

SRI MAGAZINE

SUNNYBROOK RESEARCH INSTITUTE

FOCUS ON
INNOVATION

THE HEART

IMMUNOTHERAPY

Vaccine shows promise in protecting against cancer's insidious spread

FRONTOTEMPORAL DEMENTIA

Imaging biomarker lights up traces of brain decay years in advance

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To read the online version of *Inventing the Future of Health Care* and learn more about Sunnybrook Research Institute, visit sunnybrook.ca/research.



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Messages

Delivering impact



At Sunnybrook, delivering the best care to our patients is our top priority. History shows that yesterday's discoveries are today's gold standard of care. That is why research and innovation are integral to our vision of inventing the future of health care.

Our researchers are at the forefront of finding health care solutions, and crafting them where none exist. Take, for

instance, the findings of a study published last fall by researchers in the Schulich Heart Program.

The team looked at outcomes of patients with diabetes who underwent coronary artery bypass surgery. They found patients who received a radial artery graft from the arm were five times less likely to have a subsequent blockage than those who received a vein graft from the leg. This discovery, about which you will read in this magazine, is poised to transform how bypass surgery, one of the most common heart procedures done worldwide, is performed.

Another major accomplishment last year was a visionary gift of \$20 million from the Hurvitz Family Foundation, through which Sunnybrook will strengthen its standing as a hub of cutting-edge research in neurology and psychiatry. Through this landmark investment, we are building the Hurvitz Brain Sciences Centre in which multidisciplinary experts will collaborate to accelerate research and treatment for brain disorders like stroke, dementia, depression and anxiety.

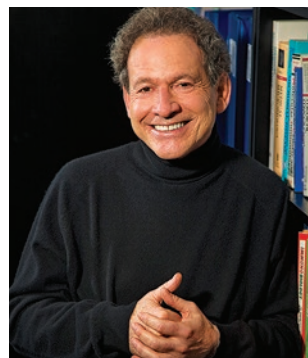
Medical breakthroughs do not happen in a vacuum. They are only possible through the dedication of our staff, and the engagement and generosity of our supporters. Thank you for partnering with us in creating tomorrow's care.

David Agnew

Chair, Board of Directors
Sunnybrook Health Sciences Centre

Barry A. McLellan

President and CEO
Sunnybrook Health Sciences Centre



Impact: That is the best way to summarize the past year at Sunnybrook Research Institute (SRI).

As a hospital-based research institute, making discoveries and getting them to patients is what drives us. We are committed to achieving an "end-to-end" solution. To do this, we need partners. Last year saw the establishment of two multimillion-dollar partnerships garnered

by the scientific excellence of our researchers. Both fall within the framework of image-guided therapeutics, an area in which we lead.

One is a \$25-million investment to develop technology that will revolutionize radiation therapy. On-beam magnetic resonance imaging (MRI)-guided radiation delivery promises to get cancer patients treated within days, not months, and reduce treatment length from months to weeks, all while lessening damage to healthy tissue.

The other is a \$41-million investment involving 29 private sector partners, which will accelerate the commercialization of SRI medical inventions to the global marketplace.

Both of these projects will ensure that the SRI discovery pipeline remains deep and broad, and will help us move forward in our goal to make care better.

To wit, the Ontario Health Technology Advisory Committee provided a strong positive recommendation for the use of MRI-guided ultrasound, pioneered by an SRI scientist in collaboration with industry and clinicians here, to treat uterine fibroids. This incision-less technology transforms a month-long ordeal into an outpatient procedure.

We have many more examples of impact: new advances, new inventions, new solutions for patients. We share some of these with you in this issue of our magazine, which has a special focus on the translational research of the Schulich Heart Program. Enjoy!

Michael Julius

Vice-President, Research
Sunnybrook Research Institute & Sunnybrook Health Sciences Centre
Professor, Departments of Immunology & Medical Biophysics
Faculty of Medicine, University of Toronto

Digest

A round-up of some notable advances and achievements at Sunnybrook Research Institute

THE CANCER'S BEEN TREATED. NOW WHAT?

Cancer therapies have improved survival, but many patients experience pain and problems with mobility and functioning after treatment. To address these challenges, **Dr. Sara McEwen**, a scientist in the St. John's Rehab Research Program at Sunnybrook Research Institute, co-authored a systematic review of rehabilitation interventions after treatment.

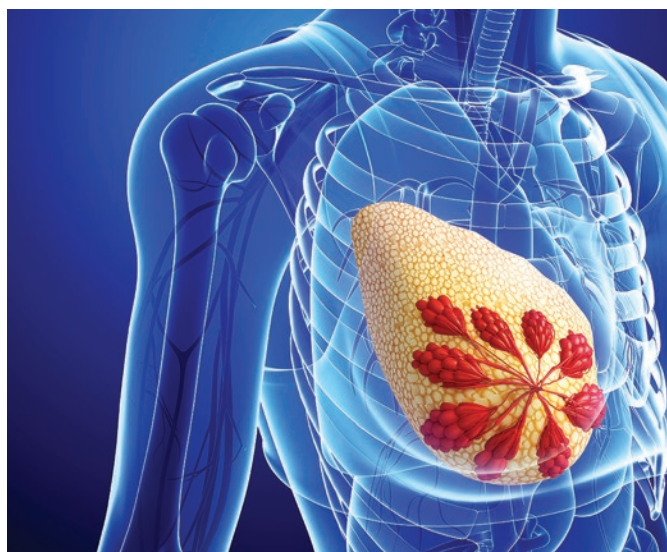
McEwen and colleagues identified areas that could be addressed by rehabilitation, including physical and cognitive functioning, fatigue, pain, depression, employment and nutrition.

The researchers observed that studies in this area are mainly on psychosocial oncology services and supportive care, which have

had limited effectiveness for rehab outcomes. They noted fatigue is a major area of study and treatment, but the related issues of physical deconditioning and cardiorespiratory impairment have not been examined.

Other areas that might benefit from attention to physical rehab include nutrition and energy conservation techniques for people with fatigue, said the researchers.

They also found an exception to the limitations in the literature: rehab after breast cancer. These studies, which have been done by physiotherapy researchers, have resulted in prevention and intervention guidelines for mobility, pain, swelling and function. On the back of this research, new rehabilitation knowledge and care for people with other types of cancer could follow.



Breast Screening: Digital Methods Contrasted

Cancer researchers at Sunnybrook Research Institute are conducting the first Canadian randomized clinical trial designed to compare a 3-D breast screening method to digital mammography as part of the North America-wide Tomosynthesis Mammographic Imaging Screening Trial.

Drs. Roberta Jong and **Martin Yaffe** are co-investigators of the 14-site study. They will compare digital breast tomosynthesis, also called 3-D mammography, with digital mammography to determine which is better at detecting breast cancer.

Digital tomosynthesis takes up to 15 low-radiation-dose images of the breast that are sliced and layered into a three-dimensional view. The technique aims to reduce false alarms, lessen patient anxiety and find up to one-third more of the small, invasive cancers that would be missed with current mammography, said Jong.

Researchers are conducting the trial at two sites in Canada; 2,000 women will be recruited and tracked over two years. An estimated 60,000 women will be enrolled overall.

Jong and Yaffe were also site co-investigators on the Digital Mammographic Imaging Screening Trial. That trial determined that digital mammography was better at detecting breast cancer among women aged under 50 years, who are premenopausal or who have dense breasts.





WHILE YOU WERE SLEEPING

Memory loss commonly affects more than one-third of patients who undergo general anesthesia for surgery. The effect can be lasting, especially in elderly patients, and is linked to poor outcomes and sometimes death.

Dr. Beverley Orser, an affiliate scientist in the Hurvitz Brain Sciences Research Program at Sunnybrook Research Institute and an anesthesiologist at Sunnybrook, and colleagues used a mouse model to look at why anesthetics can cause cognitive impairment. The study was published in *The Journal of Clinical Investigation*.

They found that memory loss receptors remain highly active long after the drugs have left the patient's body, and that this activity can persist for days or months. The results suggest sudden memory loss after surgery can diminish a patient's ability to think clearly at a time when loss of sleep and medications can also affect mental function, said Orser.

Age, health, and the type of surgery and anesthetic can also contribute to the likelihood of a patient experiencing memory loss, noted the researchers, who concluded the study with a call for more research.

Orchestral Manoeuvres of the Heart

When a doctor uses a stethoscope to listen to your heart, what does he or she hear? Most commonly, it is the “lub-dub” sound produced when the heart’s valves close with each beat. When blood flow near the heart is particularly turbulent a whooshing sound can be heard. These sounds, known as heart murmurs, are often caused by a valve that is improperly sealed, narrowed or stiffened. Murmurs are the most common abnormal sound. Irregular heartbeats can also have a galloping rhythm, distinguished by the occurrence of an additional sound, “lub-dub-ta” or “ta-lub-dub.” In young or athletic people, a racing rhythm is likely harmless, but in older patients it may be a sign of heart disease.



ON THE COUCH: Wills in Suicide Notes

Suicide accounts for about one million deaths annually. To understand the mindset of people who commit suicide, some researchers have focused on the language and themes in suicide notes.

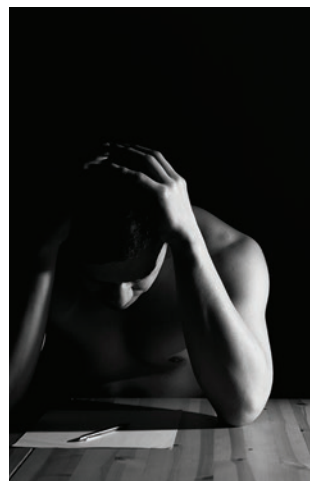
Drs. Mark Sinyor and **Ken Shulman**, clinician-scientists in the Hurvitz Brain Sciences Research Program at Sunnybrook

Research Institute, took a different approach—analyzing who left wills in suicide notes.

They studied records of 1,565 deaths ruled as suicide that occurred in Toronto between 2003 and 2009. Among these, 285 suicide notes were left behind.

Within these notes, 59 had wills. Compared with those who left no note, or a note and no will, people who left wills were more likely to be single and live alone, and be divorced or widowed.

A major mood or psychotic disorder was detected in 73% of people who left a will, but none had dementia. This is the first study to examine will content in suicide notes. The researchers concluded that the high rate of mental illness around time of death is important for understanding the psychology of people who die by suicide and has legal implications for their ability to leave a valid will.



SNAPSHOT OF AN OUTBREAK

The 2014 Ebola outbreak began in a remote area in Guinea, in West Africa. It spread to the capital, Conakry, and to bordering countries Liberia and Sierra Leone. Although at press time the epidemic was ebbing, the damage wrought has been catastrophic. It is by far the largest Ebola outbreak ever. It has infected close to 25,000 people and killed more than 10,000 people.

Dr. Rob Fowler, a senior scientist in the Trauma, Emergency & Critical Care Research Program at Sunnybrook Research Institute, led a retrospective observational study of patients with Ebola virus disease (EVD) in Conakry from March 25 to April 26, 2014. The study, the first to describe patients' demographic and clinical characteristics at the onset of the outbreak, was published in the

New England Journal of Medicine.

The primary outcome was death. During the study period, 37 patients had lab-confirmed EVD; 24 were men and 14 were health care workers. On average, patients presented to hospital five days after the onset of symptoms, which were fever, fatigue, diarrhea and fast heart rate. All patients were treated with antibiotics; 76% were given intravenous fluids for dehydration.

The mortality rate was 43%, which is lower than that of past EVD outbreaks. The lower rate could be due to adherence to new guidelines that promote interventions, including use of fluid and electrolyte replacement, certain antibiotics and targeted lab testing, said the researchers. These findings highlight the need for rapid support for infection control practices to protect patients and health care workers.



To the Bone

Radiation therapy can help reduce pain and improve quality of life for patients with bone metastases, when cancer spreads from its original site to the bone. Repeat treatment is often required, but data on the best dose are lacking.

Dr. Edward Chow, a senior scientist in the Odette Cancer Research Program at Sunnybrook Research Institute, led a study that compared two radiation doses in patients with painful bone metastases who required repeated treatment. It is the first such multicentre, randomized clinical trial to assess two radiotherapy doses and measure pain-relief scores.

The study spanned nine countries, including Canada. It enrolled 850 patients who had previously received radiation therapy and randomly assigned them to receive either 8 Gy in a single dose of radiation or 20 Gy in multiple doses. (Gy is short form for "gray unit," which is used to measure the amount of radiation absorbed.)

Chow found that 48% of all patients who received their assigned treatment had less pain at the site of repeat radiation, as well as less need for pain-relief medication. The results also suggested that a single dose with 8 Gy might be preferable to 20 Gy administered in multiple doses because of similar pain relief and lower toxicity.

The findings, published in *The Lancet*, will help inform practice, policies and future research in treating patients with bone metastases.



Dr. Rob Fowler spent weeks looking after patients at the World Health Organization Ebola isolation facility in Conakry, Guinea.

Photos: (Left) Courtesy of Dr. Rob Fowler / (Right) @iStock.com/Spondylolithesis

Non Sequitur

Dancers at the National Ballet of Canada pirouette through 120 to 150 pairs of pointe shoes per year. Depending on the role, one pair lasts two to eight hours.



THE BEAT GOES ON

In *Indiana Jones and the Temple of Doom*, there is a scene in which the heart is ripped out of a sacrifice victim and continues to pulse vigorously as its previous owner is lowered into a pit of molten lava. Can the heart continue to beat outside the body or is this made-for-movies science fiction?

Most muscles depend on electrical impulses sent from the brain to be able to move and contract. The heart, on the other hand, can generate its own electrical impulses independent of the brain. This unique characteristic allows the heart to continue beating after being removed from the body. However, without blood vessels supplying oxygen to heart cells, the heart quickly runs out of oxygen and stops beating after a few seconds.

→ WEB EXTRA

Visit sunnybrook.ca/research to read about other advances SRI scientists have made, which include new methods to predict treatment response in women with breast cancer; extended monitoring to improve detection of atrial fibrillation in stroke patients; and strategies to reduce death in patients infected with Ebola.

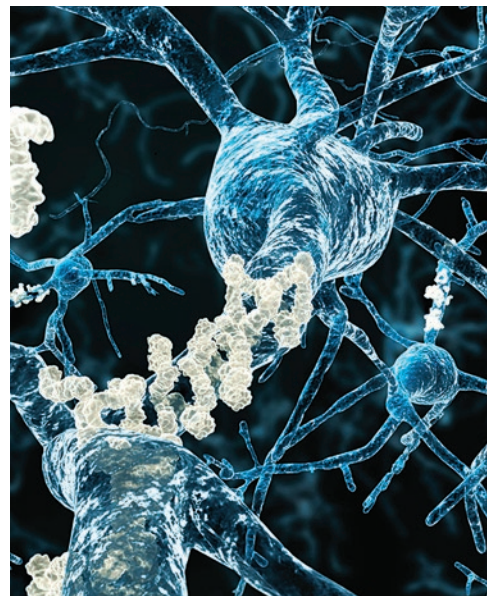
Penetrating Into Deep-Brain Territory

Scientists at Sunnybrook Research Institute (SRI) are pioneering a noninvasive approach to treating Alzheimer's disease and other brain disorders. At its essence, transcranial focused ultrasound increases the permeability of the blood-brain barrier temporarily such that antibodies and other therapeutic substances can slip through, directly to the source of the problem.

Recently, **Dr. Kullervo Hynynen**, director of Physical Sciences at SRI, and **Dr. Isabelle Aubert**, senior scientist in Biological Sciences at SRI, co-authored a study to examine whether repeated magnetic resonance imaging (MRI)-guided focused ultrasound treatments targeted to the hippocampus, a structure involved in memory and spatial navigation, could change pathological abnormalities, plasticity and behaviour.

The researchers used MRI-guided focused ultrasound to treat the hippocampus weekly in a mouse model of Alzheimer's disease. One month later, they assessed changes.

They found that repeated MRI-guided focused ultrasound targeted to the hippocampus improved spatial memory in the treated mice, which they suggest might have been the result of reduced plaque load and increased



neuronal plasticity due to the treatment. Indeed, the mice performed as well as those that didn't have Alzheimer's disease. Moreover, the hippocampus of treated mice had more newborn neurons and longer, more branched dendrites.

Published in *Radiology*, the study shows the therapy has the potential to ameliorate symptoms and abnormalities associated with Alzheimer's disease, and improve drug delivery to the brain.

ARRESTING STROKE

Scientists at Sunnybrook Research Institute were part of an international clinical trial that showed rapid endovascular treatment, a procedure used to remove blood clots in the brain, can reduce the death rate by 50% and decrease neurological disability in patients who experience a moderate to severe ischemic stroke. So compelling were interim findings that the study was stopped early. **Dr. Richard Swartz**, a scientist in the Hurvitz Brain Sciences Research Program, was an investigator on the trial.

Endovascular treatment is a minimally invasive procedure that involves inserting a catheter into the artery in the

groin, through the body and into the brain vessels to the clot. Under X-ray image guidance the clot is pulled out by a retrievable stent, thereby restoring blood flow to the brain.

The study, led by the University of Calgary and published in the *New England Journal of Medicine*, enrolled 316 patients from 22 sites who arrived at hospital within 12 hours of their stroke. Patients were randomized to receive either standard care with a clot-busting drug or the clot-busting drug plus rapid endovascular treatment. After 90 days, patients who received endovascular treatment had better outcomes—they went home after treatment and did not experience major neurological disability—and fewer of them died: 10% versus 19%

of those who did not receive the intervention.

"This is the most significant advance in emergency stroke treatment in the last 20 years, and Canada will be one of the first countries to incorporate this treatment into stroke best practice guidelines," said Swartz.





International Impact

For eight years, **Dr. Jon Barrett**, director of the Women & Babies Research Program at Sunnybrook Research Institute, led the 25-country, 106-centre trial to determine which of vaginal birth or planned caesarean section is safest for twins. The long-awaited results were clear: vaginal birth is as safe as a planned C-section for twins delivered between 32 and 38 weeks of gestation when the pregnancy is otherwise uncomplicated and the first baby presents head down.

Evidence from Barrett's trial has helped to promote the practice of vaginal twin delivery across the globe, including in Hong Kong, in a regional obstetric unit that delivers about 6,000 babies

and 100 pairs of twins annually.

As reported in the *International Journal of Gynecology & Obstetrics*, obstetricians at Kwong Wah Hospital have seen a drop in vaginal twin delivery from 70% in 1993 to as low as 10% in 2008. Since then, however, the rate in the unit has rebounded to 40% in 2012, in part because of the unit's research showing outcomes for twins delivered via C-section were not better than those delivered vaginally, which in turn led to a change in the unit's practice.

This, coupled with the results of Barrett's study, suggests the time to revisit the policy on how twins are delivered is now, concluded the researchers.

Backing Brain Sciences

The Hurvitz Family Foundation has given its name and \$20 million to establish the Hurvitz Brain Sciences Centre at Sunnybrook. The state-of-the-art facility, the first of its kind in the country, will accelerate progress into and treatment of brain disorders.

"We are the only place in Canada where world-class researchers and clinicians in all three of the most common brain disorders—dementia, stroke, as well as depression and anxiety—work closely together to

transform care," said **Dr. Anthony Levitt**, chief of the Hurvitz Brain Sciences Program and a scientist at Sunnybrook Research Institute.

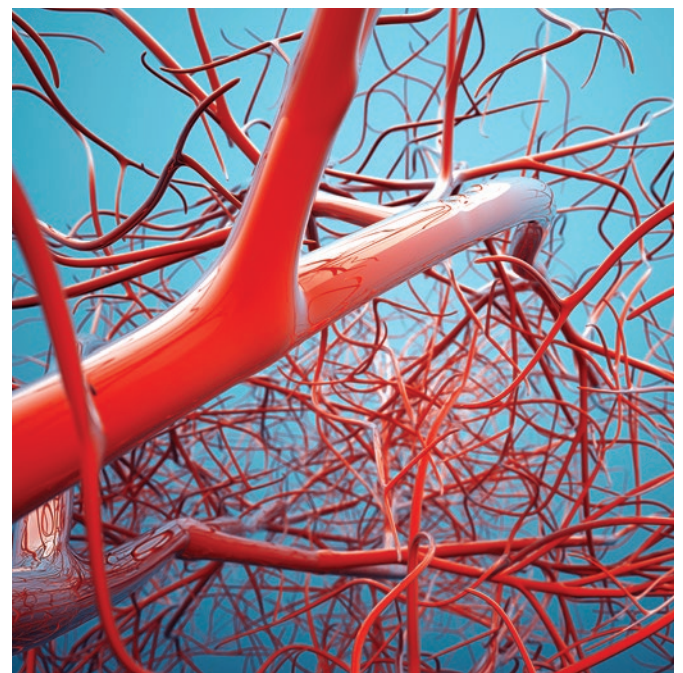
The centre of excellence in neurosciences is encouraging a collaborative approach to tackling brain conditions by linking experts across the disciplines of psychiatry, neurology, imaging, pharmacology, neurosurgery, ophthalmology and geriatrics.

The facility will cost roughly \$50 million to bring to fruition: Sunnybrook's mental health wing will be renovated, and a new building will go up beside it.

GO WITH THE FLOW

The cardiovascular system transports nutrients, gases and waste to and from cells in the body to maintain a stable environment and help fight disease. It comprises the heart, blood and three main types of blood vessels: arteries, which carry blood away from the heart; veins, which bring blood back to the

heart; and capillaries, the smallest blood vessels, which allow exchange of water and nutrients between the blood and surrounding tissues. Stretched from end-to-end the blood vessels in an adult would measure roughly 97,000 kilometres—long enough to wrap around the earth two-and-a-half times.



"The good news is that you don't have apnea. The bad news is that Fluffy sleeps on your face."

More Is Better

Intensive dialysis treatment generally safe for women with kidney failure

PREGNANCY IS often impossible in young women with advanced kidney disease. In the rare instances where women on dialysis are able to conceive, pregnancy is associated with complications and can be dangerous for mother and baby. Dialysis is a blood-cleansing procedure used when kidneys no longer function. It helps to remove toxins from the body. In women of childbearing age who are on dialysis the rate of pregnancy in some studies is less than 1%.

Looking to improve that figure, researchers at Sunnybrook Research Institute (SRI), along with colleagues at Mount Sinai Hospital, the University Health Network and community nephrologists, looked at data from a Toronto nocturnal hemodialysis program that suggested treating women with a more intensive dose of dialysis might restore ovulation cycles, thereby enabling conception, pregnancy and childbirth.

Dr. Michelle Hladunewich, an associate scientist in the Women & Babies Research Program at SRI and director of nephrology and obstetrical medicine at Sunnybrook, led the effort. It was the first retrospective cohort study to compare dialysis outcomes in pregnant women in Canada and the U.S.

The team compared data from a Toronto and an American registry. They looked at the rates of live birth, gestational age and birth weight from 22 pregnancies in the Toronto group and 70 pregnancies in the U.S. cohort.

Pregnant women in Toronto received more aggressive treatment. On average, they received dialysis for 43 hours



Meghan Kilner gave birth to a healthy boy at 37 weeks gestation after months of intensive dialysis. Leeland Allen Kilner Code was born on Jan. 18, 2015 at Sunnybrook.

per week; women in the U.S. cohort received it for 17 hours.

The results, published in the *Journal of the American Society of Nephrology*, also found a significantly higher live birth rate in the Canadian versus American cohort: 86.4% versus 61.4%. Critically, the researchers found that women on dialysis for more than 36 hours per week had a live birth rate of 85%, compared with 48% in patients who received fewer than 20 hours of dialysis per week.

"Frequent and longer dialysis sessions dramatically improved pregnancy outcomes and should be considered for dialysis patients who want to become pregnant or who are already pregnant," says Hladunewich, who is also an associate professor at the University of Toronto.

Moreover, intensive dialysis had other benefits. "Not only did we have a higher live birth rate, but these pregnancies lasted longer and the babies were a little bit bigger. That makes a big difference in terms of

neonatal intensive care and long-term outcomes for these children," says Hladunewich. The median duration of pregnancy for Canadian women was 36 weeks, versus 27 weeks for American women.

Although there were a few maternal and neonatal complications, they were manageable; overall, the study showed pregnancy is generally safe and feasible in women who are given more intensive dialysis. "This was an opportunity to say that something we're doing well here can be replicated elsewhere, so that there is more hope for women who lose their kidney function and hence their fertility during their reproductive ages," she says.

ELENI KANAVAS

→ WEB EXTRA

Read about Meghan Kilner's journey through pregnancy and dialysis at sunnybrook.ca/research.

Always Connect

Systematic approach to communication during patient care handover best: study

THE MORNING handover of patient care, whereby patient information and clinical responsibility are transferred through spoken and written communication between physicians and medical teams at the start of a shift, is a vulnerable time for patient safety. There is a perception among health care practitioners that trainees, encompassing medical students and residents, make it even riskier because they sometimes fail to communicate pertinent information. In part, this is viewed as being attributable to an overall reduction in resident duty hours, which has led to more handovers.

Few studies have looked at the quality and interaction of the morning handover at the end of an overnight shift. Given this paucity of evidence, Dr. Brian Wong, an associate scientist in the Veterans & Community Research Program at Sunnybrook Research Institute, co-led a study that assessed how frequently the overnight on-call trainee would convey clinically relevant patient issues to the daytime team. The aim was to identify factors that led to omissions in verbal handover of overnight on-call issues.

The researchers observed 26 morning handovers on the general internal medicine wards at Sunnybrook and Toronto Western Hospital. Participants were on-call third-year medical students and first- and second-year residents. Teams included one attending physician, one senior resident, at least two interns and two medical students. Each was responsible for 15 to 30 patients per day.

Of the 141 cases analyzed, Wong found that the on-call trainee omitted 40% of clinically important issues

during the handover and did not document information in the patient's medical record for 86% of the issues. Only 14% of these issues had a progress note from the on-call trainee in the chart. Results were published in *JAMA Internal Medicine*.

"What became apparent was the handover processes are very variable. There's little consistency across the teams," says Wong, who is also an assistant professor at the University of Toronto. "It's a chaotic time because it's the start of the day, so people are constantly being interrupted and asked to take care of other problems. It's disruptive when you're trying to have a conversation as a team."

The groups used three main approaches to talk about the overnight issues during morning handover.

The first, used 63% of the time, involved the team discussing each patient one by one, guided by a written list. The second, used 22% of the time, entailed giving the resident a

single opportunity to delegate issues. The third was conveying information to a senior-level team member; it was used 15% of the time.

"We found in those instances when the teams were more systematic [that] if they went through every single patient, it was more likely that the information would be conveyed back to the team," says Wong about the list approach, which had the fewest omissions.

Wong says failure to communicate and document information could cause unnecessary delays and a lack of follow-up to address important issues.

"There is a strong belief that many patient safety problems are rooted in communication-type problems," he says. "If we can improve our communication practices, there's a chance that we can improve safety for patients."

ELENI KANAVAS



First-year resident Dr. Danielle Hammond (left) reviews patient charts with Dr. Brian Wong.

Predicting Fracture Risk

Taking the guesswork out of radiotherapy technique



Dr. Arjun Sahgal (left) and Dr. Cari Whyne have partnered to understand why some patients develop a spinal fracture after undergoing stereotactic body radiotherapy and how that risk can be minimized.

PICTURE A CANCER remedy that targets a tumour with extreme precision and effectively spares surrounding healthy tissues to minimize harmful side effects. Moreover, instead of undergoing months of therapy, imagine completing treatment in two weeks.

Sounds good, doesn't it?

Stereotactic body radiotherapy (SBRT) is an emerging treatment designed to work this way. Like conventional radiotherapy, SBRT uses high-energy radiation to damage the DNA of cancer cells, thus curtailing the cells'

reproductive spree. However, instead of giving small doses of radiation over many weeks, SBRT delivers high doses of focused radiotherapy in a few days or weeks.

"We're early adopters [of SBRT]," says Dr. Arjun Sahgal, a scientist in the Odette Cancer Research Program at Sunnybrook Research Institute (SRI) and a radiation oncologist at Sunnybrook. "It's standard practice for selected indications. Our research focus is to develop new indications and ways to roll it out to more patients because it's a highly effective therapy and a new paradigm in radiation oncology."

The technique uses 3-D imaging

like computed tomography (CT) and magnetic resonance imaging to pinpoint the target area and plan treatment. The therapy is delivered at several angles and planes, which enables a greater dose to be given. Use of SBRT is normally limited to small, well-defined cancers in the body, including those of the lung, liver, spine, abdomen and prostate.

Sunnybrook has offered stereotactic radiosurgery for brain tumours for many years. In a 2015 study involving patients with brain metastases aged under 50 years, Sahgal showed that the therapy alone extended survival to 13.6 months, versus 8.2 months for patients who had stereotactic radiosurgery plus whole brain radiation treatment.

In 2007, the hospital launched an SBRT program for body sites, initially for spine and lung tumours. The program has since expanded to include treatment of cancers of the kidney, liver and prostate, and cancers that have spread to only a few sites.

In the spine, Sahgal says he is seeing local control rates of about 80% one year after treatment, even in tumours that are highly resistant to radiation, like kidney cancer metastases. A 2012 study by researchers in Japan showed the five-year survival rate of patients with lung cancer who were treated with SBRT was 41%, compared with survival rates of 13% to 22% for patients who had standard radiotherapy.

Although SBRT shows promise, it's not without risks. In the case of tumours that have spread to the spine, a troubling complication is vertebral compression fracture, which can cause debilitating pain, reduce mobility and necessitate surgery. Sahgal's research has shown that spinal fractures brought on by SBRT typically occur within three to six months of treatment, and

are likely caused by the intensity of the radiation.

Sahgal and Dr. Cari Whyne, director of the Holland Musculoskeletal Research Program at SRI, did a literature review published in 2014 in *Lancet Oncology* that showed the risk of spinal fracture after SBRT ranges from 11% to 39%, worrisome figures given that with conventional radiotherapy the risk of this complication is much lower—about 5%. In light of these findings, they sought to understand who is most likely to have a spinal fracture after SBRT.

A big piece of the puzzle is the amount of tumour in the bone itself, says Whyne, who is also a professor in the department of surgery at the University of Toronto. Her lab has engineered software that calculates the tumour volume in the spine based on a CT scan. “What we have developed over the years is a way to quantify the tumour volume within these vertebrae. When you do a volumetric quantification using this CT data, that can help us identify patients that may indeed go on to fracture versus those that don’t.”



In this spinal column, cancer has spread to the fifth and lowest vertebra of the lumbar spine, called L5. Almost 40% of patients with cancer develop spinal metastases. Stereotactic body radiation therapy shows promise as a treatment.

She and Sahgal, who is also a professor at U of T, used the software to analyze the CT scans of patients with tumours that had spread to the spine who were treated with SBRT. They then looked at clinical data on the patients’ outcomes to determine whether there was a threshold beyond which fracture was likely to occur. “It’s really about volume: How much tumour is there? How much bone is missing that’s been replaced by tumour?” says Whyne.

As they discovered, it turns out that the threshold, or amount of disease that can predict fracture risk, is between 10% and 15% tumour volume.

Having a standard measurement takes the guesswork out of identifying which patients may go on to have a spinal fracture after SBRT—something that has not been done before, notes Sahgal.

For instance, clinicians now use a classification system to determine a patient’s risk for spinal instability. One of the problems with it, however, is the variability in evaluating one of the risk factors—the amount of lytic disease, or the amount of bone that’s been destroyed by a tumour.

“The way we were looking at the spinal instability neoplastic score is if something is 50% lytic versus less than 50% lytic—but there’s no way of knowing what that is. It’s judged by the clinician’s eyeballing of 2-D scan slices. We’re using subjectivity in complex medical decision-making. We have to take the subjectivity out and put in quantifiable metrics,” says Sahgal.

Whyne says they will also try to uncover why, biologically, spinal fractures occur after SBRT. “We’re trying to understand it from a basic biomechanics perspective—the mechanism for why this is happening. Is there something we can do to reduce the impact or effects?”

Whyne developed the software for research, but she and Sahgal are working with a Toronto-based medical imaging company to develop it into a tool that can help clinicians with treatment planning.

The technology could, for example, inform a radiation oncologist’s decision to recommend a spine stabilization procedure before getting SBRT, says Sahgal.

As they discovered, it turns out that the threshold, or amount of disease that can predict fracture risk, is between 10% and 15% tumour volume.

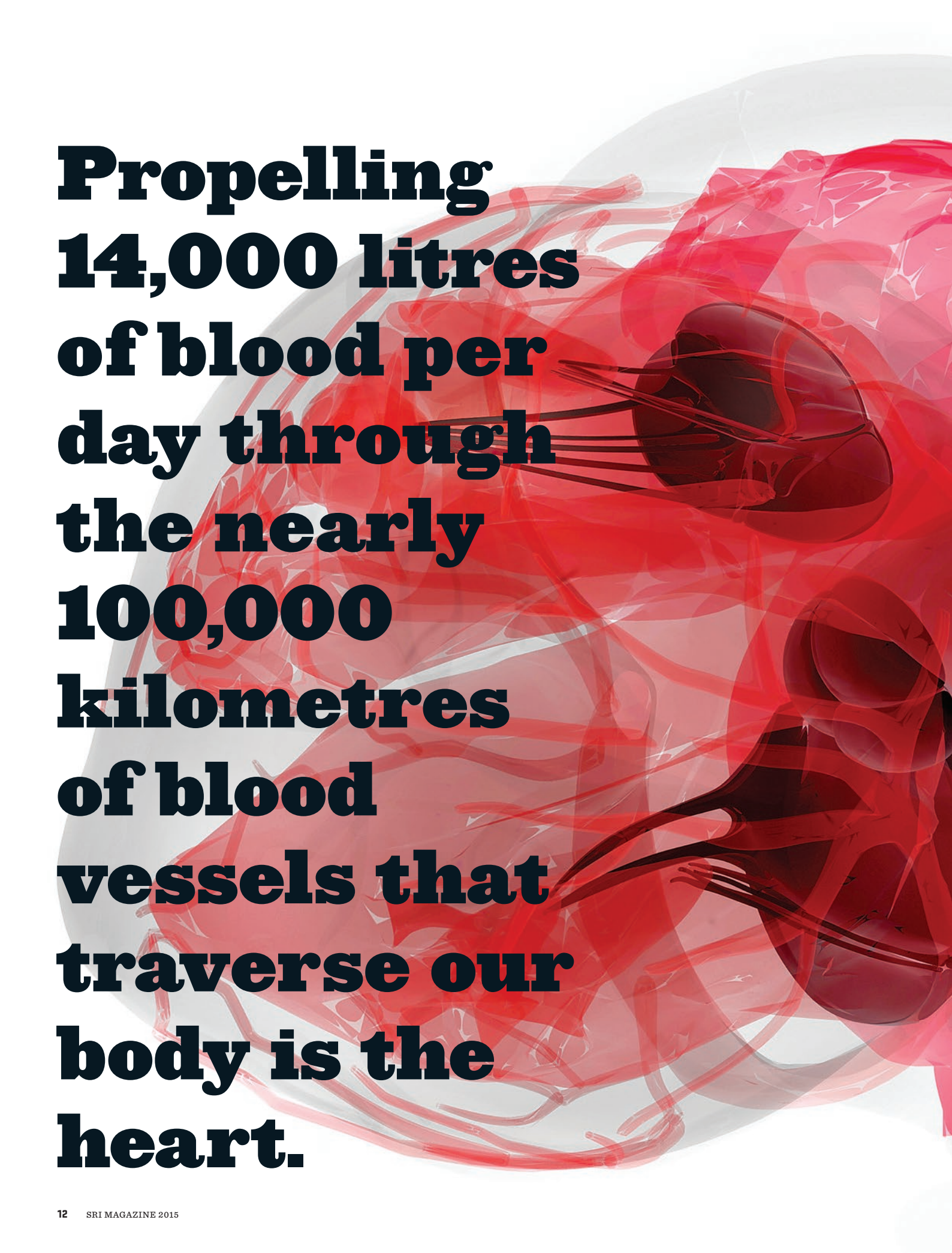
“Right now, we have no idea what the ideal clinical treatment workflow is for the patient based on their vertebral characteristics.” Moreover, the software may have broader clinical applications, he adds. “Ultimately it goes beyond radiation. It goes to surgeons or any oncologic assessment where you’re looking at the vertebrae and somebody who has pain, and saying, ‘What is the best therapy for this person?’”

In Canada, SBRT is offered in British Columbia, Alberta, Manitoba, Ontario and Quebec, generally only in large cities. Although Sunnybrook is an early provider of the therapy, Whyne says rigorous study is needed to improve patient outcomes. “We’re trying to understand and optimize it so that it benefits those patients who will benefit from it, and so that we change what we do for patients who may have complications.”


ALISA KIM

Sahgal’s research is supported by the Brain Tumour Foundation of Canada.

Whyne’s research is supported by the AO Foundation, Canadian Breast Cancer Foundation, Canadian Institutes of Health Research, Federal Economic Development Agency for Southern Ontario, Natural Sciences and Engineering Research Council of Canada, and Ontario Centres of Excellence.



**Propelling
14,000 litres
of blood per
day through
the nearly
100,000
kilometres
of blood
vessels that
traverse our
body is the
heart.**



Our cardiovascular system gives us life. Insult and injury can as easily take it away.

Most know some of the statistics, often owing to a personal trauma: heart disease has infiltrated 1.3 million Canadians and kills 34,000 each year, including 14,000 by heart attack. Another 4,300 people succumb to heart failure. That cardiac arrest kills “only” 450 Canadians is no comfort to those left behind.

Death is not the only metric that matters. For those coping with a chronic cardiac condition, quality of life can be dicey, at best. Atrial fibrillation, a mouthful to say, nonetheless has entered the vernacular of most baby boomers. It affects 350,000 Canadians, more so with age, with the knock-on effect of a three to five times higher risk of stroke, a major cause of long-term disability. All of this is costly: to families and societies.

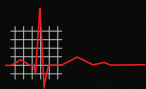
The good news is that research is chipping away at the numbers. Scientists in the Schulich Heart Program are at the forefront. Their most important tool is not a chisel, but ingenuity. Coupled with a craving to change the course of cardiac care, they are formidable.

Their research moves from the preclinical to the clinical. It is translated to patients via commercialization, and policy and practice revisions. Our scientists are spurred on by the hospital’s support of heart and vascular diseases as a strategic priority. Advances in outcomes, minimally invasive interventions and imaging—like techniques to see inside the heart and vessels in exciting new ways—are forcing this muscle to give up its tightly clenched secrets, beat by beat.

Welcome to our Focus on Innovation—the Heart—at Sunnybrook Research Institute.

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Bleeding Heart

Redefining hemorrhage as a major contributor to reperfusion injury opens up new avenues for treatment

Medicine is not perfect.

Medications often have unwanted side effects. Surgeries can have complications. Only by recognizing and understanding these obstacles can we limit their impact. Nowhere is this arguably truer than in the treatment of heart attacks.

Heart attacks occur when blood flow to the heart is restricted and oxygen-rich blood cannot reach the heart muscle. If the blockage is not removed fast enough, then the heart cells become starved of oxygen and die, leading to irreversible tissue damage.

Treatments for heart attacks aim to reestablish blood flow to the heart, either by dissolving blood clots or by

mechanically opening up obstructed arteries. However, restoring blood flow back to the heart, also known as reperfusion or revascularization, brings its own set of challenges. Between 35% and 50% of patients who have severe heart attacks experience complications following reperfusion, including hemorrhage, inflammation and injury to small blood vessels. Patients with these symptoms, known as reperfusion injury, fall into a high-risk group whose members have poor long-term prognoses. For these patients, revascularization is a double-edged sword: life-saving on the one hand, harmful on the other.

“By opening up the artery, you’re

helping the patient, but you’re also introducing these other factors that may cause additional damage. But you have to do it. The question is, how do you manage after that?” says Dr. Nilesh Ghugre, a junior scientist in the Schulich Heart Research Program at Sunnybrook Research Institute (SRI).

Under the mentorship of Dr. Graham Wright, director of the Schulich Heart Research Program, Ghugre is challenging the current paradigm that hemorrhage is a passive bystander in the adverse events following reperfusion.

Because patients who experience hemorrhage often have other complications, it is difficult to dissect the relationship between hemorrhage and reperfusion injury. To tease apart the effects of hemorrhage on these co-occurring conditions, Ghugre worked with Wright and Dr. Bradley Strauss, a senior scientist at SRI and head of the Schulich Heart Program at Sunnybrook, to develop

Restoring blood flow after a heart attack can damage heart tissue and hinder recovery. Dr. Nilesh Ghugre is examining how hemorrhage contributes to this process and if drugs called iron chelators can lessen the damage.

a new preclinical model of myocardial hemorrhage that could be used for research. In a study published in the *Journal of Cardiovascular Magnetic Resonance (JCMR)*, the scientists showed that they could induce hemorrhage in the heart with the enzyme collagenase, which weakens the blood vessel wall and makes it more likely to leak blood into surrounding tissue. Leaked blood pools in the heart muscle, thereby mimicking the myocardial hemorrhage caused by reperfusion without the other heart attack- and reperfusion-related injuries. In the course of these studies, Ghugre and Wright partnered with GE Healthcare to develop and optimize new imaging techniques that enabled them to identify areas of hemorrhage and inflammation on an MRI scan.

Building on his new model, Ghugre devised a strategy wherein he induced an artery occlusion (to mimic a heart attack) with or without hemorrhage. To test if hemorrhage by itself would cause

harm, he included a third group that only experienced hemorrhage. When he looked at inflammation and cardiac function, Ghugre found that a blocked artery with hemorrhage resulted in worse outcomes than a blocked artery without hemorrhage. More surprisingly, he found that inducing hemorrhage alone resulted in inflammation and reduced cardiac function similar to that caused by a blocked artery. The results, published last year in *JCMR*, indicate that hemorrhage is an active contributor to cell damage and inflammation.

"It's actually a combination of restricted blood flow to the heart and hemorrhage that seems to make things worse," says Wright. "This makes sense because restricting blood flow followed by reperfusion creates factors like free radicals, which are extremely damaging to cells and set the stage for inflammation. Hemorrhage may further enhance the effects of those factors to create a kind of chronic inflammation."

Wright notes that the implications of these findings are significant. "If hemorrhage is a major cause of adverse downstream events, [then] trying to only block the downstream events is like trying to stop the flood after the dam has broken. Instead, this may be an opportunity to fix the root of the other problems," he says.

During hemorrhage, hemoglobin, iron-containing molecules that trap oxygen, are released from red blood cells and broken down into iron byproducts, which creates an excess of iron at the site. This type of overload is harmful to the heart because it induces an inflammatory response and produces toxic free radicals, both of which, as Wright notes, can damage cells. Ghugre hypothesized that it was actually this flood of excess iron from the hemorrhage that was interfering with recovery. If this were true, he reasoned, then getting rid of the iron should lessen the impact of hemorrhage on inflammation and other reperfusion-related symptoms.

Drawing on his PhD research, which focused on excess iron burden in the liver and heart of patients with thalassemia and sickle cell disease, genetic blood disorders that cause anemia, Ghugre turned to examining the effectiveness of iron chelators in treating reperfusion injury.

Iron chelators are chemical compounds that track down and neutralize excess free iron circulating in the body and deposited in organs. For the pilot study, Ghugre chose the iron chelator deferiprone because it is small and can penetrate tissues easily.

Preliminary results in a preclinical model showed that deferiprone was a fast and effective remedy for hemorrhage and swelling. It also helped maintain cardiac function after a heart attack. This was the first study to show that deferiprone is successful at treating myocardial hemorrhage and reperfusion injury. The study was published in *JCMR* and done in collaboration with Children's Hospital Los Angeles and ApoPharma, a Toronto-based pharmaceutical company.

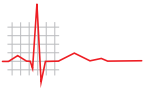
Ghugre cautions that while these early results are promising, questions remain. "We still need to confirm our results. If these ongoing studies show benefit, then we need to know why," he says.

He is now trying to figure out how deferiprone acts on the heart and how best to administer the drug. As Ghugre notes, "It's not just dosage. Timing and duration of therapy is everything."

He is working with ApoPharma to conduct preclinical studies that he hopes will pave the way for clinical trials. Because deferiprone is already authorized by Health Canada and the U.S. Food and Drug Administration to treat other iron overload diseases, Ghugre expects that if the drug makes it through to clinical trials, then the regulatory approval process will be easier and faster.

Ghugre's work has opened up new avenues of research into mitigating the harmful effects of hemorrhage on recovery after a heart attack. In the balance between the benefits and risks of revascularization, his work could help tip the scales in favour of the patient. Ultimately, Ghugre says, "You want optimal healing so that patients do better in the long term."

This research was supported by ApoPharma, Federal Economic Development Agency for Southern Ontario, Heart and Stroke Foundation, and Ontario Ministry of Research and Innovation (MRI). Equipment support came from the Canada Foundation for Innovation, GE Healthcare and MRI.



A New Dawn for Cardiac Imaging

The heart is the hardest- working muscle in the body.

It beats 100,000 times each day to pump about 10 tonnes of blood through a complex network of vessels. Our hearts drive us—our actions, thoughts and feelings—but what drives our hearts?

Our bodies contain a multitude of fuel sources derived from the foods we eat. Like gasoline in a car engine, these fuel sources are consumed in chemical reactions to generate energy that in turn power the trillions of cells comprising our tissues and organs.

The heart is an omnivore consuming whatever foods it can, including sugars and fats. “Depending on the availability and how hard it’s working, the heart can use any of those substrates. It’s very flexible in what it can use,” says Dr. Charles Cunningham, a senior scientist in the Schulich Heart Research Program at Sunnybrook Research Institute (SRI). “But in disease, that changes. Under certain conditions, the heart becomes less flexible, and that can contribute to disease progression.”

The failing heart is like an engine that is running out of fuel.

The field of cardiac metabolism

centres on the energetics of the heart: which fuel sources it uses and how it converts that fuel to energy. Although the heart can use diverse fuel sources, it prefers some to others. These preferences are purely utilitarian and driven by questions of efficiency like, “How much energy can be generated from the breakdown of this sugar versus that fat? What food source will produce the most energy when oxygen levels are low?”

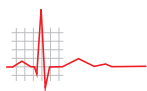
To understand how cardiac metabolism contributes to heart failure, Cunningham is studying hyperpolarized magnetic resonance imaging (MRI), a new technique that allows imaging of the biochemical reactions occurring within cells. Traditional MRI shows features like clogged arteries, swollen tissues or localized bleeding. Together, hyperpolarized and traditional MRI paint a more complete picture: one illustrates the complex network of pipes, valves and pistons in the engine, while the other measures the efficiency of the process that converts gasoline to power.

Hyperpolarized MRI could help us understand heart disease progression—and how to stop it before our hardest-working muscle wears out

Hyperpolarized MRI enables researchers to study how a fuel source is broken down and how much of it is converted into useable energy. With traditional MRI, the signals from the energy source and its byproducts are too low to distinguish from background noise. Hyperpolarized MRI amplifies these signals, making it possible for researchers to locate them and track their journey through a cell.

That SRI has one of only seven clinical hyperpolarizers in the world can be credited to Cunningham’s expertise, says Dr. Graham Wright, director of the Schulich Heart Research Program at SRI. “He’s developed methods that allow us to look at these metabolic products very quickly in a way that works in a moving heart. He’s also developed a lot of the tools that makes this approach practical in preclinical studies. Those tools are immediately translatable into patients,” says Wright, who collaborates with Cunningham.

Prior to Cunningham’s work, most research using hyperpolarized MRI focused on tumours and other static tissues, which are much easier to image than a live, beating muscle. “The motion and fast blood flow of the heart makes any kind of contrast imaging really tricky,” says Cunningham. Add to that the transient nature of the hyperpolarized MR signal, which lasts for only 60 to 90 seconds, and the need for fast and accurate cardiac MRI tools becomes obvious. Having overcome the challenges of adapting hyperpolarized MRI to the heart and large preclinical models, he is bringing the technology to patients.

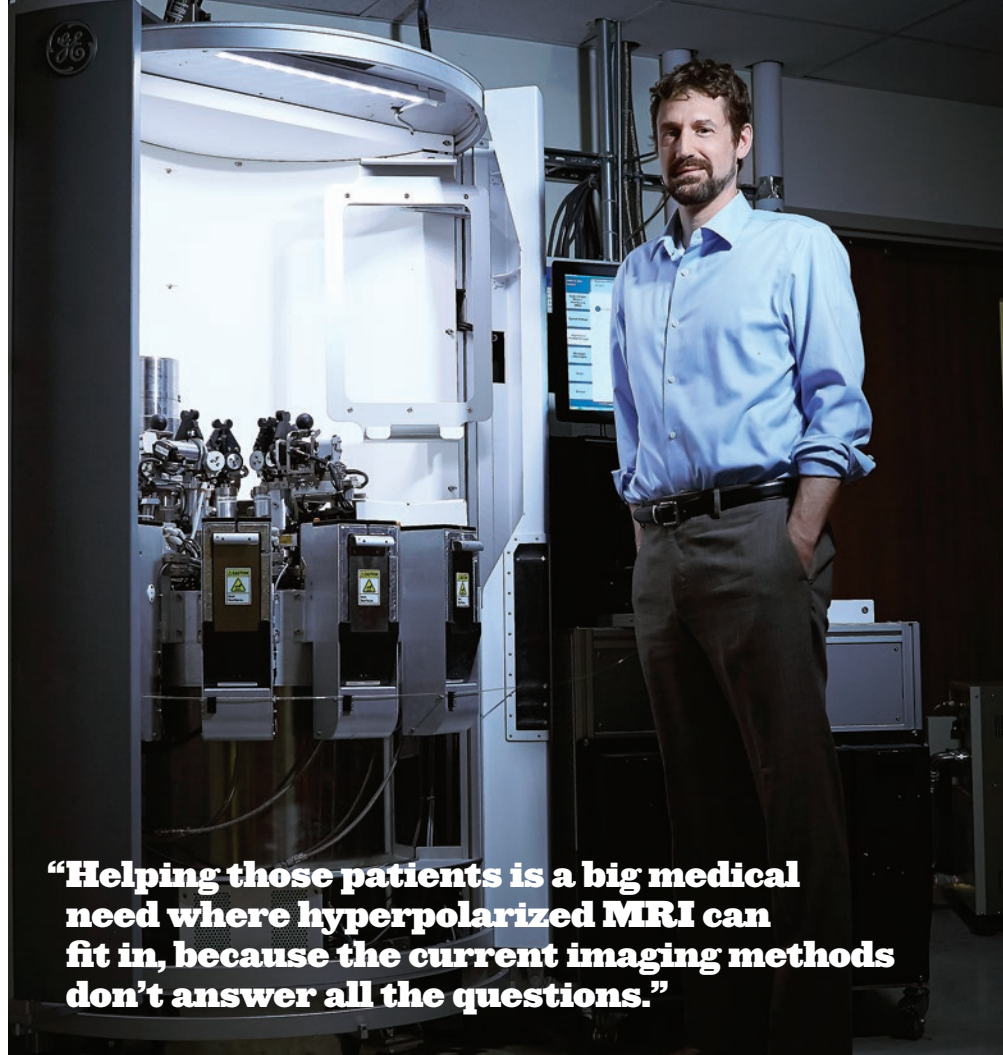


Dr. Charles Cunningham is pioneering the use of hyperpolarized magnetic resonance imaging to study cardiac metabolism and heart disease. Sunnybrook Research Institute has the only clinical hyperpolarizer in Canada.

About 500,000 Canadians are living with heart failure, with 50,000 new patients being diagnosed each year. “Heart failure is really the endpoint of a lot of diseases of the heart,” says Cunningham. “Helping those patients is a big medical need where hyperpolarized MRI can fit in, because the current imaging methods don’t answer all the questions.”

The researchers will soon be starting the first human studies of hyperpolarized carbon-13 signals from pyruvate in the heart. They chose pyruvate as the injected substance for its importance as an energy source in several metabolic pathways. As with any new technology, establishing “normal” baseline values and determining the consistency of the methods—how much variability will there be between measurements of the same patients taken on different days?—will be important to future clinical use. Cunningham and Wright will do these studies in collaboration with Dr. Kim Connelly at St. Michael’s Hospital and pharmacists at Sunnybrook, who will prepare the pyruvate mixture in SRI’s current good manufacturing practice laboratory to ensure that all products meet Health Canada guidelines.

Cunningham is optimistic about the potential of hyperpolarized MRI to help predict whether patients will develop heart failure. There’s good reason for optimism. In a preclinical study published in the *European Journal of Heart Failure*, Cunningham used MRI signals derived from hyperpolarized carbon-13 pyruvate to identify changes in cardiac metabolism; he could see how the metabolism



“Helping those patients is a big medical need where hyperpolarized MRI can fit in, because the current imaging methods don’t answer all the questions.”

changed from early- to late-stage heart disease. These results suggest that hyperpolarized MRI scans of cardiac metabolism could be a useful tool for tracking the progression of heart failure. Next, Cunningham will use the technology to look for metabolic changes in patients with hypertrophic cardiomyopathy, an enlargement of the heart often associated with a later diagnosis of heart failure.

“For the patients who are going to develop heart failure, I hypothesize that you would see a metabolic change prior to other signs and symptoms developing,” says Cunningham. “The idea is to find the people that are going to do worse and give them more aggressive therapy.”

Another area in which hyperpolarized MRI might be useful is in predicting the effectiveness of treatments like revascularization, which aims to revive damaged heart muscles by introducing blood flow back to the heart. “Shortly after a heart attack, there’s a question—is the tissue recoverable?” says Wright. “You may see a region of the heart wall that’s not squeezing properly. It may be dead or it may not be getting enough oxygen

to have the energy to squeeze. It’s often hard to tell the difference between those two states.”

While it may be hard to distinguish between dead and live heart tissues visually, metabolically speaking, the differences between them are glaringly obvious. Dead tissues have little to no detectable metabolic activity, whereas live tissues are trying to generate and consume energy. By comparing metabolic activity in different parts of the heart, hyperpolarized MRI can differentiate between tissues that are past the point of recovery versus tissues that would likely benefit from revascularization.

Like Cunningham, Wright is enthusiastic about the promise of hyperpolarized MRI. “It has huge potential to help us understand the basic biochemistry of metabolism in a situation that matters—in a patient,” he says.

This research was supported by the Canadian Breast Cancer Foundation, Canadian Institutes of Health Research, Heart and Stroke Foundation, Ontario Institute for Cancer Research and Prostate Cancer Canada. Infrastructure support comes from the Canada Foundation for Innovation, GE Healthcare and Ontario Ministry of Research and Innovation.



KEEPING THE Beat

Imaging-guided technique for complex arrhythmias could save lives

The leading cause of hospitalization in this country continues to be heart disease and stroke, and every seven minutes someone dies from one of them, according to the Heart and Stroke Foundation of Canada. One cause of cardiac arrest is triggered when the electrical circuitry of the heart malfunctions. This sparks an abnormal heart rate called an arrhythmia, which may make a heart to beat too slowly, too quickly or irregularly.

Arrhythmias can cause blood flow in the brain and body to decrease, resulting in heart palpitations, chest discomfort or pain, dizziness, fainting or even sudden death. Some arrhythmias have no symptoms or warning signs and may not be serious, while others may be life-threatening.

A team of Sunnybrook Research Institute (SRI) cardiovascular scientists is investigating therapies and techniques that could save more people from dying of arrhythmic events. Two of them—physicist Dr. Graham Wright and cardiologist Dr. Eugene Crystal—are senior co-authors of research papers that aim to enhance certain areas of heart disease management and treatment; Wright

Photo: Nation Wong



Dr. Eugene Crystal (centre) is the clinical lead on a study that aims to reduce the incidence of heart failure among patients with arrhythmias. Here, he performs a cardiac ablation inside the minimally invasive arrhythmia lab at Sunnybrook, which uses robotic imaging-guided technology and a remote control system to guide procedures.

is the technical lead and Crystal the clinical lead.

One of those papers, which was published earlier this year, revealed the findings of a study of 43 Sunnybrook patients who had received an implantable cardioverter defibrillator (ICD) after having a heart attack. A small device that's placed in the chest, an ICD uses electrical pulses or shocks to help control arrhythmias, especially those that can cause sudden cardiac arrest. The patients, who were followed-up for as long as 46 months, with a median follow-up of 30 months, were seen every three months or sooner in cases where the ICD delivered shocks.

"Many patients with chronic damage

to the heart, which usually develops after a heart attack, are at risk of sudden cardiac death when the heart stops and death occurs in minutes," says Wright, who is the director of the Schulich Heart Research Program at SRI and a professor at the University of Toronto. "We're trying to come up with more specific criteria to ensure that we're putting an ICD in the patients who would most benefit from one."

An ICD is an expensive device that costs tens of thousands of dollars; data from a few years ago in Ontario cite that 1,500 ICDs were being implanted every year, costing the health care system roughly \$50 million annually. The current criterion for putting an ICD in patients is that the heart pumps

about one-half or less of the normal amount of the blood to the body each cardiac cycle. That criterion isn't foolproof, however, and cardiologists err on the side of caution by putting ICDs into some patients who may not actually need them, while missing some patients who might benefit.

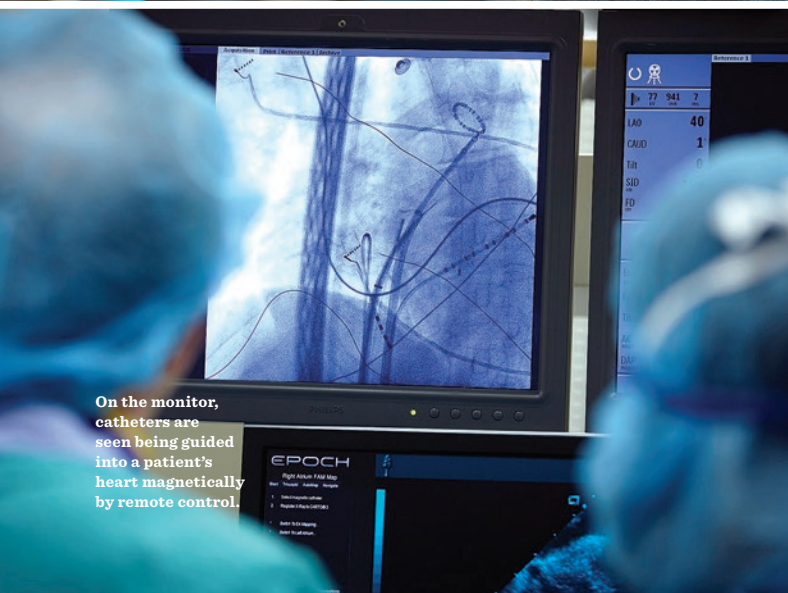
"The problem is that we have no good tools to estimate who will die suddenly," says Crystal, who is a specialist in electrophysiology, that branch of cardiology that focuses on the heart's electrical system and diagnoses and treats arrhythmias. "Right now, nine out of 10 people who get an ICD may not need it for many years. Our hope is that in the long run, with larger studies that build on our



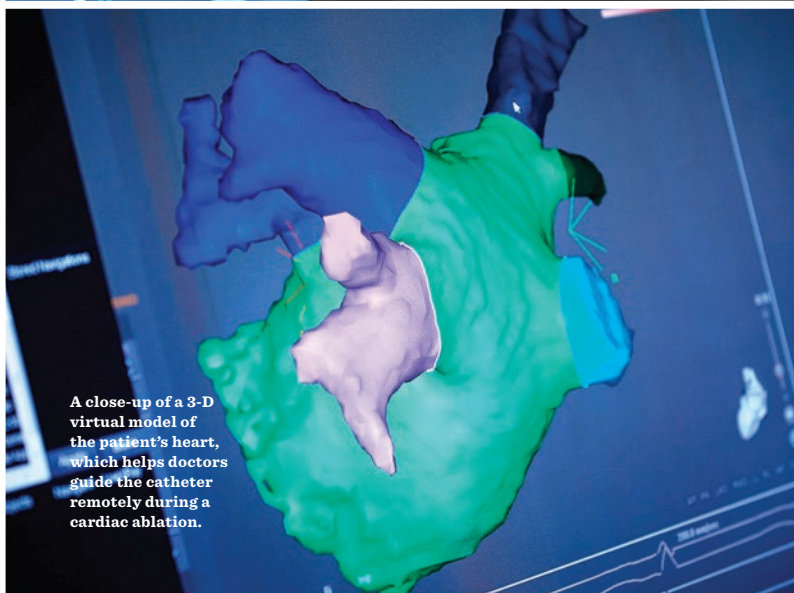
Physicist Dr. Graham Wright is developing magnetic resonance imaging techniques to identify and measure abnormal heart tissues.



Dr. Eugene Crystal (left) and his team perform a minimally invasive cardiac ablation procedure.



On the monitor, catheters are seen being guided into a patient's heart magnetically by remote control.



A close-up of a 3-D virtual model of the patient's heart, which helps doctors guide the catheter remotely during a cardiac ablation.

AN ELECTRIC PERFORMANCE

- **Cardiac electrophysiology (EP) is the study** of the electrical activity in the heart. Electrodes are placed in the heart to record its electrical signals.
- **In cases of arrhythmia, EP can be used** to diagnose the condition and pinpoint the source of the abnormal heart rhythm.
- **Once the source has been identified,** radiofrequency energy is applied through the electrodes to destroy the arrhythmia-causing tissue. This cardiac ablation procedure prevents abnormal electrical signals from moving through the heart, thereby restoring a normal, regular rhythm.
- **The most common arrhythmia targeted** by ablation is atrial fibrillation (afib), a rapid, irregular heart rate caused when the two upper chambers of the heart beat out of turn with the two lower chambers.
- **Afib is the most common cause of stroke.**
- **The risk of death from afib is higher** for women than for men.
- **Canada has 28 EP centres, three of** which perform procedures only on children, spread across nine provinces. Northwest Territories, Nunavut, Yukon and Prince Edward Island rely on external EP labs.

research, we can tell which patients will benefit the most from an ICD.”

One cause of arrhythmia is the scarring of heart tissue from a prior heart attack. In the study, scar tissue was detected in all 43 patients. The research paper that Wright and Crystal co-authored examined the potential utility of cardiac magnetic resonance imaging (MRI) to identify patients with such scarring. “There is something in the scar that helps us understand who is more prone to having further arrhythmia events,” says Crystal.

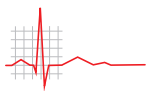
Although there have been previous studies in this area of cardiovascular research, Wright and Crystal have developed more precise ways of measuring scar tissue. “We focused on developing a quantitative measure that more accurately describes how much scar and healthy tissue there is,” says Wright. “This measure appears more specific in predicting the arrhythmia events.”

There is a broader multicentre study being led out of Calgary that is testing

the more conventional MRI approach and in which SRI will be participating. A substudy is also looking at the potential utility of the more advanced methods. “We’d like to be able to identify better who is going to have an arrhythmia event and who isn’t,” says Wright. “By developing more precise ways to measure the scar tissue, we hope to be able to save more lives.”

Another study on which Crystal and Wright collaborated aimed to take the above research one step further: to see if it was possible to prevent arrhythmia events from happening in the first place, so that an ICD wouldn’t need to be implanted. That meant trying to determine what was causing the irregular heartbeat events. There are myriad causes, including blocked arteries, high blood pressure, diabetes, and an overactive or underactive thyroid gland. This preclinical study focused on identifying the scarring of heart tissue from a prior heart attack.

It had already been established that



BASED ON A 2012 SURVEY
LED BY DR. EUGENE
CRYSTAL OF 19 EP CENTRES
IN CANADA:

17

EP centres in university-affiliated
teaching hospitals

67

Full-time EP specialists

21

Part-time EP specialists

420,000

People served by a Canadian
EP specialist

127,500

People served by a U.S. EP specialist

8,041

Ablations performed annually

104

Average ablations a Canadian
EP specialist performs each year

50

Ablations an EP specialist must perform
each year as per the Canadian
Cardiovascular Society to maintain
their competency

MRI is a powerful tool to detect scar tissue in the heart, but the existing technology isn't without limits. "One of the challenges of using MRI is that the heart is a moving target because it's beating, so it's hard to get a clear high-resolution image," says Crystal. A procedure called cardiac ablation can correct heart rhythm problems; it uses long flexible catheters or tubes inserted through a vein in the groin and threaded to the heart to correct the structural problems causing the arrhythmia.

Cardiac ablation works by scarring or destroying the tissue in the heart that's triggering the abnormal rhythm. In some cases, it prevents faulty electrical signals from travelling through the heart, stopping the arrhythmia. Once the abnormal heart tissue that's causing the arrhythmia is identified, the cardiologist will aim the catheter tip at the area of abnormal heart tissue. Energy will travel through the catheter tip to create a scar or destroy the tissue triggering the arrhythmia. In other cases, ablation blocks the electrical signals travelling through the heart to stop the abnormal rhythm and allow signals to travel over a normal pathway instead.

Although cardiac ablation can be successful the first time, some people need repeat procedures. "The problem is that it's hard to identify those regions of scar where you might want to ablate," says Wright. "Ideally, with the appropriate ablations, you get rid of the potential for further arrhythmia events. We want to put in an electrical signal that will burn or damage the suspect tissue, but we're not always sure where that tissue is."

Typically, ablation to prevent sudden cardiac death is only done in patients who have ICDs, and it often doesn't work because the techniques aren't accurate or specific enough. Crystal and Wright have developed a technique using MRI that seems to be able to identify where the damage is and the size of the scar; if so, then it could transform how such procedures are done. "We think that our measurement sees the ablated region based on temperature-sensitive changes in the

state of iron in the blood and heart muscle," says Wright. "It's very cool physics."

The preclinical study was first performed on non-beating hearts, then on beating hearts. To take it to a human-trial phase, the scientists need to be able to get to the point where they're comfortable scanning patients with ICDs in MRI machines, which they hope will happen in the next couple of years. The cardiovascular research group has submitted one-half dozen patents for approval, including one for the new MRI technology. "SRI is a world leader in imaging-guided cardiovascular therapies," says Crystal. "We have multidisciplinary collaborations with imaging specialists and experts in various areas of cardiovascular research."

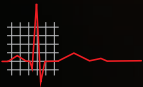
As for the potential impact of being able to use MRI in this way, the first group to benefit would be patients with ICDs who are experiencing regular arrhythmia events and shocks, which degrade their quality of life—they're always anxious that a shock may be coming, because although the shocks are brief, they can be painful. "The goal would be to get rid of the patients' stress and reduce the incidence of heart failure," says Crystal.

Another ambitious but not unrealistic longer-term objective is not to have to put an ICD in a patient at all, because ablating the scar tissue would prevent further arrhythmia events from occurring. "If the procedure worked and you only had to do it once, then it would be a one-time cost to the health care system that would improve patient outcomes," says Wright. "The MRI technique we've developed holds a lot of promise for more specific treatment."

This research is funded by the Canada Foundation for Innovation, Canadian Institutes of Health Research, GE Healthcare, Mitacs, and the Ontario Ministry of Research and Innovation.

→ WEB EXTRA

Read about how scar tissue is formed after a heart attack at sunnybrook.ca/research.



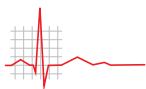
The research of Dr. Dennis Ko (centre) has highlighted the importance of physician follow-up in lowering the risk of death or heart attack among patients discharged from the ER after chest pain.

THE



**THE
HEART
OUTCOMES
TEAM IS
STEERING
PREVENTION,
PRACTICE
AND
POLICY**

New studies show Canadians have a long way to go toward achieving ideal cardiovascular health; chest pain patients do best when seen after leaving emergency room; and better criteria might be needed for selecting who should have coronary angiography



Sunnybrook Research Institute (SRI), a tightly knit team of about 30 people is working to advance cardiovascular outcomes research with the goal of improving the lives of those with heart disease and other cardiac conditions. The team includes scientists Dr. Jack Tu, Dr. Dennis Ko and Dr. Harindra Wijeyesundera of SRI's Schulich Heart Research Program, along with research coordinators, epidemiologists, statisticians and data-management experts.

While more Canadians are surviving a heart attack or stroke than ever before, some aren't able to make and maintain potentially life-saving behaviour changes, according to the Heart and Stroke Foundation's *2014 Report on the Health of Canadians*. Over the last 60 years, the death rate from these conditions has declined more than 75%, which means that now more than 90% of Canadians who have a heart attack and more than 80% who have a stroke who make it to the hospital will survive. While this is encouraging news, more work needs to be done so that even more lives can be saved, and the quality of those lives improved.

Ko, Tu and Wijeyesundera are doing some of that work as clinician-scientists, guided in their research by the patients they see. Their studies influence how cardiologists and other doctors practise, and have an impact

on the creation of policies. One such study was the CANHEART health index, a tool for monitoring the cardiovascular health of Canadians, on which Tu was the principal investigator.

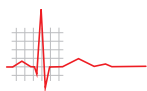
Tu and his team developed the Cardiovascular Health in Ambulatory Care Research Team (CANHEART) health index, analyzing trends in health behaviours and factors, to monitor the heart health of Canadians. "We had done a lot of previous research work in hospital settings treating cardiac patients, but we also wanted to work on prevention," says Tu, who is also a cardiologist at Sunnybrook. "We felt that this would lead to a greater contribution to population health outcomes."

The CANHEART health index, which was published in the *Canadian Medical Association Journal*, was produced in partnership with the Heart and Stroke Foundation, which has set these mission impact goals by 2020: to improve the health of Canadians significantly by reducing their risk factors for heart disease and stroke by 10%; and to reduce Canadians' rate of death from heart disease and stroke by 25%. "These are ambitious goals, and [the timeline] is only five years away," says Tu. "There was a sense of immediacy in setting this challenge for Canadians."

Prior to developing the CANHEART health index, there were no commonly accepted measures of how healthy or unhealthy Canadians were in terms of their cardiac health. Adapting the concept of "ideal cardiovascular health" first promoted by the American Heart Association and using data from Statistics Canada's Canadian Community Health Survey, the research team examined trends in the prevalence of the following six cardiovascular health factors and behaviours: smoking; physical activity; fruit and vegetable consumption; overweight/obesity; diabetes; and hypertension.

The number of ideal metrics was summed to create the CANHEART health index; the values range from 0 (worst) to 6 (best or ideal). "We found that three of the behaviours are getting worse and three are getting better," says Tu, pointing to an improvement in rates of smoking cessation, leisure-time physical activity, and fruit and vegetable consumption but worsening levels of obesity, hypertension and diabetes.

In spite of the improvements, however, the findings revealed that fewer than one in 10 Canadian adults and one in five youth were in ideal cardiovascular health from 2003 to 2011. Based on those statistics, intensive health promotion activities are needed to meet the Heart and



Stroke Foundation's mission impact goals for 2020.

"While we did see some improvements in certain health behaviours, the findings suggest that other factors are driving the obesity increase," says Tu. "Overall, diet is likely a contributing factor. For example, while we did find that Canadians are eating slightly more fruits and vegetables, they may also be consuming more of other foods that aren't as good for the heart. And total physical activity and sedentary sitting time is important, not just the leisure-time physical activity for which we had data."

These findings should help patients be more aware of their habits and show them where there is room for improvement—and there's a lot of it, considering that only 10% of the participants were in ideal health. "Some family doctors are using the findings to counsel cardiac patients," says Tu. "Often what happens is that people don't do anything to change their unhealthy behaviours until something bad happens, when what they should be doing is trying to prevent their first heart attack or stroke from happening."

DISCHARGED FROM THE ER AFTER CHEST PAIN? SEE YOUR FAMILY DOCTOR

In developed countries, chest pain is among the most common reasons for emergency department (ED) assessment. Although more than 80% of patients with chest pain are discharged from the ED after evaluation, the optimal physician follow-up for these patients remains unclear.

Ko is an interventional cardiologist at Sunnybrook, in addition to his SRI appointment. He and his team had conducted three studies on the importance of physician and cardiologist follow-up for high-risk patients with chest pain after ED assessment when they decided that a similar study for low-risk patients was warranted. Low risk was defined

as age 50 years or older with no diabetes or pre-existing heart disease; high-risk patients in that same demographic had those conditions. "We aren't sure what's the best thing to do for the low-risk patients," he says. "We're interested in understanding what the best care is for these patients after they've been discharged from the emergency room."

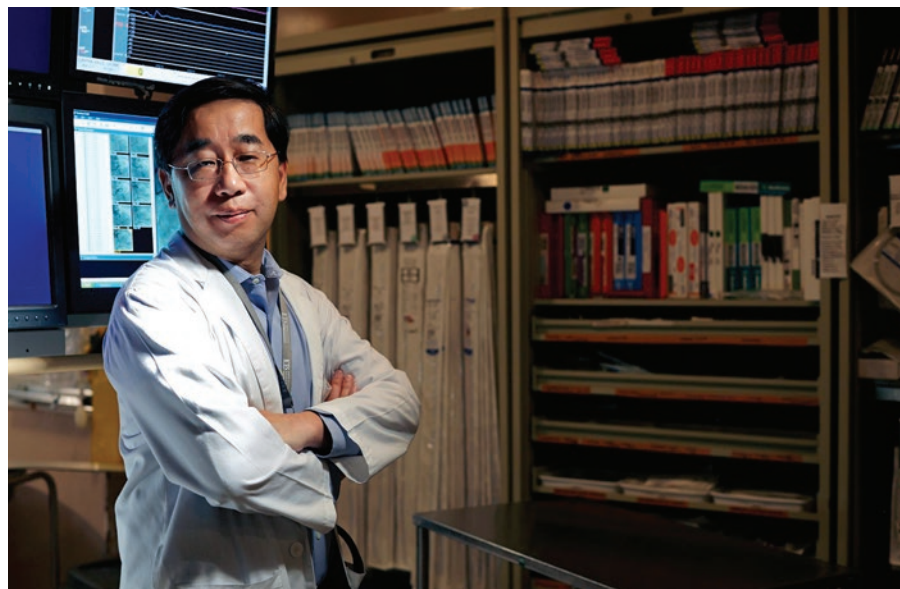
Ko, along with Tu and Wijeyesundera, performed a retrospective observational study of low-risk chest-pain patients who were assessed and then sent home from an Ontario ED. The findings revealed that following discharge, of 216,527 patients, 29% had no physician follow-up, 60% had primary care physician alone, 8% had primary care physician with cardiologist and 4% had cardiologist alone. The mean age of the patients was 64 years, and 42% of them were men.

The conclusion was that in these low-risk patients, follow-up with a primary care physician and a cardiologist in the first 30 days after being discharged was associated with a significantly lower risk of death or heart attack after one year. Specifically,

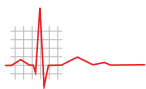
follow-up with a primary care doctor and cardiologist was associated with a 19% reduced risk of death or heart attack, and a 27% lower risk of death compared with no follow-up. Patients who saw only a cardiologist also had a significant 20% reduction in the risk of death compared with no physician follow-up. "It showed that if you follow up with a physician, the outcomes are much better," says Ko. "And if you see a cardiologist, the outcomes are the best."

Part of this, the authors noted, is that seeing a cardiologist, with or without a primary care physician, is associated with a higher use of diagnostic testing and medical therapy, like the prescribing of statins.

Additional study is warranted to investigate why some patients didn't follow up with anyone. There are myriad hypotheses, says Ko. For example, someone with several health problems could be distracted from focusing on a heart condition. Moreover, one of the strongest factors determining whether someone sees a physician is whether he or she actually has one.



Dr. Jack Tu led the development of the Cardiovascular Health in Ambulatory Care Research Team (CANHEART) health index to evaluate the heart health of Canadians.



“Not everyone has a family doctor or a cardiologist,” says Ko. “We believe that primary care follow-up is important for patients who have chest pain, as some of our studies showed primary care physician follow-up is associated with better outcomes as well, but we were surprised to learn that physician follow-up isn’t based so much on need as on access.”

Also, patients who have been told that they aren’t having a heart attack can cultivate a false sense of security. “They can’t be sure there isn’t an underlying problem unless they get additional testing,” says Ko. “It’s important for them to see someone for further evaluation and for continuation of care.”

Tu, Ko and Wijeyesundera co-authored another paper, this one on trends in short- and long-term survival among out-of-hospital cardiac arrest patients who were alive when they arrived at the hospital. People who have a heart attack at home or elsewhere, as opposed to in hospital, tend to have a poor prognosis and pose a serious burden to the health care system.

The study followed 34,291 Ontario patients older than 20 years of age who had a cardiac arrest out of hospital

and were transported alive to the ED of an acute care hospital from April 2002 to March 2012. The findings revealed that these patients were increasingly more likely to have cardiovascular risk factors but less likely to have previous cardiovascular conditions. Although the overall incidence of out-of-hospital cardiac arrest patients who arrived alive at the hospital didn’t change over the decade in which they were followed, short- and longer-term survival has improved substantially, between 25% and 30%.

“The strongest improvement was in younger patients,” says Ko. “It’s encouraging that the outcomes have improved, which could be because more early and more vigorous CPR [cardiopulmonary resuscitation] is being performed. It’s still too early to tell what the impact on the health care system could be, and further study is needed to determine that.”

BETTER CRITERIA NEEDED FOR CONSIDERING CORONARY ANGIOGRAPHY?

Health care costs, particularly in the field of cardiovascular disease, are increasing dramatically, which

“We want to find opportunities that will optimize outcomes for patients.”

is straining an already taxed system. Diagnostic cardiac catheterization, or angiography, is one widely used intervention about which there have been questions, with some studies throwing into doubt its usefulness in diagnosing stable ischemic heart disease, also known as coronary artery disease. This condition arises when arteries of the heart become blocked or narrowed, thus throttling blood supply to the heart. Coronary angiography is an invasive test that uses dye and X-rays to show the insides of the coronary arteries and how well blood is flowing into the heart. It is used to confirm the presence of coronary artery disease, but it can have deleterious effects.

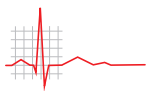
“There is potential harm or risk in these safe but invasive procedures, [harm] such as stroke, heart attack or death,” says Wijeyesundera, who also sees patients as a cardiologist at Sunnybrook. “These procedures are also expensive. So in all areas, caution must be exercised.”

In 2015, Wijeyesundera and Ko co-authored a paper on the validation of the so-called “appropriate use criteria” for coronary angiography. In theory, a procedure is defined as “appropriate” if its expected benefits outstrip its harms—yet as the researchers write in the paper, little evidence exists on if this is the case for coronary angiography, despite a set of criteria having been developed in 2012 to help guide doctors in their decision-making.

The study’s setting was the Cardiac Care Network, a registry of all patients having elective angiography at 18 hospitals providing cardiac services in Ontario between October 2008 and September 2011. (The network has 19 hospitals, but during that period only 18 were providing diagnostic angiography.)



Dr. Harindra Wijeyesundera (right) co-authored a paper showing that the appropriate use criteria for coronary angiography should not be used alone in selecting patients. Here, he performs angioplasty with Dr. Brad Strauss.



SNAPSHOT: How Research Changed Cardiac Care

Before the EFFECT study was released in 2009, despite much debate, few data existed to determine whether publicly released report cards on hospital performance improved quality of care.

The Enhanced Feedback for Effective Cardiac Treatment (EFFECT) study was a population-based cluster randomized trial of 86 Ontario hospitals of patients admitted for acute myocardial infarction (heart attack) or congestive heart failure. The decade-long trial was groundbreaking.

“This was the first time anywhere in the world that a large randomized trial had been done to rigorously evaluate cardiac report cards across hospitals to determine how cardiac patients were being managed,” says Dr. Jack Tu, the SRI senior scientist who was the study’s principal investigator. (Dr. Dennis Ko was a co-author.)

The scientists released two report cards, one deemed “early” in 2004 that reported on one-half of the hospitals and another deemed “late” 18 months later. “We found that the early report-card information was used by many of the early- and even some of the late-feedback hospitals,” says Tu. “It was helpful in that they could see how they were doing compared to other hospitals.”

The study found that, overall, there was room for improvement. A follow-up survey showed that many hospitals had changed their cardiac care practices after participating.

“Some of the hospitals introduced standardized critical care admission orders and protocols for how they managed heart attack patients,” says Tu. “They gave their patients quicker ECGs, and the emergency room doctors were permitted to give clot-busting drugs rather than wait for a cardiac specialist to arrive.” Certain hospitals opened heart failure clinics to ensure that patients got put on the right medication and stayed on it, to prevent readmission.

“The EFFECT study was a big wake-up call for the Ontario health care system,” says Tu. “We know that heart attack and heart failure mortality in Ontario has improved since then, and we believe this study was an important contributing factor. We estimated at the time of the first early feedback report that we could save 400 more lives each year in Ontario if all hospitals were providing optimal cardiac care.”

Original publication: Tu JV, Donovan LR, Lee DS, Wang JT, Austin PC, Alter DA, Ko DT. Effectiveness of Public Report Cards for Improving the Quality of Cardiac Care: the EFFECT Study: a Randomized Trial. *JAMA*. (2009);302(21):2330-2337.

The authors sought to validate the appropriate use criteria for diagnostic catheterization by examining the relationship between the appropriateness of the procedure in patients with suspected coronary heart disease and the proportion of patients later diagnosed with the disease, including those who then underwent revascularization. Revascularization is done to reinstate blood flow, either via coronary artery bypass grafting, which involves surgery to reroute blood flow, or angioplasty, which involves inserting a balloon inside a vessel to prop it open, with or without a stent.

The average age of the patients with suspected coronary artery disease that had been given an angiogram was 63 years, and 60% were men. About 81% had stress echocardiogram (ECG) testing (i.e., an exercise ECG), stress testing with imaging or ECG alone before receiving an angiogram. Findings from these tests were used to determine appropriateness scores. In remaining patients, appropriateness scores were derived from patients’ symptom status and other measures, such as one to calculate global risk for heart disease.

“After examining the angiograms of 48,000 patients, we found that more than 50% were classified as appropriate, about 30% were deemed uncertain and only 10% were considered inappropriate,” says

Wijeyesundera. “Those are very encouraging numbers.”

The researchers also found that although 53% of patients with appropriate indications had obstructive coronary artery disease, so did almost one-third of patients with inappropriate indications. Moreover, within the inappropriate category, 19% of patients underwent revascularization within three months.

“Importantly, we found that one in five patients with angiograms deemed inappropriate actually had disease severe enough to warrant revascularization,” says Wijeyesundera. “These results suggest caution in using the criteria alone to guide patient selection.”

The impact of this research—the first to study the relationship between the appropriate use criteria and diagnostic yield in patients with stable ischemic heart disease—is primarily to provide clinicians and policy-makers with information to help guide physicians’ decision-making. “As a group, we’ve spent a great deal of time on appropriateness criteria,” says Wijeyesundera. “Our study suggests that the criteria should be studied further, given that the current guidelines are three years old. Yes, they provide some insight and validation, but they can’t be used in isolation.”

All of this cardiac research has shared objectives. “We want to find

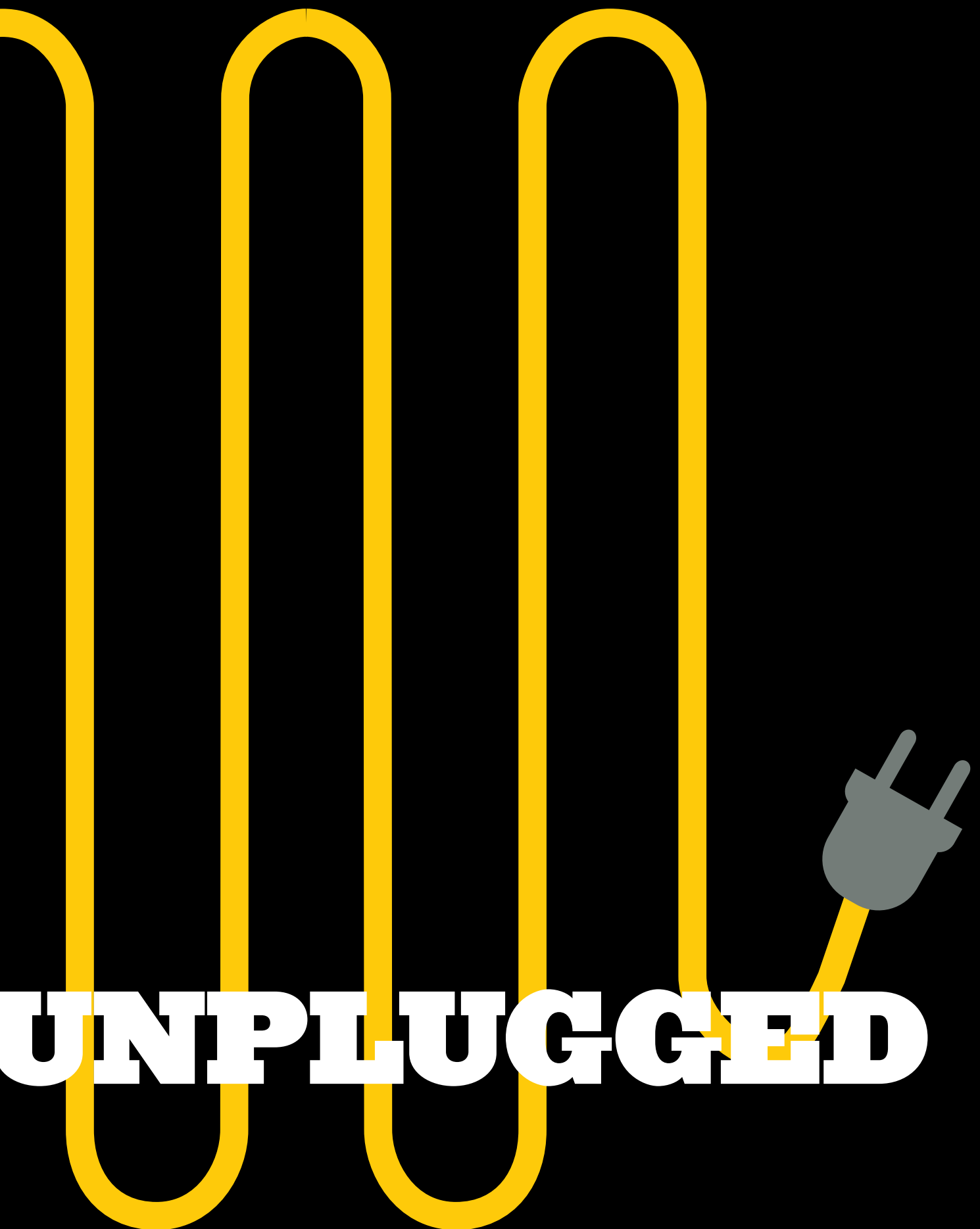
opportunities that will optimize outcomes for patients,” says Ko, “and we’re also interested in improving the efficiencies of the health care system.”

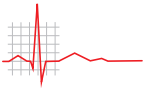
“We’re all trying to improve the quality of care to patients and provide insight to clinicians and policy-makers,” says Wijeyesundera. “My expertise lies in the uptake of new technologies and health care costing, but in different ways, we’re all working to enhance the quality of care and its effectiveness and efficiency in the health care system.”

Like his colleagues, Tu is also looking at the big picture. “The goal is to free up beds and cardiac specialists in hospitals, perform less bypass surgery and angioplasty, and prescribe fewer medications for hypertension and diabetes,” he says. “But most important, the hope is that fewer people will die of heart disease.”

Research Funding & Other Information

The CANHEART study is funded by the Institute of Circulatory and Respiratory Health of the Canadian Institutes of Health Research (CIHR). Funding for the other studies comes from CIHR and the Ontario Ministry of Health and Long-Term Care. Ko is supported by a Clinician Scientist Award from the Heart and Stroke Foundation (HSF; Ontario). Tu is supported by a Tier 1 Canada Research Chair in Health Services Research and a Career Investigator Award from the HSF (Ontario). Wijeyesundera is supported by a Distinguished Clinical Scientist Award from HSF (Canada). Each also holds an appointment at the Institute for Clinical Evaluative Sciences, which sits on Sunnybrook’s Bayview campus, and is a faculty member at the University of Toronto.





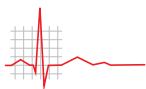
ONE

CARDIOLOGIST'S QUEST TO CLEAR CHRONICALLY CLOGGED ARTERIES AND OPTIMIZE CARDIAC CARE

Dr. Bradley Strauss has been performing angioplasty for more than 22 years. Angioplasty is an extremely common procedure that involves widening a blocked artery or vein with a balloon catheter and stent. The practice is effective for over 95% of patients, including people who've had heart attacks—acute blockages full of soft clots that can be quite easily opened up by the balloon. But in some cases angioplasty just doesn't work, particularly in older blockages that are too hard and rigid. It drove Strauss, chief of the Schulich Heart Program and head of cardiology at Sunnybrook Health Sciences Centre, to distraction that some of his patients "had poor results" after an angioplasty, and that there was no easy solution beyond surgery. "I'm always trying to figure out why I can't do something," says Strauss, who is also a senior scientist at Sunnybrook Research Institute (SRI). "I spend a lot more time dwelling on failures than the cases that do well." It's these clinical challenges that have guided much of Strauss's research, whether it's figuring out how to break through an impassable blockage, questioning long-held cardiac procedures, or tracking patient recovery using a smartphone app. Ultimately, Strauss's role as a hands-on clinician and researcher has resulted in real-world solutions at all stages of cardiac care.

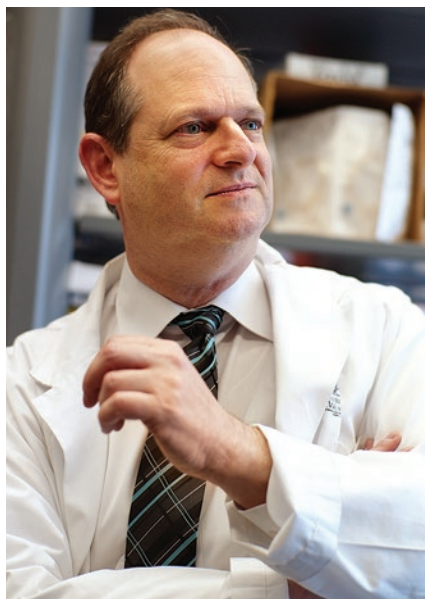
It was back in 2000 that Strauss first began tackling the problem of failed angioplasties. One of the long-known problems is a particularly durable and stubborn type of material that forms slowly in the artery over weeks—and sometimes months—until it is an unmoveable mass that not even the miniscule guide wire used in angioplasty can penetrate. This chronic total occlusion, as it's called, doesn't typically cause a heart attack, but, at its worst, the patients can't walk very far without gasping or their chest feels unbearably tight, and their quality of life becomes severely compromised. It's estimated that these obstructions show up in 15% to 20% of angiograms, affecting hundreds of thousands of patients every year around the world. Since these blockages (comprised largely of collagen and calcium) cannot be pried open via angioplasty—many doctors won't even attempt the procedure—patients usually end up on angina medications and, in severe cases, require invasive bypass surgery.

In the clinic and catheterization laboratory, Strauss had seen his share of such cases. Meanwhile, in his research laboratory, he happened to be studying an enzyme called collagenase and its role in restenosis (re-narrowing of the artery after a treatment). Collagenase is produced by the body naturally, usually as part of an immune

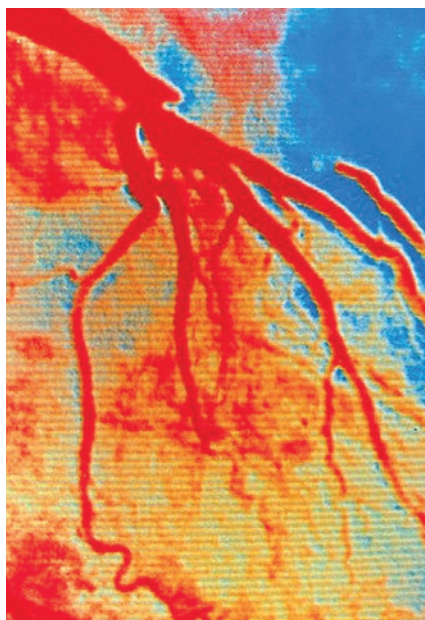


response, and works by breaking down certain cell tissues. “I started wondering whether these enzymes that exacerbate restenosis could have a *beneficial* function with this hard material in arteries,” Strauss says. “It made sense when you put the two together.” After much tinkering, Strauss and his colleagues concocted a preparation of bacterial collagenase that could be injected directly into a blockage to soften the collagen. It’s been called “Drano” for the arteries, though minus the toxicity. The treatment completed a Phase 1 clinical safety trial, called CTO-1, at Sunnybrook in 2011, and the Phase 2 efficacy study (called TOSCA-5) is underway at 13 sites in Canada (of these, Sunnybrook is the highest-enrolling), as well as two in the Netherlands and two in Israel. An anticipated 90 participants will be randomized to receive one of either collagenase or a placebo after each site receives training in how to do the procedure. The study is in its early phases, but Strauss expects results by the end of 2015. In the meanwhile, he has spun off a company from his research, Matrizyme Pharma, which is charged with the commercialization of the enzyme, MZ-004.

Martin Griedman, 69, was one of the early trial participants in TOSCA-5. Griedman had always been one of those enviably fit types. He often walked the 90 minutes home from his office. He cycled all summer. He jogged. After retiring from his stressful job running an engineering firm, Griedman kept up his fitness. But then quite suddenly, he was always out of breath. The short walk he’d done a million times to the grocery store near his condo required three or four rest stops along the way. Even just sitting still, his breathing was laboured, and he had terrible pain between his shoulders. Most terrifying was how abrupt and debilitating his physical decline was. An angiogram confirmed that he had 100% occlusion of an artery. His cardiologist attempted



Dr. Bradley Strauss has developed a treatment to make difficult-to-treat artery blockages more amenable to minimally invasive procedures and a smartphone app to improve care during patient recovery.

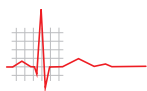


This false-colour angiogram of a heart shows a large blockage in the left anterior descending coronary artery. No contrast medium can penetrate the solid plaque that fills the inside of the artery.

an angioplasty, but after an hour-and-a-half the guide wire still could not pierce the hard blockage. (The procedure can take as little as 30 minutes.) Griedman came out of the procedure deflated and worried that his only other option would be open heart surgery.

Because he had a particularly stubborn occlusion, Griedman was put in touch with Strauss and his team. He fit the bill perfectly and was quickly enrolled in the TOSCA-5 trial. Griedman was eager to try any treatment, however experimental, that would keep him off the operating table. In September 2014, less than a month after his failed angioplasty, Griedman was injected with a dose of collagenase that had been determined to be safe and effective during the early trial, via the wrist, through the main artery in his heart directly into the blockage. The following afternoon, the angioplasty procedure began. “Suddenly I heard the doctor say, ‘We’re through!’” recalls Griedman. “I couldn’t believe it—they got the guide wire through.” The effects were instantly noticeable, he says. “Even in recovery, I felt immediately better—stimulated, not so sluggish. Friends saw me after and said my face had a different colouring.” Griedman’s was a best-case scenario, and following six months of rehab, he is now walking three miles a day four times a week, while cycling and resistance training twice a week. “I’d say I’m 75% of where I was,” he says. If Phase 2 trials go well, then collagenase could become a standard treatment of complex chronic total occlusions, and eliminate the need for invasive cardiac surgery.

Minimizing the invasiveness and possible additional damage caused by cardiac procedures has become a running theme in Strauss’s work. He has also been studying the common practice of clot removal when a heart-attack patient undergoes an angioplasty. Decade-old studies had found that extracting the offending clot boosted survival rates in the long run,



but Strauss wasn't convinced. "We weren't sure it was based on good science," he says. He wondered if the effects of the procedure were really worth the potential harm caused by opening the artery to pull out the clot. "When you go in and try to open it up, some of the clot actually moves downstream to smaller vessels and may block them up," he says, "which may extend the heart attack." While two other recent studies have confirmed clot removal doesn't improve lifespan among cardiac patients, Strauss's research delves deeper into the mechanical level of what happens to heart muscles if the whole clot is left to embolize naturally downstream. He asked: if we know the procedure provides no real benefit, would not doing it cause more harm? In other words, if the whole clot is left to run its course, what's the worst that would happen to an already damaged heart muscle?

To answer the question, he and his colleagues injected a clot directly into the artery using a preclinical model and waited to see what happened. Using magnetic resonance imaging they observed that in the short term the infarcts were a little larger, but six weeks later, the hearts had adjusted and there were no differences, except a minor amount of heart muscle wall thinning. "This suggests there is no reason to pull out the clots, because there is no long-term benefit," he says. "Our study gives molecular evidence that this is the case."

As important as acute on-the-table cardiac care is, Strauss's latest project looks farther down the continuum at patient recovery—an aspect that he feels is underserved. "We know everything that happens to the patient during the procedure and directly after," he says. "But as soon as they go home, they are off the radar." More than 1,800 angioplasties are performed at Sunnybrook every year. "That's a lot of phone calls," Strauss says. "We

Griedman was eager to try any treatment, however experimental, that would keep him off the operating table.

just don't have the resources to adequately follow up with patients in any organized way. And I think that impacts the quality of care."

In collaboration with the Cardiac Care Network, a provincial agency responsible for improving cardiac care, Strauss's idea for a smartphone app began taking shape in 2013. Rather than tasking a hospital staffer to follow up by phone, the app would do all the prompting and present an easy way for patients to answer questions that would determine how they're recovering, while also allowing them to ask questions or voice concerns. The app would be loaded onto a patient's phone (or the phone of a family member) and it would pose a series of questions at predetermined intervals (after a few days, then the following month, and so on up until six months). How do they feel? Are their symptoms abating? Are they taking their medications properly? Have they had another heart attack or cardiac event?

The app (designed for iPhone and Android operating systems) should be up and running in the next couple of months, Strauss says, and will be piloted at Sunnybrook and three other centres in Ontario. There may be some troubleshooting for elderly patients, who may not be comfortable with the technology, or people for whom English is a second language, but Strauss is confident that the technology will be successful. "It could have widespread impact and give us the opportunity to educate patients," he says. "It's a way

to improve communication between patients and doctors. And it's not often easy for patients to have access to the people who did the procedure."

Breaking down barriers, both metaphorical and physical, Strauss's research seems to advance one sweeping outcome: optimizing cardiac treatment at all stages. "I guess there's a theme to my work," Strauss says modestly. For people like Griedman, Strauss's efforts have resulted in nothing short of a second chance: "He's made me a different person," he says. "It's a gift, really."

This research was funded by the Canadian Institutes of Health Research and Heart and Stroke Foundation. The Canada Foundation for Innovation and Ontario Ministry of Research and Innovation provided infrastructure support.



"What's the next best medicine?"



VASCULAR VULNERABILITY

Using magnetic resonance imaging, Dr. Alan Moody has identified intraplaque hemorrhage as a marker of vascular disease affecting both brain and heart.

Detecting who's at risk for heart attack or stroke before it's too late

IN THE Labyrinth

beneath Sunnybrook's main building, Dr. Alan Moody confidently navigates his way down empty corridors and through unmarked doorways. Overhead, there is an exposed network of pipes—complex, interconnected and not unlike the intricate web of blood vessels supplying the human body. For Moody, head of the vascular biology imaging research group at Sunnybrook Research Institute (SRI), it's a fitting place to study the body's circulatory system and its role in disease.

On the surface, heart attack and stroke might seem like different diseases. Strip away their façades, however, and they are essentially the same disease manifested in different organs. "The poster children for cardiovascular and neurovascular

diseases are heart attack and stroke, respectively," says Moody, who is a senior scientist in the Schulich Heart Research Program at SRI. "The underlying vascular disease is the same for both. The differences are purely anatomical."

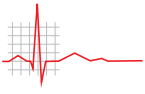
Vascular disease describes any condition that affects the blood vessels in the body. Atherosclerosis, in which plaque builds up inside the arteries, is of particular interest to Moody. Plaque is primarily made up of fat, cholesterol and calcium. Over time, as it accumulates on the artery wall, plaque hardens and narrows the artery to restrict blood flow.

But not all plaques are created equal.

Whereas traditional risk assessments focused on how much plaque is in the arteries, scientists now appreciate that the type of plaque is as important. So-called "vulnerable plaque" is more likely to create complications than others.

"We know that the plaques that rupture and cause clinical events are often not the ones that cause the greatest obstruction in the artery," says Dr. Anna Zavodni, a radiologist and affiliate scientist in the Schulich Heart Research Program. "It's really a combination of the volume of plaque as well as the characteristics of that plaque."

Building on that idea, Moody and Zavodni are using magnetic resonance imaging (MRI) to determine whether



plaque structure and composition can predict cardiovascular outcomes. The benefits of MRI are that it is noninvasive and can provide enough resolution and detail to allow scientists to detect features like a plaque's fat-filled core.

As described in a recent paper published in the journal *Radiology*, Zavodni and colleagues recruited 946 adults as a part of the Multi-Ethnic Study of Atherosclerosis (MESA) to determine if measuring vulnerable plaque components within the carotid arteries can predict the risk of a cardiovascular event such as heart attack, angina or stroke. None of the participants initially had symptoms of cardiovascular disease. In addition to a physical examination and blood tests, everyone underwent MRI to look for vulnerable plaque and changes in the artery wall.

During the five-and-a-half-year follow up, people whose plaques contained higher levels of fat or calcium, or who had thicker artery walls, were more likely to experience an adverse cardiac event. Further, plaque composition was as good a predictor of cardiovascular disease as were traditional risk factors like cholesterol, blood pressure and smoking.

MESA is the first prospective population study to examine the usefulness of plaque characteristics in predicting cardiac events. One of the strengths of the study lies in its ethnic diversity, but MESA's real value is that all of the participants were "heart healthy"—they had never had a heart attack or stroke.

Zavodni points out that for 25% to 50% of patients who experience a heart attack for the first time, this is their first presentation of heart disease. "Most people don't even know they're sick until they experience this massive, life-altering event," she says. "Being able to look at a population and decide who needs very aggressive treatment versus who can be left alone, that's important."

In another study, Moody and Zavodni asked whether they could assess cardiovascular risk based on

intraplaque hemorrhage (IPH), a feature of advanced and unstable plaques. Moody became interested in IPH when he found that patients with it in their carotid artery were six times more likely to have a neurovascular event than those without it. Given the similarities between cardiovascular and neurovascular diseases, he wondered whether IPH might also predict cardiovascular events.

By reviewing patients' charts, the researchers found that nearly three times as many patients with IPH in their carotid artery had experienced a prior adverse cardiac event than patients without it. This was a surprising finding because the carotid artery supplies blood to the brain, not to the heart. Their results also showed that the presence of IPH is a stronger indicator of risk for cardiovascular disease than risk factors like gender, age and smoking. Dr. Navneet Singh, a radiology resident at the University of Toronto, led the study, which was published in the *International Journal of Cardiovascular Imaging*. The team concluded that IPH might serve as a useful marker of systemic vascular disease that includes the brain and the heart.

Having established the usefulness of MRI in detecting features of vulnerable plaque, Moody's group is trying to define criteria by which patients should be screened. As he is quick to note, they are not advocating for all patients to undergo MRI screening. "We're trying to hone down the numbers [of patients] and look at the cost-effectiveness," he says.

Moody is also chair of the department of medical imaging at the University of Toronto and a member of the steering committee for the Canadian Atherosclerosis Imaging Network (CAIN). He is leading a study of more than 400 patients that is examining the ability of MRI to characterize plaque in the carotid artery supplying the brain and therefore predict clinical outcomes for neurovascular disease.

Moody and Zavodni's research underscores the need for better tools

to identify people before they become patients. These individuals often show no signs of cardiovascular or neurovascular disease, but nonetheless may be at risk.

"We already know what to do with the symptomatic patients," says Moody. "The bigger question is, what do we do with the asymptomatic ones?"

"The more imaging tools we have, the better we'll be able to separate patients along meaningful lines and figure out which of those patients need repeated follow up, who will benefit from an early preventive surgery, and who will be fine with a few changes to their lifestyle," says Zavodni.

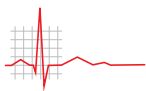
Moody's research is funded by the Canada Foundation for Innovation, Canadian Alliance for Healthy Hearts and Minds, Canadian Institutes for Health Research, Heart and Stroke Foundation (HSF), and Ontario Ministry of Research and Innovation. Zavodni's research is funded by the HSF, National Institutes of Health and Radiological Society of North America.

→ WEB EXTRA

Read about Moody's work with CAIN at sunnybrook.ca/research.



Dr. Anna Zavodni is lead author on a study that examines whether plaque characteristics can be used to predict heart attack in people without symptoms.



An Unconventional Method

Using artery from the arm rather than vein from the leg leads to better outcomes after open-heart surgery on people struck by the double whammy of diabetes and advanced heart disease

More than 10 million Canadians are living with diabetes—a population that is at a higher risk for developing diseases of the heart and blood vessels. Coronary artery disease, the most common form of heart disease, is caused when arteries that supply blood flow to the heart muscle become blocked or narrow.

Coronary artery bypass grafting (CABG, pronounced “cabbage”) is

considered the standard of care to help restore blood flow to the heart in people with diabetes and advanced coronary disease, compared to the less invasive percutaneous coronary intervention (PCI), or angioplasty. The procedure involves open-heart surgery during which doctors sew a healthy artery or vein from the chest or leg to the diseased vessel, thereby bypassing the blockage and rerouting blood to the heart. An important predictor of long-term success in CABG is persistent graft patency—the flow of

blood through the graft to the heart.

Graft patency after CABG is important for everyone, but especially for patients with diabetes, who, after the procedure, are more prone to developing atherosclerosis, plaque buildup in and on the artery walls, and who have a higher mortality rate associated with coronary artery disease than do people without diabetes. In patients with diabetes, this same process can affect the bypass grafts.

Cardiovascular surgeons at Sunnybrook Research Institute (SRI) have already shown that using the radial artery, taken from the wrist or forearm, is a better choice than using vein grafts from the leg for patients with severe blockages.

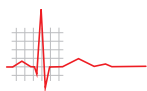
Now, extending their findings, they have determined that the radial artery is associated with better long-term outcomes on graft patency for patients with diabetes compared to the conventional method using the saphenous vein from the leg or thigh.

“Diabetes is an important indication for bypass surgery. It was very important to look at the long-term effects because there are not many studies looking at CABG for long-term effects of diabetes, especially when you’re comparing arterial grafts,” says Dr. Saswata Deb, a resident in cardiac surgery and research fellow in the Schulich Heart Program.

Deb and his mentor Dr. Stephen Fremes, a scientist in the Schulich Heart Research Program and a



Dr. Saswata Deb is studying patient and surgical factors affecting clinical outcomes after coronary artery bypass grafting surgery.



Tomorrow's Heart Surgery—Now

On the other end of the intervention spectrum, cardiac specialists at Sunnybrook are pioneering minimally invasive techniques. Transcatheter aortic valve implantation (TAVI) is one of them.

- **TAVI replaces a diseased** valve with an artificial valve that is inserted by a catheter through a small incision in the groin or chest, and threaded to the aortic valve in the heart.

- **TAVI is the “gold standard”** for elderly patients with severe symptomatic aortic stenosis—narrowing of the aortic valve, which has a one-year mortality rate of 25% to 50%—for whom open-heart surgery is too risky.

- **Dr. Harindra Wijeyesundera**, an interventional cardiologist, was part of a 21-centre study that found TAVI to be safe and feasible in selected patients with bicuspid aortic valve, a congenital heart abnormality

and the leading cause of aortic stenosis in patients aged under 65 years.

- **Wijeyesundera, Dr. Stephen Fremes**, a cardiac surgeon, and Dr. Sam Radhakrishnan, director of the cardiac catheterization labs, published the first study to evaluate the effect of delayed access to TAVI, shedding light on the impact of wait times on outcomes. Results showed that in high-risk surgical candidates a wait time longer than 60 days rendered TAVI less effective than conventional surgery.

- **Sunnybrook is one of five sites** in Canada participating in the global Surgical Replacement

and Transcatheter Aortic Valve Implantation (SURTAVI) study, which aims to recruit 2,500 patients. The goal is to assess if TAVI is a good option for people at intermediate surgical risk.

- **Fremes and Radhakrishnan are** co-leading the SURTAVI trial at Sunnybrook. Participants will receive either a Medtronic CoreValve system or a surgical aortic valve replacement.

cardiovascular surgeon at Sunnybrook, co-authored a study using data from the multicentre radial artery patency study (RAPS). The long-term RAPS study was the first Canadian randomized controlled trial to compare the radial artery with saphenous vein grafts in patients with and without diabetes.

Participants were 529 patients aged under 80 years undergoing open-heart surgery for a triple bypass, to open three blocked arteries. The aim was to determine the long-term impact of diabetes on radial artery and saphenous vein graft blockages. Each patient received angiography more than five years after CABG to evaluate the status of the bypass grafts. Angiography is a minimally invasive medical procedure to view blood vessels after injecting them with a dye that outlines them on X-ray.

Deb and Fremes reviewed a subgroup of the patient population who underwent late angiography: 269 patients, of whom 83 had diabetes. They found that five years or more after undergoing CABG, the radial artery is a much better choice for bypass grafting than is the saphenous vein in patients with diabetes.

Specifically, they found that in diabetics, 25.3% of patients who

received a saphenous vein graft from the leg or thigh developed complete blockage of their vein graft, but only 4.8% of those who received a radial artery had completely blocked radial grafts. The results were published in *The Journal of Thoracic and Cardiovascular Surgery* in 2014.

“One study usually doesn’t change practice, but given the strength of our study, we think it definitely shows good evidence for it,” says Deb, the study’s lead author. “At the end of the day, everyone wants strong long-term results, so along with other studies that will be published soon, I think that the practice will shift.”

Subsequent studies include one looking at gender investigating how the radial arteries perform in men versus women. These types of studies are relevant as women are often overlooked in the cardiac arena because they tend to present symptoms later in age.

Fremes says implementing guidelines carries weight in changing medical practice. “Our goal is to provide evidence-based recommendations for the treatment of diabetic patients, so that they receive the most effective treatment,” he says. “The guidelines will be more persuasive

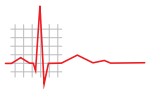
than one individual study.” Fremes is a contributing author to the guidelines, which will be published later this year.

Moreover, the improvement in intraoperative and postoperative care globally has also affected practice, adds Fremes, such that patients who would have died 10 to 20 years ago are now surviving.

“In the developed world, cardiac surgery is declining in part because of primary prevention of coronary artery disease, but also because of less invasive ways—PCI—to treat what has been formerly treated with very invasive ways—CABG. However, patients with diabetes with advanced coronary artery disease remain a group that typically has better outcomes with bypass surgery than PCI,” he says.

In a growing diabetic population facing heart disease, Deb and Fremes are hopeful that the results of their study will provide other surgeons with the evidence they need to use arterial grafting, thereby improving long-term survival rates.

This research was supported by the Bernard S. Goldman Chair in Cardiovascular Surgery at Sunnybrook, held by Fremes, and the Canadian Institutes of Health Research.



OF LIFE AND LIMB

Using high-resolution imaging to prevent amputations in patients with peripheral arterial disease



an early morning interview, Dr. Trisha Roy is bubbling with enthusiasm about her work and the day ahead. Her energy and passion undoubtedly come in handy as she juggles her dual roles as a surgical resident and PhD student.

"I've always wanted to do surgery," says Roy, who completed her first undergraduate degree in material sciences and engineering at U of T. That early experience helped her realize the potential an engineering background could have in creating better surgical devices. She then did a rotation in vascular surgery at Sunnybrook during medical school under the mentorship

of Dr. Andrew Dueck and decided that it was the field for her.

"It's a really exciting time for vascular [surgery] because it's completely changed in the last 10 years," she says. "It seems like a very promising field in terms of advanced technologies and their applications."

As a third-year resident and surgeon-scientist-in-training, Roy receives protected time during which she can focus on her research at Sunnybrook Research Institute (SRI). Under the supervision of Dueck, a vascular surgeon and researcher at SRI, and Dr. Graham Wright, director of the Schulich Heart Research Program at SRI, she is using magnetic resonance imaging (MRI) to understand the plaques that form in the arteries of people with peripheral arterial disease (PAD).

Peripheral arterial disease results when plaque buildup in the arteries restricts circulation to the limbs, most commonly the legs and feet. More than 800,000 Canadians have PAD. Risk factors include older age, smoking and diabetes. "Now that we have an aging population and more diabetes, [PAD] is becoming a growing issue," says Roy.

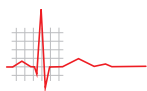
In some cases of PAD, prolonged restrictions in blood flow can lead to tissue death, or gangrene. These dead tissues are highly susceptible to infections and often require amputation to minimize the risk of infections

spreading to other parts of the body. Peripheral arterial disease is the leading cause of amputations in patients aged over 50 years and responsible for more than 90% of amputations overall.

Until recently, bypass surgery was considered the standard of care for treating patients with PAD. Similar to a bypass procedure in the heart, bypass surgery in the legs involves taking a blood vessel from another part of the body and using it to reroute blood around the blocked artery to restore circulation to the affected leg. Endovascular procedures such as angioplasty offer a less invasive alternative to bypass surgery. In angioplasty, a balloon inserted into the blocked vessel is inflated to force the vessel to widen. A stent can be also inserted into the vessel to act as a scaffold and ensure the vessel remains open.

"One of the limitations of [endovascular surgeries] is that the stents do not tend to last as long as the bypass," says Dueck. "A primary goal of our research is to determine whether the plaque itself is part of the reason why some angioplasties fail."

Imaging techniques commonly used to diagnose PAD like ultrasound and computerized tomography (CT) are able to identify blockages in the blood vessels but do not provide information about the type of blockage. Roy is using MRI to see the finer details of the



Dr. Trisha Roy is using high-resolution magnetic resonance imaging to identify types of plaque in peripheral arterial disease, a condition responsible for 90% of amputations.

artery-clogging plaques and translating that knowledge into better-informed decisions on what type of treatment a patient should receive.

Knowing whether a plaque is composed of hard materials like calcium and collagen or soft materials like fat is an important consideration when choosing the best procedure. “If you have a really hard, rigid plaque, that’s going to require different wires, stents and devices compared to if you have a soft, malleable plaque,” says Roy. “Right now, these procedures are not durable and maybe that’s because we’re not selecting our devices and approaches based on the actual [plaque] lesions.”

For the first part of her project, Roy studied human arteries donated by patients who underwent a lower limb amputation. She used ultra-high-resolution MRI to map the composition of plaques found in the isolated arteries. “We’re able to see very clearly when [the plaque] has a big chunk of calcium or collagen,” she says. “Fat appears super bright whereas calcium is quite dark.”

Roy validated her results by examining the same arteries under a microscope, where she could directly see deposits of fat or hardened calcium in the tissues. She was heartened to discover that her high-resolution MRI methods were 100% accurate in identifying fat in the plaques. In identifying collagen and calcium, the MRI techniques were about 95% accurate.

“I was surprised by the degree to which we could subdivide the plaques,” says Dueck. “I thought it would be



quite crude but the images that she’s producing are really good at differentiating different types of plaque.”

Moving forward, Roy will test the practicality of her approach in patients. Two of the biggest challenges of adapting her techniques to patient studies are resolution and scan time. In her initial work, Roy used a preclinical 7-Tesla (7T) MRI scanner to produce ultra-high-resolution images. Most clinical MRI scanners are 3T (or lower), which means the images will be much lower in resolution. Furthermore, to produce high-resolution images of the isolated arteries, each artery was scanned for four hours, a length of time that most patients would find difficult to tolerate.

“Maintaining resolution with reasonable [scan] times will be one of our biggest challenges,” says Dueck. Roy is already working on adapting and optimizing the methods she developed on the 7T scanner to produce high quality images on a clinical 3T scanner in less time.

Roy hopes that the knowledge obtained from MRI on the specific type of plaque will better equip doctors to select the most personalized treatment

for patients with PAD. “We can expand the group of patients we’re treating with endovascular interventions and maybe be able to salvage more limbs and prevent more amputations,” she says.

It’s a tall order, but if anyone can do it, it’s Roy, says Dueck: “This is very complicated work. Only a very small number of people can actually do it. She is uniquely positioned to do this work because she is a surgeon-scientist and she has a background in engineering.”

As for Roy, she sees engineering playing a bigger role in surgery. “It’s an exciting time to be able to ‘speak’ both ‘languages,’” she says. Her experiences at SRI have strengthened her desire to pursue a career in medicine and research and helped her recognize the value of a multidisciplinary environment.

“What’s nice about Sunnybrook is there are a lot of scientists who are innovators and engineers, so we have a good mentorship model,” she says. “I feel really lucky to be here.”

This research is funded by the Canadian Institutes of Health Research, Ontario Ministry of Health and Long-Term Care, and the Chair in Vascular Surgery at Sunnybrook held by Dueck.

“This is very complicated work.”



STOP-IT TRIAL SHOWS SHORT COURSE OF ANTIBIOTICS SAFE FOR TREATING INTRA-ABDOMINAL INFECTIONS

Results also relevant to global health effort to halt the overuse of antibiotics

BY BETTY ZOU

Too much of a good thing can be a bad thing, especially if the good thing is antibiotics. The overprescription of antibiotics is the main factor driving a worldwide increase in antimicrobial resistance, which poses a serious threat to global public health. On an individual level, prolonged exposure to antibiotics disturbs the resident gut flora—the community of beneficial bacteria living in your gut—and is associated with a number of ailments, including an increased risk of *Clostridium difficile* infection.

In an ideal world, patients would stop taking antibiotics as soon as their bacterial infections are resolved. In

reality, antimicrobial therapy is often extended longer than necessary for the doctors' and patients' peace of mind.

When it comes to managing an intra-abdominal infection, there is no clear consensus on what is the optimal length of antimicrobial therapy. "Some surgeons think everyone needs to be on [antibiotics] for as long as two weeks, while others believe that they can discontinue antibiotics once patients have improved clinically," says Dr. Avery Nathens, program research director of the Trauma, Emergency & Critical Care Program at Sunnybrook Research Institute and surgeon-in-chief at Sunnybrook. "Up until recently,

Photo: Nation Wong

Sunnybrook's surgeon-in-chief Dr. Avery Nathens sees a lot of intra-abdominal infections in his operating room. He was the Canadian lead on a large, multicentre trial that found shorter courses of antibiotics are safe and effective.

there hasn't been any evidence to guide us one way or another."

Guidelines for the management of intra-abdominal infections recommend patients take antibiotics until clinical symptoms are resolved and sustaining the treatment for two days thereafter. However, several smaller studies suggest that with adequate control of the infection, or "source control" as it is called, shorter courses of antibiotics might be sufficient to cure the infection while decreasing the risk of antimicrobial resistance.

Source control for intra-abdominal infections is typically achieved in the operating room. Intra-abdominal infections usually result from a perforation of the gastrointestinal (GI) tract, with common causes being a ruptured appendix or a perforated ulcer. An infection becomes complicated when it spreads beyond the infected organ to cause inflammation in the peritoneum, the thin layer of tissue lining the abdominal cavity. Surgery is required to patch the hole, drain the abscess, or in severe cases remove the damaged portion of the GI tract and reroute bowel contents. These interventions aim to remove the source of infection and restore normal physiological function to the gut. As Nathens notes, these procedures make up the bread and butter of a general surgeon's practice. "[Surgery] probably takes care of 99.9% of all the [bacteria] that are present," he says. "And the issue is, well, now that we have accomplished source control, how long do they need to be treated with antibiotics?"

Enter the Study To Optimize Peritoneal Infection Therapy, the STOP-IT trial. In collaboration with colleagues from Canada and the U.S., Nathens designed the STOP-IT trial

to test whether a short, fixed duration of antibiotic therapy would lead to equivalent outcomes as the traditional strategy of prolonging antibiotic treatment to two days after resolution of symptoms.

The study recruited 518 patients with complicated intra-abdominal infections, all of whom underwent the appropriate surgical intervention to achieve adequate source control. The patients were randomly assigned to one of two groups. The experimental group received four days of antibiotics following their source control procedure. The control group received antibiotics until their symptoms were gone and were kept on antibiotics for two days after that, for up to 10 days.

Patients in the control group received, on average, eight days of antimicrobial therapy, whereas patients in the experimental group received four. Despite the difference in therapy duration, both groups had similar rates of surgical site infection and recurrent intra-abdominal infection.

Nathens, who is also a professor in the department of surgery at the University of Toronto, was not surprised by these findings, which were published in the *New England Journal of Medicine*. "When you look at the smaller studies, many of which were not randomized, there was a hint that you would probably be fine with a shorter duration of therapy," he says. "This study provides us with fairly high-level evidence that shorter courses of treatment appear to be safe."

Although the rates of recurrent infection were similar between groups, the infections were diagnosed much later in the control group. Nathens believes that the longer treatment of antibiotics helped to hide the

INTRA-ABDOMINAL INFECTIONS

- **Intra-abdominal infections are the second most common cause of death from infectious disease in intensive care units in the U.S.**
- **Appendicitis is the leading cause of inpatient hospitalization in Canada (excluding maternal cases) among people aged 19 to 44.**
- **Globally, intra-abdominal infections cause one in four cases of severe sepsis, a life-threatening, whole-body inflammatory attack.**
- **80% to 90% of intra-abdominal infections are caused by an infection that has spread from the gastrointestinal tract via a perforation caused by disease or trauma. Of these, 70% are community-acquired and 30% are hospital-acquired.**
- **By 2050, antimicrobial resistance is predicted to lead to 10 million extra deaths annually and cost the global economy up to \$100 trillion USD.**

recurrent infection by managing some of the symptoms, such as fever. For a recurrent infection, he says, antibiotics are not effective, and surgical interventions are usually required to eliminate the source. Thus, the longer course of antibiotics might actually hinder the recovery process by delaying the diagnosis and proper treatment of recurrent infections.

Given the paucity of large, randomized controlled trials for the treatment of intra-abdominal infections, Nathens is optimistic that the STOP-IT trial will have a significant impact on clinical guidelines and help standardize practice. Moreover, he says he hopes studies such as this will facilitate dialogue between doctors in the infectious disease and surgical communities and patients on what an appropriate course of antibiotics might be.

"The patient's perspective is that more antibiotics is better, but we try to emphasize that it's probably not a good thing if you don't need them," says Nathens. "We feel more comfortable now in speaking with them and explaining that fewer days of antibiotics is actually the preferred approach, with no adverse outcomes associated with this strategy."

This study was funded by the National Institutes of Health.

Landmark study identifies imaging biomarker that can detect earliest signs of brain decay in those at risk for this devastating disease

Illuminating Frontotemporal Dementia

BY JASMINE BUDAK



At first, Jane (not her real name) didn't think much of her sister's odd behaviour. The mismatched clothes and erratic driving were benign, even comical, offenses that could easily pass for middle-aged eccentricity. At the time, Jane's sister was in her mid-50s, highly educated and fiercely independent. But then quite rapidly her judgment seemed to deteriorate. She made uncharacteristically rash and dramatic decisions. She would botch simple tasks. Her writing became like a child's, riddled with spelling errors and jumbled words. To Jane's dread, her sister's increasingly peculiar behaviour reminded her of what had happened to their father and some of his siblings, back when all dementia was considered Alzheimer's disease, or just a cruel symptom of old age.

Today there is a name for the brand of dementia that runs in Jane's family: frontotemporal dementia (FTD), the dementia you've probably never heard of, but which is one of the most common types to strike people in their 50s and early 60s, unlike Alzheimer's, which usually comes on after age

65 years. Whereas Alzheimer's most often damages the mesiotemporal and parietal lobes, gradually affecting memory and thinking, FTD swiftly attacks the anterior temporal and frontal areas, which control judgment, behaviour and language, eventually obliterating one's personality or ability to communicate. Frontotemporal dementia is highly heritable (most often caused by mutations in three genes) and has been less-studied than Alzheimer's and other more common neurodegenerative disorders. In the last several years, however, the research gap has been closing.

A new study by the Genetic Frontotemporal dementia Initiative (GENFI)—an international team that includes Sunnybrook Research Institute (SRI) scientists—has illuminated very early structural changes of the disease. By peering into the brains and behaviour of at-risk participants several years before they show symptoms, researchers have been able to locate some of the earliest sparks of FTD, so that they may one day be stamped out before igniting an uncontrollable fire. "Once the brain cells die, we can't do much," says Dr. Mario Masellis, an SRI researcher-

neurologist and the study's lead Canadian investigator. "So if we can prevent the cells from dying, treat people before they show symptoms—that is the ultimate goal of this research."

Published in *The Lancet Neurology* this past March, it is the largest and most statistically powerful presymptomatic genetic FTD study to date, involving 220 participants from five countries. This sort of collaboration is crucial, says Masellis, since FTD is reasonably uncommon and it would take one jurisdiction years to amass such a cohort.

As her sister's condition worsened, Jane became a full-time caregiver. "She couldn't be left alone," Jane says. "She had to be watched at all times otherwise she would wander off and get lost." The daily care, the constant curbing of minor catastrophes, the up-close horror of the brain disease that eventually killed her sister left Jane terrified that she would be next. "I wanted to know so I could draw up a plan for my children; there was no way I wanted them to have to take care of me." As she pursued genetic testing, Jane got word about Masellis and the FTD study. Even though she tested

Primary Progressive Aphasia



Dr. Mario Masellis is leading the Genetic Frontotemporal dementia Initiative, an international team of experts investigating this rare neurodegenerative brain disease.



“I wanted to know so I could draw up a plan for my children; there was no way I wanted them to have to take care of me.”

negative for the known familial mutation, she qualified for the study because she had a first-degree relative who'd had FTD, which meant she was at risk of developing the disease. She didn't think too long before volunteering, and even recruited nieces and nephews to participate—anything she could do to help shed light on the disease that had felled so many of their family members.

Along with blinded genetic testing and a standard clinical assessment, participants underwent behaviour and cognitive tests, for example, connecting letters on a page, naming objects, or listing animals or words that start with a certain letter—all to determine the existence or degree of FTD symptoms. But it was the 70-plus minutes participants spent lying inside the MRI

machine that showed a compelling picture of the earliest traces of brain decay, in some cases more than 10 years before symptoms would be expected.

Across all three genetic subgroups, FTD seemed to take its first blow at the insula, a region that SRI's Dr. Brad MacIntosh describes as, “the brain's brain.” The insula is a prune-sized tissue embedded deep behind where the frontal, temporal and parietal lobes meet. “It's integral to the brain-body connection,” says MacIntosh, a neuro-imaging scientist who was part of the SRI science team, rounded out by Dr. Sandra Black, head of the Hurvitz Brain Sciences Research Program. “It's a critical hub involved in everything you don't think about: the rate of your heart beat, maintaining

homeostasis, but also raw emotions and perception.” The early effect of FTD on the insula was a huge discovery. “We've introduced roughly a 10-year window where we can say there's early evidence that a patient is at risk for FTD,” says MacIntosh. (Participants will be scanned again next year to track the progression of insula damage.) As a sort of ground zero for FTD, the insula can now serve as a biomarker of the disease and could be used to test human responses to new treatments that might, for instance, slow the pace of the brain erosion, which, for Jane, could have bought at least a few more years with the sister she once knew.

Along with imaging biomarkers like the insula, Masellis hopes to find fluid biomarkers in the spinal fluid and blood samples that were also collected. (Those results haven't yet been analyzed.) Masellis suspects that spinal fluid biomarkers might be more sensitive in detecting the earliest signs of the disease.

He is also conducting a study using DNA samples from participants that will analyze genetic markers located across the genome. The hope is to identify risk factors that contribute to why one person may develop early language symptoms and why another may develop early behavioural issues. Some genetic factors may also protect against the development of disease or at least cause a later onset. These so-called modifying genes could be other potential targets for therapies under development.

Though FTD was found to erode the insula across all gene mutation groups, outwardly the disease looks different among carriers. In their study, the team found hints that mutations in the three different genes strike the brain in specific patterns, and so FTD symptoms may vary depending on from which

Dr. Brad MacIntosh used magnetic resonance imaging to identify changes in the insula region of the brain, a discovery that might be useful as a biomarker for frontotemporal dementia and to measure treatment response.

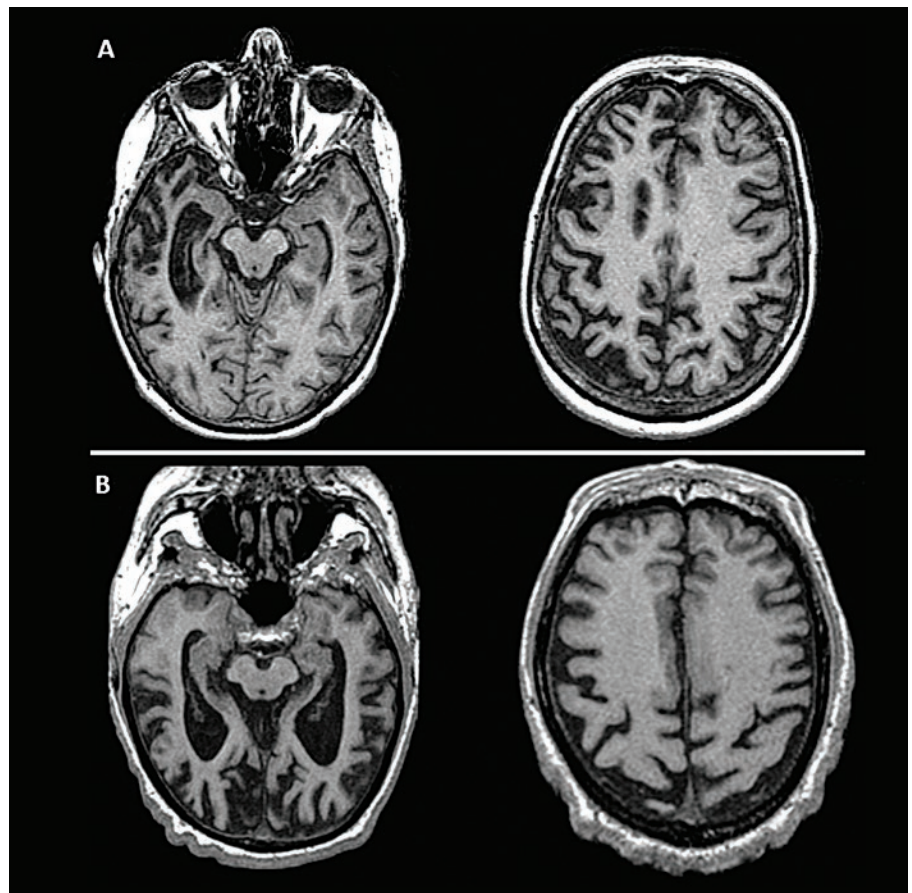


genetic subgroup you come. Mutations in the progranulin (GRN) gene tends to impair one side of the brain faster than the other. A patient with left-side damage may first lose the ability to speak, while a right-side deterioration would manifest as behavioural changes, as Jane's sister's had done. Mutations in the other two genes—microtubule-associated protein (*MAPT*) and *C9orf72*—have been found to affect both sides of the brain fairly equally, sometimes causing a broad range of symptoms all at once. (However, in asymmetric cases, as the disease progresses, it's likely that both sides would suffer eventually, says Masellis.)

These glimpses into the brain structure of presymptomatic FTD comprise just one phase of the study; subsequent papers will focus on brain *function*: blood flow and connectivity between regions, data gleaned from what's called a functional MRI. Masellis and MacIntosh are parsing the data, but Masellis has a hunch the findings will be encouraging. "It's my belief that we'll see functional changes even earlier than we see structural changes," he says, possibly paving the way for an even earlier FTD imaging biomarker.

There are no treatments for FTD beyond antidepressants and antipsychotics, which tamp behavioural and mood symptoms. And it's not like they offer long-term relief, anyway, says Masellis. Such drugs work by modulating neurotransmitters that get depleted as brain diseases progress, so the effects are fleeting. This is why dementia researchers are pinning hopes on preventive therapies, for instance, medication that targets the aggregated proteins that kill brain cells (a feature of all dementias).

In his quest to unlock the mysteries of FTD, Masellis has published several papers describing variability in clinical presentation of FTD due to mutations in progranulin, a type of protein important in brain development. Masellis found that all the mutations in this gene cause progranulin levels to drop. "So, if we can find a treatment that elevates progranulin levels," he says, "then we might be able to prevent FTD." Small clinical trials of such a drug are underway in the U.S.,



Brain scans of a patient with genetic frontotemporal dementia (FTD; top) and a patient with early onset familial Alzheimer's disease (AD; bottom). The patterns of brain decay are strikingly different in the two diseases: atrophy is asymmetric between the left and right sides in the FTD brain, whereas in the AD brain, it is symmetric. The scans were acquired using magnetic resonance imaging.

though they mark the early phases of drug testing. If the treatment should prove safe and well-tolerated, then the international FTD study participants could serve as a ready platform to launch further clinical trials, says Masellis.

During his many years as a neurologist and researcher, Masellis has seen the effects of FTD up close: the rapid robbing of lives at a time when they are still working or raising families. "They stop being who they are," he says. "You can imagine someone who's 50 years old and still has a 12-year-old child at home. They can't work, and often the spouse has to stop working to care for their partner full time. It's a huge effect on family and income." For Jane, who lost her father and, she suspects, three siblings (this was before FTD was a well-

defined diagnosis), it's an unfathomably cruel disease that leaves the caretakers and surviving family members in ruins. The best thing she can do now in service of her family is to be part of studies that continue to shine a light in the shadows and make important advances. "The progress on FTD has been spectacular," says Jane. "I think back to my sister [some 20 years ago], and she got a different diagnosis every time she saw the doctor. And now they know what it is, they've got it down to the genetic level; they're finding biomarkers so the disease is more predictive, and when it's predictive they can do something about it."

The work of Masellis for this study is funded by the Canadian Institutes of Health Research and the Ontario Ministry of Research and Innovation.



IMMUNOTHERAPY

Engineering a vaccine to thwart cancer

BY ALISA KIM

PHOTOGRAPHY BY NATION WONG

Dr. Aws Abdul-Wahid developed a therapeutic vaccine that effectively restricts tumour growth and halts the spread of cancer cells. He is working to bring his vaccine to clinical trials.

The first things you notice in Dr. Jean Gariépy's office are the giant yucca plants perched on his filing cabinets and windowsill. Their lush, shiny green leaves stand out in the soft-spoken scientist's cozy office, which overlooks Sunnybrook's Bayview campus.

Outside his office, there's a flurry of activity. Voices and the whirring of machines can be heard as the 10 members of his lab work on their projects. Under Gariépy's direction, they are engineering biomolecules like proteins, peptides and nucleic acids for imaging and targeted treatment of cancer.

The research in Gariépy's lab is basic and applied. Ultimately, it is translational. His recent work on the protein carcinoembryonic antigen (CEA) in particular is pushing its way to the fore of clinical realization.

Gariépy, a senior scientist in the Odette Cancer Research Program at Sunnybrook Research Institute, and his postdoctoral fellow, Dr. Aws Abdul-Wahid, are studying the molecular biology of CEA and its role in metastasis, the spread of cancer from its original site to elsewhere in the body. In metastasis, cancer cells most often migrate to the liver, lung and bone.

Discovered in 1965 by Drs. Phil Gold and Samuel Freedman, CEA is an established tumour marker that is associated with cancers of the colon, rectum, pancreas, stomach, breast,

lung, thyroid and ovaries. "It's typically present in humans at birth, but after that it disappears and it's only weakly expressed along the gastrointestinal tract. After you're born, that marker is very rare. That's why it's a useful [tumour] marker," says Gariépy, who is also a professor of medical biophysics and pharmaceutical sciences at the University of Toronto.

Cancer cells teem with CEA. So much of the molecule is expressed on cancer cells that some of it is shed in the blood, which is how it is measured clinically. Oncologists check CEA levels in the blood to assess a patient's response to therapy and likelihood of disease recurrence, rather than to detect cancer.

For years researchers have suspected that CEA plays a role in metastasis, but they had yet to nail down the precise mechanisms by which it did so—until recently.

In a study published in *Molecular Oncology* in 2014, Abdul-Wahid and Gariépy showed that one piece of the CEA molecule on the surface of tumour cells—called the N domain—bound to its counterpart on nearby cancer cells. "We found it actually made cancer cells 'stickier.' They tended to clump with each other. When cancer cells clump, they aggregate [and] expand [just] as seeds sprout," Abdul-Wahid explains.

The researchers are the first to show that this particular region of CEA also binds to fibronectin, a protein that is part of the extracellular matrix, which provides structural and biochemical support to the cells it surrounds. This interaction allows cancer cells floating in the bloodstream to attach themselves to secondary sites in the body; disrupting this interaction, therefore, could well be the key to blocking metastasis, Gariépy surmised, correctly as it turned out.

What's more, they were surprised by the strength of these interactions. "If you have a cancer cell that's covered with this molecule, you don't just have an affinity of this binding to that and forming these 'zippers.' It's more like an avidity of having thousands, if not more, of these molecules trying to strap [themselves] to this thing and that with pretty good affinity for each individual interaction.



Dr. Jean Gariépy (right) and postdoctoral fellow Dr. Aws Abdul-Wahid are trying to harness the power of the body's immune system to fight cancer.

“So these cells have this propensity to want to stick together, to stick to the matrix. We don’t see this on normal cells because they don’t express CEA,” says Gariépy.

MARSHALLING ONE’S NATURAL DEFENSES

Armed with these discoveries, Gariépy and Abdul-Wahid set out to develop a vaccine to interfere with these interactions to block the implantation of cancer cells, thereby preventing metastasis.

Cancer vaccines fall into two categories: preventive and therapeutic. Preventive vaccines are given to healthy people to protect against infections associated with cancer. Examples are vaccines against the human papillomavirus to ward off cervical cancer, and vaccines against the hepatitis B virus to prevent liver cancer.

Preventive vaccines are similar to traditional vaccines that protect against polio or chicken pox, for example, in that they are based on antigens—substances that induce an immune response, like the

production of antibodies. The immune system recognizes the antigens as foreign and “remembers” them to prevent future infections.

Therapeutic cancer vaccines, on the other hand, are given to people who have the disease, with the aim of preventing recurrence, destroying residual cancer cells after another type of treatment, or stopping a tumour from growing or spreading. They are a type of immunotherapy designed to enlist the body’s natural defenses to fight cancer.

Most therapeutic vaccines have failed mainly because cancer cells elude the immune system’s natural ability to spot and destroy that which is foreign, says Gariépy. “Most cancer cells express ‘self’ antigens—molecules that are normally found in humans. So your immune system does not want to raise an immune response against that. Your body basically rejects the idea of mounting a significant immune response.”

To get around the problem of cancer cells not “looking” harmful to the immune system, Gariépy and Abdul-Wahid created a vaccine that

targets CEA’s pro-metastatic properties, but disguised the molecule to trigger an immune response.

“We’ve focused on the tiny N domain of CEA that is involved in cell-cell adhesion with the view that it’s going to kind of look foreign. We’re making it look like an ‘altered self’ so that the immune system says, ‘That’s probably not something that’s in my body so I will raise an immune response against it,’” says Gariépy.

Making effective treatment vaccines has proven much more difficult than developing preventive vaccines. A major obstacle has been the lack of understanding of how the immune system will respond to a therapeutic vaccine. To be effective, a vaccine must prompt a specific immune response against the right target.

By focusing the vaccine-elicited immune response to the CEA N domain, the researchers have shown they can thwart cancer cells’ ability to settle elsewhere. “It’s almost like we’re teaching the immune system to reject the cancer from ever implanting,” says Abdul-Wahid.

They tested their vaccine in mice that

“It’s almost like we’re teaching the immune system to reject the cancer from ever implanting,” says Abdul-Wahid.

were genetically modified to express CEA. Animals treated with their vaccine showed delayed onset of metastasis and limited tumour growth. The tumour volume of vaccinated animals was about one-half that of unvaccinated animals 24 days after implantation of cancer cells.

“We were able to protect animals from developing cancer in the peritoneum and the lung. In vaccinated animals, we were able to stabilize tumour growth. The tumour cells, once injected in unvaccinated animals, would grow out of control. The vaccinated animals, on the other hand, were able to control their tumour burden much better. That highlighted that vaccination is feasible as a strategy.

“Other people have attempted this kind of a vaccine for over 20-something years with very modest results—practically no successes. They were targeting the whole [CEA] molecule, not the ‘business’ end of it,” says Abdul-Wahid with a smile.

NEXT STOP: PATIENTS

Having proved in principle that their strategy can prevent metastasis, the researchers are now developing a formulation for patients. They are working with pharmaceutical companies to obtain clinically approved adjuvants, which are substances that help activate the immune system, to use along with their vaccine. These adjuvants stimulate activity by B cells and T cells, which allow the body to remember and recognize invaders, and eliminate them.

One of the difficulties in evaluating whether the vaccine works in patients is the time needed to complete a clinical trial. Choosing patients with aggressive disease is one way around the problem, notes Gariépy.

“This sort of vaccine faces more challenges than other types of treatment because you’re looking at an event that occurs fairly far in the future, so you have to pick your group of patients such that the disease tends to progress more rapidly than others in terms of metastasis,” says Gariépy. “That is why triple-negative breast cancer and ovarian cancer are interesting candidates for us to test the vaccine, because the outcome of metastasis would be quicker in these patients. This way, within a reasonable timescale of a trial—it may be three to five years—we’d start to see curves changing between vaccinated and unvaccinated [patients].”

Triple-negative breast cancer is hard to treat because it lacks the three receptors known to promote tumour growth—estrogen, progesterone and HER-2. Thus, therapies that target these receptors don’t work. It occurs in 10% to 20% of diagnosed breast

cancers, and is more likely to spread and return.

It could be a year or two, or even longer, before clinical trials of the vaccine begin. Abdul-Wahid says if they can prove that it works, then the vaccine could be a viable strategy because it doesn’t require elaborate infrastructure and can be given by nurses. “My wish is that I would see patients—soon after diagnosis—immunized and then put into whatever first-line treatment that is needed. Then just like we do with the flu shot every year, these patients would be ‘boosted’ periodically, so that we can prevent or delay the onset of metastasis. Wouldn’t that be great?”

This research is supported by the Canada Foundation for Innovation, Canadian Breast Cancer Foundation, Canadian Cancer Society, Canadian Institutes of Health Research, Federal Economic Development Agency for Southern Ontario, and Ontario Ministry of Research and Innovation.

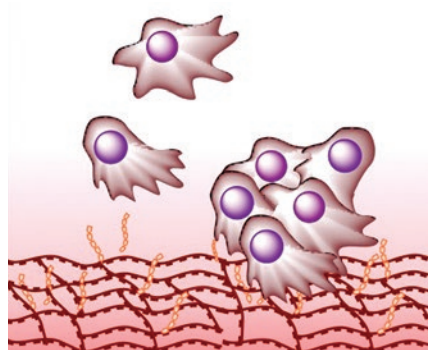


Figure 1: Expression of CEA on cancer cells renders them more aggressive and prone to metastasizing. Presence of CEA helps cancer cells aggregate with themselves as well as adhering to fibronectin present on target tissue (represented as brown filaments).

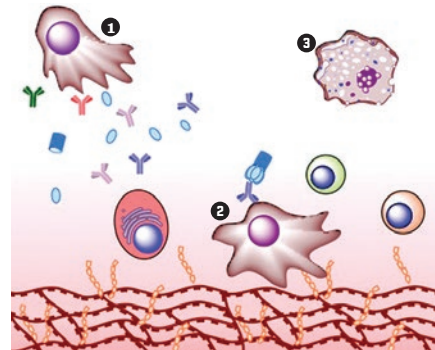


Figure 2: Giving the metastasis-preventing vaccine to patients helps the patient’s immune system recognize metastasizing cancer cells and limits their ability to spread to other parts of the body. On one level, antibody molecules tackle cancer cells, thus preventing their “clumping” and ability to implant (1). On a second level, cells of the immune system attack cancer cells that manage to escape the first wave of defenses (2), ultimately leading to the killing of the cancer cells by the patient’s immune system (3).



Project Guidance

Made-in-Ontario imaging devices seek to redefine the landscape of interventional cardiology

BY ALISA KIM
PHOTOGRAPHY BY NATION WONG

If a picture is worth a thousand words, then what is the value of one that helps doctors navigate the heart's delicate terrain to repair lethal conditions?

That's the million-dollar question Dr. Brian Courtney, a clinician-scientist in the Schulich Heart Research Program at Sunnybrook Research Institute (SRI), is investing his time and energy into answering. Courtney is compelled to provide better image guidance so that doctors like him can manoeuvre through the heart and its channels with greater safety and precision.

"I love looking after patients and trying to provide them with some solution to the challenges they face. If I were to do clinical work 100% of the time, knowing how many technical challenges we face and how many conditions we'd like to be able to treat better, I'd be a bit frustrated. I studied engineering as my initial profession—I like to go after problems and solve them with technical and other solutions," he says.

Courtney has spent much of his career developing devices to improve outcomes of minimally invasive procedures. In 2007, he founded Colibri Technologies to put these tools in the hands of those who mend ailing hearts and vessels.

Colibri's first product is an ultrasound catheter that makes 3-D pictures inside the heart in real time. It's used for intracardiac echocardiography, a technique whereby a catheter with an ultrasound probe at the tip is inserted into a leg vein and guided up into the heart. Intracardiac echo is gaining traction in procedures for structural heart disease and arrhythmia, when the heart beats irregularly.

First, a primer on the heart. This fist-shaped pump is divided into four chambers. The left and right atria, which receive and collect blood, form the upper chambers. The lower chambers, the left and right ventricles, pump blood out of the heart to the rest of the body. An internal wall called the septum divides the right and left sides.

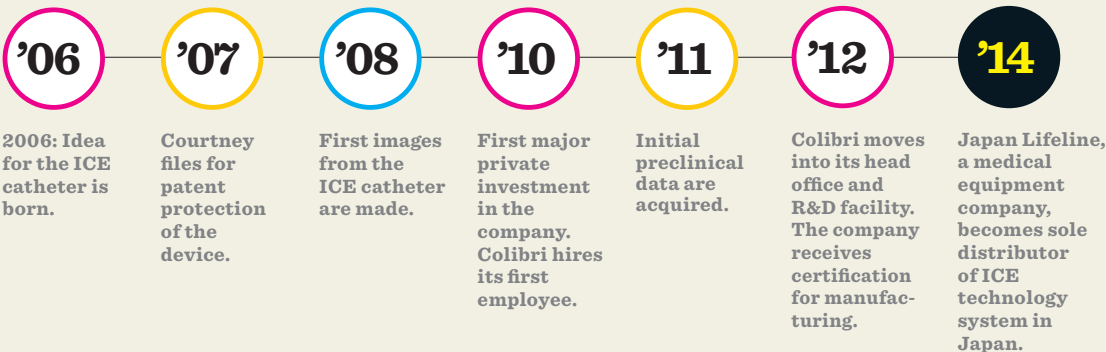
Atrial fibrillation (AF) is when the heart beats abnormally—too fast, too slow or somehow out of sync. It affects about 250,000 Canadians, which makes it the most common heart rhythm problem. It's caused by an electrical disturbance in the atria.

A prolonged too-fast heartbeat can lead to heart failure when the weakened muscle can't pump enough blood throughout the body. Atrial fibrillation also increases the risk of stroke five-fold. This is because the atria contract

Dr. Brian Courtney founded Colibri Technologies to develop and commercialize better image guidance devices for cardiac care.

Staying the Course

Moving a medical innovation from an idea through to a saleable product takes dedication and time—lots of it. Here, a look at some milestones in Colibri's commercialization pathway of the intra-cardiac echocardiography (ICE) system.



in a chaotic pattern; thus, the heart doesn't pump effectively, causing blood to pool, which could lead to the fatal ascent of a clot to the brain.

Anticlotting drugs and medication to control heart rate and rhythm are a first-line strategy for reducing the risk of stroke and symptoms caused by AF. If patients can't tolerate them, then they might undergo cardiac ablation, a procedure that's done in Canada several thousand times annually. The aim is to alter the heart muscle that initiates and propagates faulty signals that cause the arrhythmia.

Some electrophysiologists, who are cardiologists specialized in treating such problems, rely on X-ray guidance during ablation procedures, especially if the patient's anatomy is normal. That often isn't the case, though, says Courtney. "That's one of the reasons why people might have atrial fibrillation, because they have something different about their heart."

For common heart procedures, including AF ablation, doctors move from the right side to the left by making a small hole in the atrial septum. The left atrium is the trickiest chamber to enter, and where ultrasound guidance is advantageous, says Courtney.

Dr. Bradley Strauss, a senior scientist at SRI and chief of the Schulich Heart Program at Sunnybrook, where he works as an interventional cardiologist, agrees. "Sometimes you go through [the septum] where you don't want to go through, and puncture the heart or do something that's very dangerous, especially for people who don't have

as much experience doing it. The idea that you can actually see where you're going is very helpful."

Other companies make catheters, but Courtney's intracardiac catheter is the only one that is forward-viewing and can do 2-D and 3-D imaging.

Strauss, who has evaluated the device and made a minority investment in Colibri, says being able to see ahead of the catheter is a game-changer. "Imagine doing some of the dangerous things we do and not knowing precisely where you're going. That we can do it without that guidance is amazing, [but] every once in a while, even with experience, you get misled or make a mistake. This will ensure it's safer and more accurate."

The device could also transform how catheter-based mitral valve procedures are done. Here, doctors stop leakage of blood from the left ventricle to the left atrium by attaching a clip to the mitral valve to keep it closed. It's guided by a technique called transesophageal echo, which uses ultrasound to see inside the heart but goes in through the esophagus and requires general anesthesia. Using intracardiac echo instead requires only local anesthesia, a faster, cheaper option.

In addition to providing more anatomical context, the 3-D component of the imaging could help doctors do their work more handily.

"When you're doing these procedures, you have one device that's either burning, sensing or clipping, and you have another catheter that takes pictures. If you have a 3-D

catheter, that gives you more flexibility in being able to position your imaging catheter in other locations that are less likely to interfere with the movement of the catheter that's doing the therapy," says Courtney.

WELCOMING THE HYBRID AGE

Colibri's second product, its intravascular catheter, is an innovation that could help cardiologists to determine better the nature and extent of coronary artery disease, narrowing of the coronary arteries that is the leading cause of death worldwide. The device combines two complementary ways of seeing inside blood vessels: ultrasound and optical coherence tomography (OCT).

Intravascular ultrasound can identify attributes such as plaque build-up or calcifications on the artery wall that are difficult to make out on an angiogram, a picture of the coronary arteries made using X-rays and a dye. It's also used to see whether a stent has been placed correctly or to determine the right-sized stent.

Optical coherence tomography, which makes pictures by sending light into tissue and collecting the reflections, is a newer technique that provides higher resolution and better contrast than does ultrasound. Where ultrasound prevails is being able to see deeper into tissue and looking through blood.

Colibri's intravascular catheter aligns the ultrasound and OCT beams exactly so that they look in the same direction concurrently. The design enables data from both modalities to be matched

precisely for a more detailed image inside the vessels.

The device offers hope in detecting “vulnerable” plaque, which is prone to rupturing. If this happens, then a life-threatening clot forms inside the artery, which can lead to a heart attack or stroke. Catching the buildup before it bursts—which can be symptom-less, as was the case for the plaque that caused the death of NBC journalist Tim Russert in 2008—isn’t possible with current diagnostic methods.

Courtney has presented research on the technology at conferences, which has generated buzz from his colleagues. “It’s clear that there’s a need. We have a path to get there. It’s just a matter of putting the fuel in the tank to get to that point.”

NEARING THE FINISH LINE

Development of the intracardiac catheter is the company’s primary focus, says Courtney, who began working on the technology seven years ago. In the early stages, he and his team built a prototype and did validation testing and preclinical experiments at SRI.

Since then, Colibri has moved into its own space. Its 25 employees are working to propel the technology from a prototype to a market-ready product. The team has concentrated on image quality and reliability, and making the device sterile and biocompatible. In addition to ensuring safety, the team has miniaturized the catheter and modified the design so it can be manufactured. Colibri will seek regulatory approval for clinical use, with an eye to doing patient studies later in 2015.

While the first two products target applications in cardiology, there are plans to expand into other clinical domains. Colibri has acquired the rights to an ultrasound probe for imaging in the ear that was developed at Dalhousie University in Halifax, N.S. The device will become part of a pipeline of products. “The philosophy is to make a company that has a broad technology platform so we can be the best at

providing imaging guidance for minimally invasive procedures,” says Courtney.

The global market is paying attention: Japan Lifeline, a firm specializing in cardiovascular medical equipment, recently agreed to become the exclusive distributor for Colibri’s intracardiac catheter in Japan. The deal gives Colibri a foothold in the world’s second-largest medical device market.

The company’s dogged pursuit of success is remarkable against the somewhat gloomy backdrop of commercialization of innovations in Canada.

A study by the C.D. Howe Institute shows that per capita patent filings in Canada are declining. Moreover, the country’s medical device sector operates at a \$5 billion trade deficit; we buy \$7 billion worth of medical

equipment from the rest of the world while selling just \$1.8 billion of our own.

The path to bringing his inventions to market has been bumpy, and the stakes are high, but Courtney says the cost of sitting on the sidelines is even greater. “If people get too fearful of participating in the innovation process, then Canada will not be the one to innovate and we’ll be buying expensive technologies from elsewhere in the world, or not, and therefore not treating our patients as effectively.”

He’s all in.

Courtney’s research was supported by the Canada Foundation for Innovation, Canadian Institutes of Health Research, Federal Economic Development Agency for Southern Ontario, Health Technology Exchange, Natural Sciences and Engineering Research Council of Canada, Ontario Centres of Excellence, and Ontario Ministry of Research and Innovation.

Colibri’s first product is this catheter with an ultrasound probe at the tip that can take 3-D pictures inside the heart in real time.



Undeterred

Today's science trainees and their supervisors say their postgraduate education is worth it, despite a changed and challenging job terrain

IS

Canada producing too many PhDs? That was the question posed at the 2011 Canadian Science Policy Conference. Then-president of the Natural Sciences and Engineering Research Council of Canada, Dr. Suzanne Fortier, responded: "If you asked me, are we training too many people to become university professors, I think the answer is yes.

Are we training too many highly educated people who are encouraged to be creative and push the advancement of knowledge? I'd say definitely not."

How many PhDs is Canada producing? According to the Conference Board of Canada, 6,000—which might seem like a lot, but which the board notes is proportionately fewer than in comparator countries, and worth a "D" grade.

Most doctoral students pursue their degrees to become a university professor; however, employment outside academia is the norm for PhDs in Canada. Only 19% of PhDs work as full-time professors.

Against a backdrop of lower research funding and a scarcity of faculty positions, scientists at Sunnybrook Research Institute (SRI) are steadfastly training the next generation of researchers. They do so because they know that without them Canada loses its capacity to innovate and understand the world. Trainees at SRI recognize the odds of joining the tenure track are not in their favour. Still, they press on.

For Dr. Isabelle Aubert, nothing beats life as a scientist. Aubert is a brain biologist at SRI who is developing therapies to stop degeneration of neurons and promote their regeneration in Alzheimer's disease. She knew early on that she wanted to become a scientist.

Despite the long hours and the pressure to publish and get funding, Aubert says she finds the job stimulating. As a graduate student, such challenges weren't front of mind; rather, she was attracted by the collegial atmosphere modeled by her supervisor, and the opportunity to be productive and work toward achieving a worthy discovery. "I thought, 'Wow, there's no better job than this. We travelled a lot, so yes, it's demanding, and you work all the time, but you also have a lot of flexibility,'" says Aubert, who is also a professor at the University of Toronto.

It's an optimism shared by some of

today's trainees, who are nonetheless all too aware of the challenging path in front of them.

Catherine Schrankel is a fifth-year PhD student in the lab of Dr. Jonathan Rast, a senior scientist in Biological Sciences at SRI. Her focus is on identifying the factors that specify the immune system of the developing embryo in the sea urchin.

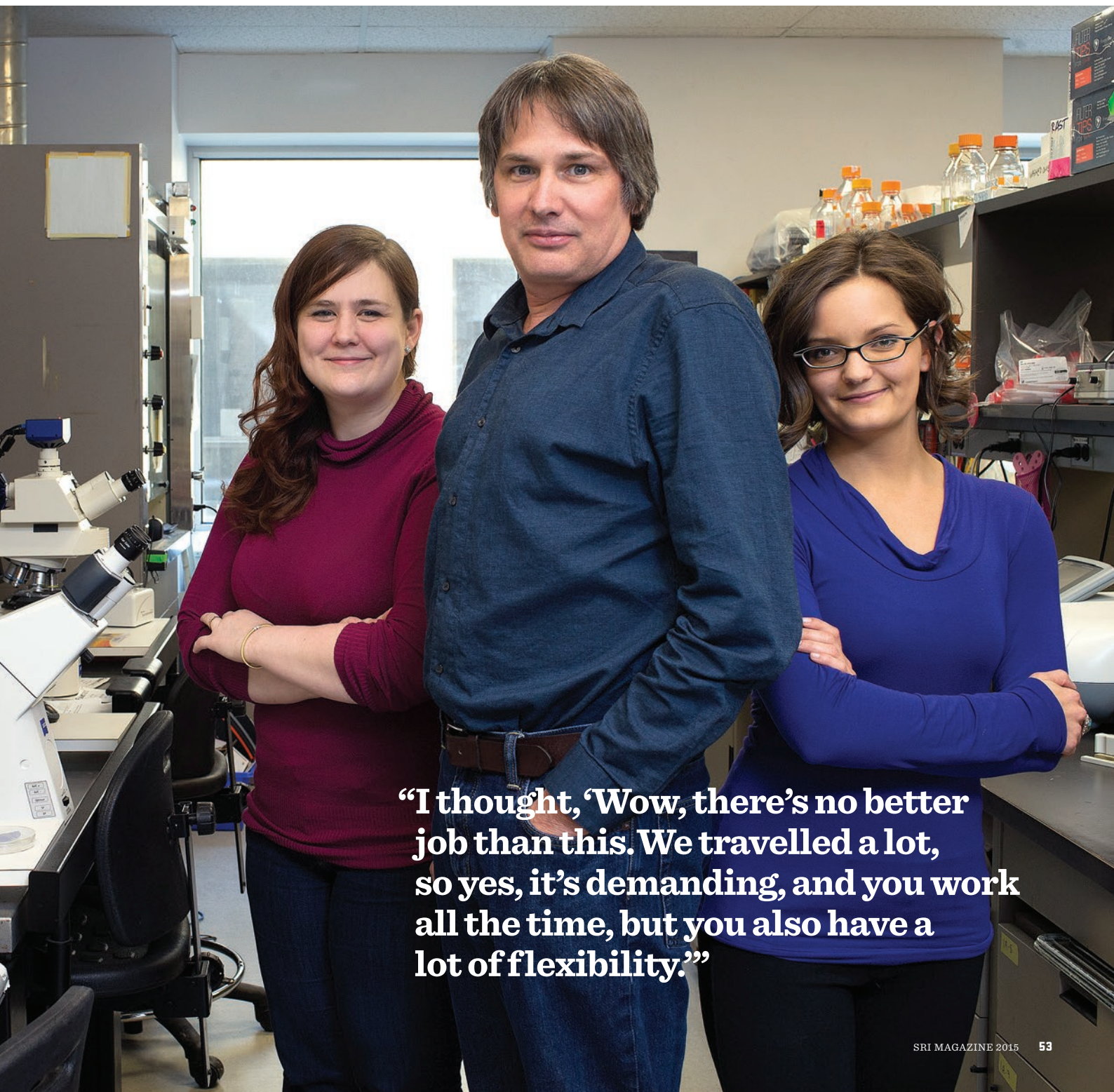
She says she hopes to become an academic researcher, but has broadened her options because of the tough job market: "I'm starting to look at back-ups, which I didn't come in thinking I would [do]. But they would still be related to science. I don't know if I'd be happy if I didn't have science somehow incorporated into what I do every day." She is also looking at careers in scientific illustration and communication, and advocacy.

Most of Rast's trainees have gone on to other academic positions, including a former postdoc who is a professor in Japan. Yet he says some trainees are disillusioned at their prospects and will leave research, which he considers a significant loss.

"It's starting to feed back into the morale of the students. When a student comes out of here, I imagine you spend about \$250,000 in training, with salary and materials. If they go into a field that doesn't use that training, all of that is lost."

Schrankel says anxiety over the

Dr. Katherine Buckley (left), a postdoctoral fellow in the lab of Dr. Jonathan Rast (centre), and Catherine Schrankel, a PhD student in the Rast lab, are persevering in their pursuit of an academic position.



“I thought, ‘Wow, there’s no better job than this. We travelled a lot, so yes, it’s demanding, and you work all the time, but you also have a lot of flexibility.’”

“I just wouldn’t want to do anything else. My motivation for this was never about money.”

shortage of academic jobs is common among her peers. She discusses her concerns with Rast because he faced similar uncertainty. Rast studied marine sciences and had aspirations of running his own lab, but was unsure about a future in basic research. “It was exciting, but at the same time you kind of knew that the funding was very limited for this type of stuff because it was distant from the practical, although it had huge implications,” he says.

Things worked out. As a scientist in the departments of medical biophysics and immunology at U of T, Rast uses the purple sea urchin as a model in which to study interactions among genes involved in immune response. “In retrospect, almost everybody I know that stuck with it and really wanted it ended up in an academic position. It was more attainable than it seemed,” he says.

THE TIMES, THEY ARE A-CHANGIN’

Graduate enrolment in Canada has risen in the last 30 years. In 1980, there were 25,000 full-time masters students and 9,800 full-time PhD students. By 2010, the last year for which data are available, these numbers had ballooned to 82,400 and 45,000, respectively.

Moreover, with the end of mandatory retirement and budget cutbacks at universities, it’s no surprise there are more PhDs than the market can absorb.

Given the fierce competition for jobs, Aubert tells trainees they must be the best in their area. “You cannot be in the ‘excellent average’ category anymore. You need to be outstanding,” she says. She counsels students to publish, network with leaders in their fields, and seek a postdoctoral position sooner rather than later during their PhD training. Some labs have a waiting list for postdoctoral fellows to join. Applying early will increase their chances to get into the lab of

their choice, where they can acquire specialized skills, expertise and publications.

Dr. Paul Nagy, who finished his PhD in Aubert’s lab in 2014, entered graduate school with a less conventional career path in mind. Before coming to SRI, Nagy worked for a pharmaceutical company. He became interested in drug development, but was advised by management that he would need an advanced degree to be promoted. “The motivation to get the PhD was never to become a principal investigator,” he says. “I did my undergrad, found a job and then found out I needed more to keep on moving up. The PhD was always related to that industry job.”

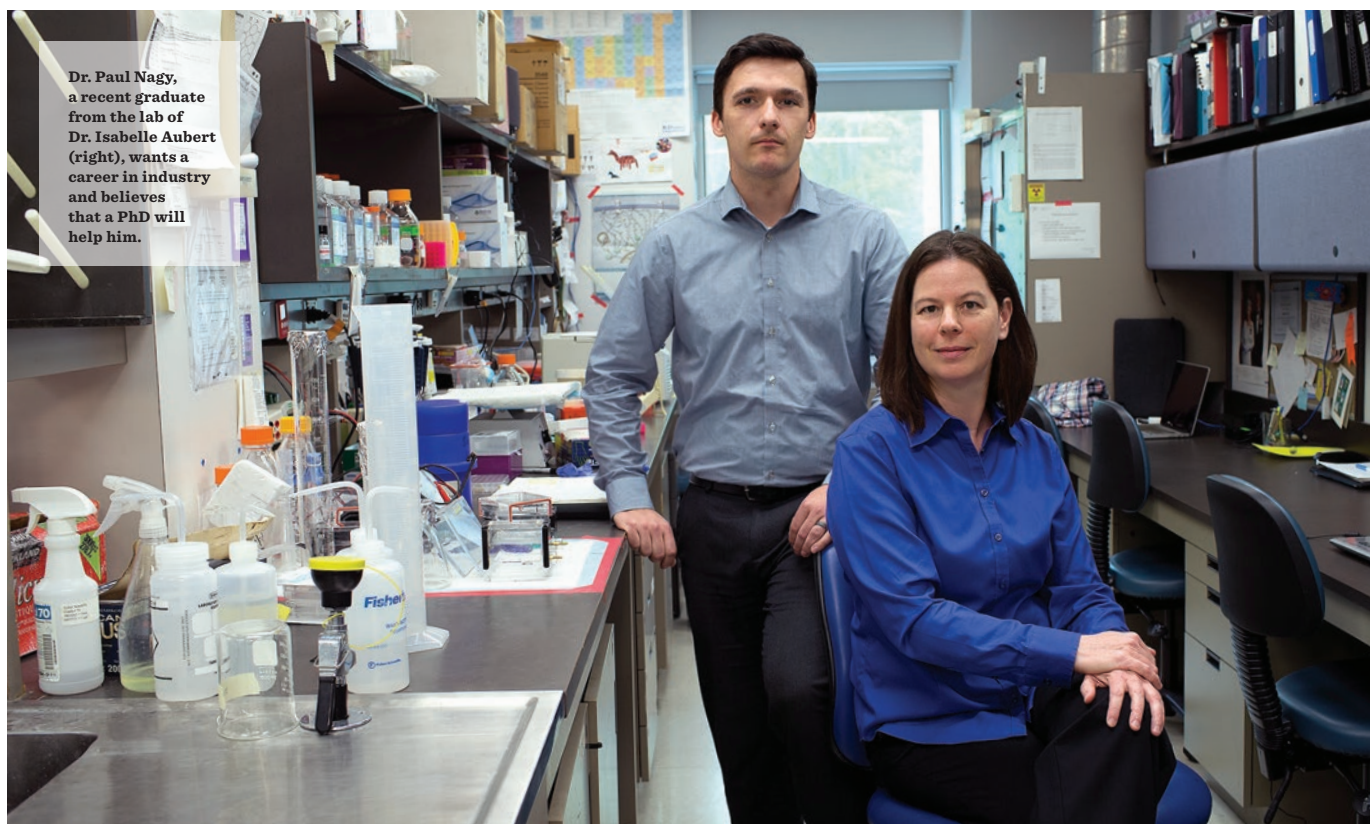
Nagy’s doctorate was on limiting and reversing neuronal damage in aging. He now works as Aubert’s research manager, a temporary position tied to one of her grants. With an emphasis on project management, Nagy thinks the role will help him make the transition back into industry.

He says getting his PhD was rewarding, but now that he has it, are the job offers from the private sector rolling in? Not quite yet. “I feel like I have the ticket to move up; I just don’t have the ticket to get in,” says Nagy.

SCIENCE FOR SCIENCE’S SAKE

Aubert acknowledges there aren’t enough jobs for PhDs, but she says it’s crucial to keep training young people in science for Canada to thrive as a knowledge-based society. “Canadian neuroscientists have a solid reputation. We want to stay competitive at the international level. If research goes down, then creativity, knowledge and our well-being go down.”

The threat of losing our edge looms as support for researchers—particularly basic scientists—diminishes. Over the past decade, success rates of grant competitions held by the Canadian Institutes of Health Research (CIHR)



Dr. Paul Nagy, a recent graduate from the lab of Dr. Isabelle Aubert (right), wants a career in industry and believes that a PhD will help him.

have fallen steadily. In 2005, about 25% of proposals were approved for funding; today, it's 17%.

Furthermore, CIHR recently revamped its funding model, replacing the open grants program with programs geared toward applied research—a change many scientists, including Rast, find worrisome.

“What’s going to happen is that 20 years down the road, you’re going to end up with no new material to make advances on because there’s not going to be that basic science to start out from,” he says. “The majority of ideas being used in applied science came out of things that were not clearly connected to those applications early on. There’s also cutting-edge training of students. Those types of things will start to disappear, and you’ll have a bunch of people working more on something akin to engineering than discovery-based science.”

Dr. Katherine Buckley, a postdoc in Rast’s lab, says in spite of such challenges, she is pursuing an academic career. She is studying how genes are turned on and off during an immune response in various species of animals.

“I just wouldn’t want to do anything

else. My motivation for this was never about money. All my friends are in their early 30s and have huge houses and nice cars, and I live in a tiny apartment. But we get to do what we want, and we have freedom. We get to be creative. That makes it worth it,” she says.

For Buckley and other postdocs, the licence to explore projects of interest come at the expense of reduced wages. A 2009 survey by the Canadian Association of Postdoctoral Scholars shows that most postdocs in Canada are aged 30 years or older and earn less than \$45,000 annually (before taxes), which is equivalent to the pay of a clerical assistant.

“To be brutally honest, for the amount of time spent in school, had I gone into another field, the returns would have been much higher,” says Dr. Aws Abdul-Wahid, a postdoc in the lab of SRI senior scientist Dr. Jean Gariépy.

He and Gariépy study the biology of a molecule found on cancer cells with the aim of developing a vaccine to stop the spread of cancer to distant sites in the body. They have engineered a vaccine that works

in preclinical models and are collaborating with drug companies to develop a formulation that can be tested in patients. After his postdoc, Abdul-Wahid plans to continue doing research in vaccine immunology.

What motivates him? The work itself. “For the first time, we’re giving a blueprint of an immune response that needs to be generated to prevent metastasis or decrease its severity. Metastatic cancer—this is what kills patients, and we’ve found a way to stop or limit it. I think this is worthwhile,” says Abdul-Wahid.

As for Buckley, she is wrapping up her postdoc and applying for jobs. She is hopeful a suitable position will open up, especially since she is willing to relocate. In spite of discouraging circumstances, she is concentrating on her work and maintaining a positive outlook. “It’s better to focus on the science and let the funding situation happen around you. I’m focusing on being good at what I do and doing interesting things, and going from there.”

ALISA KIM

Dr. Clare Atzema is a scientist in the Trauma, Emergency & Critical Care Research Program at Sunnybrook Research Institute and an emergency physician at Sunnybrook, where she sees 15 to 30 patients in an eight-hour shift. She is also a scientist at the Institute for Clinical Evaluative Sciences (ICES) and an assistant professor at the University of Toronto. She spoke with Eleni Kanavas about her research.



What is the focus of your research?

I have two foci. One is atrial fibrillation (a common arrhythmia of the heart) and how we manage it in the emergency department, as well as after people leave—the continuity of care between the emergency department and primary care, for example.

The other focus is, more broadly, cardiovascular disease in the emergency department. Again, I'm focused on the continuity of care with primary care, particularly because we're trying to help these patients avoid being admitted to hospital. If you're going to avoid that high level of care and send these patients home, where potentially no one's looking after them, then you need to have a system in place to ensure that they get timely follow-up care.

Right now, the patient is the system. We say, 'Please make sure you see your family doctor within a week,' and hope they pick up the phone. Sometimes we can call the family physician, but most people are in the emergency department after 5 p.m., when primary care is not open.

This "system" is especially important for the elderly and frail—they are the ones who are likely to have the most difficulty navigating the system, unless they have someone to advocate for them. They often aren't good at advocating for themselves. It's those patients in particular who I'm focused on, to try and establish some system of care such that we know they'll get seen after discharge from the ER. We know that with an aging population there will be a lot more ER visits in the next few decades, and we don't want to admit them all to hospital, but you can't just send them home and say, 'Hope that works out for you.'

Over the years, have you seen progression in better patient outcomes?

I've done a study that shows that the number of afib [atrial fibrillation] patients in Ontario's emergency departments has gone up by 30% between 2002 and 2010. If we continue to admit

the same proportion of those patients that we admit now (about 40%), and we do that for every disease, then we are going to overwhelm the hospital, so we have to send more patients home.

But what actually happens after ER discharge is a problem. For example, we did a study on patients with a new diagnosis of atrial fibrillation, who are at increased risk of stroke and heart failure. Some emergency physicians start them on something, while others don't, and we tell these patients to see their family doctor to continue the care we may have started.

We found that only 50% of these new patients with afib were being seen in Ontario by their primary care physician or a relevant physician [e.g., cardiologist] within seven days, which is the period within which the emergency doctors want them seen. By 30 days, 82% had been seen. So 18% with a new diagnosis of atrial fibrillation still had not seen anyone, which is disconcerting.

Why did you become an emergency doctor?

It's a privilege to be offered that incredible trust, to be a part of someone's life during that high acuity moment when they are showing up in the emergency department and giving you their complete trust.

Everyone works together, [that] is the other great thing about emergency. You're surrounded by smart people—nurses, doctors and the staff I work with on a daily basis. It's a can-do environment, because we're all working toward helping the patient, and that is incredibly fortifying.

What are some ways to prevent emergency department visits?

In the winter, for shoveling snow, call someone, hire someone or get a snow blower.

I feel there aren't that many ER visits that are not justified. The media talk a lot about patients who come to the ER who don't need to be here,



FACTS ABOUT EMERGENCY DEPARTMENT VISITS (AND ONE ABOUT ACCESS TO FAMILY PHYSICIANS)

- About 12 million people visit an emergency department (ED) in Canada each year, with the highest rates among the elderly.
- There were more than 57,000 visits to the Sunnybrook ED in 2013–2014.
- One in five Canadians visits an ED every year.
- Chest pain is the second most common reason for ED visits, behind abdominal pain.
- Minor trauma injuries such as cuts and head injuries are the most common diagnoses in the ED.
- 33% of Canadians wait six or more days to see their family doctors.



“Don’t shovel snow if you are over 65 and have heart disease!”

and I find that some of my patients apologize for coming, but you can’t diagnose what your chest pain is; that’s my job.

Not to mention that if they made it through what is sometimes a six-hour wait, then most people have a pretty good reason for being here. It might be nothing in the end, but it might have been something. That’s my job—to figure out which it is.

That’s unless you can see your family doctor right away (and that would be fine—if you have same-day access to your family physician). We need to ensure better access because as the Commonwealth [Fund] Study shows, we are pretty low down for being able to obtain an appointment in a timely way. [Canada ranked last of 11 advanced industrial countries on timeliness of care, for all levels of service.]

That said, there’s nothing like working over the holidays in emergency to make you really appreciate family physicians and all that they do. For example, influenza went around over the holidays, which caused a spike in ER visits: it makes you realize that what usually happens is those people do see their family doctor and then we don’t see them. But without those family doctors we are overflowing. There are no chairs left in the waiting room or beds to put patients in, and it’s standing room only.

I’d like to do a study showing that—to look at how we are completely hit [during the holidays]; the numbers are incredible, all because some of the family doctors are away. It makes me appreciate how much work they take off us normally.

Why is it important to examine the relationship between early care in the emergency department and outcomes in patients with cardiac illnesses?

Some of the things that we do in the emergency department are time dependent. We know that with heart attacks, for example, the sooner the better, in terms of patient outcomes; same with strokes.

However, while we do good work in the emergency department, and we fix the problem at hand, I suspect that for most patients what really matters is what happens *after* they leave the ER. Did they get to see the family doctor in a timely way? Did they get started on the evidence-based medications that we all know will help their disease?

Depending on what brought you to the ER, I feel that what happens after the visit is often more important than what happens to you in the emergency department.

Is most of your work provincial?

I generally only focus on Ontario, although I also examine Canada-wide data, and I have collaborated with other people. One example is a recent paper where we did a direct comparison of the proportion of visits to the ED for afib that result in hospitalization in Ontario versus the U.S. We discovered that 69% of the U.S. ED visits for afib end up in admission, whereas in Ontario it’s 37%. The big difference was in young patients [aged 18 to 64 years]; whereas we admit only about 26% of those people to hospital, in the U.S. it was around 63%.

What are some of the next steps in your research?

We need to mine the data on who gets follow-up care more extensively. As well, we assume that getting such care matters, and we have some longer-term studies that show that it does matter if you get seen in a timely way after you leave the emergency department, but we can’t say for sure whether or not seeing your family doctor within seven days has an impact on your mortality five years later, for example.

Is there anything else you’d like to add?

Don’t shovel snow if you are over 65 and have heart disease!

Atzema’s research is funded by the Canadian Institutes of Health Research and the Heart and Stroke Foundation of Canada. For more on her research, visit sunnybrook.ca/research.

Investing in the Future of Children

Gift bestows recognition on maternal-fetal medicine research

TORONTO PHILANTHROPISTS Fred and Linda Waks were delighted and surprised at the news of becoming first-time grandparents when their eldest daughter Jessica and her husband David Goodman announced they were expecting identical twins. In the months that followed, Jessica braved a high-risk pregnancy. A team of obstetricians and maternal-fetal specialists within the Women & Babies Program at Sunnybrook Health Sciences Centre monitored her carefully. On Jan. 27, 2014, Jessica gave birth to two healthy boys, Jack and Charlie.

"I felt the care my daughter received was of the greatest quality, and when there was a concern at one point in time for the two babies, the reaction, expertise and bedside manners that the hospital provided was beyond compare," says Fred, who serves on Sunnybrook Foundation's board of directors.

In recognition of this care, Fred, Linda and their four daughters decided to give back with a generous donation that was matched by family, friends and close business associates.

Together, they established the Waks Family Chair in Maternal-Fetal Medicine Research. The \$2-million Chair will enable 10 years of specialized research focusing on patients with high-risk pregnancies and births. The main areas of study will be very small preemies, multiple births, early fetal ultrasound, and the process and service of high-risk patient transfers.

Dr. Jon Barrett, director of the Women & Babies Research Program at Sunnybrook Research Institute and chief of maternal-fetal medicine at Sunnybrook, was appointed as the inaugural chair-holder. Barrett is a world-leading expert in high-risk births and was one of the physicians on Jessica's care team.

"It's an honour to be named Chair. There is a feeling of excitement about how we can take the program to the next level of international recognition of the excellence that we [achieve] here," says Barrett, who is also a professor in the department of obstetrics and gynecology at the University of Toronto. "We will create new knowledge of the best way to look after pregnant women, and then we will be able to translate that to other people who are looking after high-risk women and their babies throughout the world. By doing this we improve the quality of care of women in Toronto and internationally."

"This much-needed research Chair is a reality because a small group of donors who felt a deep commitment to improving the health of women and babies rallied to make it happen," says Dr. Jon Dellandrea, president and CEO of

Sunnybrook Foundation. "We're very grateful, in particular to Fred and Linda Waks. Without their leadership and passion for the project, the Waks Family Chair in Maternal-Fetal Medicine Research would not have been possible."

When asked what impact he hopes his philanthropy will have, Fred responds, "The most important thing is to set an example to your children in terms of community, and family is part of community. Giving back is a part of our heritage, and it's something that defines you. We are fortunate to be able to support various philanthropic endeavours in our community."

The Women & Babies Program at Sunnybrook is unique. Barrett says they see 4,200 patients a year, one-third of which are high-risk pregnancies. Obstetricians within the program deliver the largest number of premature babies in Canada and provide care to the smallest and sickest infants. The program is also a leader in clinical trials.

"It's an investment in the future of children in Canada," says Fred about Barrett's role as Chair of the research program. "As long as his vision fulfils what he's looking for, then I'm satisfied. That's what I hope for."

ELENI KANAVAS



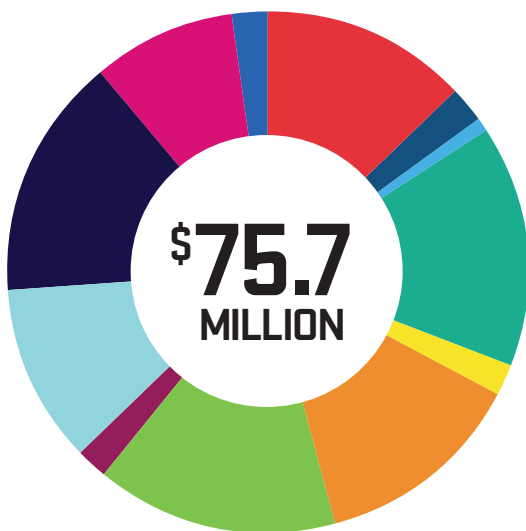
Fred and Linda Waks established the Waks Family Chair in Maternal-Fetal Medicine Research at Sunnybrook.

Photo: Hudson Taylor

Quick Statistics

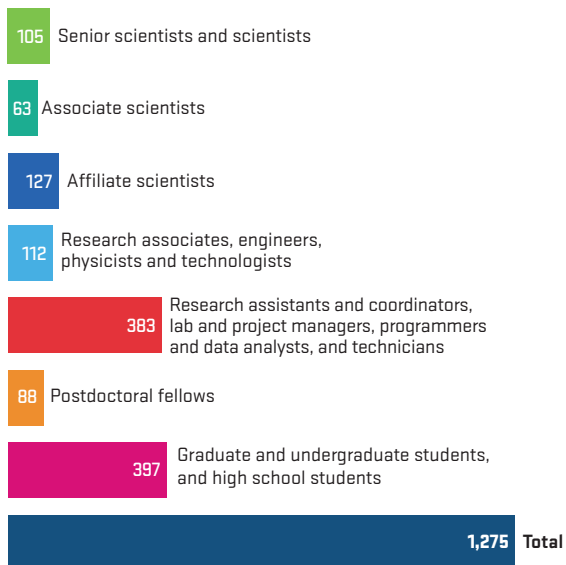
Sunnybrook Research Institute is grateful to its many sponsors. Each dollar we receive supports the achievement of high-impact discoveries and innovations.

MAJOR SOURCES OF EXTERNAL FUNDING 2013-2014

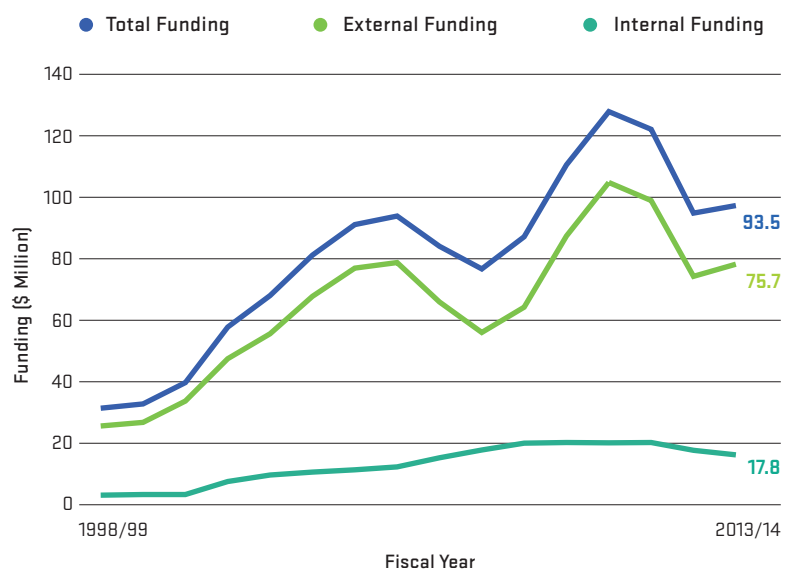


Sources	\$(M)	%
Canada Foundation for Innovation	9.7	13
Canada Research Chairs Program	1.6	2
Canadian Cancer Society Research Institute	0.7	1
Tricouncil Funding: Canadian Institutes of Health Research, and Natural Sciences and Engineering Research Council of Canada	11.1	15
Donations and Trust Income	1.8	2
Foundations	9.7	13
Industry	11.1	15
Ministry of Health and Long-Term Care	1.9	2
Ministry of Research and Innovation	8.5	11
Other Funding Sources	11.5	15
Other Government Sources	6.8	9
U.S. and International Sources	1.3	2
Total	75.7	100

RESEARCH STAFF



HISTORY OF RESEARCH EXPENDITURES AT SUNNYBROOK RESEARCH INSTITUTE



What Is the Greatest Challenge Facing Science?

Three scientists weigh in on what's weighing research down

EDITED BY STEPHANIE ROBERTS



JOANNE MCLAURIN

Reproducibility. It may seem ludicrous that science, an exacting field, has reproducibility problems. Yet, however exacting an individual, laboratory or country, there are factors outside of one's control. Reagent variability as a result of lot-to-lot variability, company acquisitions leading to alterations in production or lack of industry standardization leads to variable results and lost time spent trying to determine the cause. I have noted that hidden within every successful experiment is a detail that defies a written explanation. This is easily communicated within a laboratory in which techniques are shared between members. However, it can create reproducibility problems among laboratories, institutions and countries. Other technical fields have developed apprenticeship programs to circumvent this problem, and science should not be excluded from such a system. Science is a global collaboration with ready electronic communication among laboratories and countries. Access to an in-person training experience has lagged behind other fields, however, and requires support from government, philanthropists and private organizations to facilitate knowledge transfer.

Dr. McLaurin is developing small molecule therapies that target the toxic protein aggregates commonly found in the brains of patients with neurodegenerative disorders. One of her drug discoveries is in clinical trials to treat neuropsychiatric symptoms of Alzheimer's disease. She is also working on improved methods to diagnose and track the formation of these protein aggregates.



MEAGHAN O'REILLY

I think the issue of financial support will always be a major challenge for science. Funding opportunities are highly competitive and, unfortunately, there are typically more great research ideas than there is money to go around. Further, what is researched is heavily dictated by what opportunities are available—it's not enough to have a brilliant research idea if there is no funding body interested in the work. For an individual scientist to have the best chance at success they need to be able to adapt their work to align with the interests of the funding bodies, but without sacrificing the unique aspects that define their research program. In the bigger picture, for science to survive, we must continue to convince the funding bodies, and ultimately the public, that research remains a worthwhile investment.

Dr. O'Reilly is using microbubbles and focused ultrasound to deliver drugs across the blood-brain barrier. She has optimized techniques to monitor and control microbubble activity to ensure that drug delivery is targeted and effective. Her focus is primarily on the physics and engineering aspects. She is also applying these approaches to the spine and treatment of spinal cord diseases, using her expertise to tackle the challenges posed by the geometry of the spinal column, which is more complex than the skull.



ROBERT SCREATTON

The major challenge facing health science today is insufficient financial support. Canadians overwhelmingly recognize research as critical to health care, yet the main federal funding mechanisms for biomedical research have been reorganized to support preferentially targeted areas, with a focus on the "applied" end of the spectrum. While applied research is important, it should not come at the expense of providing consistent support for outstanding curiosity-based research in Canada that is recognized as such internationally. History shows that transformative discoveries stem from curiosity-based research, and that groundbreaking work requires taking risks. Being able to take risks requires a steady stream of operating funds, which should properly be viewed as investment in the resulting intellectual property, training of the next generation of researchers and novel therapies. My concern is that if the current trend continues, we may find ourselves revisiting the "brain drain" era, with leading Canadian scientists once again looking elsewhere to set up shop.

Dr. Screatton studies how cells communicate with each other to respond to their environment and ensure their survival and function. Among his research interests are pancreatic beta cells that produce and secrete insulin and mitochondria, the energy generator of the cell. One project focuses on pancreatic beta cells and how they sense and respond to changing blood sugar levels.



Through the Wormhole

Journey into a different
time in medical science

In 1999 Elton John cancelled several performances due to poor health. Tests revealed he had an irregular heartbeat. In July of that year he had pacemaker surgery. He resumed his concert schedule the next month.

Pacemakers, used routinely to regulate abnormal heart rhythms, are now taken for granted, but before 1950 cardiac patients were not so lucky.

The external pacemaker is a Canadian innovation. John Hopps, an engineer from the National Research Council of Canada, designed one of the first electronic pacemakers. Hopps collaborated with Drs. Wilfred Bigelow and John Callaghan, of the University of Toronto, who were studying how to keep the heart beating during hypothermia.

In 1950, the researchers “paced” the heart of a dog—prompting the heart to beat regularly—using Hopps’ device, which was powered by a wall outlet and the size of a small table radio.

Hopps’ pacemaker worked, but was too bulky to be carried by a patient.

In 1960, an implantable pacemaker invented by Wilson Greatbatch, was inserted in a 77-year-old man, who lived another 18 months thanks to the device.

Today, next-generation wireless pacemakers are being tested clinically. These devices, which are the size of a vitamin, are implanted using catheters rather than via surgery.

Like John, about four million patients are “still standing” because of an implanted pacemaker.

COVER SLIP

A high-magnification histological image of a cross-section of a blood vessel. The vessel lumen is almost entirely filled with a dense, light purple-stained mass, which is a blood clot. This clot is surrounded by a thick, multi-layered wall of the vessel, stained in various shades of purple and pink, indicating different tissue components like muscle and connective tissue. The overall structure is circular, with the clot occupying the central part of the vessel's cross-section.

Microscopic view

of a blocked leg artery harvested from a patient with peripheral arterial disease (PAD) who underwent a below-knee amputation. A blood clot (light purple, middle) is completely blocking the artery, which is surrounded by hard plaque materials like calcium (white). The blockage of leg arteries does not allow sufficient blood flow to the lower leg and resulted in limb loss for this patient. Clinician-scientists at Sunnybrook Research Institute are working to prevent amputations in patients with PAD by using magnetic resonance imaging to improve the success of minimally invasive procedures that restore blood flow. See page 36, inside.

Tissue sectioning and staining was done by Lily Morikawa. Imaging was done by Dr. Trisha Roy using a Leica DM2500 microscope with a Leica EC3 camera.

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