics who note that SonoSite represents yet another U.S. company buying out a Canadian business, Amlani has a quick response. "There is no such thing as borders for financials and financing these days. Canadians sell to Americans; Americans sell to Canadians. The question becomes, 'What is the best way to take this technology to the human market, to lessen suffering?'"

With the clinical potential of VisualSonics' technology manifest, the answer to that question came down either to raising capital—which Foster estimates would have been up to \$50 million—privately or through an initial public offering on the stock market, or to finding a corporate partner with clinical capacity.

The latter option was more attractive for three reasons. First, the economic downturn meant securing capital had become especially difficult. Second, despite its profitability, VisualSonics was under pressure to sell from the venture capital firms that had supported it. Third, SonoSite could provide the ideal mix of technical know-how and financial and regulatory resources to push the technology into the clinic.

With profits from multiple products, SonoSite could fund VisualSonics' continued expansion into the preclinical medical device market, forecasted to grow from 8% to 15% annually over several years. They also had experience with regulatory approvals from the U.S. Food and Drug Administration (FDA). More importantly, they had a proven ability to compress large-footprint ultrasound systems, such as the 350-pound Vevo, for point-of-care clinical medicine.

"It was a perfect marriage," says Amlani.

SonoSite liked the deal because VisualSonics had a healthy, profitable business model, with further potential in the preclinical research market, and what Goodwin calls a "strong group of people who accomplished a lot with limited resources." Goodwin was confident that SonoSite could converge VisualSonics' technology with his company's silicon application-specific integration circuit technology to produce a cost-effective, convenient device weighing less than 15 pounds. "We got very excited about what we thought we could do with that technology, between expanding it in the preclinical world of research and bringing it into clinical medicine," says Goodwin.

In the global clinical market, Goodwin expects revenues for the new technology could approach \$1 billion. It's a big opportunity, he says, because it brings physicians something they can't have today, and it fits into the cost-safety paradigm toward which medicine is moving.

SonoSite will put that new technology into their manufacturing and supply chain, then attempt to get FDA approval, which Goodwin anticipates will be quick. "Then I think it's 'Katie bar

the door," he says. "There are a lot of people very interested in this technology for very good reasons. It has the potential to completely transform one's ability to look from the skin line to three centimetres deep in the body, and as the saying goes in our industry, 'Get the anatomy books out again.'"

Foster, for his part, is now focusing his research on photoacoustics, which also holds huge potential for medicine. The idea is that light can be converted into sound, and as it enters the body in nanosecond-length laser pulses, it creates an ultrasound signal. The result is an imaging hybrid that combines the sensitivity and specificity of optics with the readout of ultrasound.

Foster will maintain a scientific advisory role with SonoSite while pursuing photoacoustics research, and he isn't ruling out another commercial venture. Overall, he says he's "quite positive" about the trajectory of his research and the deal with SonoSite, which he calls educational. "I've learned a lot about business and how ideas get translated into things people can use," he says. "And I've come to appreciate what people do in creating commercial instrumentation. There's a lot more to it than straightforward engineering."

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ANIL AMLANI



WOMAN

IT'S A TREND WITH STICKING POWER: MORE AND MORE, PATIENTS ARE CONTRACTING SEVERE AND EVEN FATAL INFECTIONS AGAINST WHICH ANTIBIOTICS ARE IMPOTENT. LEST YOU THINK THIS IS HYPERBOLE, THINK AGAIN: WE SHOULD BE VERY, VERY CONCERNED, SAYS ONE SRI SCIENTIST WHO IS LEADING THE CRUSADE AGAINST 21ST-CENTURY SUPERBUGS BY JIM OLDFIELD

WORLD

DRUGS

In 1940, a British police officer named Albert Alexander was admitted to an Oxford infirmary with a *Staphylococcus aureus* infection. The disease began as a small sore on his lip a few weeks before, but had spread to his face, eyes, scalp and neck, leaving tracts of dead tissue. All treatments failed, including repeated surgeries to drain abscesses, so Alexander's doctors administered an experimental course of penicillin—the first-ever use of this now-iconic antibiotic—in a final attempt to save him. Remarkably, Alexander stabilized and began to recover—until five days later, when his doctors ran out of the miracle cure despite repurifying remains of the compound from his urine.

A few weeks later, as Dr. Brad Spellberg describes in his 2009 book, *Rising Plague: the Global Threat From Deadly Bacteria and Our Dwindling Arsenal To Fight Them*, Alexander died—a common outcome at the time for patients with infectious disease. An autopsy showed the bacteria had spread to almost every part of his body.

Fortunately, as penicillin supplies increased over the next decade, physicians saw unqualified success with previously untreatable infections, including the *S. aureus* that consumed Alexander. Spellman, a physician at Harbor-UCLA Medical Center, notes in his book an ecstatic quality in medical reports from the time:

“These doctors knew they had harnessed a power heretofore unseen in the millennia-long annals of medicine, as if drawing forth and bottling manna from the heavens.”¹

That euphoria did not last long. About one year after the first clinical use of penicillin, doctors reported a case of penicillin-resistant *S. aureus*, and within 10 years similar cases appeared throughout the world. Although the next three decades were a golden age for antibiotics, owing largely to the discovery by pharmaceutical companies of penicillin derivatives, by the 1990s bugs resistant to all combinations of antibiotics had emerged and were spreading through hospitals and the broader community.

Today, antibiotic resistance continues to grow—particularly in hospitals. The U.S. Centers for Disease Control and Prevention reported that in 2002 hospital-acquired infections afflicted 1.7 million Americans; stunningly, 99,000 of them died from those infections, most of which were antibiotic-resistant. Rates of infection in Canada are lower, but antibiotic-resistant strains of *S. aureus*, *Clostridium difficile*, vancomycin-resistant enterococcus and other serious infections are increasingly present in Canadian health care facilities, and previously healthy patients are dying from them. The World Health Organization recently listed

"IT'S A HUGE PROBLEM, AND IT UNDERSCORES WHY IT'S SO IMPORTANT THAT WE USE OUR ANTIBIOTICS APPROPRIATELY," SAYS SIMOR.

antibiotic resistance as one of the top three threats to human health, and in Ontario, government-mandated public reports of hospital infection rates frequently produce alarming—and sometimes alarmist—media coverage.

Into this jittery milieu, the *Canadian Medical Association Journal* in 2009 published a review paper by Dr. Andrew Simor, director of clinical integrative biology at Sunnybrook Research Institute (SRI) and head of microbiology at Sunnybrook Health Sciences Centre.

Simor's paper, "Antimicrobial Resistance in Hospitals: How Concerned Should We Be?" surveyed biological mechanisms of resistance in bacteria and examined the growing impact of antibiotic resistance on patients and hospitals. It also added a Canadian-specific, globally relevant plan of action to the increasingly urgent call from infectious disease experts on what must be done to limit the impending calamity of 21st-century superbugs.

In this article, Simor, who is also a professor in medicine, and laboratory medicine and pathobiology at the University of Toronto, details three approaches that could curtail antibiotic resistance quickly. The first is surveillance—accurately tracking antibiotic resistance rates to compile region- and patient-specific data on risk. "We need baseline and ongoing measurements to see how infection rates are changing over time, and to gauge the impact of our interventions," says Simor. "Canada does not, at the moment, have an adequate, national surveillance system for antibiotic resistance." While we have some rudimentary measures in place, he says, some countries in Europe know their resistance rates for several major organisms, and therefore have a much stronger grip on the problem.

Second, Simor recommends better methods of infection prevention and control. This involves improved cleaning of contaminated environments and more effective isolation of infected patients,

among other methods. Unfortunately, not all of these measures are evidence-based, so progress is challenging. More research in this area is necessary, says Simor, to determine which infection control practices and interventions are likely to be most effective.

Third, Simor calls for more judicious use of antibiotics. "There is no question that one of the major drivers promoting the emergence and spread of antibiotic-resistant organisms in the community and health care settings is antibiotic use," says Simor. "Study after study, globally and in Canada, has documented a substantial amount of inappropriate use."

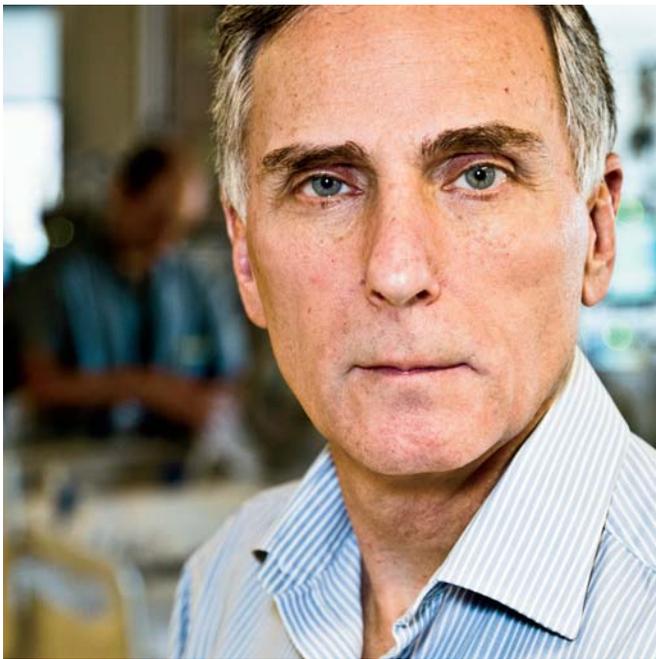
Scientists refer to this problem as "selective antibiotic pressure." To illustrate, Simor points to the role of genetic mutation, one of two main avenues by which bacteria become resistant. Most of the microbes in a particular infection may be susceptible to a particular antibiotic, with perhaps only 1% of them resistant. A physician may treat the infection with that antibiotic and kill 99% of the bacteria, but the remaining resistant microbes no longer have any susceptible competitors, so they become the dominant organism.

More worryingly, superbugs can also develop by acquiring mobile genetic elements from other types of bacteria. Use of one antibiotic can then drive resistance in other classes of organisms—and to other antibiotics that target those other classes. "It's a huge problem, and it underscores why it's so important that we use our antibiotics appropriately," says Simor.

The problem of antibiotic resistance has become so acute in large part because far fewer new antibiotics are coming onto the market precisely when resistance is rising, as Simor notes in his paper. Over the last two decades, pharmaceutical companies have put more resources into developing drugs for increasingly manageable chronic conditions like diabetes, hypertension and heart disease than they have for antibiotics, because the return on investment is far greater: a patient with a chronic condition may require a particular medication every day for decades, for example, while a typical course of antibiotics runs only days to weeks.

Compounding this profit-driven shift are tighter safety regulations and testing requirements for new agents. Greater awareness among consumers and physicians of drug toxicities, potential adverse effects and drug-drug interactions, spurred in part by more robust studies of large patient-record databases, has added tens of millions of dollars to the cost of bringing a new drug to market. Drug development expenses now range from hundreds of millions to billions of dollars per medication, so identification of a problem at a late testing stage can inflict significant financial damage.

Shrinking numbers of approvals for new antibiotics tell the story.



TOP TO BOTTOM: DR. NICK DANEMAN; DR. ANDREW SIMOR

The U.S., for example, approved 16 antibacterial drugs from 1983 to 1987, but only four from 2003 to 2007. Yearly decline between those two periods was consistent; moreover, there are few promising agents in the pipeline. The need for new drugs has become so critical that early in 2010, the Infectious Diseases Society of America, extending its “Bad Bugs Need Drugs” campaign, published a statement called the “10 x ’20 Initiative,” which set the goal of developing 10 new antibiotics by 2020 through cooperation among industry, government and academia.

While the issue of antibacterial drug development is gaining traction with policy makers in the U.S., Simor and Dr. Nick Daneman, a scientist in clinical epidemiology at SRI and doctor specializing in infectious diseases at Sunnybrook, are leading a pilot program based on the third tenet Simor outlined in his paper that could become a model for Canada. With critical care staff and pharmacists at Sunnybrook, they are monitoring antibiotic prescriptions in the hospital’s intensive care units to reduce antibiotic use.

The initiative is an active intervention that contrasts with passive approaches to overprescription like physician education, which research suggests is less effective. On the third day of any prescription for a broad-spectrum antibiotic (one able to fight a range of infection-causing bacteria), a team led by senior infectious disease pharmacist Dr. Sandra Walker and antibiotic stewardship

pharmacist Marion Elligsen reviews the patient’s charts, pharmacy information, and lab culture and susceptibility results. If the pharmacists believe the prescription may not be needed, then they discuss it with the infectious disease physicians on call, and feed a recommendation back to the critical care team. “It’s been very successful, very much because the critical care teams have been involved from inception to implementation,” says Daneman. “Our intervention has been tailored to their needs.”

Six months after starting the program, the research group had reviewed more than 400 prescriptions, and critical care staff had accepted nearly 90% of their recommendations; the immediate result was a 16% reduction in antibiotic use that saved \$140,000 in drug costs. The team will soon have data on the most important outcome — infection rates — which preliminary numbers suggest will be lower.

Over the next year, contingent on funding, the group has two goals: to extend the program to the whole hospital, and to compare long-term data on infection rates before and after the rollout in various Sunnybrook units, thereby adding scientific rigour to a research field that Daneman and Simor say lacks it.

That research on such interventions is insufficient is yet more evidence that the greatest challenge in containing infectious diseases is the remarkable shiftiness of microbes—which while pathogenic are also essential for life. Biological study has shown the genetic pathways on which antibiotics are based, and their corresponding resistance mechanisms, are more than two billion years old. Entering the stage a mere seven decades ago, medicine must indeed step quickly in this evolutionary tango. “We can no longer treat without thinking, in the belief that antibiotics have no potential for harm,” says Simor. “Those days are long gone.”

The Ontario Ministry of Health and Long-Term Care funded Sunnybrook’s antibiotic stewardship initiative through its program, Alternate Funding Plans for Academic Health Science Centres.

1. Brad Spellberg, *Rising Plague: the Global Threat From Deadly Bacteria and Our Dwindling Arsenal To Fight Them* (New York: Prometheus Books, 2009) 50.

BACK FROM AFRICA

It was an easy decision to make, but a difficult one to carry out.

In 2006, Drs. Michael Schull and Josée Sarrazin arranged to take a sabbatical in 2009, resolving to do something “radically different” in their time off. That was the easy part. It would take two years for the married Sunnybrook doctors to work out the logistics of moving their family to Malawi in southeast Africa for one year.

“There were times when I thought, ‘This is impossible. It’s too complicated work-wise.’ By far the toughest thing is not getting settled over there, but disengaging from your professional life here,” says Schull, an emergency physician and senior scientist at Sunnybrook Research Institute (SRI).

With the cooperation of their respective departments, and colleagues agreeing to cover their absences, the couple set out for Zomba, Malawi in July, 2009. Schull spent the year volunteering as a research fellow with Dignitas International, a medical humanitarian organization working to improve human immunodeficiency virus and acquired immunodeficiency syndrome (HIV/AIDS) treatment and prevention programs in developing countries. Sarrazin, a radiologist and professor of medical

imaging at the University of Toronto, had two goals: training technicians to use ultrasound to diagnose disease, and establishing a partnership between her department and the Queen Elizabeth Central Hospital in Blantyre, for consulting and teaching purposes.

Though their work was different, the main difficulty they shared was a severe shortage of health human resources. “Physicians are so rare that in primary care they hardly factor in the public [health] system,” says Schull. And, as Sarrazin learned, there is only one radiologist in all of Malawi, a country of 14 million people.

Moreover, health care workers in Malawi do not receive adequate training. This, combined with a dearth of staff and heavy workloads, leads to low morale, poor relationships among primary health care teams and low rates of job retention, says Schull.

His research seeks to address these problems by developing a training program that combines HIV/AIDS care with primary care for diseases such as malaria, pneumonia and tuberculosis—major global health concerns. The program is designed to improve care in rural health centres by simplifying the work of frontline clinicians and improving communication with patients.

Schull is collecting the data and is encouraged by the changes he observed at some of the sites that received the intervention (of the 30 health centres chosen for the study, 14 received the training and 16 did not).

“The [professional] highlight of the trip was when I went to health centres in remote areas. I would meet a nurse or medical assistant who was in a building with a couple of rooms and a desk—a blood pressure cuff, if they were lucky. They see 200 patients a day, and they’d be using the guidelines and training and say how much easier it made their clinical work. Anything you can do to make the clinical life of those guys easier is satisfying because they have a very tough work life,” says Schull.

While Schull made headway in his research, Sarrazin knew that her academic agenda would need to be scrapped in favour of clinical work and training. She had hoped to study placenta previa—a complication in pregnancy resulting from placenta that is close to or covering the cervix—but realized that with no scheduled imaging for pregnant women in Malawi, there would be no control group for her research. She would have had to restrict her clinical activity to women who presented with symptoms of the condition, something she felt was not a good use of her time.

“With the lack of radiologists in Malawi, to conduct something so precise would have been a loss of resources,” says Sarrazin. “The need was so enormous for

basic diagnoses of acute diseases in patients of all ages that I didn't want to spend time in that niche just so I could bring back numbers to be able to write a paper.”

She focused on teaching technicians in Zomba and Blantyre to use ultrasound, bringing along the portable system given to her by lab members of SRI senior imaging scientist Dr. Peter Burns. “You’re quite humbled when you arrive in a setting like Malawi, by how big your contribution can be in a single year,” she says. There were definite challenges—limitations in the trainees’ knowledge of anatomy and diagnostic techniques—but overall Sarrazin was pleased. “By the end they were really capable of doing abdominal examinations properly,” she says.

She also found that in the resource-scarce environment, feelings of insecurity sometimes prevented people from sharing knowledge with one another. She therefore wanted to impart the value of mentoring. “Part of the teaching I was trying to do was to say that if your colleague is struggling with a case, you should help him, or try to share your skills and teach and help each other.”

At the same time, she learned to adjust her goals and expectations to the situation at hand. Due to the lack of radiology residents in Malawi, her plan to establish a teleradiology program between the hospital in Blantyre and U of T was set aside. And though it wasn’t part of her original plan, Sarrazin spent two days a week doing rounds in the hospital in Zomba helping clinicians diagnose patients.

“You have to be flexible and open-minded,” she says. “I intended to do a bit of teaching. I did not intend to put a lab coat on and do clinical work. But I ended up doing it. You arrive and assess very rapidly the main needs and where your help can be best used.”

It was not just Schull and Sarrazin who showed that they could “go with the flow.” The couple was pleasantly surprised by how quickly their children—Camille, 11; Gabriel, 9 and Juliette, 6—took to their new surroundings. Playing games in the yard, looking at insects and pulling fruit off trees were some of their pastimes.

“They rarely said they missed computer games or TV,” says Schull. “Each child adapted differently, but they all settled in and enjoyed the year. I think they recognized that they were experiencing something very different.”

The opportunity to travel to Africa with his family was also personally meaningful for Schull, who has worked there as a volunteer with Doctors Without Borders.

“What was most novel about the whole year was to experience with it Josée, with the kids—to see it through their eyes and listen to their experiences.”

The pair returned to Toronto last July and resumed their professional duties at Sunnybrook. Reflecting on their year abroad, they say that one of the things they appreciated most was the more relaxed way of life and time to themselves.

“It’s freeing a lot of your mental space,” says Sarrazin. “Allowing yourself to not run constantly from point A to point B is a luxury. It was the absence of constant stress and taking your time the whole year. When will I do that again?”

Over the next two years Schull will analyze data from his research to assess the effectiveness of the training program. He will return to Malawi as a follow-up to his work with Dignitas International, but another long-term stay isn’t in their immediate plans. Sarrazin says they would like to return one day. “We see ourselves going back to Africa at the end of our careers. In between there will be other adventures, but we don’t know what they are.” —Alisa Kim

PHOTOS: JACQUIE LABATT



DR. JOSÉE SARRAZIN



DRS. MICHAEL SCHULL AND JOSÉE SARRAZIN WITH THEIR CHILDREN;
FROM LEFT TO RIGHT: GABRIEL, CAMILLE AND JULIETTE

BLOOMING WHERE SHE'S PLANTED

If success as a scholar depends on being adaptable, then Dr. Chlöe Milsom may be more suited to academia than most.

Milsom, who is doing her postdoctoral fellowship at Sunnybrook Research Institute (SRI), was born in Singapore, raised in England and has lived in Canada with her husband since 2000. After working as a research technician for a few years, Milsom earned her PhD from McMaster University. She moved to Toronto in June 2009 to join the lab of SRI senior scientist Dr. Robert Kerbel, whom she sought for his pioneering work on the use of antiangiogenic therapy—halting a tumour's growth by disrupting its blood supply—to treat cancer.

“He’s so well known throughout the world, particularly for tumour angiogenesis and advanced metastatic disease,” says Milsom of her mentor. “If this is the area you want to study, to come to his lab to do the training is such a fantastic experience. It’s very exciting to be able to do this work and become more independent and established.”

Part of becoming a successful researcher involves securing funding, a skill Milsom is learning quickly. She has already received two prestigious awards: a postdoctoral fellowship from Ontario’s Ministry of Research and Innovation (MRI) worth \$100,000 over two years and a L’Oréal Canada Women in Science fellowship worth \$20,000.

Competition for the awards was intense. Milsom was one of only six postdocs from the University of Toronto’s faculty of medicine to receive the MRI fellowship; moreover, only two L’Oréal Canada Women in Science fellowships were handed out this year.

Together, the fellowships will cover her salary. “I’m very pleased,” says Kerbel. “Graduate students or postdoctoral fellows who obtain such competitive awards



DR. CHLÖE MILSOM

invariably have their development as future independent investigators facilitated. The awards naturally boost the self-confidence of young investigators at a critical point in their training.”

Milsom will use the funds to study a curious phenomenon that occurs in the use of chemotherapy to treat cancer, particularly breast cancer. Chemotherapy, the use of toxic drugs to kill cancer cells, is the most common and, often, the most effective treatment for the disease. Although these drugs are initially helpful in shrinking tumours, the benefits of chemotherapy are compromised not only by harmful side effects, but sometimes also by the rapid regrowth of tumours.

Using preclinical models designed to mimic these responses to chemotherapy, Milsom seeks to identify the processes involved in a tumour’s regrowth by zeroing in on the blood cells known to be involved in the spread of cancer.

“One of the things that has been observed is that there’s an influx of cells from the bone marrow which home into the tumour

and contribute to tumour angiogenesis,” says Milsom. “So the patient’s own body is then helping the tumour to grow. I want to know what factors are being produced by these drugs that lead to this homing of the bone marrow-derived cells into the tumour.”

The chance to do research that can be translated from the lab to the clinic is one reason Milsom came to SRI. “Sometimes when you’re doing research you’re so far removed from helping patients. One of the thrills of coming to this lab is that Dr. Kerbel’s work is very relevant to the clinic,” she says.

She would like to run her own lab one day, but like so many women, Milsom faces the challenge of balancing her personal life with her professional goals. “I would love to have children,” she says. “My next challenge will be incorporating a family with my career. I’d like to do as much as I possibly can. I really want to make the most of my time in this lab and generate some good publications. It’s a fantastic opportunity so I want to use it to the fullest.” — Alisa Kim

WHAT MAKES A SCIENTIST A SCIENTIST?

Three researchers at Sunnybrook Research Institute (SRI)—each of whom holds a Canada Research Chair—offer their insight on the essential ingredients of a scientist.

“When the pieces fall into place, there is euphoria—an Archimedes’ Eureka moment—that inspires you to continue the quest.”

Dr. Bob Kerbel

Senior Scientist
Odette Cancer Research Program, SRI
Professor, University of Toronto
Canada Research Chair in Tumour Biology,
Angiogenesis and Antiangiogenic Therapy

Perhaps it might be better to ask, “What makes a scientist a really good scientist?” Many of the qualities of successful scientists are similar to those of individuals who achieve success in other professions. They include intelligence (brilliance definitely helps), drive and ambition (some would call it ego), the ability to communicate and inspire, perseverance and dedication. But perhaps above and beyond all of these, at least for scientists, is intense curiosity. All successful scientists have in common an enduring passion to discover and learn about new things—to create new knowledge that might actually be useful. For them, reading scientific papers, for example, is not “work,” nor is it a burden—it is both an obsession and a hobby.

Dr. Jack Tu

Senior Scientist
Schulich Heart Research Program, SRI
Professor, University of Toronto
Canada Research Chair in Health
Services Research

Several features distinguish those who become scientists. In general, scientists have an innate curiosity about nature and how things work. They enjoy learning new things, solving challenging problems and expanding their knowledge base.

In their search for knowledge, their novel ideas and solutions often challenge the status quo. Clinician-scientists enjoy helping patients and bringing new discoveries to the bedside. They get very excited about a new treatment or having a paper published as they try to improve patient care and outcomes. Their ability to focus on a complex problem for months or years often results in new ideas or innovative solutions that save lives.

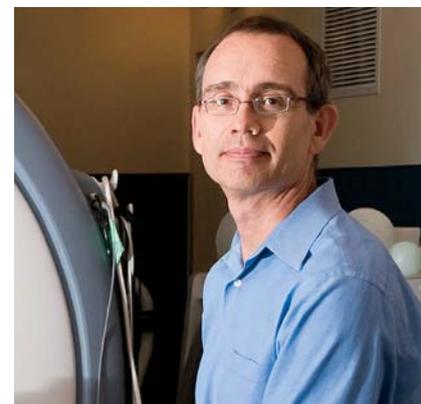
Dr. Graham Wright

Senior Scientist
Schulich Heart Research Program, SRI
Professor, University of Toronto
Canada Research Chair in Imaging for
Cardiovascular Therapeutics

Curiosity. A compulsion to make sense of experience. Perhaps it starts with solving puzzles and progresses to understanding how things work. You make an observation that doesn't fit with your internal picture of the world. I remember in my doctoral studies imaging blood vessels for the first time with MRI [magnetic resonance imaging] and noticing arteries and veins behaved differently. Why? You search the literature to see what is known—often, the answers you find don't quite fit your situation but provide signposts for further enquiry. You start to put together possible explanations, then you do an experiment to see if your explanation holds up. When the pieces fall into place, there is euphoria—an Archimedes' Eureka moment—that inspires you to continue the quest.



TOP TO BOTTOM:
DR. JACK TU; DR. BOB KERBEL

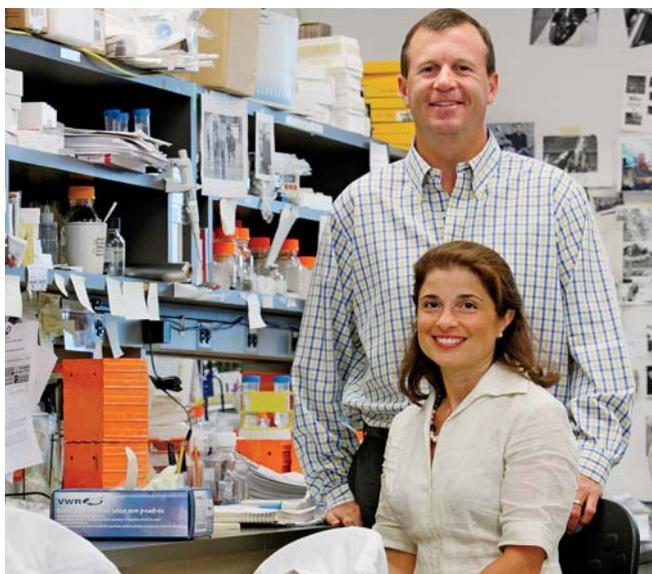


DR. GRAHAM WRIGHT

GIVING TO RESEARCH: A SMART INVESTMENT IN A HEALTHIER FUTURE

Gerrard Schmid and Linda Mantia feel fortunate to be able to support research at Sunnybrook

“It’s a responsibility to give back to the community,” says Gerrard. “And it’s more than just financial support—it’s helping Sunnybrook advance to the next level. Canada needs more world-class leaders, and Sunnybrook is well-positioned to continue to become a world-class research facility.”



GERRARD SCHMID AND LINDA MANTIA

“We’ve always believed that research is an important contributor to how we can improve health care,” says Gerrard, the chair of Sunnybrook’s Research Cabinet. “It’s fascinating to see the range of ideas that the scientists are exploring, and the significant impact they’ll have on patient care in the future.”

After living in England, the couple feels especially appreciative for Ontario’s health care system, and for having Sunnybrook in their backyard. Inspired by the staff and impressed by how swiftly Sunnybrook’s research has an impact on people in need, they are happy to invest in Sunnybrook’s innovation. “With an aging population, we both feel strongly that research is important in developing new alternatives to existing patient care—alternatives that will be minimally invasive, reduce the cost of care and increase the reach of new treatments,” says Linda.

“It’s a responsibility to give back to the community,” says Gerrard. “And it’s more than just financial support—it’s helping Sunnybrook advance to the next level. Canada needs more world-class leaders, and Sunnybrook is well-positioned to continue to become a world-class research facility.”

“This is a very special hospital,” says Linda. “The story needs to get out.”

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

Sunnybrook’s vision is to invent the future of health care. Sunnybrook Research Institute is dedicated to making new discoveries and getting them to patients. The \$470-million Campaign for Sunnybrook is investing \$64 million into new research facilities, including the Centre for Research in Image-Guided Therapeutics; scientists and their highly skilled teams; and specialized research equipment. To support our fundraising goal, please visit www.sunnybrook.ca.

Q&A

Dr. Samira Mubareka

Dr. Samira Mubareka is a scientist at Sunnybrook Research Institute in the Veterans & Community Research Program, and a microbiologist and infectious diseases consultant at Sunnybrook Health Sciences Centre. She is also an assistant professor at the University of Toronto. She spoke with Dilys Chan about her research.

What's the connection among *Staphylococcus aureus*, bacterial pneumonia and influenza?

In recent years, about 30% of cases of severe influenza have been associated with bacterial pneumonia, which in the past was associated with *Streptococcus pneumoniae* and *Haemophilus influenzae*. Since the 1950s, we've seen more bacterial pneumonia that is due to *Staphylococcus aureus*. We don't know why this is—it may be due to vaccination programs for *Streptococcus pneumoniae* and *Haemophilus influenzae*; or the emergence of MRSA [methicillin-resistant *Staphylococcus aureus*], which wasn't present decades ago.

Our research question is: 'Are people colonized with *Staphylococcus aureus* more likely to transmit influenza than people who are not?' If we find this is true, then we could reduce transmission of influenza in patients who are colonized with *Staphylococcus aureus*. The potential secondary outcome would be the reduction of bacterial pneumonia after influenza virus infections.

What do researchers know about influenza compared to 10 years ago?

There has been an amazing amount of new information, thanks to a reverse genetic system. Essentially, you can clone the virus and look at how each segment contributes to viral pathogenesis. We know more about how viruses evade the immune system.

The generation of the 1918 virus has given us insight into virulence factors, mechanisms of disease, and how they differ from one strain to another. We also have a better

understanding of modes of transmission.

We're also gaining an appreciation for different strains of influenza in animals—characteristics of swine or avian influenza virus—and how those can reassort (mix genetic material into new combinations) with human influenza viruses. In addition, with sequencing and surveillance now available globally, we're getting a better sense of which parts of the virus have evolved.

What's been your most interesting finding?

During my fellowship, we looked at aerobiology of viruses and noted that some strains transmit better than others. The more transmissible a virus, the more likely we were to recover it from the air. This is an area I intend to pursue as a research project.

How do you measure the transmission in the air?

We use a liquid impactor, which is a pump that sucks air into a sampler. Then you can culture a virus from that sampler. There are also dry impactors, where you can do polymerase chain reaction assays on sampled air and look for viral RNA [ribonucleic acid, the influenza virus genetic material].

How do your research projects relate to your clinical work?

It's important to me that our work has clinical impact. I think the more clinical work I do, the more our research will be based on clinical questions. It's nice to go from the bedside to the bench, and ultimately back to the bedside with a solution. That's thinking long-term, because it happens over years and years of research. Ultimately, we want to be able to say, 'These are the differences that we've made.'

In addition, understanding the biology of the virus for the sake of advancing our knowledge of the natural world is also important. There are direct and indirect benefits to this, including gaining

insight into how other RNA viruses are transmitted, and what the molecular and environmental determinants for transmission are. Understanding the interactions among host, pathogen and environment will allow us to develop approaches to stop transmission and disease.

Sunnybrook Research Institute provided start-up funding for Mubareka's research. She also received a grant from the Canadian Institutes of Health Research.



DR. SAMIRA MUBAREKA

LIFTOFF

A new model for technology transfer at Sunnybrook Research Institute helps enterprising scientists and their innovations soar

A one-stop shop for commercialization — it's just what enterprising scientists need to ensure their discoveries are moved out of the lab and launched into the marketplace quickly and efficiently.

For scientists at Sunnybrook Research Institute (SRI), MaRS Innovation is that shop. It brings experts together through a partnership that creates “deal teams” to speed scientific discoveries to the market in a new approach to commercialization.

And for those who wonder why a hospital-based research institute would be involved in the business end of medical innovation, Dr. Michael Julius, vice-president of research at Sunnybrook Health Sciences Centre, explains: “SRI is dedicated to making discoveries and delivering them to patients. It's foundational to our vision of inventing the future of health care. We can only do this by going through the rigours of commercialization.”

In April 2008, Canada's National Centres of Excellence for Commercialization and Research program funded the establishment of MaRS Innovation with \$15 million over five years. Now, MaRS Innovation supports 16 member institutions — research-intensive universities and health care centres in Ontario — all of which, in turn, have committed \$10 million to this not-for-profit institution.

“The success and legitimacy of our part-

VASCULOTIDE This compound, a peptide mimetic, stimulates new blood vessel growth, a process known as angiogenesis. The compound has potential in several therapeutics areas, including wound healing, acute lung injury, antimetastatic therapy, asthma and atherosclerosis. The most developed indicator at this time is that for wound healing, especially in the treatment of chronic ulcers that are common among diabetics. Preclinical studies have shown that the compound speeds the healing or closure of wounds—and keeps them closed.

nership with member institutions is based on the quality of science we support,” says Dr. Raphael Hofstein, president and CEO of MaRS Innovation. “Sunnybrook has generated several high-quality scientific breakthroughs, and we offer improved tools for adding value to advanced technologies that are the outcome of scientific research at Sunnybrook.”

MaRS Innovation is applying this new approach via an integrated economic platform, which includes packaging new technologies, protecting intellectual property with patents, advancing project development through brokering industry partnerships and helping with licensing.

The driving force behind MaRS Innovation is to see a return on investment in the research it supports. Accordingly, whenever improvement of a technology prior to commercialization is required, it works to create a company around the innovation, transfer intellectual property

to it, provide money for research development within it and then out-license the innovation. “We help Sunnybrook become the entity that creates the company, which adds significant value to the product,” says Hofstein.

This process, in turn, helps advance the vision of SRI. The research institute receives royalties on the technologies its scientists develop, which it invests in further research, thus perpetuating the innovation cycle, all with the ultimate aim of improving patient care. “Through commercialization, we boost our capacity to extract economic value from the discoveries we make. All the revenue we receive goes directly toward supporting research overhead at SRI,” says Julius.

In March 2010, MaRS Innovation and SRI announced their first agreement: to commercialize four discoveries by SRI scientists. These innovations have broad commercial potential and show promise

TRACKING CATHETER This catheter can create a three-dimensional image of the body's internal structures, which, when combined with traditional fluoroscopic X-ray imaging, would allow a doctor to place the catheter precisely during surgical procedures. The technology could help overcome current limitations of two-dimensional images for catheter positioning in critical procedures such as removal of damaged tissue during cardiac surgery.

COMPUTER DEVICE COMPATIBLE WITH FUNCTIONAL MRI

This device enables scientists and clinicians to measure a patient's brain functions while he or she performs cognitive tasks, to see how the brain works and how it is affected by trauma. Graham and his team are refining the system's design, electrical components and associated computer software.

for treating many clinical conditions, including diabetes, heart disease and traumatic brain injuries.

Dr. Daniel Dumont, senior scientist at SRI and professor in medical biophysics at the University of Toronto, and his research team have developed a compound they've named **vasculotide**.

In the Schulich Heart Research Program at SRI, two new technologies to help with visualization in cardiovascular procedures are in the works.

Electrophysiologist Dr. Eugene Crystal, associate professor in medicine at U of T, and his research team have invented a **tracking catheter**.

Dr. Charles Cunningham, an imaging scientist at SRI and assistant professor in medical biophysics at U of T, has designed a catheter-based technology that can be used in a magnetic resonance imaging (MRI) system — an innovative **guide wire**.

Traumatic brain injury exacts a heavy toll on patients, their families and societies. In an effort to diagnose and understand the severity of such injuries, SRI imaging scientist Dr. Simon Graham, who is also

an associate professor in medical biophysics at U of T, and his team have developed a **computer device compatible with functional MRI**.

These advances build on a successful history of commercialization at SRI that dates back over a decade. During that time several spinoff companies have emerged from innovations at the institute, including VisualSonics Inc., Sentinelle Medical Inc. and Profound Medical Inc.

Dr. Stuart Foster, senior imaging scientist at SRI and professor in medical biophysics at U of T, created the world's first high-frequency microultrasound system. Responding to demand, he formed VisualSonics in 1999 to manufacture the systems for universities, research institutes and drug companies worldwide. In 2010, SonoSite purchased VisualSonics for \$71 million to adapt the technology for neonatal care, early detection of skin cancer and skin-graft rejection, and diagnosis of eye diseases.

In another success story, SRI senior imaging scientist Dr. Donald Plewes, a professor in medical biophysics at U of T,

and Cameron Piron, his former graduate student, established Sentinelle Medical in 2004 based on MRI technology they invented for improved detection and biopsy of breast cancer. In 2010, Hologic acquired Sentinelle for \$85 million, with plans to grow sales of existing products and develop technology to treat other diseases in women and men. (To read more about the rise of VisualSonics and Sentinelle, see page 34 of this magazine.)

Also over the last decade, SRI imaging scientists Drs. Michael Bronskill and Rajiv Chopra, professor and assistant professor, respectively, in medical biophysics at U of T, developed an MRI-guided, transurethral ultrasound system that uses high-intensity focused ultrasound to treat prostate cancer. The treatment is quick to do, safe and less invasive than current treatment options. It's being tested in clinical trials. The pair formed Profound Medical in 2008 to bring the technology to patients.

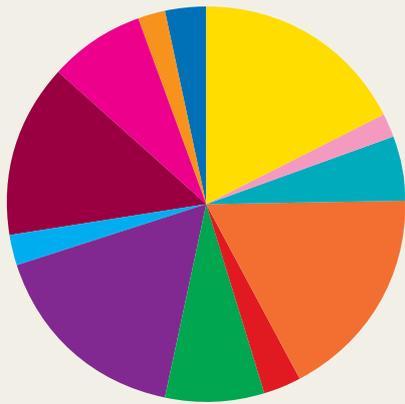
Looking ahead, Hofstein is optimistic about SRI's future inventions. "Technologies that are exported into companies we create in the province and that reach the marketplace will eventually contribute to economic development and return investment to Sunnybrook," he says. "MaRS Innovation will continue supporting SRI, and we will utilize their scientists' brilliant ideas to improve health care in Canada." — Eleni Kanavas

GUIDE WIRE The device enables the marker at the catheter's tip to be turned on and off to visualize more clearly the tissue areas that surgeons need to see during vascular procedures. The technology is early stage; with help from two proof-of-principle grants, including one from MaRS Innovation, Cunningham is working to miniaturize the device and validate it preclinically. The hope is that cardiologists will be able to use the system to treat blocked coronary arteries and peripheral vascular disease.

QUICK STATISTICS

Major Sources of External Funding

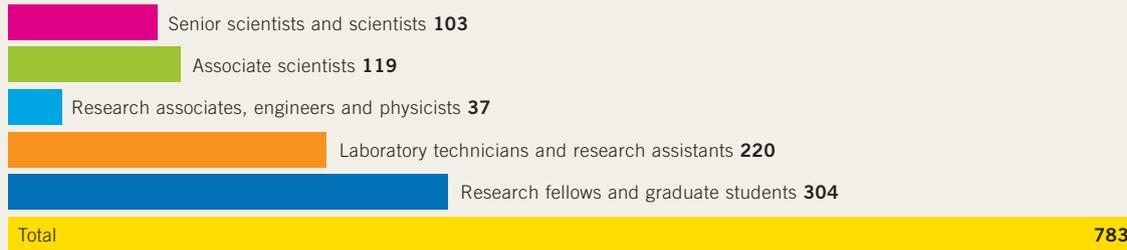
Sunnybrook Research Institute is grateful to the many sponsors who, with each dollar they give, help support research here.



\$84.3 MILLION (2009–2010)

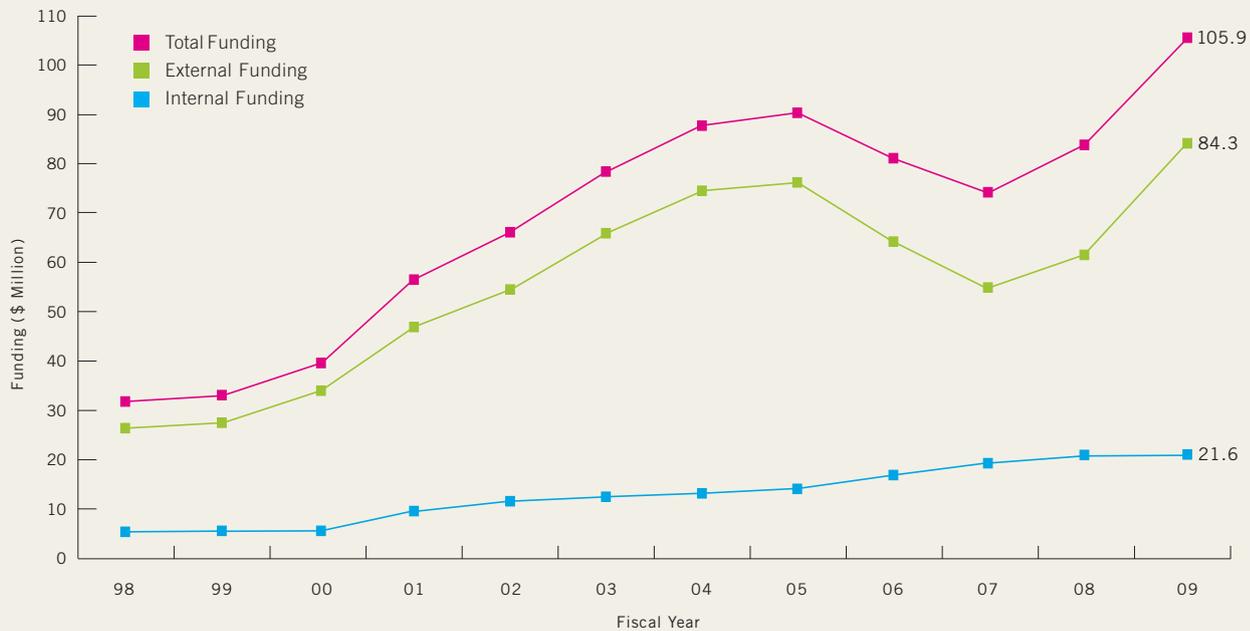
- Canada Foundation for Innovation 18%
- Canada Research Chairs Program 2%
- Canadian Cancer Society Research Institute 6%
- Canadian Institutes of Health Research 17%
- Donations and Trust Income 3%
- Foundations 8%
- Industry 17%
- Ministry of Health and Long-Term Care 2%
- Ministry of Research and Innovation 14%
- Other Funding Sources 8%
- Other Government Sources 2%
- U.S. Sources 3%

Research Staff



History of Research

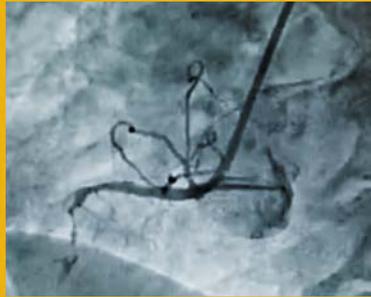
Expenditures at Sunnybrook Research Institute



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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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