TAMING A BEAST
Relieving acute pain while minimizing opioid use

BUZZWORTHY
Brain stimulation for stroke patients

GUT FEELING
Imaging suggests bacteria calm the brain

SRI MAGAZINE

SUNNYBROOK RESEARCH INSTITUTE **2016**

TARGET: CANCER

Researchers are taking precise aim at a ruthless, invasive and pervasive killer. They seek to master it, while making care for patients better now

SRI MAGAZINE 2016

Inventing the Future of Health Care

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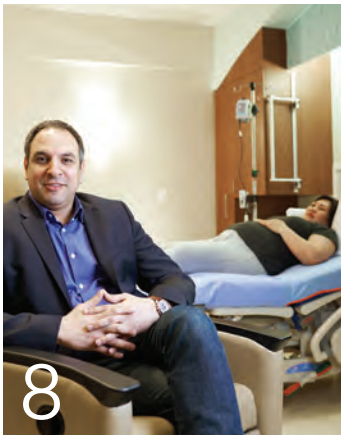


FEATURES

DEPARTMENTS

Messages

Delivering impact

WHETHER IT'S DISCOVERING a new therapeutic or tailoring a treatment to curtail side effects, teams at Sunnybrook are inventing tomorrow's health care now. Our strongest exemplifier of this last year was showing that we could breach the blood-brain barrier to deliver chemotherapy to the brain of a patient with brain cancer. This was a world first. (See story on page 4.)

We have many more advances of which we are proud. As the story on high-impact clinical trials at Sunnybrook's Odette Cancer Centre shows, researchers are striving to ensure treatments are more effective and better suited to each patient. For example, they have shown taking the drug everolimus for neuroendocrine tumours, a disease with debilitating symptoms and few treatments, held progression at bay for 11 months—more than twice as long as a placebo did.

The trial spanned 97 centres in 25 countries, underscoring that collaboration is integral to what we do. That is why our scientists are partnering with a medical device company to develop systems that pair real-time imaging with radiation therapy. These systems will be tested in trials at Sunnybrook, which will be the first centre in Canada where doctors will be able to see tumour response as therapy is given.

The potential benefits to patients from these advances and the others highlighted in this issue are cause for optimism. Such breakthroughs stem from the ingenuity and dedication of our staff, and the generosity of our community. Without you we could not create the future of health care.

Blake Goldring
Chair, Board of Directors
Sunnybrook Health Sciences Centre

Barry A. McLellan
President and CEO
Sunnybrook Health Sciences Centre

WE ARE AT the precipice of the most profound change in how we diagnose and treat disease.

Precision medicine seeks to treat and ultimately prevent disease by taking into account individual variability. For example, how patients respond to a therapy—even one that is widely used—is all over the map: it might work brilliantly for some and not at all for others; even when it works, it might have serious adverse effects.

Precision medicine seeks to minimize this ambiguity. It works by collecting and using personal health information to give care that "fits" a person much more closely, based on one's genetic, cellular and molecular makeup; physiology; lifestyle; environmental influences and other factors; as well as how these factors interact with each other.

One's genetic profile is perhaps the most important of these, because it is our biology that holds many of the answers regarding the origins and mechanisms of health and disease. Certainly, the most notable advances have been in this arena, emerging from the extraordinary opportunities afforded by the genomics era in which we now live.

Bottom line: precision medicine means focusing on an individual's disease and a tailored plan for care based on one's unique "measurements." We have some distance to travel to get there, but the journey is well underway, as you'll read in some of the stories in this issue, with its special focus on the research of the Odette Cancer 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

Photos: **Doug Nicholson**

Digest

A round-up of notable advances at Sunnybrook Research Institute

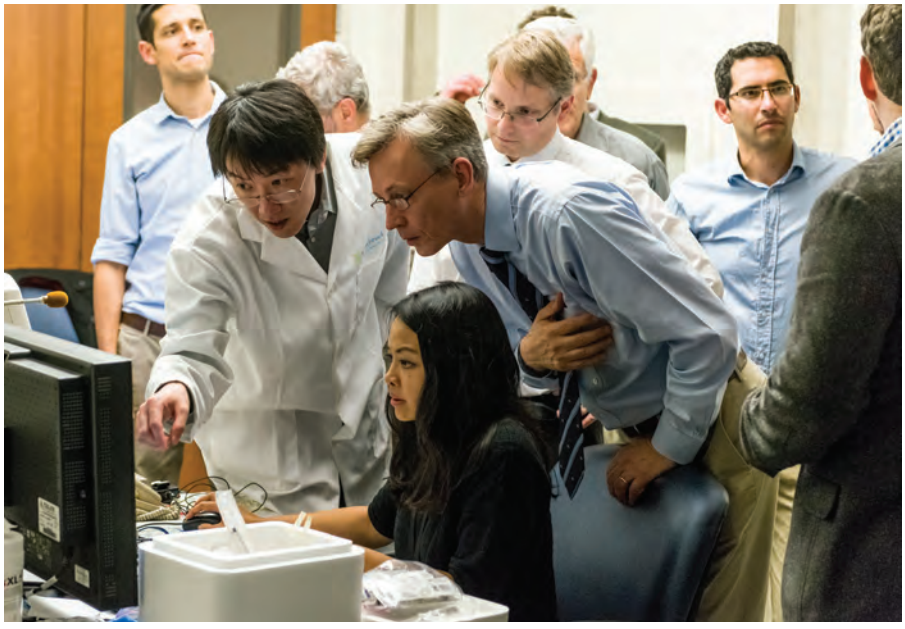
Breaching the Blood-Brain Barrier Noninvasively: an Historic First

ROUGHLY 20 YEARS: that's how long it took for Dr. Kullervo Hynynen to see his research do what he always knew it could do, if he just kept working at it. On Nov. 5, 2015, something extraordinary happened, something that heralds a new era of hope for treatment of the most intractable brain diseases. On this day, neurosurgeons and physicists at Sunnybrook successfully breached the blood-brain barrier of a patient with brain cancer, to deliver chemotherapy directly into her brain. It was the first time in the world that this had been done. For Hynynen, it was a culmination of two decades' worth of invention, experimentation and validation, first in the lab, then in preclinical research and finally with industry to commercialize the device.

In 1996 he was the first to describe a controlled, reversible and reproducible way of using focused ultrasound to open the blood-brain barrier under the guidance of MRI. This was once deemed impossible, given the impenetrable nature of the barrier, which protects our brains but also blocks access to 97% of drugs that might save our lives. Hynynen, director of Physical Sciences at Sunnybrook Research Institute (SRI), did not think it impossible. Now, the skeptics don't, either.

The patient, Bonnie Hall, has lived with brain cancer for eight years; recently, her tumour became aggressive. Under the care of Dr. Todd Mainprize, the lead neurosurgeon of the clinical trial testing if the strategy can be done and is safe, she agreed to be the first patient to have the procedure, even though it won't change her prognosis. Her motivation, she said, is to help others. During the procedure, the team, sardined in the MRI control room, on the other side of which lay Hall in the scanner with the helmet-like device attached to her head, was as one, glued to the monitors. They held their collective breath, only to exhale exultantly when they saw the focused ultrasound and microbubbles do just what they were designed to do: open the blood-brain barrier, through which the chemotherapy slipped, travelling to its plotted destination, the tumour. Hynynen gave a thumbs up. There wasn't a smileless face in the room.

Hall came out of the procedure tired but happy to hear that it had succeeded. The Phase 1 clinical trial continues, as does Hynynen's life's work. Next in line is harnessing focused ultrasound with a different scourge top of mind: Alzheimer's disease. Partnering with him is SRI neuroscientist Dr. Isabelle Aubert. Together, they have already scaled several "firsts": They delivered antibodies into the brains of mice to clear the "sticky plaque" that marks the disease; they used focused ultrasound alone and with therapeutics to restore memory and learning, and create new brain cells; and they used focused ultrasound to deliver gene therapy to targeted brain regions, where it reduced plaque load—seminal advances, indeed, given that by 2030 this pitiless condition will hit 75 million people globally. **SR**



Dr. Kullervo Hynynen (right-centre) and **Dr. Todd Mainprize** (centre-back) watch intently as focused ultrasound and microbubbles are used to open the blood-brain barrier in a patient with a brain tumour, so that chemotherapy can be delivered, a world first. Hynynen developed the technology. Mainprize is the lead investigator on the clinical trial.

Photo: **Doug Nicholson**

Getting Timely Post-Emerg Care: What Best Predicts It?

JUST BECAUSE SOMEONE has been discharged from the emergency department (ED) doesn't mean they're out of the woods. Unfortunately, though, patients often don't get that continued care. Dr. Clare Atzema, an emergency doctor at Sunnybrook, looked at what happens after discharge to patients newly diagnosed with atrial fibrillation, an irregular heart rhythm; guidelines recommend these patients get timely follow-up care to prevent serious outcomes like stroke.

The researchers defined timely care as being seen by a family doctor, cardiologist or internist within seven days of leaving the ED. They looked at almost 15,000 adults in Ontario across five years and 157 EDs. They found that one-half of those discharged with a new atrial fibrillation diagnosis had timely care—leaving a full 50% behind. Worse, after one month 18% still hadn't been seen by anyone.

Not having a family doctor was the strongest predictor of not getting timely care. Digging into what model of family practice worked best, patients whose doctors were remunerated through a primarily capitation model, where doctors get a flat payment for each person under their care regardless of the number of visits or services provided, were 14% to 28% less likely to be seen within seven days, compared with those in a fee-for-service practice. These findings suggest further study is needed to understand the reasons behind these differences, and that any solutions ultimately must be systems-based. SR

"I appreciate the concept of universal health care, but there are limits."

SPECIAL DELIVERY

GENE THERAPY IS advancing preclinically and clinically, showing promise to treat debilitating diseases like amyotrophic lateral sclerosis and Parkinson's disease, as well as spinal cord injury and chronic pain.

Getting any therapy into the spinal cord is a problem of access. The spinal cord is protected by a barrier, which, just like the blood-brain barrier, keeps out unwanted agents, but also blocks helpful agents from entering. Moreover, direct injection of therapies carries risks like infection, incorrect needle placement and nerve trauma. Sunnybrook Research Institute (SRI) scientists are pioneering the use of focused ultrasound to deliver gene therapy into the spinal cord.

Dr. Isabelle Aubert, senior scientist in Biological Sciences at SRI, led a study on focused ultrasound guided by MRI to deliver gene therapy across the blood-spinal cord barrier. The team included head of Physical Sciences Dr. Kullervo Hynynen, and musculoskeletal researchers Drs. Meaghan O'Reilly, Cari Whyne and Albert Yee. Under MRI guidance, the researchers injected microbubbles into the circulation of adult rats. When the bubbles reached the target area, the cervical spine or neck region of the spinal cord, the researchers applied focused ultrasound, thereby loosening the tight junctions of the blood-spinal cord barrier.

This loosening resulted in a temporary opening of the barrier to usher therapeutic genes tagged with a coloured protein into the targeted side of the cervical spine. Expression of the coloured protein in 87% of neurons and 36% of oligodendrocytes—cells only in the desired areas—confirmed passage through the blood-spinal cord barrier. This proof of concept study suggests MRI-guided focused ultrasound could be a valuable tool in the delivery of noninvasive gene therapy to promote nerve cell regeneration or improve nerve function in disease or after spinal cord injury. SR

Caring for Caregivers Critical

SERIOUS ILLNESS DOESN'T just affect those who are sick. Their caregivers at home suffer, too, yet resources generally aren't flowed that way to help these caregivers through the challenge of nursing their loved one after discharge. A Canadian critical care powerhouse of five centres, including Sunnybrook, with a gaggle of six critical care doctors, studied what aspect of patients and caregivers best predicted who was likely to need help. They looked at different times within the immediate one-year period after patients were sent home. They included 280 people whose family member had been on mechanical ventilation in the intensive care unit for at least seven days.

They found that 67% of caregivers reported high levels of depression at six months, which tumbled but gently to 43% at one year. Symptoms of depression decreased a bit with time in 84% of the caregivers, but 16% experienced no such reduction. Worse mental health outcomes were linked to being younger; patient care having a greater impact on other activities; and having less social support, less sense of control over life and less personal growth. Results were published in the *New England Journal of Medicine.* They underscore that intervention to improve family outcomes after critical illness should address the support needs of not only survivors, but also their caregivers. SR

Non Sequitur

Vibrissae, otherwise known as whiskers, are an essential sensory tool for cats. They help them navigate through dark and tight spaces, in part by detecting changes in air currents. Loaded with nerves at their root, their exquisite sensitivity even helps kitty sense danger. These stiff hairs are found not only framing damp little noses, but also on forelegs and jaws, and atop the eyes.

Aerobic Exercise: as a "Biological Probe" in Bipolar Disorder

IMPAIRED THINKING, PARTICULARLY in executive decision-making, is common in adolescents with bipolar disorder. It adds insult to injury, as it were, and makes social and other activities even harder to carry out, beyond the effect of mood symptoms. While anecdotal evidence suggests that exercise might help to improve mood and cognition, there is a dearth of studies that drill down into the specifics, to try to understand just what the effects of exercise are, and the biological mechanisms behind those effects.

Brain scientists at Sunnybrook Research Institute (SRI) published the first study to examine the effects of aerobic exercise on executive function with neuroimaging in teens with bipolar disorder. Drs. Benjamin Goldstein and Brad MacIntosh, scientists in the Hurvitz Brain Sciences Research Program at SRI, and Dr. Arron Metcalfe, a postdoctoral fellow at SRI and the study's lead author, compared two groups of teenagers: 30 with bipolar disorder and 20 with no major psychiatric disorders. They evaluated them on tasks commonly used to test executive function, which is the brain's control centre, in a way, and is compromised in bipolar disorder. It enables people to plan, organize and act on information; and to pay attention. The team looked at the teens' brains before and after exercise, to see what effects, if any, the exercise had.

For the study, teens rode a recumbent bicycle for 27 minutes, 20 of which got their heart rates up to a defined aerobic level. The attention tests were done before and 25 minutes after exercising. Their brains were scanned using functional MRI, which allows scientists to look at brain activity and response. Results, published in the high-impact journal *Translational Psychiatry*, were fascinating. The team was able to see that just 20 minutes of aerobic exercise improved neural markers of attention and inhibition, and did so in specific brain areas of interest.

About 1% of Canadians will experience bipolar disorder in their lifetime.

The implications are that exercise is not only a potential treatment in this arena, but also that its effect can be used as an objective marker—a "biological probe"—to expose differences in the brains of adolescents with bipolar disorder. Imaging can thus provide a window into the brains of these teens, to see just what is going on. This in turn could help scientists develop treatments that don't—as is the case now—rely on subjective reporting of symptoms, but instead could target specific brain systems. SR

Photo: Marcel De Grijs / Dreamstime.com

Surveying New Territory:
Physician-Assisted Death & Amyotrophic Lateral Sclerosis

WITH THE FEDERAL government this year releasing draft legislation on Supreme Court-sanctioned physician-assisted death, the issue is on many people's minds. Arguably, this is no truer than for doctors, many of whom are already fielding questions from their patients. Dr. Lorne Zinman, a clinician-scientist in the Hurvitz Brain Sciences Program at Sunnybrook Research Institute, was the senior author of a survey of health professionals who care for people with amyotrophic lateral sclerosis (ALS) to find out what they think about it. Zinman is the head of the ALS clinic at Sunnybrook, which is the largest such in Canada. He and his colleagues, led by Sunnybrook neurologist Dr. Agessandro Abrahao, asked doctors and allied health professionals from the 15 academic ALS centres across Canada for their thoughts on the court ruling, how willing they were to participate in physician-assisted death and about the process for it.

An estimated 2,500 to 3,000 Canadians live with this fatal disease.

Of the 231 respondents, 64% of doctors and 80% of allied health professionals agreed with the ruling. Most—77% of doctors and 81% of allied health professionals—agreed that someone with moderate to severe ALS and physical and emotional suffering would qualify for physician-assisted death. Eight percent of doctors and 2% of other care providers said that no patient with ALS should be eligible.

When it came to the process, most said they would not provide a lethal prescription or injection. Even among doctors who support physician-assisted death, only 26% were willing to write a prescription for a lethal dose of an oral medication in moderate-stage ALS. In severe-stage ALS, 34% were willing to prescribe a lethal dose of oral drugs; 31% said they were willing to give a lethal injection.

Most said they would prefer the patient get a second opinion from an ALS expert to confirm eligibility, have a psychiatric assessment, make the request twice at least 15 days apart and then be referred to a third party for administration of the lethal drug or injection. Most also said they felt unprepared to deal with the new legislation, and advocated for training and guidelines. In their conclusion, the authors noted that it was imperative to include the perspectives of patients with ALS and their caregivers as legislation moves ahead. SR

On Feb. 6, 2015, the Supreme Court of Canada unanimously struck down the prohibition of physician-assisted dying (PAD). Here is what doctors and allied health professionals (AHP) from ALS centres across Canada think about the ruling and PAD.

Source: Abrahao A et al. *Neurology*. Epub 2016 May 13.

Timing Is Everything

Mom-to-be has gestational diabetes. When is the best time for her to deliver?

GESTATIONAL DIABETES AFFECTS up to 15% to 20% of pregnant women. It is often clinical practice to induce labour in these cases at 38 or 39 weeks to decrease complications that include cesarean delivery, birth trauma and shoulder dystocia, a severe obstetrical emergency, whereby, after delivery of the head, the anterior shoulder of the infant gets stuck against the woman's pubic bone. This condition can lead to nerve injury and paralysis of the arm, as well as fetal asphyxia and death. Doctors are not sure, however, whether inducing labour actually improves outcomes because only a few studies with small sample sizes have looked at the issue.

This lack of clarity led Dr. Nir Melamed, a clinician-scientist in the Women & Babies Research Program at Sunnybrook Research Institute (SRI) to investigate.

"The purpose was to determine whether routine induction of labour at 38 or 39 weeks can decrease the risk of cesarean section and improve the baby's outcomes," says Melamed. "The rationale is that gestational diabetes can lead to accelerated growth of a baby who might be exposed to high levels of glucose and insulin." A large infant increases the risk of serious complications, he notes.

Melamed led the study using data from the Better Outcomes Registry & Network Ontario, or BORN, a registry of all births in Ontario. He looked at 14,600 women with gestational diabetes who delivered babies between April 2012 and March 2014.

He and his colleagues compared the outcomes of women who were induced at 38 weeks with those who were managed expectantly and did not deliver until at least 39 weeks. Separately, they looked at women induced at 39 weeks and compared them with those who were managed expectantly and did not deliver until at least 40 weeks.

Dr. Nir Melamed with his patient Cherrylou Bautista. Melamed is a clinician-scientist at Sunnybrook Research Institute specializing in maternal-fetal medicine.

"We found that at either 38 or 39 weeks, induction of labour decreased the rates of cesarean section quite dramatically—by about 27%, a finding which may have huge implications in terms of complications, costs and resources," says Melamed.

Inducing labour at 38 weeks, however, was not risk-free. It came with a higher rate of neonatal morbidity and admission to the neonatal intensive care unit for jaundice and low blood sugar levels.

"Our study provides more support to induce labour at 39 weeks because it results in a similar decrease in cesarean section rate like 38 weeks, but at the same time it doesn't have adverse effects on the baby," he says.

Melamed notes the results provide a foundation to establish guidelines and protocols. Dr. Jon Barrett, director of the Women & Babies Research Program at SRI, agrees. "This will change practice and impact the timing of delivery of patients with gestational diabetes," says Barrett. "A very basic question: 'When is the best time to deliver?' was extremely well answered by Dr. Melamed and his team. It gives clear direction to a common practice."

The study will help inform future trials supported by the Greater Toronto Area-Obstetrical (GTA-OBS) Network, which Barrett established in 2013. Sunnybrook leads the 16-hospital-strong network, which accounts for more than 65,000 births annually.

ELENI KANAVAS

Melamed's research is supported by the GTA-OBS Network. Barrett holds the Waks Family Chair in Maternal-Fetal Medicine Research.

Photo: **Nation Wong**

CO-OP-erative Strategy

Therapeutic technique goes beyond what is trained to have a more meaningful impact on stroke patients' skills

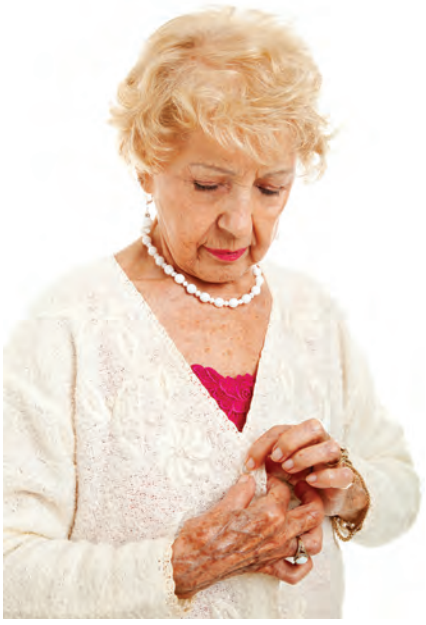
PEOPLE LIVING WITH the effects of a stroke face a challenging road to recovery. Evidence suggests treatments that incorporate task-specific training are effective in helping to improve walking and upper-arm and hand function. An approach called CO-OP, which stands for cognitive orientation to daily occupational performance, teaches patients to use cognitive strategies in addition to task-specific training. Adding these cognitive problem-solving techniques might help people to learn better and retain important skills. There is not a lot of research, however, that has evaluated this new concept.

Dr. Sara McEwen is a scientist in the St. John's Rehab Research Program at Sunnybrook Research Institute with a background in physiotherapy. She led a randomized controlled trial that compared the CO-OP approach with typical rehabilitation that aims to help patients improve function in everyday living. Participants who had a stroke less than three months before the study received outpatient rehabilitation at St. John's Rehab in Toronto and The Rehabilitation Institute of St. Louis in Missouri, U.S.

"CO-OP is a problem-solving approach that focuses on actual performance of meaningful activity, and we use something called 'guided discovery' as our main therapeutic technique," says McEwen. The approach was originally designed for children with a motor learning disability, but McEwen adapted it for adult stroke patients. "There are few direct instructions. We coach patients and ask questions. We also teach them a problem-solving framework that is: goal, plan, do, check, [which] they use to learn every activity."

Participants each established five personal goals that were specific to them. Examples included getting dressed independently, washing the dishes, throwing a football and playing the drums. In the CO-OP group, three goals were specifically trained and two were untrained tasks that the therapists did not work on with the patients. In the usual care control group, the therapists determined how many of the goals were trained or not.

A video-recorded performance test rated the quality of tasks completed. McEwen found the CO-OP group improved about three times as much on performing trained goals compared with the control group, and twice as much on untrained goals. The study suggests the CO-OP approach not only enhanced performance on skills trained during therapy, but also helped patients transfer skills such that they were able to learn additional activities outside of the rehab setting. Results were published in *Neurorehabilitation and Neural Repair* in 2015.



Getting dressed independently is an example of a personal goal participants aimed to achieve during the study.

McEwen co-authored another study using the same trial participants that was published in *The American Journal of Occupational Therapy*. Researchers compared CO-OP with standard therapy on upper-arm and hand movement, cognitive ability and the effect of stroke on health-related quality of life.

"This study showed early evidence that CO-OP is associated with a moderate effect compared to usual care on aspects of cognition, and arm and hand function in stroke patients, even though we did not train those components," says McEwen. "This is a really big deal because generally rehab therapies work specifically on the thing we train, but don't generalize well to other impairments and activities."

McEwen is collaborating with Elizabeth Linkewich, who is the director of the Regional Stroke Centre and the North & East GTA Stroke Network. They are studying how CO-OP can be implemented at five in-patient rehabilitation sites across Toronto, including St. John's Rehab.

"We are teaching people to do what's meaningful to them. We're giving them the tools to transfer and generalize that learning to their home and community environment," says McEwen.

ELENI KANAVAS

McEwen's research is funded by the Canadian Institutes of Health Research.

Photo: iStock.com / lisafx

PoP! Goes the Funding

Innovative technologies need early-stage investment

A REPORT BY the Council of Canadian Academies, whose assessments inform public policy, shows that Canada punches above its weight in science and technology: despite having less than 0.5% of the global population, Canada produces nearly 5% of the world's most frequently cited papers. When it comes to commercializing research, however, we could be doing much better.

Critics of this innovation gap point the finger at the risk aversion of Canada's venture capitalists, who often require that technologies be well-developed and validated many times over before they consider investing in them. How, then, does a researcher with a promising idea get to that point?

This is where proof-of-principle (colloquially referred to as "PoP") funding, comes in. These grants finance early-stage research and, critically, technology transfer activities that accelerate commercialization of intellectual property.

Scientists at Sunnybrook Research Institute (SRI) know that bringing the products of research to the marketplace is the only way patients can benefit from breakthroughs made in the lab. They are developing technologies to improve patient care and seizing opportunities to move them through the innovation pipeline.

Doctors trying to fix deformities of the face and skull during reconstruction surgery know all too well the drawbacks of using metal plates and screws to repair fractures of delicate facial bones. The hardware neither attaches well to thin bone, nor is suited to the complex geometry of the facial skeleton. Moreover, complications, including infection and prolonged pain, occur frequently.

Dr. Cari Whyne, a biomedical engineer and director of the Holland Musculoskeletal Research Program at SRI, is working on an elegant solution: bone tape. As its name suggests, the technology adheres to bone and can reattach fractured pieces with enough stability until they heal.

DR. CARI WHYNE engineered bone tape so that surgeons can reattach fractured facial bones, as if fixing a broken vase.

"It works kind of like the way you'd expect a Band-Aid to work," says Whyne. "[It's] like duct tape for bones—to be able to tape multiple fragments together as if you're fixing a broken vase, for example. It's complicated, and there are a lot of parts that need to fit together. You need some flexibility to put that 'puzzle' back together in three dimensions."

She is developing the bone tape with Dr. Jeff Fialkov, an associate scientist at SRI and a plastic surgeon at Sunnybrook, and researchers at the Institute of Biomaterials and Biomedical Engineering at the University of Toronto, where Whyne is also a professor.

Their preclinical studies show bone tape is effective, safe and easy to use. Over time, the technology, which is made of a polymer and ceramic, dissolves.

She was awarded a PoP grant from the Canadian Institutes of Health Research (CIHR) to optimize bone tape and make headway in commercializing it.

The researchers have filed a patent and done a workflow analysis to understand how the device would function in the operating room. Whyne notes they've made prototypes in the lab and are looking at ways of scaling up manufacturing. They will also do longer-term studies of how bone tape biodegrades.

She secured funding in the final competition of CIHR's PoP program. As part of reforms made by the agency, the program, which gave out about $5 million annually, was subsumed within CIHR's general "Project Scheme." Critics argue shutting down the niche program, which covered non-research costs, including patenting and market studies, will hamper innovation.

Whyne says funding from the defunct program will be instrumental in proving the usefulness of bone tape, which will help attract an industry partner. Although commercialization is long and difficult, she is committed to seeing it through. "It's the best way to get new technology into the operating room," she says.

Dr. Simon Graham, a neuroimaging scientist at SRI, was awarded a PoP grant in 2011 to develop a technology for use during functional MRI(fMRI). Conventional MRI visualizes anatomy; in contrast, fMRI shows physiological processes. It depicts changes in blood flow and blood oxygenation, which researchers use to map brain activity.

The tablet-based technology will enable people to do neuropsychological tests, used to assess thinking and normally done with pencil and paper,

Photo: shutterstock.com

during fMRI scans.

The idea is to use the test results and the map of brain activity together to gain a comprehensive look at brain impairment early on in people with Alzheimer's disease or mild cognitive impairment. "You combine the two and you might get improved sensitivity and specificity for characterizing a brain abnormality," says Graham. The test would indicate cognitive impairment, and the brain activity map would pinpoint which regions are responsible for that impairment.

The MR environment is exacting. Patients must remain still during scans, which makes paper-and-pencil testing impossible. Using a tablet computer within the system has its own challenges, however. "You don't want attractive magnetic forces causing the tablet to be pulled into the magnet and hurting the patient. You also don't want the electronics of the tablet to interfere with the MRI signals and vice versa," he says.

As a workaround, he separated the response aspect of the tablet (its writing surface) from the display component (its screen). Participants do tasks on a touch-sensitive surface that is fixed to a table. Through a mirror, they look at a projection screen that's connected to a computer, which shows their responses and the test questions—a phone number they have to copy, for example.

A video camera inside the MRI system lets people see their hand and the writing instrument as they write. The visual feedback helps them make responses in the right spot, notes Graham.

He and his team have validated the technology on young, healthy adults. Next, they will use it to study healthy elderly adults and people with mild cognitive impairment.

Another exciting application is in neurosurgery. The technology has been used by patients who were awake during a part of surgery to remove a brain tumour. When combined with electrical stimulation of the cerebral cortex, the outer layer of the brain, it enables intraoperative brain mapping for safer, more effective surgery. In a well-documented case at St. Michael's Hospital in Toronto, a surgeon used Graham's technology to remove a seizure-causing tumour lodged deep within the brain of a 23-year-old woman.

The device is 10 years in the making. Graham says PoP money helped him to move forward with commercialization and technology development. Will the loss of this funding opportunity mean Canada's performance on innovation—middling, according to the Conference Board of Canada, which ranked Canada ninth of 16th among peer countries on this measure—slip even further? Only time will tell, but much more is at stake than dollars and cents.

ALISA KIM

Graham's work on the tablet was supported by the Canada Foundation for Innovation (CFI), Canadian Cancer Society, CIHR and Heart and Stroke Foundation of Canada. Whyne's work on bone tape is supported by CFI, CIHR, MaRS Innovation and the U.S. Department of Defense.

FROM POP TO PRODUCT

How to turn an invention into a commercial device

BASIC RESEARCH

- Study technology's characteristics.
- Perform proof-of-principle studies.

MARKET STUDIES

- Research the customer.
- Analyze the competition.

INTELLECTUAL PROPERTY

- File patent application. Receiving patent protection can take from 18 to 36 months.

PROTOTYPE DEVELOPMENT

- Make basic prototype and test it in lab.
- Fix any bugs.
- Repeat as needed.

COMMERCIALIZATON

- License technology/attract commercial partner.
- Scale up manufacturing.
- Transfer to medical marketplace for benefit of patients.

Target: Cancer

Researchers in the Odette Cancer Program at Sunnybrook are taking precise aim at a ruthless, invasive and pervasive killer.

They seek to master it, while making care for patients better now

KNOWLEDGE IS STRENGTH

Bigger-picture research helps patients with blood cancers and their doctors battle uncertainty and decide on treatment

By **Betty Zou**

"I will remember *that I do not treat a fever chart, a cancerous growth, but a sick human being, whose illness may affect the person's family and economic stability.*"

When graduating medical students recite the modern version of the Hippocratic Oath they are pledging to treat their patients as more than a presentation of ailments and symptoms. Each person has a unique story that can affect the course of the disease and treatment. In conversations frequently dominated by jargon and numbers, however, the patient's voice can sometimes be lost.

At Sunnybrook Research Institute, Drs. Rena Buckstein and Matthew Cheung are striving for change. These scientists are showing how inclusion of patient-specific traits and perspectives can improve risk assessment and treatment decision-making.

Buckstein is an oncologist who specializes in haematological cancers, those of the blood. She is also the co-director of the myelodysplastic syndrome (MDS) research program at Sunnybrook's Odette Cancer Centre. Myelodysplastic syndromes are a group of cancers that have in common faulty blood stem cells. In healthy people, blood stem cells mature into new red and white blood cells and platelets, which deliver oxygen, fight infections and form blood clots to stop bleeding, respectively. In patients with MDS, the stem cells fail to develop properly, leading to a shortage of healthy blood cells and platelets. Consequently, patients with MDS are prone to anemia, infections, bleeding and bruising. Most will require blood transfusions, and one-third will develop acute leukemia.

"The average age of diagnosis [for MDS] is about 72," says Buckstein. "The prevalence is increasing because more and more people are living beyond the age of 70."

The elderly patient presents a unique set of challenges when it comes to assessing risk and determining prognosis. Chief among them are frailty and the chronic health conditions, or comorbidities, many patients have in addition to MDS. The tools physicians use to calculate risk, like the revised International Prognostic Scoring System (IPSS-R) app Buckstein pulls up on her iPhone, rely primarily on lab test results. She types in a few numbers for a fictitious patient—age, platelet counts, blood cell counts, percentage of immature blood stem cells, genetic abnormalities—and almost instantly, the app generates a risk score and projected survival.

"You can't treat the disease in isolation."

"Haematologists love risk scores," she says. While handy, the IPSS-R score is incomplete. "You have no real good way of telling someone how their level of comorbidity or frailty is going to impact on their disease course. That's never been incorporated into any scores."

To determine whether comorbidity and frailty could be used to refine the IPSS-R, Buckstein and Dr. Richard Wells, co-director of the MDS research program, founded a national MDS registry, the first of its kind in Canada. In addition to their medical history, patients enrolled in the registry were asked about their quality of life and other medical conditions such as heart disease, diabetes and previous cancers. Patients were also evaluated for disability and frailty using a variety of tests done when they first joined the registry and once a year thereafter.

By following patients an average of 20 months, the researchers found that combining IPSS-R with new scores for frailty and other health conditions generated a comprehensive score that could predict overall survival more accurately. The addition of frailty and comorbidity scores to the IPSS-R increased its predictive power by 35% relative to the IPSS-R score alone. This study is the first to examine the effects of frailty on predicting survival in patients with MDS. It was published in the *British Journal of Haematology*.

"You can't treat the disease in

Drs. Matthew Cheung and **Rena Buckstein** test a hand dynamometer, a device used to measure grip strength. In elderly populations grip strength predicts frailty and mortality.

Photo: **Nation Wong**

isolation," says Buckstein. "Patient-related factors [like frailty and comorbidity] have to be incorporated into our scoring systems that predict outcome so that we can better counsel our patients and inform our physicians."

Cheung, a scientist and physician at Sunnybrook who specializes in blood disorders, is also advocating for a patient-centred approach. He recently completed an evidence-based review to address the controversy surrounding radiation therapy in treatment of early-stage Hodgkin lymphoma (HL), a cancer that originates in white blood cells called lymphocytes.

The standard of care for patients with early- or limited-stage lymphoma is chemotherapy followed by radiation. Despite being a mainstay of HL therapy, radiation carries considerable risk—it can damage DNA and cause healthy cells to turn cancerous. Most cases of HL start in lymph nodes found in the neck and chest. Irradiation of these areas not only kills the cancerous lymphocytes, but it can also increase the risk of early heart disease and secondary cancers developing in neighbouring tissues like the breast, thyroid and lung.

"In the last decade, we've become very successful at treating HL, especially limited-stage HL," says Cheung. "These patients have a very good long-term prognosis. But then we worry that in the five-, 10-, 15-year timeframe, are they going to run into these [other] problems that we caused?"

Concerns over secondary cancers and early heart disease have pushed into practice guidelines that reduce the area receiving radiation and the dosing of this treatment, thereby lessening exposure. Cheung wanted to go one step further by asking: Can you minimize risks from radiation exposure by forgoing it altogether?

He combed through the scientific literature looking for studies comparing survival of patients with HL who received chemotherapy and radiation to that of patients who received chemotherapy alone. He found that although fewer patients treated with both therapies saw their lymphoma progress after treatment, patients who received only chemotherapy had lower incidences of secondary cancers and heart disease and higher survival rates overall. In other words, patients treated with chemotherapy alone fared just as well in the long term as those who received combination therapy.

Still, Cheung points to an important caveat of the earlier study comparing the two treatment strategies: the dose of radiation given to the patients was much higher than the dosing typically used today. While more research is needed to compare directly chemotherapy with and without modern radiation therapy, his findings have led to a new Cancer Care Ontario guideline on how physicians should discuss treatment options with patients who have early-stage HL.

"Because of [this review], our general feeling is that a chemotherapy-alone approach is a reasonable option in some patients," says Cheung. "Obviously, there's still some controversy, and there's no 100% certain approach. That's why we really value the patient's thoughts in this process."

He notes some patients might prefer the more aggressive approach with chemotherapy and radiation to try and cure the lymphoma at any cost. Others, such as those with a higher risk of developing breast cancer, might opt for a more conservative approach and choose chemotherapy alone. Although chemotherapy alone may be slightly less effective at treating HL upfront, it is still an excellent option offering a high likelihood of cure and potentially is safer in the long run.

"In the past, a lot of decisions were set out in HL and almost dictated to the patient," he says. "Our hope is this paper gives both physicians and patients a chance to have a dialogue where patients can make a decision."

Buckstein's research is funded by the Canadian Institutes of Health Research, Celgene Canada and the Crashley Estate. Cheung's research is funded by the Cancer Care Ontario program in evidence-based care and the support of Roy and Majorie Linden, and Joan Fisher and James Rowland.

Overcoming Treatment Resistance

It's bedevilling: cancer therapy can simply stop working, to devastating end. New research gets closer to why and offers some solutions

By **Betty Zou**

Imagine you have cancer. You go through multiple rounds of treatment, enduring nausea, fatigue and other sickening side effects. Nothing works. The cancer continues to grow.

Now imagine yourself as another patient with cancer. Your treatment is working. The tumour is shrinking. Your doctors are optimistic. Then, one day, you learn the treatment has stopped working. The tumour has started to grow back. You try other drugs, but it's always the same: they work for a while; then, inevitably, they lose their effectiveness and the cancer rebounds. These scenarios describe treatment resistance. In the first case, the cancer cells have intrinsic resistance to the treatment—they are resistant from the get-go without previous exposure to the drug. In the second scenario, the cancer develops resistance to the drug after being exposed to it. Think of this acquired resistance as cancer cells evolving in response to a danger in their environment. For many people with cancer, these scenarios require no imagination. It is their reality.

At Sunnybrook Research Institute (SRI), Dr. Robert Kerbel, a senior scientist, is studying the biology of treatment resistance to find ways of overcoming it. "The mainstay of cancer treatment to this day is still chemotherapy," he says. "There are certain cancers where a high proportion of patients respond to chemotherapy, and there are a couple of cancers that are just notoriously resistant to chemotherapy drugs. One of them is kidney cancer. It just doesn't respond."

Renal cell carcinoma (RCC) is a common type of kidney cancer. Roughly 90% of all kidney cancer is RCC. A major gain in the treatment of advanced RCC has been the approval of four

Dr. Bob Kerbel is studying how tumours become resistant to therapy, and how to thwart that resistance.

Photo: **Curtis Lantinga**

therapies that function as tyrosine kinase inhibitors (TKIs). These drugs target a growth factor protein that enables cancer cells to attract and build a blood supply to the tumour, thereby allowing it to grow bigger. By blocking the protein, TKIs deprive the tumour of nutrients and prevent its growth.

These TKIs are not, however, a cure-all. About one-fifth of patients with kidney cancer are intrinsically resistant to TKIs. One gets the sense that these are the patients that inspire Kerbel's research.

Recently, Kerbel and his team showed that pazopanib, one of the approved TKIs for advanced RCC, has potent anti-tumour activity in TKI-resistant cancer cells when given in combination with the chemotherapy drug topotecan.

To do this work, the researchers created the first preclinical model for metastatic RCC in which the cancer had spread from the kidneys to other organs. Using this mouse model, when they tested pazopanib alone, they found the drug had no effect on tumour growth, disease spread or overall survival. These cancers were innately immune to pazopanib.

In contrast, when the researchers gave pazopanib with topotecan, the tumours shrank in size and spread to fewer organs compared to treatment with either drug alone. Overall survival was also significantly extended. They observed these effects when the drugs were given in two scenarios: early on to treat the primary tumour and after the cancer had spread extensively from the kidney to other sites.

"It's been hard to find any other agents [to give alongside TKIs] because of toxicity. There are really no good combinations," says Dr. Georg Bjarnason, a senior scientist at SRI and an oncologist at Sunnybrook's Odette Cancer Centre. Bjarnason specializes in kidney cancer and worked with Kerbel on the study. The researchers overcame the issue of toxicity by lowering the dose of topotecan given with pazopanib. "[This study] discovered a potentially new combination that can be active in tumours that seem to be intrinsically resistant," says Bjarnason.

These results, which were published in 2015 in *Science Translational Medicine*, challenge the very notion of intrinsic resistance. "It really raises this [question] of whether the cancer cells are really truly resistant to TKIs," says Kerbel. "Maybe there are also chemotherapy drugs [that], depending on the nature of the drug and the way it's scheduled and dosed, might make a cancer that is generally thought to be intrinsically resistant not resistant."

The possibility of as-yet undiscovered TKI and chemotherapy drug combinations offers new hope to the 20% of RCC patients whose tumours are unresponsive to TKIs.

Kerbel's research is also shedding light on how tumours become impervious to drugs following treatment. To study this question, he focused on a type of liver cancer known as hepatocellular carcinoma (HCC). The only approved therapy for advanced HCC is a TKI drug called sorafenib. Like the TKIs used to treat kidney cancer, sorafenib works mainly by inhibiting the process of new blood vessel formation, or angiogenesis. Without angiogenesis, the tumours starve and cease to grow. While sorafenib can prolong overall survival in patients with advanced HCC, it inevitably stops working because the tumours develop resistance.

Kerbel and his colleagues, including former PhD student Elizabeth Kuczynski, compared sorafenib-sensitive tumours with those that were sorafenib-resistant under a microscope. They saw a key difference that explained why the drug stopped working.

In the drug-sensitive tumours, the researchers could see signs of angiogenesis. On the other hand, in the drug-resistant tumours, the researchers were surprised to see that, instead of making new blood vessels, the tumours were co-opting—stealing, in effect—blood vessels from healthy neighbouring tissue in the liver to supply them with the oxygen and nutrients they need.

"That was a 'Eureka!' revelation moment for me," says Kerbel. "It's like an evolutionary selection pressure. [The tumours] are angiogenic at the beginning, but you're sort of forcing them to switch to [using] the normal, existing [blood] supply."

In the drug-resistant tumours, the researchers were surprised to see that, instead of making new blood vessels, the tumours were co-opting—stealing, in effect—blood vessels from healthy neighbouring tissue.

Because the tumours were no longer relying on angiogenesis to grow, sorafenib, an antiangiogenic drug, lost its effect. These results provide the first evidence for vessel co-option as the cause of acquired resistance to sorafenib in HCC. The study was published in April 2016 in the *Journal of the National Cancer Institute*.

The researchers also found that the sorafenib-resistant HCC cells had turned on a set of genes that enabled the tumour cells to be more mobile and invade adjacent tissues to steal their blood vessels.

As a next step, Kerbel is trying to figure out a way of overcoming acquired resistance by targeting the hijacked vessels themselves. "They're not new blood vessels so antiangiogenic therapies won't work," he says. "But that doesn't mean some other type of anti-vascular therapy won't."

Kerbel's research is funded by the Canadian Breast Cancer Foundation, Canadian Institutes of Health Research, Israel Cancer Research Fund and Worldwide Cancer Research.

The Doctor Can Aspirate You Now

Study supports doing ultrasound-guided thyroid biopsy in the clinic

By **Eleni Kanavas**

Head and neck specialists at Sunnybrook's Odette Cancer Centre are leading the way in endocrine surgery through use of point-of-care ultrasound and fine-needle aspiration, a minimally invasive procedure for evaluating disease in thyroid nodules.

The thyroid is an endocrine gland located at the base of the neck, in front of the throat. It has two lobes on either side of the windpipe connected by a narrow strip of tissue. The butterfly-shaped organ releases hormones that regulate metabolism, body weight, cholesterol levels and heart rate.

Dr. Kevin Higgins, a head and neck surgical oncologist at Sunnybrook, specializes in performing thyroid biopsies using 2-D ultrasound imaging that enables him to assess the lymph nodes and thyroid, and determine whether a patient needs a biopsy.

"Being able to do my own ultrasound not only allows me to speed up the process, but to be more accurate, efficient and capable at time of operation," he says. "[It] allows us to identify the thyroid with structures at the root of the neck, into the thoracic outlet, and its relationships with the surrounding blood vessels, trachea and esophagus that we would not have appreciated from just reading a report. It gives a dynamic portal into the surgical anatomy in advance."

During the 30-minute procedure, which is done during a patient's first visit, Higgins moves the ultrasound transducer with one hand along the neck to locate the nodule on the thyroid. He places the needle on the thyroid, to aspirate with the other hand, a practice similar to drawing blood. Cells from the nodule are removed using a hollow needle and sent to a pathologist. Results are available in about a week.

Higgins recently co-authored the largest Canadian study to review the adequacy rate and learning curve for a single surgeon adopting ultrasound-guided fine-needle aspiration biopsy into practice. Adequacy in this case was defined as obtaining enough cells from the sample to allow a cytopathologist to interpret and provide a diagnosis.

Researchers looked at 423 biopsies of 289 patients who received the procedure at Sunnybrook between 2010 and 2015. They found an overall adequacy rate of 87%. There was a clear learning curve: adequacy improved each year, starting at 71% in 2010 and peaking at 94% in 2015. The learning curve was demonstrated by the proportion of patients each year who eventually received the procedure, regardless of the number of attempts.

"We showed that we are on par with, if not exceeding, what are considered acceptable norms for accuracy and adequacy of sample," says Higgins. The study concluded that surgeons are capable of performing ultrasound-guided fine-needle aspiration of the thyroid. This is important, he says, as the procedure offers clear benefits. "Patients appreciate the convenience, and it ultimately allows for a dramatic wait times reduction," he says, noting that a referral to a radiologist to do the imaging can take four to six weeks.

Carly McCready, a patient of Higgins', says immediate testing lessened her anxiety. "I didn't expect to have action taken so soon. I was pleasantly surprised the first day I met Dr. Higgins I had an ultrasound and biopsy. The next time I had an appointment, I had the information right away."

Dr. Kevin Higgins performs a thyroid biopsy under ultrasound guidance on a patient in the head and neck clinic at Sunnybrook.

Photo: **Nation Wong**

Higgins' research is supported by donations through the Head and Neck Initiative at the Sunnybrook Foundation.

Read about Carly McCready's treatment for thyroid cancer at **sunnybrook.ca/research**.

SpotON

Using molecular markers to quash lung cancer

By **Betty Zou**

Dr. Yee Ung led the creation of new guidelines for targeted therapies in lung cancer.

Photo: **Nation Wong**

Cancer care is changing.

Technological advances have made it easier, faster and cheaper to draw the genetic profile of tumours, transforming the way cancers are diagnosed, classified and treated. The favoured therapies of yesteryears—blunt treatments killing healthy and diseased cells alike—are being pushed aside by a new type of care: precision medicine.

Precision medicine challenges the one-size-fits-all approach to treating disease. Instead, it advocates for therapies tailored to each patient, taking into account her genes, environment and lifestyle. One area in which precision medicine has had meaningful impact is lung cancer, the leading cause of death from cancer in Canada and worldwide.

The last 10 years has seen significant changes in treatments for lung cancer, particularly for non-small cell lung cancer (NSCLC). In the past, patients with advanced, stage four NSCLC had two options: chemotherapy, which has limited effectiveness and serious adverse effects, or palliative care. "If [patients] are stage four, unfortunately, we don't have a cure," says Dr. Yee Ung, a radiation oncologist at Sunnybrook's Odette Cancer Centre. "However, there are newer therapies depending on whether they have different molecular markers."

These molecular markers are small changes in a patient's DNA that point to the underlying cause of her cancer. In 10% to 35% of patients with NSCLC, small typos are found in the epidermal growth factor receptor (EGFR) gene. These receptors sit on the cell surface where they transmit signals to the cell that tell it to grow and divide. The EGFR mutations seen in patients with NSCLC often render the receptors overactive, leading to uncontrolled cell growth and, ultimately, cancer.

The discovery of EGFR as a driver of disease led to the development of a new class of drugs that target the receptor and block its activity. These EGFR inhibitors have mainly been deployed in advanced NSCLC, where they have proven more effective and less toxic than chemotherapy.

Together with colleagues in the program in evidence-based care at Cancer Care Ontario (CCO), Ung published a review of 96 clinical trials to determine whether EGFR inhibitors are more suitable for some patients versus others. He found that in patients with an EGFR mutation, those who received an EGFR inhibitor as their initial therapy were able to stave off disease progression longer than those who received chemotherapy. Among patients whose EGFR mutation status was unknown, however, treatment with an EGFR inhibitor led to worse outcomes: their cancers progressed sooner than those treated with chemotherapy. These results underscore the growing role of molecular markers in determining the most appropriate course of treatment for a patient.

Another advantage of targeted therapies like EGFR inhibitors is reduced toxicity, which translates into fewer and less severe side effects. For patients with advanced NSCLC, that can have a dramatic impact on their life. "We still can't cure [the cancer], but at least we can improve the prognosis and quality of life," says Ung.

The team's findings provided the basis for a new CCO guideline on use of EGFR inhibitors to treat NSCLC. "The value of the guideline is that it consolidates the evidence and it helps us make a stronger recommendation for funding," he says. Funding from the government to cover the costs of these drugs will ensure these therapies are available to those that stand to benefit. With the evidence compiled and the recommendations submitted, all that's left to do is wait.

This research was supported by the Cancer Care Ontario program in evidence-based care.

FOCAL HERO

Dr. Arjun Sahgal specializes in stereotactic radiotherapy, a treatment that uses high-dose, focally delivered radiation to kill tumours.

A new kind of radiotherapy kills brain tumours with pinpoint precision. Researchers say it will only get better once they add MRI to the mix

By **Alisa Kim**

In 2010, just before her daughter's fifth birthday, Annie Parker was diagnosed with breast cancer. The battery of treatments she received—chemotherapy, radiation and mastectomy—seemed to be working. Early in 2014, however, she was beset with excruciating back pain.

Parker had spinal metastasis—the disease had spread to her vertebrae. (Bone is the most common site of secondary breast cancer; malignant cells stray to areas such as the spine, ribs, skull and pelvis via the blood and lymphatic system.) The tumour had put such pressure on her spinal cord that she had emergency surgery to remove it. Her husband feared she'd never walk again, but there was a silver lining.

"She came in with very limited disease," says Dr. Arjun Sahgal, a clinician-scientist at Sunnybrook Research Institute (SRI) and deputy chief of radiation oncology at Sunnybrook's Odette Cancer Centre. "I treated her with postoperative stereotactic ablative radiation, and she's been perfectly controlled for years. She's an example of somebody who would otherwise have been told, 'You're going to die. Let's use palliative radiotherapy.' But we took an aggressive approach, and we treated her for cure. As time goes on, we'll know whether she's truly cured, but for now nothing else has come up," he says, smiling.

Fortunately, Parker was a good candidate for this fairly new therapy, which uses advanced 3-D imaging to deliver higher-than-normal doses of radiation to the target. Conventional radiotherapy is given in small doses over many weeks. In contrast, the high-dose, focally delivered ablative radiation used in stereotactic radiotherapy allows for fewer treatment sessions. It's usually limited to patients with small, well-defined cancers, including those of the lung, liver, spine, abdomen and prostate. Sunnybrook is an academic leader in spine stereotactic body radiotherapy and one of the few institutions developing the postoperative indication used to treat Parker. Saghal notes doctors perform the procedure on about 200 patients annually, making the hospital one of the largest single-site practices in the world.

When performed on the brain, it's called stereotactic radiosurgery. At Sunnybrook, stereotactic radiosurgery is performed on as many suitable patients as possible—about 500 yearly—to spare them the negative effects of whole-brain radiation. These include seizures, memory loss and extreme fatigue. As evidence in support of focal radiation in the brain mounts, Sahgal is training clinicians from other Canadian centres in how to use it.

His passion (obsession, one could argue) is to understand fully when it is best to treat with stereotactic radiation and how to deliver it more effectively.

"[For] the last seven years, all our research has been on safety and developing the technique, learning

Photo: **Nation Wong**

what our outcomes are, the adverse effects [and] how to manage those effects. We've advanced the field to where we have good patient selection," says Sahgal.

His research shows cause for optimism. In 2015, he published a review of Phase 3 trials involving patients with fewer than five metastatic brain tumours. He found that patients aged 50 years and younger treated with only stereotactic radiosurgery had better survival rates than those treated with radiosurgery and whole-brain radiation. The results provide strong evidence of the benefit of stereotactic radiosurgery for younger patients with limited disease.

The cancer ablation therapy program at Sunnybrook, of which Sahgal is director, is conducting practice-changing research into treatment of central nervous system (CNS) cancers. At its core is a partnership with Elekta, a company that is investing in its brain radiosurgery device, known as a gamma knife, and magnetic resonance (MR) linear accelerator technologies. In all, three systems, including Elekta's, will be installed by autumn 2016. [See sidebar.]

The technologies integrate MRI into the therapy systems. "It's not only going to improve our ability to be accurate in terms of how to target the tumour, but it also allows real-time [tumour response] assessment using high-field-strength MRI for the first time," says Sahgal.

Sunnybrook is the only Canadian centre within a seven-member global consortium that has partnered with Elekta to optimize use of the MR linear accelerator technology.

As the lead centre for CNS trials, one order of business will be a randomized study comparing radiosurgery with whole-brain radiation plus radiosurgery in patients who have between 10 and 20 metastatic brain tumours.

"This is at the real forefront because you need the technology to deliver the radiosurgery, and there is a question as to whether more therapy in this indication is better," says Sahgal, who adds the study is about two years away.

Before it can begin, researchers must develop more efficient therapy planning strategies. Sahgal notes treating patients with more than 10 brain tumours is extremely complex; the sheer number of lesions makes it difficult for doctors to distinguish between tumours that have already been treated and those that are new. He is working with Dr. Anne Martel, a senior scientist at SRI, to develop software that uses image segmentation to identify new lesions automatically.

Sahgal points out such advances are a team effort. The program fosters collaboration among oncologists, medical physicists, radiologists and imaging scientists at SRI to validate the advantages of MRI-guided radiotherapy. He notes another example: a project with Dr. Greg Stanisz, a physicist at SRI, on functional imaging to measure therapy response. "At any time, about one-third of our department is working on the MR [linear accelerator] and gamma knife in some way or another," he says.

His next focus will be to develop the first-in-human trial using the MR linear accelerator to treat glioblastoma, the most common and aggressive primary brain cancer. This is a major challenge, as the technology has not been used on patients.

His ultimate goal is to be able to roll out new radiation applications to more patients so that they, like Parker, can have options. Parker's journey highlights the promise of stereotactic spine radiotherapy; even so, Sahgal says further proof is needed before it can be made widely available. In addition to his research on the brain, he is the lead investigator of a national trial comparing stereotactic body radiotherapy with conventional radiation in patients with painful spine tumours. "It's an important study to ensure that we're not just using new technology indiscriminately and believing in it without evidence."

Parker describes her health as "excellent." On the snowy February morning on which we chat, she has shoveled the driveway of her home in Ajax. The road to recovery has been gradual, but not painful, she says. She is grateful for the care she received at Sunnybrook, the effects of which differed markedly from the conventional radiation she had the first time around. "I had five weeks of radiation for breast cancer. I was tired. I could fall asleep anywhere. I had four [sessions] with [Dr. Sahgal], and it's like I went for coffee."

Her lifestyle is that of a busy stay-at-home parent. She also goes to the gym three times a week. "If you saw me, you'd never think I was ever sick."

Sahgal's research is funded by Elekta, the Federal Agency for Economic Development for Southern Ontario, and Ontario Ministry of Research and Innovation.

Hunks of Steel

By 2016's end, the Odette Cancer Centre (OCC) will be the first in Canada to offer radiation therapy guided by real-time imaging. Here's how.

Gamma Knife Icon

The Icon uses real-time computed tomography to home in on brain lesions. The system, which weighs about 20 tonnes, will enable treatment of more patients, including those with up to 30 brain tumours. Bonus: instead of screwing a metal frame into patients' heads to keep them still during treatment, patients will don a custom-fitted mask.

Magnetic Resonance Linear Accelerator (MR-linac)

Currently, doctors use pretreatment scans to estimate a tumour's location during therapy. The MR-linac will enable doctors to see the tumour during treatment for precise delivery. Applying the dose more accurately reduces the size of the safety margins around the tumour, thereby minimizing exposure of healthy tissue. They will even be able to zero in on moving targets, such as pancreatic tumours. Installation won't be easy; the massive system will be delivered via a hole in the ceiling with a diagonal nearly four metres long.

Magnetic Resonance-Guided Brachytherapy

Brachytherapy is the placement of radioactive substances in or near tumours. The OCC treats about 300 patients with brachytherapy annually. It is the largest single-institution program of its kind in North America. In the summer of 2016, the centre will install an MR imaging machine in its brachytherapy suite. For the first time, doctors will be able to monitor the effects of radiation on the tumour—at a cellular level—at the moment it is delivered.

It's Personal

Edging closer to individualized breast cancer care

By **Alisa Kim**

About 25,000 Canadian women are diagnosed with breast cancer annually. If you're one of them or know someone who is, there is hope: about 88% of women are alive five years after a diagnosis; furthermore, deaths from breast cancer have decreased by 44% since 1986 due to earlier detection and better treatments.

Despite these promising trends, the disease strikes deep fear in women. This fear has consequences that extend far beyond the psychosocial. Researchers from Brigham and Women's Hospital in Boston, U.S. have found thousands of women with breast cancer are removing a healthy breast as a preventive measure without evidence that doing so is beneficial.

For these women, watchful waiting isn't good enough. Dr. Eileen Rakovitch, a scientist at Sunnybrook Research Institute (SRI) and radiation oncologist at Sunnybrook's Odette Cancer Centre, is developing a treatment strategy that aims to mitigate uncertainty and empower women with information and choices for optimal care.

She's looking at ductal carcinoma in situ (DCIS), where cancer is confined to the lining of the milk ducts, and the most common type of noninvasive breast cancer. The upside of DCIS is that, for most, treatment will be successful. The downside: DCIS raises the risk of developing an invasive breast cancer.

Doctors can only estimate this risk using factors including a patient's age and tumour size—an approach that's unreliable, according to Rakovitch, who is also the medical director of the Louise Temerty Breast Cancer Centre at Sunnybrook. "There's been a lot of variability and even confusion in management of DCIS—overtreating some women, undertreating others," she says. "We know we overtreat many women with DCIS; how do we improve that? By better identifying women at risk so they can get treated, and then [with] those at low risk, backing off—de-escalating therapy."

She led research on the Oncotype DX DCIS Score, a test that measures the expression of 12 genes in breast tumours to indicate a woman's recurrence risk; the higher the score, the greater the likelihood of a cancer's return. She looked at women diagnosed with DCIS in Ontario from 1994 to 2003 who had a lumpectomy. Their tumour samples were sent to a lab for genetic testing and scoring. She compared the women's risk scores with their outcomes. She found those with a low-risk score had a low probability of recurrence; those with a high-risk score had a higher risk of recurrence. "We're moving beyond clinical factors and pathological features to molecular features. That's what's exciting. This is the first molecular-based assay in DCIS that's associated with outcomes," says Rakovitch.

Showing the test works could overhaul treatment of DCIS, which is diagnosed in about 13 out of 100,000 Canadian women annually. For instance, in addition to surgery, women with DCIS are offered radiotherapy and medication to stave off recurrence. Many opt for more therapy—enduring adverse effects—in the hopes of

Illustration: **Lisa Henderling**

Dr. Martin Yaffe developed a technique that aims to make pathology more accurate so doctors can determine the best way to treat patients. It uses whole slices of tumour tissue.

Photo: **Nation Wong**

pre-empting disease, even if the benefits are uncertain. Knowing which women with DCIS are most likely to develop invasive breast cancer could change all that.

"It's creating individualized medicine where women have their score on their own DCIS, and they can have better information about their own risk of recurrence, rather than some generic estimate, which is what we've been doing up until now," says Rakovitch. "We're hoping that lower-risk women will then choose not to have [additional] treatment and, conversely, we're identifying higher-risk women who really do need the treatment."

Her research shows that the genes on which the test is based could serve as biomarkers to identify women at greatest risk of recurrence. This knowledge could in turn improve care and optimize use of resources.

There are also policy implications. She is working with the Ontario Clinical Oncology Group (OCOG) to evaluate how the test, which costs about $4,000 and is not covered by provincial funding, might change treatment decision-making and women's satisfaction with their decision. With OCOG, Rakovitch is doing a cost-effectiveness analysis to determine whether paying for the test makes sense owing to potential savings from lower-risk women not needing radiation treatment.

If Rakovitch is reducing uncertainty by identifying the odds of recurrence, then her colleague, Dr. Gregory Czarnota, is decreasing it in the realm of treatment response monitoring. Czarnota is director of the Odette Cancer Research Program at SRI and a radiation oncologist at Sunnybrook. He and Dr. Ali Sadeghi-Naini, an imaging scientist at SRI, have developed a technique that uses quantitative ultrasound (QUS) to indicate early on how well women with breast cancer are responding to chemotherapy.

Most of us associate ultrasound imaging with pictures of a developing fetus. These pictures, known as B-mode images, are made by sending sound waves into the body. As the sound waves bounce off internal structures, the echoes are collected and processed by a computer to make an image. Czarnota and Sadeghi-Naini's technique takes the raw data collected (and discarded) by ultrasound machines, and uses it to depict dying cancer cells in response to therapy. "We get, if you like, a digital fingerprint or readout of what the structural states of various cells are," says Czarnota.

There are other ways of imaging tumour cell death, including single photon emission computed tomography and positron emission tomography. These methods are costly and require injections of radioactive contrast agents. Quantitative ultrasound, on the other hand, does not use contrast agents.

Czarnota and Sadeghi-Naini were the first to show that QUS could detect tumour cell death in women with locally advanced breast cancer (LABC), an aggressive subtype characterized by large tumours. Typically, these patients receive chemotherapy to shrink tumours before having surgery to remove them. It can take up to six months before this change—if it happens—is visible on standard imaging scans. Czarnota and Sadeghi-Naini have shown QUS can identify which women with LABC will respond to therapy within one week of the start of treatment.

How can they tell so soon? A cancer cell's death is heralded by the destruction of its nucleus, the storehouse of genetic information. When this happens there is increased echogenicity, or return of the ultrasound signal, says Sadeghi-Naini. "When cell death, or apoptosis, starts, the size of the cells changes, and their morphology alters. The nucleus starts to be more condensed and fragmented. These are the microstructures within tissue that scatter back the ultrasound signal," he explains. "The intensity of the ultrasound signal that is detected increases by about 25 decibels—fivefold, so it's very significant," says Czarnota.

To validate the predictive value of QUS, Czarnota turned to Dr. Martin Yaffe, a senior scientist in Physical Sciences at SRI. The idea was to compare their findings against the gold standard in cancer diagnosis: pathology. "If you're developing a new technique, you need to test it. The best way to test it is against truth, which is usually found in the tissue in pathology," says Yaffe.

Yaffe's method uses whole slices of tissue cut from tumours that are removed during surgery. The whole-mount technique gives pathologists an overview of tumour margins and lets them see where the margins are in relation to normal tissue. Lab-developed software digitizes the slides,

making it easy to store, retrieve and work with images of the tissue slices. In addition to getting the "big picture" of a tumour, pathologists can zoom in on single cells, which are only a few thousandths of a millimetre in size. "We can go back and forth between those two scales simply using the computer mouse. It becomes an easy way of looking at an enormous amount of information," says Yaffe.

The whole-mount technique is already making the job of pathologists easier. ("They love working with large slides," notes Yaffe.) It provides contextual information that tells doctors where the disease ends and whether all of the cancer has been removed during surgery, for example. His goal is to make pathology more accurate and to provide greater insight into disease so doctors can determine how best to treat patients.

Yaffe notes a second application: validating new in-the-body imaging tools, including the QUS method developed by Czarnota and Sadeghi-Naini. The researchers published a study in *Clinical Cancer Research* that highlights this collaboration. In it, they verify that tumours of women classified as "responders" through QUS imaging had indeed disappeared or shrunk considerably, as confirmed by Yaffe's whole-mount technique, which was done about six months after the start of chemotherapy. The implications are significant: rather than waiting months to learn that a therapy isn't working, doctors can determine this within weeks and switch patients to a treatment that might work. On the flip side, patients who are responding to treatment can have peace of mind.

Rather than waiting months to learn that a therapy isn't working, doctors can determine this within weeks and switch patients to a treatment that might work.

Having proved the technique in breast cancer patients at Sunnybrook, Czarnota and Sadeghi-Naini are evaluating it in a multicentre trial that, in addition to Sunnybrook, includes Princess Margaret Hospital, St. Michael's Hospital and the University of Texas MD Anderson Cancer Center. Preliminary data are promising and consistent with previous findings.

Along with publishing research on QUS, Czarnota and Sadeghi-Naini are working to ensure that the technology has widespread impact through development and commercialization. They have engineered software that uses raw data from ultrasound imaging to generate and analyze QUS "maps" of cancerous tissue for computer-aided prognosis. They are working with GE Healthcare to adapt the software for use in its ultrasound devices.

Although their work has focused on breast cancer, they have shown that QUS also can differentiate between benign and malignant disease in prostate cancer. It has the potential to be used in multiple cancers, says Sadeghi-Naini. "[Tumour] cell death is the main goal of many anticancer therapeutics, so it can be adapted for various applications in different cancer sites."

Research Funding

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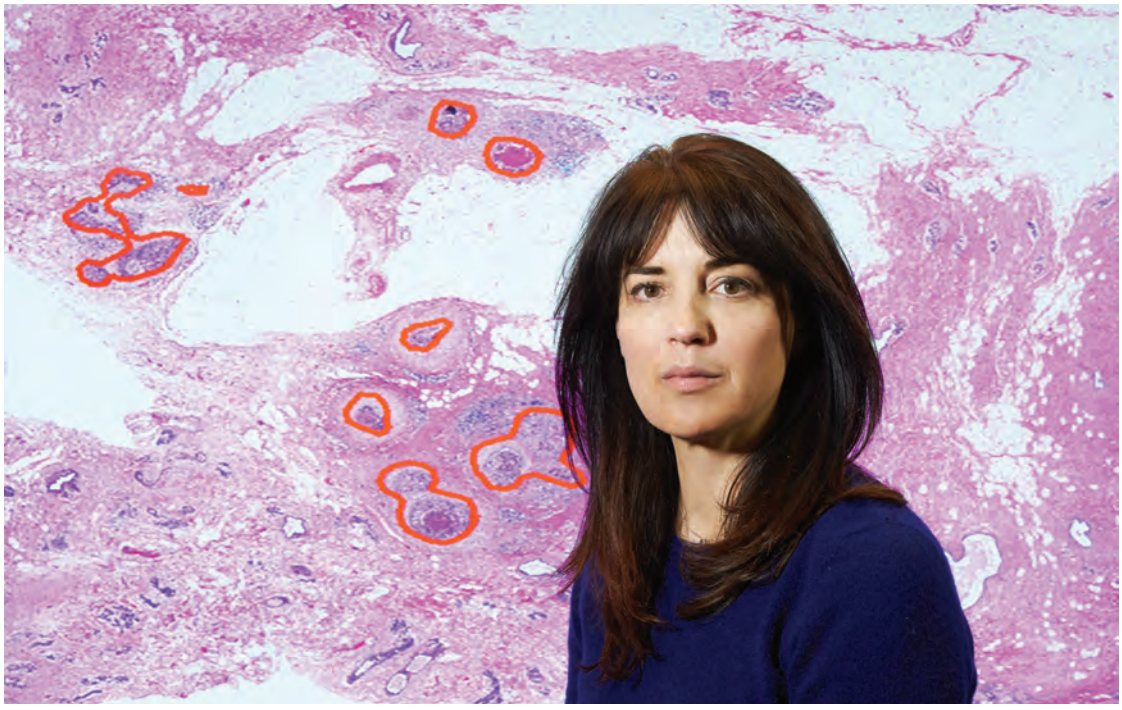


Dr. Eileen Rakovitch validated the Oncotype DX DCIS Score, a test that indicates a woman's risk of cancer recurrence. Shown behind her is a slide of a lumpectomy sample. Ductal carcinoma in situ cells are circled.

Photo: **Nation Wong**

Dr. Laurent Milot is one of only a handful of radiologists in Canada with expertise in using MRI-ultrasound fused targeted biopsy to locate hidden tumours in the prostate.

MAN by MAN

Genomics and imaging tools are cracking the tough nut of prostate cancer, exposing which patients are most likely to get worse, and where tumours might be concealed

By **Betty Zou**

Photo: **Nation Wong**

"How do we diagnose prostate cancer more responsibly and avoid overdiagnosis?" Dr. Masoom Haider pauses, having arrived at this crucial question midway through the interview. "We've talked about screening, overdiagnosis and PSA [prostate-specific antigen test] not being recommended for a number of years now," says Haider, a senior scientist at Sunnybrook Research Institute (SRI) and chief of medical imaging at Sunnybrook. "What's a man supposed to do?"

Since 1994, the PSA test has been used to screen for prostate cancer. The test is based on PSA levels in the blood. In healthy men, these are very low, whereas men with prostate cancer typically have elevated PSA levels. High levels can also result from a noncancerous condition, like an enlarged or infected prostate, and cannot, by itself, distinguish between aggressive cancer, which needs immediate treatment, and slow-growing disease that can be left untreated. "If you screen for prostate cancer you lower the mortality [rate], but you also find a lot of cancer that is clinically insignificant," says Dr. Laurence Klotz, a urologist at Sunnybrook and a researcher at SRI. "If you treat all those patients aggressively, screening is not palatable because you have so many patients who are overtreated."

Aggressive treatment for prostate cancer involves radiation and surgery to remove the prostate. Both therapies can have side effects, most commonly, erectile dysfunction, loss of bladder control and problems with rectal function. These effects may be acceptable when the treatment is life saving, but in men for whom the disease poses no threat, they are unnecessary and harmful. Despite the risk of overtreatment, Klotz and Haider say there is value to PSA screening. They, along with other doctors and researchers, are trying to make screening practices more effective. Their work is shedding light on the biology of prostate cancer and how doctors can treat patients based on their individual risk.

In a sun-lit office tucked away in the research wing of Sunnybrook, Dr. Arun Seth is working to turn his scientific discoveries into prognostic tools to predict a patient's prostate cancer risk and outcome. Seth is a senior scientist at SRI. He studies microRNAs, small molecules in the cell that help regulate gene function by controlling protein production. "There are some microRNAs known to either increase disease spread or contribute to development of prostate cancer," says Seth. "[Then] there are some microRNAs that go the other way; they inhibit the progression of prostate cancer."

In 2015, Seth and Dr. Robert Nam, an associate scientist at SRI and head of the genitourinary group at Sunnybrook's Odette Cancer Centre, published a study on the role of microRNAs in predicting prostate cancer outcomes. They used tumour samples from 31 patients who had their prostates removed. Thirteen were cancer free five years later, whereas cancer returned and metastasized in 18 men. The scientists compared tumour microRNA levels between these two groups and identified five microRNAs that were strongly associated with disease spread. In a cohort of 515 patients, abundance of these five microRNAs in the prostate tumour predicted the likelihood of metastasis and recurrence.

One microRNA, miR-301a, was the most accurate in predicting recurrence after surgery—miR-301a levels were significantly higher in prostate tumours that recurred than in tumours that did not come back. The researchers discovered that miR-301a promotes tumour formation and cancer growth, but they wondered: How does this small molecule make cancer cells grow faster and spread more widely?

To answer this question, the researchers grew prostate cancer cells in a Petri dish. They engineered one group of cells to make lots of miR-301a and compared them to cells with little or no miR-301a. Cells that overproduced the microRNA grew faster than those with low miR-301a. Fascinatingly,

Dr. Arun Seth's work on the biology of prostate cancer has led to the discovery of new biomarkers that predict disease recurrence.

Photo: **Curtis Lantinga**

the high miR-301a levels caused the cells to morph from rounded blobs into long missiles—a sign of their increased mobility and invasiveness. Cells overproducing miR-301a also had much lower levels of a protein called p63, which suppresses tumour formation. The team showed miR-301a directly inhibits production of p63, which in turn sets off a cascade of events that leads to the cancer cells becoming more virile.

The researchers are now exploring whether miR-301a can be used for prognosis. "Since [miR-301a] predicted recurrence, we're going to look in blood, serum and urine to see if we can detect miR-301a early enough that we can classify patients into different [risk] groups," says Seth. Knowing a person's risk profile could help patients and doctors choose between aggressive treatment like surgery and a conservative approach like active surveillance.

Klotz is considered by many to be the father of active surveillance. A self-described contrarian, he rides to work every day on his electric scooter, undeterred even by the lashing freezing rain of a late Canadian March. In the mid-1990s, Klotz and fellow Sunnybrook physicians Drs. Richard Choo and Cyril Danjoux came up with the idea of active surveillance to address a gap in care. With the approval of the PSA test, the number of prostate cancer diagnoses rose dramatically. In the U.S. and Canada nearly 95% of these patients were treated aggressively. On the other hand, the U.K. and Scandinavian countries adopted a "no treatment" approach, leading to the highest prostate cancer mortality rates in the world.

"The question was, was there some middle ground?" says Klotz. He knew that, in most cases, prostate cancer is extremely slow growing. Together, the researchers devised a strategy for men with low PSA whose cancer was confined to a small area. Instead of undergoing radical treatment, these patients would be monitored with regular PSA tests and biopsies. If tests showed cancer progression, then they would be treated right away. And so active surveillance was born. "That seems, in retrospect, like such an obvious idea," says Klotz. "[But] at the time, it was very controversial. Many of our opponents truly felt this would result in unnecessary deaths."

Dr. Laurence Klotz is the co-creator of active surveillance, a strategy that has changed the treatment landscape for men with prostate cancer.

Photo: **Nation Wong**

Klotz enrolled the first patient in active surveillance in 1995. He has been recruiting and following patients ever since. In two reports published in 2015, Klotz analyzed the outcomes of 993 men on active surveillance, one-quarter of whom had been in the program for more than 10 years. Of these men, 27% quit to receive treatment when their PSA tests and biopsies showed their cancer was progressing. While there were 149 deaths during the follow-up period, only 15 were due to prostate cancer. Thirty patients developed metastatic disease, including the 15 that succumbed to prostate cancer. At 10 years, the probability of surviving cancer was 98%. At 15 years, the odds dropped slightly to 94%.

"One of the criticisms of our program was, 'you guys are just reporting too early,'" says Klotz. Long-term studies like this one have helped convince even his toughest adversaries that active surveillance is a safe approach for men with low-risk prostate cancer. Today, active surveillance has been adopted all over the world, and Klotz is tackling other challenges. "The Achilles heel of this approach is about 25% of patients [on active surveillance] have high-grade cancer elsewhere in the prostate," he says. A high-grade cancer is more likely to grow and spread faster than a low-grade one, but it's often missed in the biopsy. This creates a false sense of security, leading patients and doctors to choose a conservative approach when more aggressive treatment is needed.

To address this problem, Klotz is working with Haider and Dr. Laurent Milot to improve detection of high-risk prostate cancers. The current technique for prostate biopsy relies on ultrasound imaging for guidance. An ultrasound scan locates the prostate, from which 12 biopsy samples are taken systematically by following a grid-like pattern. The samples are then sent to a pathologist for diagnosis and grading. "Ultrasound is a great tool to see the prostate, but it's not so great to see the cancer," says Milot, a radiologist and researcher at SRI. He compares the ultrasound-guided systematic biopsy to navigating without a map. With no idea of where the disease might be, chance determines whether one of the 12 biopsy needles will hit cancerous tissue.

Magnetic resonance imaging is changing that. A new method fuses MRI with traditional ultrasound-guided biopsies to create GPS-like navigation for radiologists. "[Magnetic resonance imaging] gives you two things: it tells you whether there's a cancer, but also where it is," says Haider.

Milot is the only radiologist at Sunnybrook—and one of a handful in Canada—with expertise in MRI-

ultrasound fused targeted biopsy. He recently performed the procedure on a patient who travelled to Toronto from Newfoundland expressly to get it. With this new technique, patients first undergo an MR scan to pinpoint the cancer. Newly developed fusion systems merge the MR and ultrasound images to generate a live map of the prostate with an "X" marking the tumour. With map in hand, Milot is able to guide the biopsy needle directly to the target site and take three or four samples instead of the standard 12.

Sunnybrook was the first hospital in Ontario to have an MRI-ultrasound fusion biopsy system, and the first in the world to do a prospective study comparing the two biopsy methods. In this work, Haider, Klotz and Milot tested how well MRI-ultrasound fused targeted biopsy and systematic biopsy could detect high-grade prostate cancer in men on active surveillance. Out of 72 patients, high-grade cancer was detected in 10 patients using both methods. An additional seven patients were found to have high-grade cancer revealed only by targeted biopsy. The study showed MRI-ultrasound fused targeted biopsy was six times more likely to detect a high-grade cancer. "[This] was really the landmark work for us in terms of saying, 'Yes, we can do it. Yes, it makes sense to do it,'" says Milot. Based on these results, MRI scans are now given to nearly all patients on active surveillance at Sunnybrook.

"There are some parts of the prostate that are hard to get to," says Klotz. "That's where we think most of these bad cancers are hiding. We think going forward with MRI we will find most, if not all, of them early enough that they're still curable." The researchers recently finished recruiting patients for a large trial in which men on active surveillance were randomly assigned to receive either MRI-ultrasound fused targeted biopsy or systematic biopsy. They believe that the results will change practice and establish a role for MRI in prostate cancer care. "We've had an incredible influence in an area of oncology that affects a huge number of patients," says Klotz. "That's been unbelievably rewarding for everyone here that's been involved."

Haider's research is supported by the Cancer Imaging Network of Ontario and the Ontario Institute for Cancer Research. Klotz's research is funded by the Canadian Institutes of Health Research and Prostate Cancer Canada. Seth's research is supported by the Canadian Cancer Society Research Institute and Cancer Research Society. The Canada Foundation for Innovation and Ontario Ministry of Research and Innovation provided infrastructure support.

Photo: **Nation Wong**

Dr. Masoom Haider is integrating MRI into existing treatment strategies to make prostate cancer screening smarter and more effective.

Masterpieces are not created in a day. Neither are better, kinder medical therapies, prized treasures in their own right. Researchers at Sunnybrook's Odette Cancer Centre are leading the charge through clinical trials that seek to help patients with cancer live stronger, longer lives. Their mantra? Only the best is good enough.

Standard treatment for breast cancer involves surgery to remove the tumour and radiation to prevent recurrence. Adjuvant therapies are then typically given to reduce the odds of cancer coming back, and include chemotherapy and hormone, or endocrine, therapy. Endocrine therapy, which blocks estrogen from stimulating breast cancer cell growth, is relatively gentle and well-tolerated. Most patients with early-stage, hormone-sensitive breast cancer receive adjuvant endocrine therapy, some in combination with chemotherapy, the more toxic and gruelling of the two. "With chemotherapy, we're probably treating a bunch of people that we don't need to treat," says Dr. Kathleen Pritchard, a medical oncologist and researcher at Sunnybrook Research Institute (SRI). "We need to know which patients are low enough risk that we don't need to give them adjuvant chemotherapy."

Concern for overtreatment is at the heart of the Trial Assigning Individualized Options for Treatment, or TAILORx study, which sought to determine whether the Oncotype DX Recurrence Score could predict which patients need additional chemotherapy. The test examines the activity of 21 genes in tumour tissue to generate a score between zero and 100—the higher the score, the greater the risk of the cancer returning. More than 10,000 women with invasive breast cancer (stages 1 to 4) took the Oncotype DX test. Of those, 16% had a score of less than 11 and were given adjuvant endocrine therapy alone. At five years, the risk of recurrence in this group was less than 2%; overall survival topped 98%.

"Those patients have a very, very low risk of recurring even though they were just treated with surgery, radiation and a hormone," says Pritchard, who led the trial's Canadian team. "Many of them [were] patients that we might otherwise have given chemotherapy to because they had large or high-grade tumours." These results confirm that Oncotype DX is a useful test to give patients to help them decide whether they need adjuvant chemotherapy. In Ontario, the province covers the cost of the test for patients with hormone-sensitive breast cancer. "We will do it if we're not certain whether to give chemo or not," says Pritchard.

The TAILORx study is ongoing to determine the outcomes of the 67% of women who had a mid-range score between 11 and 25. These women were randomized to receive either adjuvant endocrine therapy alone or with chemotherapy. The results, expected within two years, will shed light on whether endocrine therapy alone is sufficient to prevent recurrence in patients at intermediate risk.

On the opposite side of the treatment spectrum, Dr. Georg Bjarnason is testing a strategy to address a seldom-recognized problem: underdosing. Bjarnason, a senior scientist at SRI and medical oncologist, focuses on kidney cancer. The standard of care for these patients is an oral drug called sunitinib, which stops tumour growth by staunching the flow of nutrients. "Traditionally, oncologists attempted to give the same dose and schedule of sunitinib to every patient," says Bjarnason. "It doesn't make any sense based on what we know about the pharmacology of oral drugs."

While chemotherapy dosing is calculated based on a patient's height and weight, dosing for oral drugs like sunitinib is fixed at a predetermined level. Sunitinib is typically given at a dose of 50 milligrams per day for 28 days, followed by a two-week break to allow patients to recover from any ill

A Tapestry of Trials

Oncologists are interlacing the threads of greater effectiveness, more precision, less harm and cost-consciousness to create an enduring legacy of care

By **Betty Zou**

Illustration: **Betty Zou**

Dr. Kathleen Pritchard led the Canadian portion of a study that showed the Oncotype DX genetic test can determine which patients with breast cancer would benefit from adjuvant chemotherapy.

effects. Not everyone, however, endures the same degree of adverse effects. For some, the toxicity is so severe that they cannot complete the full course. Others are able to stay on the drug with minimal discomfort.

In an earlier study, Bjarnason found a correlation between the severity of side effects and a patient's outcome. "We were the first to observe that in patients with minimum side effects the drug controlled the cancer for a much shorter time," he says. Patients who required dose and schedule changes to manage adverse effects did much better, suggesting that those who experienced minimal toxicity were, in effect, underdosed. These findings spurred Bjarnason to develop a new strategy. "We hypothesized that we could use toxicity as a surrogate for adequate drug exposure to individualize the therapy for every patient," he says. With this approach, doctors modified a patient's dose and schedule such that the level of toxicity was not too much, not too little, but just right.

To evaluate the safety and feasibility of individualized sunitinib treatment, Bjarnason led a Phase 2 trial with 117 participants from 13 centers across Canada. Patients with advanced kidney cancer were started on 50 mg of sunitinib for 28 days. Those unable to tolerate the full dose for 28 days received an individualized lower dose, whereas patients experiencing minimal side effects were given a higher dose. The study is ongoing, but early results show a response rate exceeding 50%, one of the highest reported for advanced kidney cancer. Further, over 90% of patients saw their tumours either stabilize or shrink. "Patients get to take more control of their therapy. They understand that having a bit of toxicity shows that they're taking an adequately high dose so they accept a degree of toxicity," says Bjarnason. He hopes these results will give doctors more confidence to individualize and escalate the dose of similar oral cancer drugs if necessary.

Fighting for recognition of a new concept is a struggle that Drs. Edward Chow and Carlo DeAngelis know well. When they first described the phenomenon of pain flare more than 10 years ago, they were met with disbelief. Cancer that has spread to bone can cause debilitating pain. Radiation therapy provides effective relief to patients with agonizing bone metastases. In 30% to 40% of patients, however, radiation therapy induces a temporary worsening of their aches, or a pain flare, in the first week after treatment. "We noticed that for the first few days, we actually made the pain worse," says Chow, who is a radiation oncologist and senior scientist at SRI. "Everyone else said, 'No, Edward. You're just joking.' People did not believe that."

It took two studies involving three centres to convince their peers that pain flares were a legitimate—and common—effect of radiotherapy. In a 2009 study led by Chow and DeAngelis, the clinical pharmacy coordinator for oncology at Sunnybrook, patients reported that pain flares interfered with daily activities. Nearly 85% said they would prefer to prevent the pain flare rather than take painkillers, which were often less effective.

A decade after they identified the phenomenon, in 2015, Chow and DeAngelis published results of a Phase 3 trial looking at the effectiveness of dexamethasone in preventing radiation-induced pain flares. Dexamethasone is a corticosteroid used to treat brain tumours, and inflammatory and autoimmune conditions such as

Photo: **Nation Wong**

rheumatoid arthritis. The drug is cheap—it costs less than 20 cents a pill—and has well-known and minor side effects if used cautiously.

In the study, 298 patients with painful bone metastases were randomly assigned to receive either dexamethasone or a placebo. Patients who received dexamethasone were 9% less likely to experience a pain flare in the first five days after treatment than those who received a placebo. While a reduction of less than 10% might not seem critical, it's the only treatment that has been shown to have any effect in preventing these flares, says Chow, underscoring the perhaps obvious point that for these patients any difference is welcome. Moreover, the drug reduced pain severity in patients who experienced a flare, and those who took the drug had, on average, less nausea and better appetite. The study was chosen by the Canadian Cancer Society as one of its top 10 research publications of 2015.

"These patients are palliative," says DeAngelis. "Our best hope is to improve and maintain quality of life for the short period that they have left." With the next step, he will move into the realm of precision medicine. He will analyze saliva from more than 70 patients in the Phase 3 trial to search for genetic markers that can predict whether a patient will experience a pain flare.

"I call it a neglected cancer with limited treatment options," says Dr. Simron Singh. "[It's] a complex disease—hard to understand, hard to treat." The disease to which he is referring is neuroendocrine cancer, a once-rare condition with one of the fastest rising incidence rates among cancers.

The neuroendocrine system comprises cells that receive instructions from the brain to produce hormones. These cells are distributed throughout the body with high concentrations in the digestive and respiratory systems. When the machinery in these cells runs amok, cancer develops in the form of neuroendocrine tumours (NETs).

Singh is a medical oncologist and co-head of Sunnybrook's Susan Leslie Clinic for Neuroendocrine Tumours, the largest NET clinic in Canada and one of five major centres in North America. He is also an affiliate scientist at SRI who is the global lead of the gastrointestinal portion of the RAD001 in Advanced Neuroendocrine Tumours, Fourth Trial (RADIANT-4), an international Phase 3 study on the efficacy and safety of the drug everolimus to treat advanced NETs originating in the lung or gastrointestinal tract. More than 300 patients from 25 countries were randomly assigned to receive either everolimus or a placebo, and then tracked to determine when their cancer progressed.

What the researchers found blew them away. Patients taking everolimus staved off progression for an average of 11 months, whereas those receiving the placebo saw their disease advance in less than four months. Overall, patients who took everolimus were 49% less likely to worsen or die. The impact of delaying disease progression also extended to quality of life. Throughout the trial, patients completed questionnaires that assessed their physical, social, emotional and functional well-being every eight or 12 weeks. The results from these surveys were used to generate a quality of life score. The overall score dropped by nearly five points after the cancer worsened, with the biggest differences seen in physical and functional well-being.

"We imagined it to be a positive trial, but I didn't anticipate such a dramatic result," says Singh. The RADIANT-4 study was the largest Phase 3 trial for NETs and the first to identify an effective treatment for patients with advanced NETs originating in the lung. "There was no treatment option before for these particular patients," he says. "This opened up a new door and hope for them." The strength of these results convinced the U.S. Food and Drug Administration to approve everolimus as a treatment for advanced NETs. As this story went to press, the drug received approval from Health Canada, and new results from the second interim overall survival analysis were released at the annual meeting of the American Society of Clinical Oncology. These data showed that the estimated two-year survival rate for patients on everolimus was 77% compared to 62% for patients taking the placebo.

When the trial is done, the results analyzed and the papers published, it's

Dr. Georg Bjarnason is testing an individualized approach to the oral cancer drug sunitinib. By adjusting the dose and schedule for each patient, he achieved one of the highest response rates for kidney cancer.

Photo: **Nation Wong**

easy to file everything away and move on. Not so for Dr. Laurence Klotz, who is turning to old data to answer new questions. Klotz is a researcher at SRI and a urologist at Sunnybrook. In 2012, he led a landmark study called the PR-7 trial that showed intermittent hormone therapy was as effective as continuous hormone therapy in prolonging survival for men with prostate cancer.

The goal of hormone therapy is to reduce testosterone levels as much as possible so that the hormones cannot stimulate prostate cancer cells to grow. At the time, there were six or seven different drugs used for hormone therapy, with some claiming that they could lower testosterone levels more than others. The key question was, did it matter? Do testosterone levels need to reach a minimum threshold?

"It occurred to me that we had an opportunity with this PR-7 trial," says Klotz. He revisited the data, focusing on the 626 Canadian patients treated with continuous hormone therapy. During the original study, they collected blood samples from these men to track their testosterone levels over the first year of treatment. In the secondary analysis, Klotz examined how testosterone levels in the first year correlated with long-term outcomes. "To my surprise, it vindicated the hypothesis that testosterone mattered," he says. "The patients whose testosterone was fully suppressed did much better than ones whose testosterone levels were not."

Men whose testosterone reached an all-time low of less than 0.7 nanomoles per litre (nmol/L) had a significantly lower risk of developing hormone therapy-resistant prostate cancer or dying from the disease than men whose testosterone levels failed to reach that point. "Historically, we didn't measure testosterone in patients on hormone therapy. The message is that testosterone should be measured frequently," says Klotz. "If it's not fully suppressed below 0.7 nmol/L, then do something to suppress it."

Finding new and better therapies is all well and good, but cancer drugs are notoriously expensive. Cancer Care Ontario estimates that in 2010 to 2011, the New Drug Funding Program and Ontario Drug Benefit program covered more than $430 million in cancer drugs, a figure that does not include money spent by hospitals, individuals or insurance companies. Despite this, most trials do not examine the potential savings associated with a new drug or treatment strategy. The Clinical Trials Group at the National Cancer Institute of Canada is one of the few cancer cooperative groups in the world with a team dedicated to studying the economic impact of new therapies. "In Canada, we have the perspective that it's very important to do, especially in our current environment where new drugs are coming in at such huge expense for the system," says Dr. Matthew Cheung, a haematologist and researcher at SRI.

In an earlier trial, researchers found that a newer regimen known as GDP—gemcitabine, dexamethasone and cisplatin—was as effective as the historical standard DHAP—dexamethasone, cytosine arabinoside and

Dr. Simron Singh talks with his patient Agnes Basemera. Singh is one of the global leads for a trial that showed the drug everolimus cut the risk of disease progression or death in half for patients with neuroendocrine tumours.

Photo: **Nation Wong**

WEAVING IT ALL TOGETHER

GOAL: To test the effectiveness of a genetic test in identifying patients who need adjuvant chemotherapy

WHO: 10,253 women with breast cancer

RESULTS: Patients with a low test score had an overall survival of 98% without chemotherapy.

TAKE-HOME: In certain women, the test can help decide whether adjuvant chemotherapy is worthwhile.

GOAL: To test the safety and feasibility of individualized drug dosing for an oral cancer drug

WHO: 117 patients with kidney cancer

RESULTS: Individual dosing led to tumour shrinkage or stabilization in more than 90% of patients.

TAKE-HOME: Being able to tailor the dose and schedule helps ensure that each patient receives an appropriate and effective dose.

GOAL: To measure the effectiveness of a steroid in preventing pain flares

WHO: 298 patients with bone metastases

RESULTS: The steroid reduced the likelihood of pain flares by 9%.

TAKE-HOME: Taking this steroid before radiotherapy can help prevent pain flares.

GOAL: To determine the effectiveness of everolimus in treating neuroendocrine tumours (NETs)

WHO: 302 patients with NETs

RESULTS: Everolimus reduced risk of disease progression or death by 52%.

TAKE-HOME: This is the first targeted agent that has been shown to be active against different types of NETs.

GOAL: To determine if testosterone levels need to reach a minimum level during treatment

WHO: 626 men with prostate cancer

RESULTS: Men whose testosterone dropped below a certain level were less likely to develop treatment resistance or die.

TAKE-HOME: Testosterone levels should be measured often to ensure that it reaches a minimum threshold.

GOAL: To compare the cost-savings of two drug regimens for lymphoma

WHO: 619 patients with lymphoma

RESULTS: The new GDP regimen was roughly $14,000 cheaper per patient than the standard DHAP treatment.

TAKE-HOME: With lower costs and similar outcomes as DHAP, GDP is now becoming the standard.

cisplatin—in treating patients with aggressive lymphoma whose cancer had returned after initial therapy. Cheung led a secondary analysis evaluating the costs and benefits associated with each treatment. To calculate the cost of each treatment, the researchers tallied up the expenses at each step along the way. These include costs from drug pricing and administration, staff wages and hospitalizations due to adverse events.

Benefits were measured using questionnaires administered to patients during the trial, taking into account not just how long patients survive on a given therapy, but also whether they're able to spend less time in the hospital and more time at home doing activities they enjoy. "If one treatment makes a patient live a lot longer, but it causes them to have a poor quality of life and suffer, then it may not offer all the benefits that we would like patients to have," says Cheung.

Given the similar results obtained for GDP and DHAP in the original trial, Cheung was shocked to see big differences in his study. The average per-patient cost for GDP was nearly $14,500 lower than the cost for DHAP. This was largely due to longer hospital stays for patients on DHAP because of drug administration protocols and increased toxicity, which led to more hospital visits. The reduced toxicity of GDP also led to patients reporting a higher quality of life. "So GDP is actually both beneficial and less costly for the system," says Cheung. "It's the best of all worlds." These results have begun to change practice in Canada. At Sunnybrook, GDP is prescribed as the standard chemotherapy regimen for patients with recurrent aggressive lymphoma.

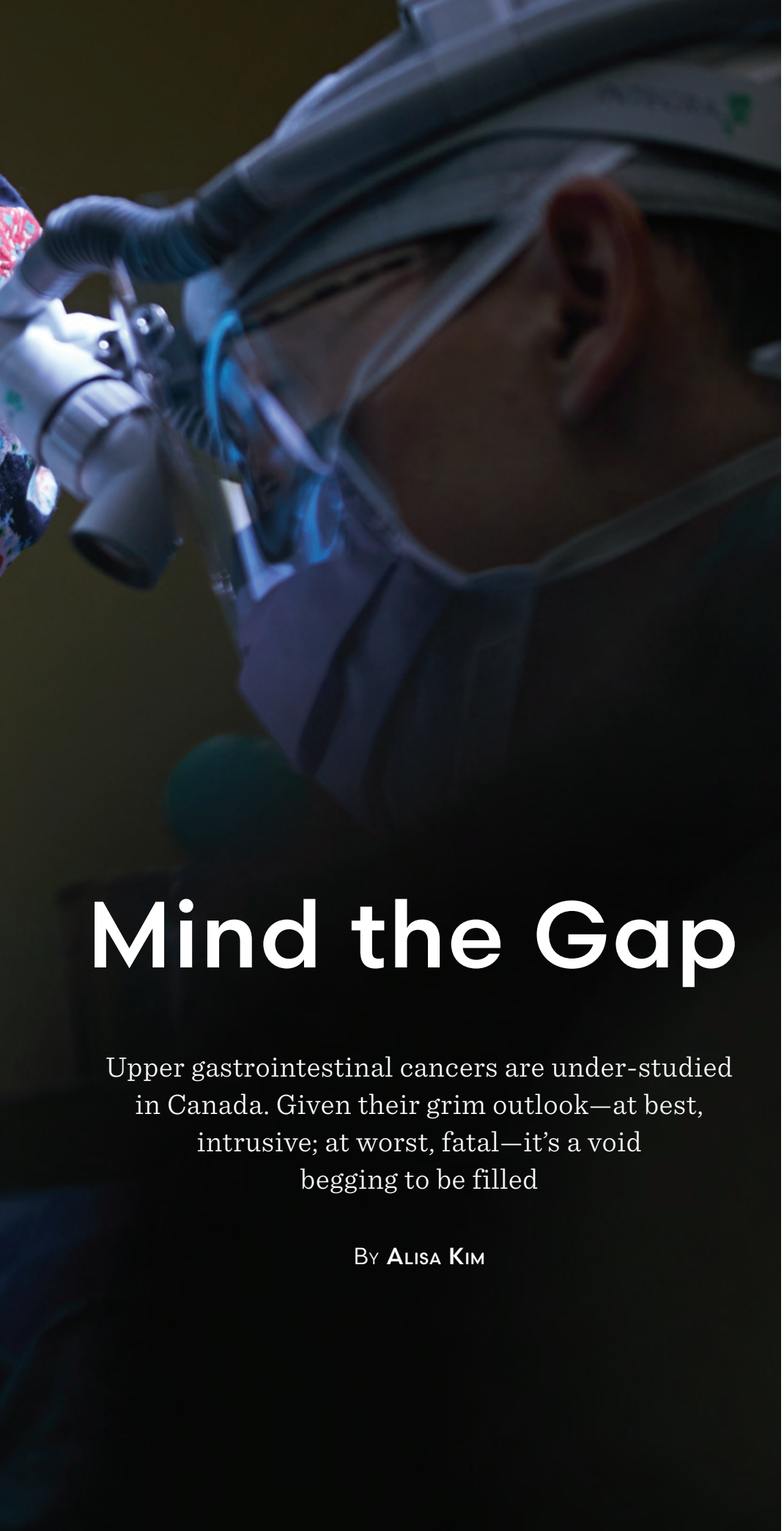
All clinical trials seek to solve a common riddle: how can we best care for this patient? In some trials, the answer is clear-cut and obvious. Others require a more nuanced interpretation. For the researchers fabricating a treatment plan person by person, each effort is a step closer toward victories big and small—a pain-free month, an extra year of independence or the ultimate reward: a life unburdened by disease.

Research Funding

Bjarnason: Anna-Liisa Farquharson Chair in Renal Cell Cancer Research, Canadian Institutes of Health Research (CIHR) and Pfizer. Cheung: Canadian Cancer Society Research Institute (CCSRI), Eli Lilly Canada and Hoffman-La Roche Limited. Chow and DeAngelis: CCSRI through the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG). Klotz: CCSRI through NCIC CTG, National Cancer Institute and National Institute of Health Royal Marsden Institute for Cancer Research Biomedical Research Centre. Pritchard: Canadian Cancer Society through NCIC CTG and National Institutes of Health. Singh: Novartis, the Ontario Institute for Cancer Research and Susan Leslie Fund for Neuroendocrine Cancers.

Dr. Julie Hallet excises a liver tumour. Her research has shown that blood transfusions during surgery to remove liver tumours are associated with lower rates of survival and higher rates of cancer recurrence.

Photo: **Nation Wong**



Mind the Gap

Upper gastrointestinal cancers are under-studied in Canada. Given their grim outlook—at best, intrusive; at worst, fatal—it's a void begging to be filled

By **Alisa Kim**

In 2009, U.S. Supreme Court Justice Ruth Bader Ginsberg had a routine CT scan that showed a one-centimetre-wide tumour in the middle of her pancreas. The finding was part of Ginsberg's yearly exams after having beaten colon cancer a decade earlier. She had surgery to remove the lesion and was back in the courtroom less than three weeks later. The veteran Supreme Court Justice, who'd experienced no symptoms, was lucky it was caught early. Pancreatic cancer most often is diagnosed when people report symptoms like abdominal pain and weight loss, at which point the disease has already spread, or metastasized.

Upper gastrointestinal cancers, including those of the esophagus, stomach, liver and pancreas are uncommon in Canada, but they can be fatal. Stomach cancer is often diagnosed at advanced stages, with more than one-half of patients presenting with incurable disease. Pancreatic cancer is even more pernicious; nearly 80% of these patients have disease that is so advanced that surgery cannot be offered. Moreover, it accounts for only 2.4% of all new cancer cases in Canada, yet it is the fourth leading cause of cancer death, killing 4,600 Canadians yearly—more than even prostate cancer, which arguably gets more public attention.

The challenge of managing these potentially deadly diseases is what drew Dr. Natalie Coburn, a surgical oncologist at Sunnybrook's Odette Cancer Centre and clinician-scientist at Sunnybrook Research

Surgeon-scientist **Dr. Natalie Coburn** found that people with advanced stomach cancer who were treated by a specialist with a high volume of patients had a rate of death that was 15% lower than that of people who did not receive such treatment.

Photo: **Nation Wong**

Institute (SRI), to the field. In particular, Coburn is working to unravel the complexities of treating stomach cancer in North America. "It's a really interesting cancer to study epidemiologically. Worldwide it's very common, but not one that is commonly seen in North America," she says. Stomach cancer represents less than 2% of all new cancers in Canada, but it is the fifth most common cancer worldwide. The disease is not screened in North America, Coburn notes. "It is useful to screen for colon or breast cancer, because these are common cancers. Since stomach cancer is so rare in Canada, screening programs are not effective. In Asia, where the prevalence of stomach cancer is nearly 10 times higher, screening is effective. Unfortunately, lack of screening leads to the disease presenting at advanced stages."

This challenge of late-stage presentation with linked metastasis prompted Coburn to lead a study on factors influencing the prognosis of people with advanced stomach cancer. The aim was to help doctors provide more accurate prognoses and identify modifiable factors that might improve outcomes. She looked at people with stage four cancer in Ontario between 2005 and 2008. Older age, tumours in the middle of the stomach and cancer that had spread widely were associated with lower rates of survival. Those who had surgery, chemotherapy or radiation, as well as those who were treated by a stomach cancer specialist with a high volume of patients, had significantly better survival, with this last factor accounting for a 15% reduction in the rate of death.

Why do these findings matter? "We can give [doctors] a 'road map' for the best way to treat patients," says Coburn. "If we can identify a group of patients that exceeds expectations, that were treated in a certain manner—so with chemotherapy upfront, for example, or with aggressive therapies—then we can let other physicians know this seemed to work best across our population."

To define these road maps, Coburn helmed the largest review of processes of care of patients with stomach cancer. The project culminated in a special issue of *Gastric Cancer* and a meeting of global experts who developed guidelines for best practices. Coburn is leading adaptation of these guidelines for Cancer Care Ontario's program in evidence-based care. Having a research-based guide to treatment may be helpful especially in Ontario, where, according to Coburn, there is variation in care. "Wait times at one centre might be longer for radiation; wait times at another might be a little bit longer for surgery. Doctors' philosophies [with respect to] aggressiveness of treatment also likely varies between centres. Those subtle differences affect what happens to patient care and outcomes," she says.

Sometimes, even where there are guidelines to help standardize care, they are not always followed, as Coburn and her colleague Dr. Julie Hallet know. They, along with Dr. Paul Karanicolas and Dr. Calvin Law, chief of the Odette Cancer Program, form the upper gastrointestinal surgical oncology team at Sunnybrook. Hallet is also an associate scientist at SRI. One of her aims is to reduce unnecessary blood transfusions in the operating room. Blood transfusions can save lives but come with risks. They can make people more susceptible to bacterial or viral infection. In people with cancer, transfusions may stimulate isolated cancer cells to grow, leading to tumour enlargement and spread. Guidelines suggest blood transfusions only when hemoglobin, a protein in red blood cells that carries oxygen throughout the body, falls below a certain level, at which point the body is not getting enough oxygen.

Hallet cites research that found one-half of all blood transfusions during surgeries to remove tumours of the liver, pancreas, gallbladder and bile ducts are avoidable. Some reasons why guidelines aren't always followed include lack of understanding of the risks and a doctor's belief that transfusion is critical, notes Hallet. "Often people know about guidelines but don't use them because they don't see the relevance to their practice," says Hallet. She led a large study highlighting the

"People who don't have access to neuroendocrine centres of expertise may not be getting the optimal care that they deserve."

risks of transfusions during surgery to remove liver tumours arising from colorectal cancer. Coburn, Karanicolas and Law are co-authors of the study, which was published in the *Annals of Surgical Oncology*. It focused on 483 people who had the operation at Sunnybrook between 2003 and 2012. People who received a blood transfusion during or right after surgery had a five-year survival rate that was 15% lower than that of people who didn't have one, Hallet found. Moreover, the percentage of people who remained cancer free five years after surgery was 32% among those who didn't get a transfusion—twice that of the transfused patients. "The reality is that some patients will never avoid a blood transfusion. But for some people, if it can be avoided, why give it and expose them to unnecessary potential risks? That's what we're trying to highlight," says Hallet, who shows no signs of fatigue from having performed an emergency appendectomy late the night before.

Hallet and Coburn are working with the department of surgery at the University of Toronto to create best practice guidelines for transfusions around the time of surgery to reduce the percentage of patients who are transfused annually in Toronto. Hallet is also filling a knowledge gap for a relatively rare and poorly understood disease: neuroendocrine tumours (NETs). About one-third of her practice is devoted to people with NETs, which is cancer that's found in the cells of the hormonal and nervous systems. Neuroendocrine tumours are most common in the lung or gastrointestinal tract, although they can occur anywhere in the body. She is one of two surgical oncologists in Sunnybrook's Susan Leslie Clinic for Neuroendocrine Tumours. It is the only multidisciplinary clinic of its kind in Canada where people with NETs see specialists in radiation, surgery and medical oncology simultaneously. The clinic, which treated more than 300 new patients in 2015, is co-led by Dr. Simron Singh.

"It's actually the second most common gastrointestinal cancer in terms of prevalence," notes Singh. Neuroendocrine tumours often grow slowly, with symptoms that are vague, including diarrhea and flushing, which contribute to misdiagnosis. Hallet says she sees patients who have lived with the disease for years before it is identified, at which point symptoms are intrusive and have a severe impact on people's lives. Singh recalls one patient who was given a psychiatric diagnosis before she came to the clinic and was diagnosed with a small bowel NET. Unfortunately, it was beyond the stage where cure was an option, he says. A distinctive feature of NETs is excess production of hormones. Chronically high hormone levels can damage the heart's valves or cause heart failure, when the muscle is too weak to pump blood as it should.

Using databases of provincial health records, Hallet and Singh looked at 5,619 cases of NETs in Ontario that were diagnosed between 1994 and 2009. They found the rate of new cases more than doubled in Ontario in those 15 years. They also found people from a low socioeconomic background and who lived in rural areas had worse overall survival. The results of the research are compelling, says Law, who co-authored the study and also treats NETs. "Sometimes people forget that the population of Ontario is as large as a lot of the European countries … . What's powerful about that [study] is not just the number, but the ability to start understanding what are the barriers to getting better treatment and how to deliver better care to these people," says Law.

On the back of this research Hallet, Singh, Law and Karanicolas compared outcomes of people with NETs living in rural versus urban areas. They found those in rural regions and who had lower socioeconomic status had worse overall survival and were more likely to have cancer that returned—even though they didn't have more advanced disease at presentation. "It's important to study because we worry that people who don't have access to neuroendocrine centres of expertise may not be getting the optimal care that they deserve," says Singh. They are looking into whether poorer outcomes in this patient group is due to less follow-up care, as treatment of NETs occurs over many years. "We have to keep patients enrolled in surveillance and active maintenance therapy programs. Maybe that's where we're missing something with patients with lower incomes or living in rural areas, and that's where we should focus our efforts in improving outcomes for them," says Hallet.

The NET clinic at Sunnybrook sees most of the people in Ontario who have this cancer. Such a high volume of patients provides an opportunity to do groundbreaking clinical trials. Singh led the gastrointestinal portion of the RADIANT-4 trial, a global Phase 3 study of the safety and efficacy of the drug everolimus in treating advanced NETs in the lung or gastrointestinal tract (for more on this see p. 30). Researchers found treatment with everolimus was associated with a 52% reduced risk of disease progression or death compared to placebo, astonishing results that led to regulatory approval of the drug in the U.S. "I don't think [the trial's organizers] expected our centre to be anywhere near the powerhouse of a recruiter it was. For this particular trial of a relatively rare disease, they actually stopped Simron because he was recruiting too fast, and they couldn't believe it," says Law, smiling.

Singh says the next step is to study the cost of NETs treatment, research that is challenging to do because of, well, costs. Funding for research into NETs is hard to get because it is less common, says Hallet. With incidence of the disease rising worldwide, however—in the U.S., it has increased nearly fivefold since 1974—we can't afford to ignore it.

Coburn's research is supported by the Canadian Cancer Society Research Institute, Canadian Institutes of Health Research and the Ontario Ministry of Health and Long-Term Care. She holds the Sherif and MaryLou Hanna Chair in Surgical Oncology Research. Hallet and Singh's research is supported by the Ontario Institute for Cancer Research.

COLORECTAL CANCER ADVANCES

Including DIY kit in the mail raises screening rates and taking a break from chemotherapy OK

By **Eleni Kanavas**

Regular colorectal cancer screening can save lives. That's the take-home message from Dr. Jill Tinmouth, a scientist in the Odette Cancer Research Program at Sunnybrook Research Institute (SRI) and a physician at Sunnybrook who specializes in screening for gastrointestinal cancers.

Small lumps of precancerous cells called polyps often form in the colon or rectum as we age. Over time, some of these polyps can become cancerous and spread to other organs in the body, making them harder to treat. Colorectal cancer is the third most common cancer and the fourth-leading cause of death worldwide. It doesn't have to end that way, however.

"The good thing about colorectal cancer is that it can be caught early with screening. There are large, grade-A randomized controlled trials that show screening with fecal tests can reduce colorectal cancer-related death," says Tinmouth, who is also the lead scientist of the ColonCancerCheck program at Cancer Care Ontario (CCO).

ColonCancerCheck was launched in 2008. It is Canada's first province-wide colorectal cancer screening program. It enables family physicians to give patients aged over 50 years who are at average risk of colorectal cancer (meaning no family history) a guaiac (pronounced gwai-ak) fecal occult blood test (gFOBT). The test comprises a stool-collection kit that is used to look for small amounts of blood. Individuals who have an abnormal test should undergo a colonoscopy to determine the source of the bleeding, which can result from a cancer, polyp or other cause, such as ulcers, haemorrhoids or colitis, an inflammatory bowel disease.

The program conducted a pilot project to test the feasibility of mailed invitations for cancer screening. Invitations from 102 family physicians were sent to their patients who were due for screening asking them to visit and obtain a gFOBT stool sample kit, or get a referral for a colonoscopy based on family history. Invitations were mailed to 11,000 people aged between 50 and

Photo: **Nation Wong**

Dr. Jill Tinmouth holds an at-home stool-collection kit. Kits were mailed to patients at average risk of colorectal cancer, in a study looking at increasing screening rates.

"We can now reassure patients that if they want to take a break, it will help their quality of life and not have an impact on their overall survival."

74 years; a gFOBT kit was not included. Only 22% of invitees responded and completed the gFOBT kit. Researchers concluded that better strategies were needed to get people to participate in colorectal cancer screening.

In 2011, Tinmouth led a randomized controlled trial to build on ColonCancerCheck's pilot study. She looked at whether making it easier to do the screening would help with participation. To test this theory, the trial studied the impact of including a gFOBT kit along with a second mailed invitation compared to a second invitation alone among people who did not respond in the pilot project.

The participants were randomly allocated to one of two arms: the intervention group received a second mailed screening invitation along with the gFOBT kit from their family doctor; and the control group received a second mailed invitation alone from their family doctor.

Tinmouth and colleagues found that the completion rate of a gFOBT test within six months of the mailing date was twice as high in the intervention group at 20% compared to the control group at 10%. The findings suggest that mailing gFOBT kits to participants increases colon cancer screening in harder-to-screen persons; only 10 additional kits need to be sent to screen one more person. Results were published in the *International Journal of Cancer*.

"This research is at the cusp of policy," says Tinmouth. "It has the potential to have an impact in the very near future, because it's actually studying how we're delivering health care to Ontarians in the here and now."

But how are patients treated when prevention measures are too late and the cancer has spread?

Improving survival rates and quality of life for patients with inoperable colorectal cancer is a priority for Tinmouth and Dr. Scott Berry, a researcher at SRI and medical oncologist at Sunnybrook.

Since the late 1990s, many new chemotherapy and biologic agents have emerged to treat metastatic colorectal cancer. These new treatments have improved the median life expectancy for people whose colorectal cancer has spread from 12 months to about 29 months. With patients living longer, however, concerns have emerged about the side effects associated with extended exposure to chemotherapy and the impact on patients' quality of life.

Researchers have conducted trials looking at a "stop-and-go" approach to treatment to see whether patients can take "chemotherapy holidays" to improve their quality of life without negatively affecting survival. These trials have compared the outcome of patients receiving therapies continuously to those receiving breaks from treatment for three to four months, and then receiving treatment again.

Berry and his colleagues in CCO's gastrointestinal disease site group and program in evidence-based care did a meta-analysis of the randomized clinical trials in this arena. They identified 11 trials that looked at variations in the continuity of drugs given during chemotherapy. The meta-analysis included more than 3,800 patients. The researchers found there was no significant reduction in overall survival when patients took breaks from treatment. Intermittent chemotherapy, moreover, maintained or improved quality of life compared to continuous treatment. The results were published in the *Annals of Oncology* and used to craft an evidence-based guideline to provide direction for practitioners caring for patients with metastatic colorectal cancer.

"Based on the results of this meta-analysis, we can now reassure patients that if they want to take a break, it will help their quality of life and not have an impact on their overall survival," says Berry, noting patients often ask for time away from the hospital to enjoy a holiday down south or up north at the cottage. "Giving breaks from chemotherapy is a reasonable option that maintains the benefits of the therapy but reduces the toxicities."

Careful clinical assessment is important, however, as treatment breaks are not for everyone. For some patients with more aggressive disease it may not be suitable to take a complete break, notes Berry. Patients who are off treatment also require careful monitoring so physicians know when to reintroduce therapy.

Berry says the results are practice-affirming. Physicians who may have hesitated to give breaks are now able to have an informed discussion with their patients about treatment options based on the data.

"The goal of our work was to help inform practice in an area of clinical controversy using the power of meta-analysis to collect data from multiple trials and thousands of patients to answer a clinical question: Do treatment breaks have an impact on overall survival?" says Berry. "The answer is no."

Berry's research was supported by Cancer Care Ontario (CCO). Tinmouth's research was supported by CCO and the Ontario Institute for Cancer Research.

Oncologically Adept

Specialist care critical for women with vulvar cancer

By **Eleni Kanavas**

Drs. Lilian Gien (left) and **Lisa Barbera** are part of a collaborative team of specialists who treat women diagnosed with vulvar cancer, a rare gynecological disease.

Gynecologic and radiation oncologists at Sunnybrook's Odette Cancer Centre have conducted the largest Ontario population-based study evaluating patterns of care for women diagnosed with a rare gynecological disease.

Vulvar cancer is the growth of abnormal cells in the vulva, the skin tissue that forms the external female genitalia. It accounts for 5% of gynecological cancers and usually occurs in postmenopausal women.

Research has shown most women with vulvar cancer should undergo lymph node dissection in the groin, a surgical procedure to remove one or more of the oval-shaped glands that are part of the lymphatic system.

"We know lymph node status and the management of it is critical for patient outcome and overall survival," says Dr. Lilian Gien, a gynecologic oncologist-surgeon and clinician-scientist at Sunnybrook Research Institute (SRI). Preliminary work showed only 62% of patients in Ontario were getting a lymph node dissection upon presenting with invasive vulvar cancer, but it was impossible to determine from the limited information in the databases the reasons why groin node dissection (GND) was not done, she notes.

To understand this better, Gien and colleagues, in conjunction with the Institute for Clinical Evaluative Sciences, conducted a detailed clinical and pathologic review of 1,038 patients diagnosed with vulvar cancer over a 10-year period in Ontario.

"We found about 68% of patients got a node dissection and 32% did not," she says. Reasons why patients did not receive a GND included older age, obesity, presence of advanced disease, care by a nongynecologic oncologist-surgeon and referral to a centre not specializing in gynecologic cancer surgery.

Of these, they concluded that the most significant factor determining whether patients were more likely to have a GND was the presence of a gynecologic oncologist at the time of vulvar resection. Results were published in the journal *Gynecologic Oncology*.

Although there is a 90% survival rate for patients whose cancer has not spread to the lymph nodes of the groin, survival drops to 50% for patients whose cancers have metastasized.

In cases like these, surgery is required to remove the vulvar skin lesion and to determine the status of the lymph nodes. "It's important that gynecologic oncologists evaluate those patients along with radiation oncology at initial consultation," says Gien.

Dr. Lisa Barbera, a radiation oncologist and senior scientist at SRI, is co-principal investigator of the study. "The surgery helps us decide which patients need radiation; not every patient gets the combination. It depends what is found in the lymph nodes," she says. "The radiation treatment is a very important part of the whole management when there is cancer in the lymph nodes."

Moreover, Barbera notes, collaboration is important in treating vulvar cancer. "Sunnybrook has a very large gynecologic practice, and we have multidisciplinary teams for making decisions. I think the concern with provincial studies like this is that the care may not be the same everywhere," she says.

Barbera and Gien say they hope their research will address any knowledge gaps.

"When we're focused on gynecological cancers and the improvement in the quality of care, it's important to take a look at what's going on in our province right now, and where the potential deficiencies are and how to make that better," says Gien.

This research was funded by the Canadian Cancer Society Research Institute, the Gynecologic Disease Site at Odette Cancer Centre and the Ontario Institute for Cancer Research.

More gynecological research: Dr. Danielle Vicus is striving to extend survival in women with ovarian cancer: **sunnybrook.ca/research**.

Photo: **Nation Wong**

The Incredible Shrinking Lesions

Immunotherapy for melanoma works over the long term: study

By **Eleni Kanavas**

Melanoma is the most serious type of skin cancer that can spread to other organs. It develops in the cells, known as melanocytes, that produce melanin, the pigment that gives skin its colour. Melanocytes are found in the deepest part of the epidermis, the top layer of skin, and can reach the dermis, the layer underneath. From here, cancerous melanocytes can spread through the bloodstream and lymphatic vessels.

Although the number of cases is increasing each year, survival rates are high when melanoma is detected early. Surgery is the cornerstone of treatment.

"At the Odette Cancer Centre, we see about 20% of the province's surgical melanoma [cases]. It's a large program, the largest in Ontario by far," says Dr. Frances Wright, a surgeon and scientist at Sunnybrook Research Institute (SRI).

Wright works with Dr. Teresa Petrella, a medical oncologist. One of their areas of research is in-transit disease.

"About 3% to 10% of patients with melanoma over one millimetre in depth will develop these deposits of disease on their skin that's between the primary site and the nearest lymph nodal basin," says Wright. "If you had a melanoma on your ankle, then the nearest lymph node basin would be your groin." In-transit lesions would be deposits of melanoma between the ankle and the groin, Wright explains.

Therapies for these lesions include surgery, radiation, regional chemotherapy, and injection of immune-modulating agents and systemic therapies, drugs that treat the whole body to fight cancer cells.

The five-year survival rate for melanoma with in-transit disease is 50%; it plummets to 25% in those whose cancer has spread to the lymph nodes and have in-transit metastases.

Since 2009, Wright has been treating these patients using an agent called interleukin-2 (IL-2), which is injected into the lesions. This immunotherapy is used when surgery is no longer viable—that is, for patients who have many skin lesions or new lesions appearing weekly.

"It works well for patients, and for those that get a good response, it tends to last for a long time," says Petrella.

"We see about 20% of the province's surgical melanoma [cases]. It's the largest program in Ontario by far."

To understand better the long-term effects of IL-2 therapy, an unexplored area, Wright and Petrella co-authored a review of patients treated with IL-2 between 2009 and 2012 who had in-transit disease. Most were between 60 and 80 years of age with primary melanoma lesions from one millimetre to 20 mm deep.

Results suggested patients who had a good response to IL-2 had longer overall survival. "About one-third of all patients had a complete pathological response, meaning the IL-2 activated the immune system to get rid of the melanoma," says Wright. "About 80% of those one-third did well in the long-term and are likely to live longer and be disease-free." Patients were monitored for five years.

The study showed IL-2 decreases the size of the skin lesion or makes it disappear completely, says Petrella. Most side effects were minor, such as fever and chills.

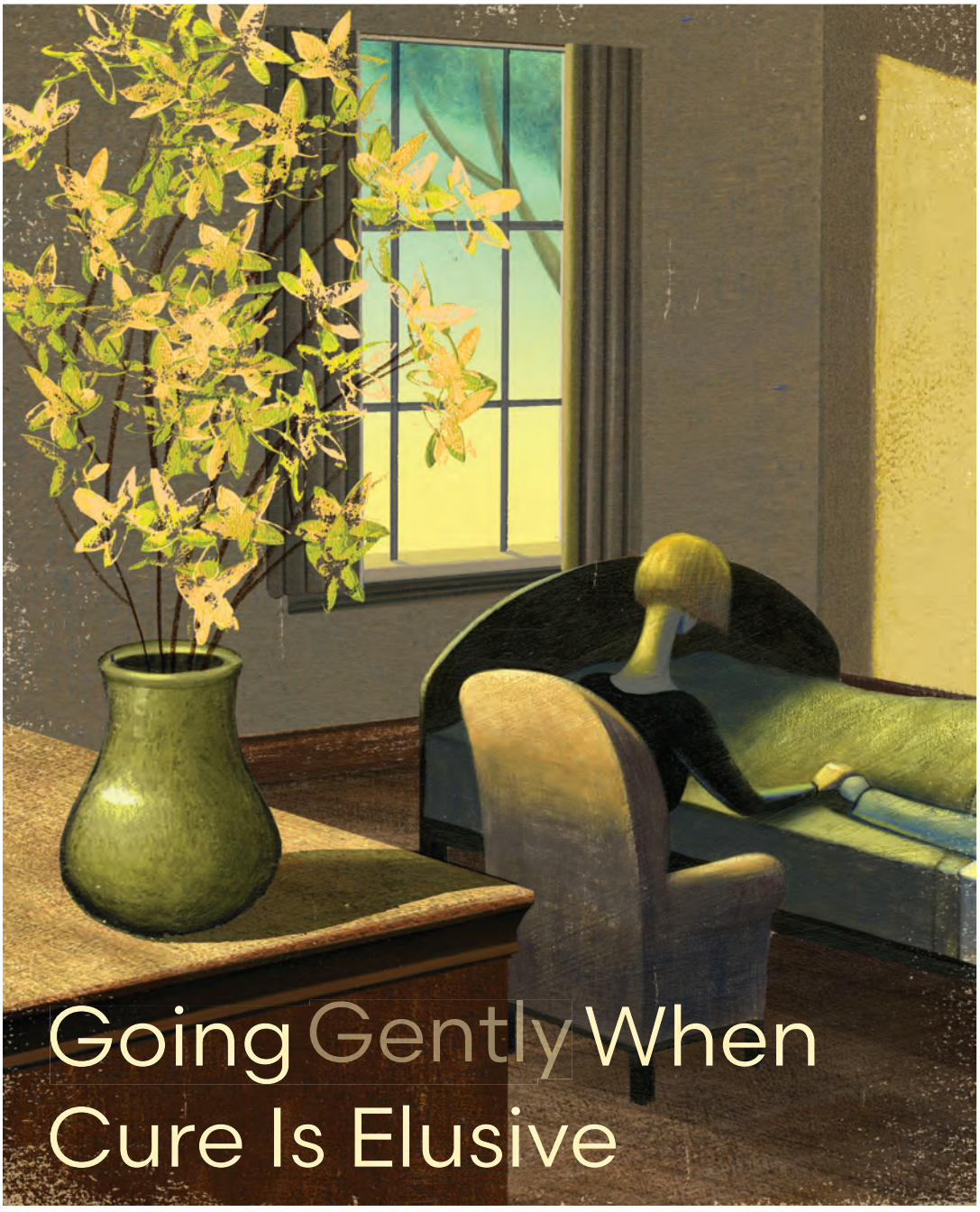
These results paved the way for Wright to solicit support for IL-2 therapy to be covered by provincial funding. They submitted a request to the pan-Canadian Oncology Drug Review that, if successful, means patients will not have to pay.

"Each injection costs $600 every two weeks. You need about six to eight injections depending on how well the treatment is going," says Petrella. "You can imagine by the end of the treatments, if you're paying each time, [especially] for someone on a fixed income, it can get really expensive."

Given the drug is already approved by Health Canada, Wright and Petrella say they are hopeful funding from the province will come through shortly.

Drs. Frances Wright (left) and **Teresa Petrella** led a study that found patients with melanoma unable to be treated surgically had longer overall survival when given immunotherapy.

Photo: **Nation Wong**



Going Gently When Cure Is Elusive

Death is beautiful when seen to be a law, and not an accident. It is as common as life
—*Henry David Thoreau*

By **Alisa Kim**

It would seem that as a society we are uneasy about death. In a 2013 survey by Harris/Decima of nearly 3,000 Canadians, more than one-half had never discussed end-of-life care preferences with a family member, doctor, lawyer, friend or financial advisor. Respondents attributed their reticence to fear of death, not wanting to upset family members, discomfort in talking about death and lack of knowledge about options.

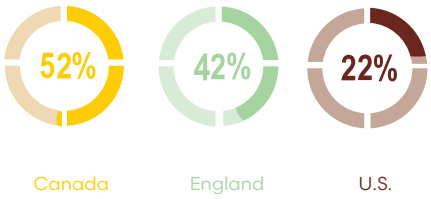
Furthermore, although most Canadians would prefer to die at home, more than 60% of all deaths in Canada occur in a hospital.

People who die in an acute care setting do not have adequate symptom control, communication with doctors and emotional support, notes Dr. Lisa Barbera, a senior scientist at Sunnybrook Research Institute (SRI) and radiation oncologist at Sunnybrook's Odette Cancer Centre. She says hospitalization when someone is dying focuses on acute medical problems, whereas palliative care treats the whole person, not just the illness.

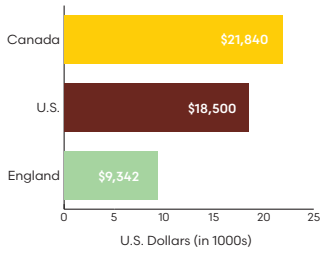
Palliative care, also known as supportive or comfort care, aims to improve quality of life by relieving pain and other symptoms. It can be given at any stage of illness to anyone with a life-threatening disease. The approach integrates psychological and spiritual care, and provides caregiver support.

Illustration: **Jon Krause**

Among seven developed countries, Canada has the highest proportion of people with cancer dying in hospital. *



Among these countries, Canada has the highest average hospital costs for a person with cancer in the last six months of life. *



Cost of treatment in Canada for a person with cancer in the final month of life. **

Aggressive treatment $18,131

Palliative care $12,678

* Bekelman et al. *JAMA*. 2016;315(3):272–83.
** Cheung et al. *Cancer*. 2015;121(18):3307–15.

Barbera says knowing which health services people receive before death can indicate whether they are receiving appropriate care. In a study published in *Current Oncology*, Barbera looked at health services used by people approaching death owing to cancer in British Columbia, Alberta, Ontario and Nova Scotia. These services included palliative care, home care, emergency department (ED) use, admission to the intensive care unit (ICU) and death in hospital.

Across all four provinces, 54% of patients died in hospital, and 46% received supportive care such as home care nursing and personal support worker visits. She also found that ED use ranged from 31% in Nova Scotia to 48% in Ontario.

"We're trying to understand what kinds of services cancer patients are receiving near the end of life to have an idea of where is there a problem, how big a problem and where there are opportunities for improvement," says Barbera. She notes the holistic nature of palliative care is important in dying because it addresses physical and emotional needs.

One of the challenges in accessing supportive care is fragmentation of services, says Barbera. "Some areas are well-resourced and others aren't. How do you make sure that the services are widely available, and that people are getting referred to them and making use of them?"

Part of the problem is not knowing how many palliative care doctors there are. Barbera notes most are family physicians. Using administrative data, she developed an algorithm to identify physicians in Ontario who provide this care. The method can be used to determine the number of palliative care doctors in Ontario, their distribution, how much work they are doing and the nature of their work. Policy-makers could then use this information to improve access to supportive services.

Misconceptions about the definition of palliative care are also a hindrance, as a study out of the University Health Network in Toronto suggests. People with cancer who were interviewed for the study equated the term with certain death, an impression they said was derived from their doctors and nurses.

Dr. Clare Atzema, a scientist at SRI and an emergency medicine physician at Sunnybrook, says she routinely sees people with terminal cancer waiting for hours in the ED, something she finds extremely regrettable.

Atzema says that these patients often come to the ED because their health is declining and their families don't know what else to do. Unfortunately, the problem is beyond her scope. "The ER's a great 'quick-fix' kind of place: you have pain, I'll give you pain medicine; nausea, I'll give you anti-nauseants. There is a lot that we do well, but something as big as a sense of poor well-being, that's hard to fix in the ER," she says.

In addition to enduring long wait times, people with cancer—whose immune systems are weak—are at risk of picking up an infectious disease in the ED. For these reasons, the ED is not the best option, says Atzema.

Increased uptake of palliative care, on the other hand, which provides pain relief and emotional support, would not only improve treatment, but also reduce costs. A study co-authored by SRI critical care researcher Dr. Robert Fowler shows that among seven developed countries, Canada has the highest average hospital expenses for a person with cancer in the last six months of life. Canada also has the highest proportion of people with cancer dying in hospital.

Dr. Matthew Cheung, a clinician-scientist at SRI, compared the cost of aggressive care with that of comfort care in the final month of life. Looking at records of people who died of cancer in Ontario between 2005 and 2009, Cheung found the cost of providing major medical interventions to dying patients was 43% higher than that of supportive care.

That finding was intuitive, he says. What surprised him was that early use of palliative care was associated with fewer life-prolonging measures such as admission to the ICU, ED visits and chemotherapy; and less expensive care in the final stages of illness. "If you invest in palliative care early on, it saves money down the road, but more importantly, it ends up refocusing the care to make patients more comfortable," says Cheung.

He says the research provides a rationale for investment in supportive care. When asked why he thinks people with cancer are receiving active treatment near death, Cheung says that communication around end of life between doctors and patients is challenging and needs improvement, an issue he wants the research to highlight. "Part of my hope with this paper is it identifies that need to have these conversations to make sure that patients who are dying are dying with comfort and dignity."

Barbera's research was supported by the Canadian Cancer Society Research Institute and the Canadian Centre for Applied Research in Cancer Control. Cheung's research was supported by the National Institutes of Health and the Ontario Institute for Cancer Research.

Taming a BEAST

Doctors are grappling with how to relieve acute pain while minimizing opioid use and averting descent into chronic pain

By Jasmine Budak
Photography by Nation Wong

In September 2015 Anita Shedletsky's lumpectomy revealed cancer cells in her left breast. Very quickly her surgeon, Dr. Frances Wright of Sunnybrook's Odette Cancer Centre, had Shedletsky, 67, back on the operating table to determine if the cancer had spread to nearby lymph nodes. The surgery was quick and the results encouraging; Shedletsky's sentinel nodes were cancer free. But soon after the procedure, Shedletsky developed swelling in her armpit. "It felt like I had half a tennis ball under my arm," she says. The pain was sharp and radiated into her breast and back. She couldn't sleep and feared picking up her grandkids or even a grocery bag. For the pain Wright prescribed gabapentin, an anticonvulsant drug that helps with some neuropathic pain. After 10 days, Shedletsky felt good enough to quit the drug. She'd had the model experience—immediate pain relief without the side effects. And, she didn't have to take opioids. "The idea of opioids does not thrill me," she says. "There's no way I wanted to go near them unless I really had to."

Opioids—Hydromorph Contin, morphine, fentanyl, codeine and the like—are a mainstay treatment for acute surgical pain and, controversially, for many chronic pain conditions. Long-term use can lead to dependence, severe addiction and even death. Although fatal overdoses via the illicit opioid market get most of the media attention, physical dependence and other harms resulting from well-intentioned treatment of chronic pain remain an insidious problem that the medical community is working to solve.

Dr. Bev Orser is concerned with the effects of opioid use, but wants to ensure her patients get the pain relief they need.

This year the Centers for Disease Control and Prevention (CDC) published a stark recommendation: prescribe opioids for chronic pain only for exceptional cases and in limited doses. It harkens back to a level of caution held some 30 years ago, when opioids were prescribed for either severe acute pain or cancer pain, generally at moderate doses. This caution began loosening in the 1990s, after a few scientifically weak but influential studies suggested opioids could be safely used to treat chronic pain, and the pharmaceutical industry heavily marketed "safer," slower releasing opioid products. Altogether, it was enough to sway the pain management field, which was undergoing a shift, moving to more assertive treatment of all types of pain. In this climate, opioids steadily became commonplace for most types of pain, whether the result of minor dental surgery, a knee replacement or a litany of chronic conditions.

Since 2008 opioid consumption in Canada has increased by 70%, and we now have the second highest rate of opioid prescriptions in the world. (The U.S. has the highest.) "It's easier to prescribe a drug than to not prescribe one," says Dr. David Juurlink, a Sunnybrook internist and scientist at Sunnybrook Research Institute (SRI). "In the context of pain, doctors were taught that prescribing opioids more liberally was the right thing to do."

Not only has prescription frequency skyrocketed, but doses have, too. A recent study led by Dr. Hannah Wunsch, a critical care doctor and senior scientist at SRI, analyzed some 14 million U.S.

pharmacy and medical claims of 18-to-64-year-olds who'd undergone various low-risk surgeries. (She used an American database that captures people younger than 65.) She found that about 80% of the patients filled an opioid prescription within one week of surgery, though Wunsch cautions that the data do not confirm whether the patients actually consumed the drugs. The study also found that the prescribed daily doses for those surgeries have jumped significantly in 10 years. "These surgical procedures [hernia repair, knee arthroscopy, carpal tunnel release] haven't changed much over the years—in fact, they're getting less and less invasive, so one shouldn't expect to see such an increase in dosing," Wunsch says.

Speculating on the reasons, she says, "it may be easier to ensure someone has more opioid from the outset rather than having patients come back to be reassessed for pain control." Of course, this practice can be counterproductive as patients become increasingly tolerant. "Sure, people will often tell you they feel better for a week or two," says Juurlink. "But over time, the effects of the drug attenuate and doses tend to creep up. Before you know it, patients are on high doses and that's when the harms can mount."

Research published in the last several years has looked not only at the harmful effects of sustained opioid use (deaths, addiction rates, car accidents), but also the efficacy of other types of pain medications, which could work together in smaller doses to lessen the need for opioids, particularly after surgery. Even acute pain from minor procedures can become chronic, potentially setting patients up for the vicious cycle of opioid therapies. Using this multimodal approach medical researchers are hoping to stem pain at the outset, with the broader goal of reining in a culture of lenient opioid-prescribing practices.

Dr. Hannah Wunsch found doses of opioids are getting stronger for low-risk surgeries.

One of these alternatives is gabapentin, which got Shedletsky through her persistent postsurgical pain. Along with a similar drug called pregabalin, gabapentin was first used to treat seizures; it was also found to do well with certain types of neuropathic pain. More recently, as wariness builds around opioid use, gabapentinoids have been increasingly prescribed to treat acute postsurgical neuropathic pain. Shedletsky's surgeon, Wright, has been prescribing gabapentin preoperatively along with Tylenol since the early 2000s. Wright specializes in breast cancer and melanoma. For certain procedures that carry the risk of chronic pain—mastectomies, groin or axillary lymph node dissections, an amputation for a melanoma—she'll prescribe gabapentin for one month after surgery. Wright has found gabapentin to be helpful. "The nurses in the recovery unit tell me that patients are using less opioids, and studies support these observations," she says, adding that gabapentinoids could play a role in preventing lingering pain. "If acute pain is controlled more aggressively immediately after surgery, patients may be less likely to develop chronic pain."

These drugs, however, are not a panacea. Gabapentinoids alone aren't sufficient to treat severe postsurgical pain. Dr. Beverley Orser, Sunnybrook anesthesiologist and researcher in SRI's Hurvitz Brain Sciences Research Program, has been studying gabapentinoids to understand how they work in the brain and spinal cord, and how they interact with other drugs. Gabapentinoids, she says, "have some narcotic-sparing effects postoperatively and may be helping prevent the transition from acute to chronic pain. But, these drugs can cause memory loss, intense fatigue and dizziness, so they have to be

tailored to the patient and the condition." For example, Orser's lab has been finding that gabapentinoids may increase the severity of sleep apnea when used with opioids. "As our population becomes larger and sleep apnea becomes more of a problem, combinations of classes of drugs must be used with caution," she says. "We're still learning how to optimize the use of gabapentinoids for perioperative care; it hasn't found its place yet in practice."

Orser's lab is also looking for new targets, to understand the receptors that are involved in pain pathways in an effort to develop new drugs. "We have many more modalities than were available in our mothers' time, but the challenge is to keep expanding that armamentarium, while optimizing the use of the drugs we have now."

Orser calls the multimodal approach "one of the most impactful changes I've seen in practice. There's awareness and investment in ensuring our patients are as comfortable as possible in the postop period, as safely as possible."

ANOTHER IMPORTANT TOOL has been celecoxib (Celebrex), a nonsteroidal anti-inflammatory drug (NSAID) in the same class as acetylsalicylic acid (Aspirin), ibuprofen (Advil) and naproxen (Aleve). Unlike Aspirin and Advil, however, Celebrex doesn't increase bleeding, which is crucial during surgery. It's most effective for inflammatory pain—from arthritis, broken bones or other musculoskeletal damage. Dr. Stephen Choi, a Sunnybrook anesthesiologist and researcher with SRI's Holland Musculoskeletal Research Program, was part of a team that analyzed the effects of administering celecoxib before non-cardiac surgery. "We found that it does decrease pain and opioid consumption somewhat," Choi says. "The takeaway is that it helps best in combination with other adjuncts, like pregabalin, to make a real difference in opioid use." In his practice, Choi takes a cautious approach to pain management, starting with Tylenol and NSAIDs, and supplementing as needed. "The majority of people are fine with Tylenol, NSAIDs and some opioids," he says. "But on their own, these alternative medications just do not provide enough pain relief for most people after major surgery."

Safely maximizing pain treatment while minimizing opioid consumption can be tricky business. Tinkering with drug combinations and doses must happen on a case-by-case basis in a way that balances side effects with patient expectations, needs and existing conditions. Recently Choi treated a former heroin addict who was undergoing major orthopaedic surgery. Although drug-free for three years, the patient was naturally terrified of being exposed to opioids that could awaken their addiction. Choi was sympathetic but realistic with his patient. "The likelihood of not using opioids for a surgery like this was nil," he says. "So we had a very aggressive tapering schedule, and I called the patient every day to check in." Along with opioids, Choi prescribed Tylenol, anti-inflammatories and pregabalin.

Before resorting to opioids, however, Choi was able to administer what's called a nerve block, in which a local anaesthetic is injected around the surgical site, effectively freezing the nerves so they're unable to transfer signals to the brain. Patients feel zero pain for 12 to 18 hours, but they also lose mobility in that region, which is problematic for recoveries involving physical therapy. For Choi's formerly addicted patient the nerve block was a worthwhile treatment; it delayed opioid use at least for a short time, and during the most painful time of recovery. As a researcher, Choi is looking for ways to extend nerve blocks. "We've put catheters in that can extend infusions for anywhere up to two to seven days," he says, noting that this method is most useful for upper extremity procedures—like shoulder surgery—after which patients are immobilized in a sling for several days. Long-term nerve blocks are less useful for knee or hip replacements that require intense physiotherapy.

Individually, nerve blocks, gabapentinoids and NSAIDs are nowhere near a glaring replacement for opioids; for most acute surgical pain, opioids are too effective. Researchers now have a better handle on the trajectory of acute pain, however, which could ultimately help curb opioid use in the long run. "There's been a real transition in the way we view pain," says Orser. "Not only are we striving to keep patients comfortable to the point that we have a dedicated team in the post-op period, but we recognize that it's important to prevent the transition to chronic pain."

Part of the solution has been the thoughtful deployment and combination of adjunct therapies, which, along with a growing caution around opioid use, signal a philosophical shift among the medical community and an acknowledgement of past wrongs. "There's been a gradual evolution of thought in the last several years," says Juurlink. "We have the benefit now of 20 years of hindsight to realize exactly how wrong we were about the safety and effectiveness of long-term opioid use."

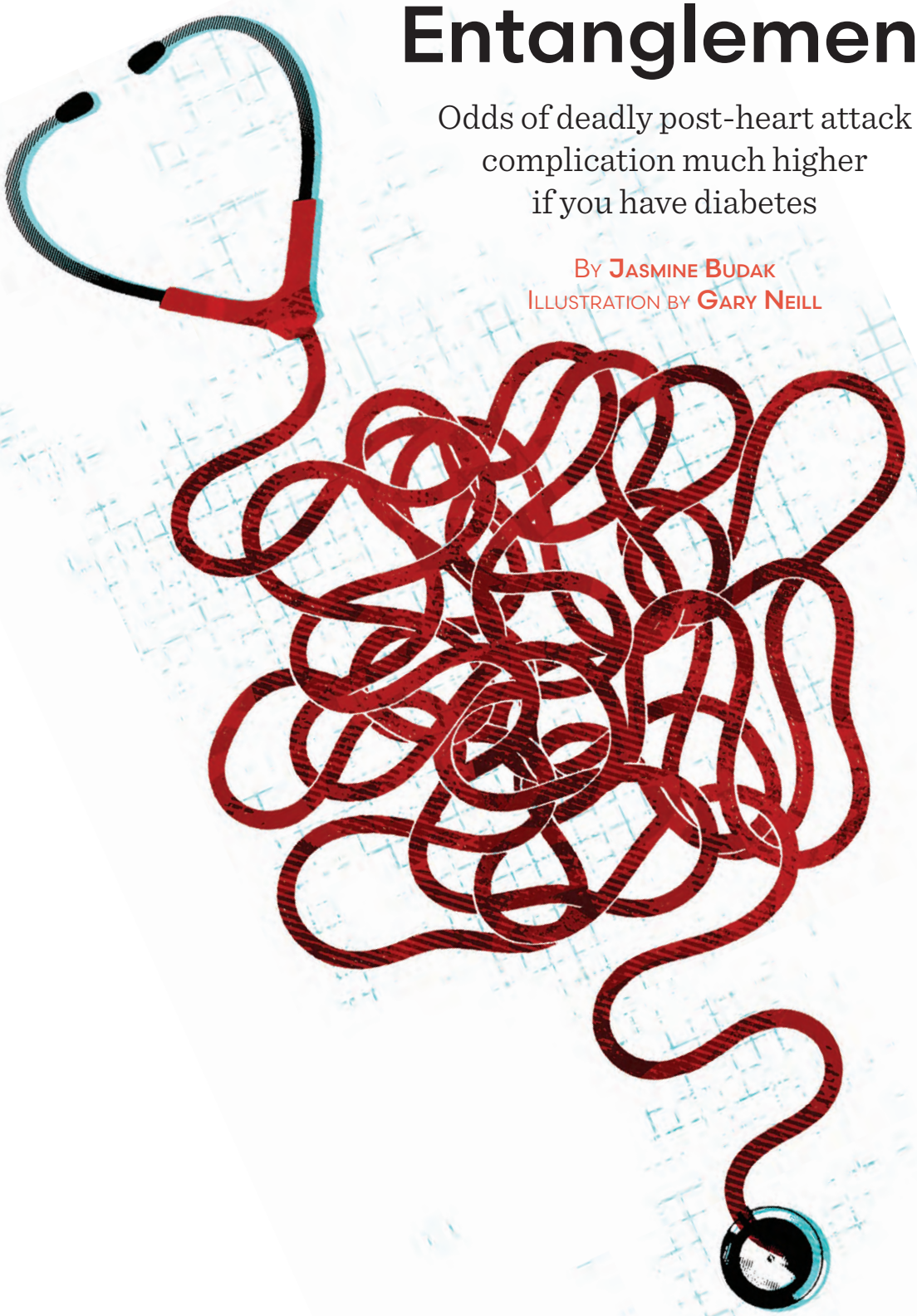
DR. STEPHEN CHOI takes a multimodal approach to pain relief, which he says is needed when it comes to major surgery.

Wunsch was funded by the (U.S.) NIH's Eunice Kennedy Shriver National Institute of Child Health and Development.

Fatal Entanglement

Odds of deadly post-heart attack complication much higher if you have diabetes

By Jasmine Budak
Illustration by Gary Neill



ACCORDING TO PROJECTIONS by the World Health Organization, diabetes will be the seventh leading cause of death by 2030, affecting some 350 million people. In Canada, one in 10 deaths are diabetes related, and 10% of the population has a diagnosis of Type 2 diabetes, with many more in the prediabetic phase. People with diabetes are prone to blindness, kidney damage and, most dangerously, heart disease—called the frequently forgotten but often fatal complication. Researchers know little about why cardiac outcomes are so grave among these patients, but a study led by Dr. Idan Roifman, a cardiologist and scientist at Sunnybrook Research Institute in the Schulich Heart Research Program, is forging a new path in the diabetes-cardiac connection.

Roifman and his team looked specifically at right ventricular dysfunction (RVD), an often deadly complication following a major heart attack. A cardiac MRI was performed on 106 patients who'd suffered a heart attack a few days earlier. Of those who were found to have RVD, the presence of diabetes was shown to be a strong independent predictor, conferring an approximate threefold greater odds. "None of the other major risk factors, like smoking or hypertension, predicted the development of RVD," says Roifman. "Only diabetes. So the question is, why?"

The answer, Roifman surmises, has to do with the microvasculature—the small blood vessel system—which is particularly vulnerable in diabetes. "Small vessel disease is a hallmark of diabetes," he says. And because the right ventricle is fed more heavily by micro vessels than the left ventricle, diabetic patients may be more prone to develop RVD after a heart attack. He adds, "Perhaps diabetic microvascular disease is also weakening some of the natural protective mechanisms of the right ventricle."

Though the underlying basis of the diabetes-RVD link will instigate future research, Roifman's study is the gateway to solving a major clinical problem. His was the first study to look at predictors for RVD as measured by cardiac MRI, which he calls a game-changer in the field. "In the past 10 years, the MRI technology has matured and allowed us to look at the right ventricle in a much more accurate and detailed manner. We've discovered that there's more RVD than we had initially thought." Comparably little is known about the right ventricle; historically, cardiac research has focussed on the left side, because it was easier to image and its disorders were thought to be more prevalent. A better understanding of RVD and at-risk patients will be crucial in informing screening and treatment strategies.

"Finding out the predictors of RVD is an important first step," Roifman says. "Because then we can predict which patients in the coronary care unit are at higher risk of developing this complication. In the long run, if microvascular disease is the culprit, we can try to develop novel therapeutics to target the problem."

"We've got a huge clinical problem," says Dr. Kim Connelly, a cardiologist and scientist at St. Michael's Hospital, and a senior author of the study. "And right now, we have no specific treatments for the right ventricle. If you're a diabetic and your right ventricle is falling apart, there are various blanket treatments we can give you, but nothing specific."

Connelly notes that there is a promising new Type 2 diabetes drug on the market (empagliflozin; trade name Jardiance), a SGLT2 inhibitor that in a large clinical trial was shown to reduce substantially heart failure hospitalizations and cardiac deaths. It's huge news in the field. Most diabetes drugs work to lower blood glucose levels—important for reducing blindness and kidney damage—but in isolation have no effect on the risk for cardiovascular disease. Connelly is enthusiastic about the new drug, but cautions that the mechanisms remain a mystery. "We don't know how this drug actually works," he says. "We don't know how it affects the microvasculature. And we need to know this so we can start to personalize treatments."

More research to elucidate the connection between diabetic microvascular dysfunction and cardiac events is already underway. Roifman's next study will look at how people with diabetes and microvascular disease fare after suffering a smaller, less severe heart attack. (These have been found to cause higher rates of death among diabetics compared with non-diabetics.) Roifman and his team will use cardiac MRI to study the microvasculature damage of participants and determine if it can be associated with heart attack death.

"A better understanding of the relationship between diabetes, microvascular disease and clinical outcomes will hopefully allow us to develop better treatment options," says Roifman. "Our hope is to eventually be able to improve both the quality and length of life of those patients suffering from diabetes."

Roifman is supported by an AstraZeneca Impact Challenge Grant in Cardiovascular Research, which is jointly provided by the Heart and Stroke/Richard Lewar Centre of Excellence in Cardiovascular Research, and the Banting and Best Diabetes Centre. Connelly is supported by a New Investigator Award from the Canadian Institutes of Health Research. Infrastructure support for Roifman was provided by the Canada Foundation for Innovation, and the Ontario Ministry of Research and Innovation.

"I limit myself to one glass of wine a day."

BUZZWORTHY

Direct brain stimulation paired with rehab helps stroke patients regain mobility

By Jasmine Budak
Photography by Nation Wong

THE PRACTICE OF stimulating brain cells with a mild electrical current has been around for centuries, but recently transcranial direct current stimulation (tDCS) has been undergoing a bit of a renaissance. Google "tDCS" and you'll find plenty of device manufacturers, DIY kits (a 9-volt battery and a couple of electrodes) and articles on the various benefits, from boosting math skills to treating tinnitus. Internet hype aside, the science is still catching up. Researchers are seeking to understand how or whether this kind of noninvasive stimulation can induce neuroplasticity—the brain's ability to change and adapt in response to injury and experience.

Dr. Joyce Chen, a scientist in the Hurvitz Brain Sciences Research Program at Sunnybrook Research Institute, has been studying the use of tDCS among stroke patients undergoing rehab to recover mobility. Though physical exercise alone can help reinvigorate neural pathways, Chen wondered, "what if you can stimulate the brain with tDCS during rehab exercises? Would that be akin to giving a double dose of therapy?"

In this small pilot study, Chen recruited five patients who'd suffered a stroke at least six months earlier, after which the brain's natural healing process would have tapered and any mobility improvements could be attributed to the tested therapies. The patients had moderate to severe mobility impairment, but to be eligible for the study they had to be able to muster a flicker of movement, says Chen. "We needed some neural cell activity to work with."

Over the course of two weeks, patients underwent 10 tDCS sessions of 20 minutes while doing their usual physical and occupational therapy exercises. The tDCS device is portable and compact: patients wore a battery pack and two electrode pads that were wrapped against their scalp—in this case, a few inches above each ear, covering the brain's motor-function regions. The electrical current, just 1.5

milliamps, causes a slight and fleeting tingling or itchy sensation. Brain cells can either be excited or inhibited, and Chen's study did both. A positive electrode worked to enhance cell activity in the stroke-affected cortex, while a negative electrode worked to hamper the unaffected, overactive side. (One theory is that the healthy, overactive region may be inhibiting the affected side.)

Improvement in mobility among the participants was dramatic, says Chen. Using statistical modelling, as well as subjective accounts, all patients showed significant improvements in their ability to engage with their arm or hand. Most notably, resting state functional MRI (fMRI) showed increased connectivity between two important areas of the brain involved in motor control. "The fact that the motor and premotor cortices are talking to each other may be the reason these patients improved," says Chen. "But at this point, we don't really know the mechanism behind this." Because the premotor cortex has been shown to play an important role in the recovery of movements after a stroke, Chen is encouraged by the fMRI results and what they could mean for future studies. "Maybe then this premotor region could be used as a target to refine the brain stimulation," she says. "What if we excite that particular region more? Would we see even more benefits?"

Chen's is the first stroke study to examine brain connectivity changes related to the combination of tDCS and another therapy. By understanding the brain's response to tDCS, Chen hopes to begin to elucidate its mechanism of action. "A lot of research, including ours, is showing that if you simultaneously couple the therapy—in our case rehab—with brain stimulation, it has an additive effect," she says.

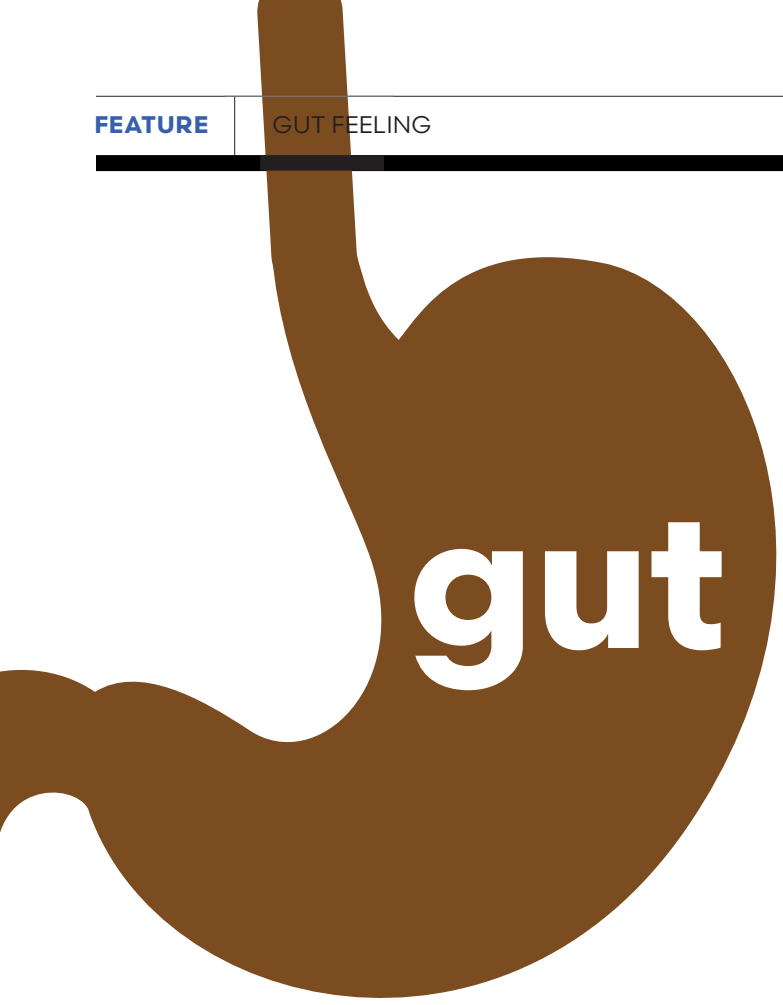
Participants in the study reported feeling effects of the therapies (better mobility) for at least one week. Because tDCS devices are compact, portable and simple to operate, Chen can foresee brain stimulation becoming a practical home-based therapy that patients could self-administer. "You can envision sending this home with the patient for regular booster sessions," she says. But these are early days, she adds. "There is debate in the field of brain stimulation. There's enough evidence showing effects if you couple tDCS with therapy, but results from meta-analyses of all the studies is equivocal—it works for some people, but not for everyone." Chen attributes this ambivalence to a lack of understanding for how parameters of brain stimulation (for example, duration, intensity, whether to enhance or inhibit cells) and individual differences affect overall response to this therapy. "Each study ends up doing something a little different, so there's a big push to standardize the protocols so that we can compare apples with apples."

Brain cells can either be excited or inhibited, and Chen's study did both.

In the meantime, Chen's stroke research continues with a new study that will test a personalized, targeted approach to tDCS therapy, reflecting different theories about the neural underpinnings of mobility repair. "Up until now, researchers have been applying a one-size-fits-all approach. However, different people may require different methods: for some people, we may enhance only the unaffected side of the brain; for others, excite the affected side," she says, clearly delighted by the myriad study prospects in the realm of stroke recovery alone. Beyond which, the very old and very low-tech practice of brain stimulation seems to offer unending fodder for research and potentially innovative therapies that could literally change the way we think.

Chen's research is supported by the National Institutes of Health, the Mary Crown and William Ellis Foundation, and the Rosalyn and Richard Slifka Family Foundation.

Dr. Joyce Chen works with a volunteer to place items during a transcranial direct current stimulation session.



gut feeling

Ultra-high-resolution imaging suggests bacteria produce a calming effect on the brain

By **Betty Zou**
Photography by **Nation Wong**

What weighs around three pounds and controls your behaviour?

The bacteria in your gut.

Surprised? You could be forgiven for thinking that the answer is your brain, but scientists are more and more recognizing the effects of gut bacteria on our thoughts and actions.

The human gut is home to a complex community of bacteria, known collectively as the gut microbiome. While researchers have known about the existence of these bacteria for a long time, they have only recently begun to understand the profound impact of these microbial dwellers on the body. The gut microbiome helps break down food into nutrients that would otherwise be inaccessible. It trains the immune system to recognize and defend against harmful pathogens. Now, a study by Dr. Greg Stanisz, a senior scientist at Sunnybrook Research Institute (SRI), has shown that the gut microbiome can alter brain chemistry to modify mood and behaviour. The preclinical study, published in the journal *NeuroImage*, is the first to use magnetic resonance spectroscopy (MRS) to measure changes in brain metabolites caused by gut bacteria.

In 2011, scientists at McMaster University in Canada and University College Cork in Ireland showed that mice fed a daily supplement of the bacterium Lactobacillus rhamnosus were less anxious and depressed than mice that did not receive the supplement. They had no way of looking into the brains of these mice, however, to see what was causing the changed behaviour. That's when a family dinner saved the day.

"We never actually talk science at all," says Stanisz about the relationship between he and his brother Andrew, a member of the McMaster group led by Dr. John Bienenstock who conducted the 2011 study. As it turned out, Stanisz' expertise in MRI was exactly what the McMaster group needed. "They knew that probably the right approach is to use MRI or spectroscopy. They had been looking for a year or two [for someone who could help them do it], but my brother didn't contact me. Finally during dinner we started talking, and here we are."

An offshoot of MRI, MRS is a noninvasive technique that allows scientists to see directly into the metabolic factories of tissues and organs. An MRI scan provides structural information like the number and density of blood vessels leading to an organ. On the other hand, MRS offers snapshots of the biochemistry within an organ. It allows scientists to measure how different metabolite levels shift as nutrients are broken down and converted into useable compounds and waste.

In this case, Stanisz wanted to use MRS to look for chemical changes in the brains of mice fed the Lactobacillus bacteria. "I was a little bit skeptical about the whole project," he says. "I had never done MRS in my entire life." When he presented his idea to the lab, his PhD student Rafal Janik jumped at the chance to take on the challenging project.

Janik started by recreating the experimental setup of the 2011 study. He used the same breed of mice and fed them the same dose of L. rhamnosus for the same period. At various times during and after the four-week treatment, he put the mice in an ultra-high-resolution MRI scanner to measure the

levels of different chemicals in their brains.

He found that concentrations of three chemicals—gamma amino butyric acid (GABA), glutamate and total N-acetyl aspartate (tNAA)—were higher in the brains of mice that received a bacterial supplement than those that did not receive it.

"The one we were most happy about was GABA, [because it is] the main inhibitory neurotransmitter in the brain and is implicated in the pathophysiology of depressive disorders," says Janik. The primary role of GABA is to quiet overexcited neurons, thereby producing a calming effect. Benzodiazepines, a commonly prescribed class of drugs that includes Valium and Xanax, decrease anxiety in patients by enhancing GABA's actions.

These results suggest that the alterations in neurotransmitters seen in animals with anxiety or depression are related to changes in their gut bacteria, says Stanisz, who is also a professor of medical biophysics at the University of Toronto. If that is true, then it might be possible to restore neurotransmitter levels and therefore normal behaviour by adding certain bacteria to their diet, he adds.

Stanisz and Janik's study contribute to a growing body of work on the so-called microbiome-gut-brain axis, a bidirectional communication pathway linking the gut and brain. Specifically, it adds to research that seeks to understand why people with stress-related psychiatric disorders like anxiety and depression are far more likely to suffer from gastrointestinal ailments than are their healthy peers. Disorders like irritable bowel syndrome and inflammatory bowel disease often arise when the microbial community within the gut is thrown off balance by changes in diet, antibiotic exposure or stress. Based on these observations, groups like the one at McMaster University are now exploring the possibility that a disturbed gut microbiome may be contributing to an individual's off-kilter state of mind.

Laboratory studies are increasingly pointing to a definitive link between the gut microbiome, mood and behaviour. In one experiment, scientists showed that feeding a normally calm mouse gut bacteria from a more high-strung mouse causes the calm mouse to exhibit more anxiety-like behaviours and vice versa. Studies of germ-free mice—those born and raised in completely sterile environments—found they were less anxious than mice whose guts were colonized by the normal spectrum of bacterial species.

Stanisz and Janik are now exploring the possibility of using MRS to find other bacteria that produce a calming effect on the brain. The metabolites they identified—GABA, glutamate and tNAA—will serve as biomarkers, helping them to predict which bacteria can reduce anxiety and depression. They will test different bacteria by first feeding them to mice. Then, instead of doing behavioural tests to measure anxiety and depression, they will put the mice in an MRI scanner to look for changes in neurotransmitter levels. This strategy is a faster and more objective way to test many different bacterial species. Promising candidates will then undergo behavioural tests to confirm whether the mice are less anxious and depressed.

"There are probably more bacteria that have a similar effect," says Stanisz. "[L. rhamnosus] was a good start."

Stanisz' research is funded by the U.S. Office for Naval Research. Janik's research is supported by a Frederick Banting and Charles Best Canada Graduate Scholarship from the Canadian Institutes of Health Research. Infrastructure support comes from the Canada Foundation for Innovation.

Dr. Greg Stanisz (right) and his PhD student **Rafal Janik** work on a 7 Tesla magnetic resonance scanner. The researchers used this ultra-high-resolution imaging device to measure biochemical changes in the brains of mice fed bacterial supplements.

Data dig unearths unexpected findings

By **Betty Zou**

SHORTLY AFTER HE was elected, Prime Minister Justin Trudeau gave a speech in London, U.K. on Canada's response to the Syrian refugee crisis. He spoke behind a podium bearing the sign "Diversity is Canada's strength." With one of the highest per capita immigration rates among wealthy countries, Canada is a diverse nation, with roughly 250,000 immigrants arriving each year. Yet we know surprisingly little about the health of these immigrants after they settle in.

For Dr. Jack Tu, the desire to learn more about how settlers fare in their new country comes from his own story. He and his parents left Taiwan and moved to Canada when he was one year old. "As an immigrant myself, I've always been interested in cardiovascular health in different immigrant groups," he says. "Historically, there's relatively little data on this topic."

Tu is a cardiologist and senior scientist at Sunnybrook Research Institute (SRI). He leads the Cardiovascular Health in Ambulatory Care Research Team (CANHEART) at the Institute for Clinical Evaluative Sciences (ICES). He was the first author of the CANHEART Immigration Study, which looked at the incidence of major cardiovascular events like heart attack or stroke in immigrants to Ontario. A research agreement between Citizenship and Immigration Canada and ICES gave him access to the government's permanent resident database. By linking those data to the health databases at ICES, Tu and his team could look for differences between immigrant and non-immigrant populations.

What they discovered was surprising. "Most studies in Europe show immigrants there do worse than people born in Europe, but we found the opposite with immigrants here," says Tu. Major cardiovascular events occurred 30% less often in newcomers than in long-term residents. This so-called "healthy immigrant" effect is partly explained by a lower cardiac risk factor score for newcomers, which takes into account things like diabetes, hypertension, cholesterol level and smoking.

Within the immigrant population, the researchers found startling differences between ethnic groups. For example, the incidence of major cardiovascular events was nearly four times higher in South Asian immigrants—those from Pakistan, India and Sri Lanka—than in East Asian immigrants from China and Korea, who had the lowest overall incidence. Tu puts his results into perspective. "If you're a smoker or diabetic, or [have] high blood pressure, that doubles your risk," he says. "If you're a South Asian compared to an East Asian, that quadruples your risk." For some immigrant groups, where you come from puts you at greater risk for heart problems than smoking or being obese.

As for why immigrants to Canada seem to be healthier than their European counterparts, Tu says there are two main reasons. The first is Canada's rigorous screening process, which includes extensive health requirements. This means that newcomers to Canada are likely healthier at the outset than those in Europe, whose porous borders allow easier entry and movement of people from one country to another. The second reason is Canada's universal health care system, which ensures that all residents have access to preventive care.

"For the first time, we know the incidence of [cardiovascular] events for the different groups in Canada," says Tu. Using this knowledge, he and his team are building better prediction models that incorporate ethnicity to assess cardiac risk. The currently used Framingham risk score was developed based on a predominantly Caucasian population, which is "potentially misleading for people from other ethnic groups," he says.

While the CANHEART Immigration Study found that newcomers had better heart health and were less likely to have a heart attack or stroke, it did not provide insight into how well they do after suffering a major health setback. Specifically, how did their survival rates compare to those of long-term residents?

That's the question that prompted Drs. Matthew Cheung and Simron Singh to study the impact of immigration status on cancer outcomes. Using the same databases as Tu, they looked

Illustration: **Betty Zou**

at mortality rates in immigrant and non-immigrant populations between 2000 and 2012 in Ontario. Their analysis controlled for factors that might influence cancer mortality, like age, type of cancer and stage at diagnosis. "We found that there was a considerable reduction in mortality in individuals who had immigrated to Canada," says Cheung, who is an associate scientist at SRI and a blood specialist at Sunnybrook's Odette Cancer Centre. Recent settlers—those arriving within the last 10 years—were 14% less likely to die from cancer than non-immigrants. For immigrants who had been in the country for 11 to 25 years, their odds of dying from cancer were 9% lower than non-immigrants. "They seem to have some sort of advantage in terms of both cancer-related survival as well as overall survival," he says.

"We weren't expecting to find this 'healthy immigrant' effect in cancer," agrees Singh, a medical oncologist and affiliate scientist at SRI and ICES. "We were very worried when we did this study that we would find results that show immigrants did worse." The researchers feared that unfamiliarity with the health care system would hinder newcomers from accessing the care they needed. "We were, in a way, pleasantly surprised that Canada's public health care system works. It works for people who are new to the country. It works for people regardless of socioeconomic status and colour of their skin."

For some immigrant groups, where you come from puts you at greater risk for heart problems than smoking or being obese.

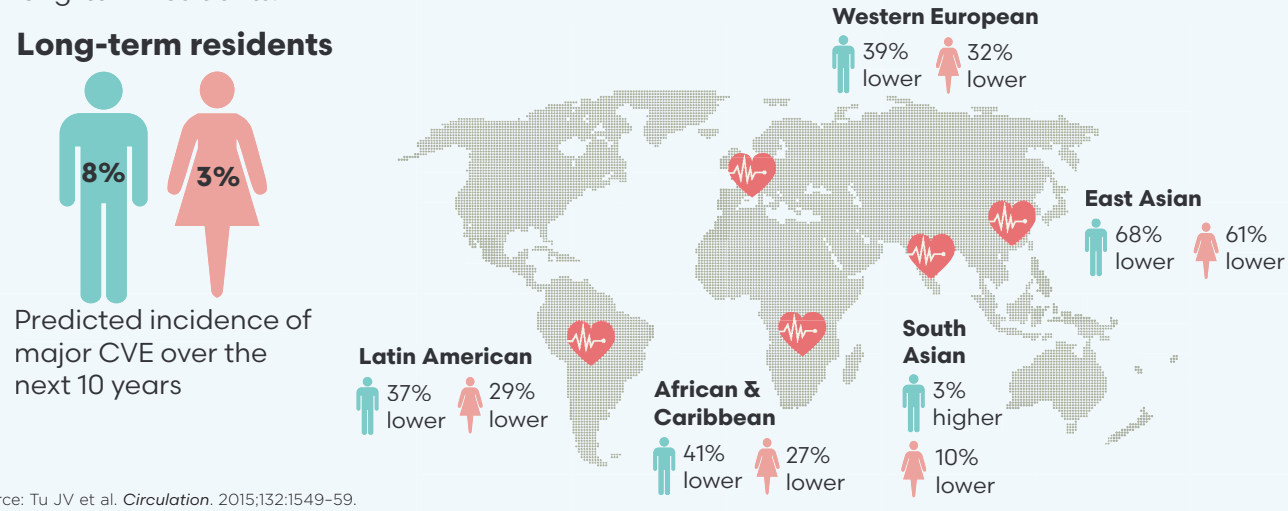
The researchers also found that immigrants' survival advantage decreased with time, possibly owing to lifestyle changes in their new home. The longer they stayed in Canada, the closer their survival rates were to the non-immigrant population. As the next step, Cheung and Singh are taking a closer look at specific cancers and how survival rates differ between the two groups. They are also trying to identify factors that contribute to the healthy immigrant effect in hopes of using those traits to help all cancer patients better their odds.

As the researchers note, this study was the first to find a consistent link between immigration status and reduced cancer-specific mortality. It contrasts with American studies, which showed that immigrants to the U.S. typically do worse than U.S.-born people. The researchers note that Canada's public health care system is likely responsible for the improved outcomes seen in our immigrant population. "I want people to have confidence in the Canadian health care system," says Singh. "[This was] a study on the cancer system, and the system gets a passing grade from us."

Cheung and Singh's research is funded by the Canadian Cancer Society, and Ontario Ministry of Health and Long-Term Care. Tu's research is funded by the Canadian Institutes of Health Research, Heart and Stroke Foundation of Canada, and Public Health Agency of Canada.

The Healthy Immigrant Effect

Immigrants are less likely than long-term residents to have a major cardiovascular event (CVE) like heart attack or stroke. Here, a closer look at the risks of different ethnic groups compared to long-term residents.



Source: Tu JV et al. *Circulation*. 2015;132:1549–59.

All for One

Portrait of a lab family

BEHIND EVERY SUCCESSFUL scientist is a family; not just husbands and wives, or parents and siblings, but a lab family. When it comes to scientific training and research, this second family can turn a good experience into an unforgettable one.

The path to becoming a scientist can be difficult and lonely: hours spent in a dark room looking down a microscope; late nights in the lab processing samples; weeks holed up writing a manuscript or thesis. Your lab family understands you in ways that, try as they might, your parents and partners just can't—failed experiments, the whims and idiosyncrasies of your supervisor, the stress of distilling three years' worth of work into 250 words. It's not easy, but with the right lab family it can be fun and rewarding.

When Myuri Ruthirakuhan applied to be a research assistant in Dr. Krista Lanctôt's lab three years ago she felt intimidated by the big group of students and researchers she met. In particular, she remembers the two women who sat on opposite sides of her during the meeting. "They were asking me the more difficult questions," she says. Fast-forward to today: Ruthirakuhan is now a first-year PhD student supervised by Lanctôt, a senior scientist in the Hurvitz Brain Sciences Research Program at Sunnybrook Research Institute (SRI). That intimidating group of people has become her second family, and those two women—PhD students Mahwesh Saleem and Sarah Chau—are like sisters to her now.

The lab family of Ruthirakuhan, Saleem and Chau is made up of fellow graduate students and research assistants in the Neuropsychopharmacology Research Group at SRI. The group is led by Lanctôt and Dr. Nathan Herrmann, who is head of geriatric psychiatry at Sunnybrook and an associate scientist at SRI. Among labs, theirs is particularly close. This intimacy is partly born of physical proximity. Thirteen people work side-by-side in two small rooms under the watchful eyes of a colossal stuffed monkey, a souvenir from a previous lab outing.

The group studies how best to manage the neuropsychiatric symptoms commonly associated with central nervous system disorders such as cerebrovascular disease, dementia and stroke. Their goal is to identify the best drug- and behaviour-based interventions to treat the mood and cognitive changes that accompany these illnesses. At any given time, the researchers are recruiting patients for clinical trials to test the effectiveness of different therapies in alleviating symptoms.

"We are a tight-knit group," says Saleem. "We stick together and we help each other out." As the most senior students in the lab, Saleem and Chau frequently provide guidance and support to the younger students. They read grant and scholarship applications, and act as a sounding board for new ideas. "I ask them a lot for advice," says Ruthirakuhan. "I benefit a lot from having them in the lab." The benefits are mutual. When Saleem is late for a meeting with a patient, she often asks Ruthirakuhan to sit and chat with her patient while they wait.

A spirit of collaboration is instilled

Illustration: **Betty Zou**

early into new recruits to the lab. "I remember Mahwesh saying to me during my interview that you need to know how to balance working independently as well as collaborating," says Chau. "If there's a deadline, nobody is slacking." By pulling together and working as a team, tasks are accomplished faster. The key to successful collaborations and enhanced productivity is the camaraderie within the lab, notes Chau. "It's important to like the people that you work with," she says. "That adds a layer of trust which will translate into your work." Saleem agrees. "I also think it creates an environment where you can be more creative as well," she says. "We come up with new ideas in terms of how to solve problems related to our projects or what's the next step." Members of the lab are comfortable sharing and talking about ideas openly. These fruitful discussions often lead to a clearer understanding of what's going on and better solutions to the problem at hand.

But how do you build a trusting environment? One way is to take your team treetop trekking. The activity, which forces groups to work together to complete an obstacle course high among the tree canopy, was Saleem's favourite outing with the lab. "It was challenging," she says. "We had to support and help each other so you don't fall off the tree." With the encouragement of their friends, group members overcame their fear of heights and finished the adventure course. In addition to going treetop trekking, lab members take turns organizing social events like barbeques, dinners and ski trips. These field trips help everyone to let loose and get to know each other outside of work. Over time, colleagues become friends and then, family. Together they celebrate personal milestones like birthdays and engagements, and academic achievements like getting a paper published and graduation. When the times get tough, they are there for each other. "Someone is always there to just sit there and listen to you when you need it," says Saleem. "People are good listeners in the lab, which is great because once you get it off your chest, you feel so much better."

All three women credit their supervisor, Lanctôt, and Herrmann, who serves as their advisor, for creating an inclusive and friendly environment. For her part, Lanctôt says it's all about "hiring the right people, promoting team work rather than competition and having exceptionally good luck. I really have the honour of working with the best, the brightest and the nicest. We put so much time and heart into our research that the importance of a close group cannot be overstated. A supportive environment is not only the foundation of lab productivity, but it is also an important life lesson."

It's a lesson that Saleem and Chau will take with them as they prepare to graduate later this year. "We have a trusting relationship," says Chau. "That's something I hope to find

Lab mates **Myuri Ruthirakuhan** (left), **Mahwesh Saleem** (centre) and **Sarah Chau** (right) take a break from their work to unwind with some YouTube videos. All three are PhD students in the lab of **Dr. Krista Lanctôt**.

wherever I go." Their departure will leave a hole in their lab. "We're losing two fantastic mentors," says Ruthirakuhan. "It'll take some adjusting to get used to that." Saleem pipes up: "But then you can be the mentor." And with that, a new family will evolve and come together as families do.

BETTY ZOU

Lanctôt's lab is supported by the Alzheimer's Drug Discovery Foundation, Alzheimer Society of Canada, Canadian Institutes of Health Research (CIHR), Heart and Stroke Foundation, National Institutes of Health, and Ontario Ministry of Health and Long-Term Care. Chau is supported by a Glaxo/Sunnybrook Drug Safety Award. Ruthirakuhan is supported by a CIHR Doctoral Research Award. Saleem is supported by a scholarship from the Alzheimer Society of Canada.

"Since we switched from discovering new lifesaving antibiotics to discovering new daiquiri drinks, our funding has tripled."

Photo: **Nation Wong**

Tell us about your lab family

Andrea Datu
Research technician
Jeschke lab

"We fight sometimes over trivial things. We get on each other's nerves just like brothers and sisters but in the end, we all have a common goal—research—and we work it out.

I really like when we're poking fun at each other. We're close enough to do that to each other without any feelings getting hurt."

Catherine Schrankel
PhD student
Rast lab

"We see each other every day. Just going through the really high highs and the really low lows of research and publishing really forms a tight-knit group.

We cook together sometimes. Every once in a while, we'll have a lab cookout. We'll go to someone's house, listen to music, pick a good recipe and just hang out."

"My favorite moments come from our annual lab beach days when we all drive up to Wasaga together, have a barbeque, swim, and play bocce ball or volleyball. This really brings the lab family together.

I won't forget the time I beat [my supervisor] Jean [Gariépy] at a virtual boxing match on Nintendo Wii for the championship title during our makeshift Christmas potluck in a conference room at Sunnybrook."

Nick Fischer
PhD student
Gariépy lab

"It's like a second home. We had to learn how to live with each other. Everyone is different; everyone has different personalities. It takes a while to work it out, but then it's OK.

Even though everyone has their own project, we're always interacting with each other. Help comes from every side. It speeds up our work a lot. It's no longer, 'I'm working on it for my own benefit.'

We have each other's backs."

Dr. Marzena Cydzik
Research associate
Gariépy lab

Photos: **Alisa Kim, Curtis Lantinga, Nation Wong, Betty Zou**

"Talk about tough days: Your results didn't pan out. You didn't get the grant. What do you do to decompress after days like this?"

EDITED BY STEPHANIE ROBERTS

DAVID ANDREWS

WHEN I REALLY need to de-stress and the opportunity arises, live music is my destination of choice. Most recently it was Stick Men live at the Mod Club; before that, King Crimson—I am in the audience in the pictures King Crimson bassist Tony Levin took from the stage on November 19 and 21, 2015, their first appearances in Toronto since 2003.*

If recorded music is the agenda, then I have a choice of about 1500 CDs, 1000 vinyl LPs [aka records] and about 100 live shows that I have recorded over the years. Right now I am ripping all the CDs and recordings of live shows onto a server, and have wired the house for sound so that I can control the music in every room with my phone. But it's when I head for my 'fancy' stereo in the basement that it can get pretty loud—and is ultimately most cathartic.

Andrews, director of Biological Sciences at Sunnybrook Research Institute (SRI), recently was awarded close to $2.7 million over seven years in the first Canadian Institutes of Health Research (CIHR) Foundation Scheme competition. Of the 1,375 applications CIHR received, 150 were successful. Andrews is studying the assembly of apoptotic and protein complexes on subcellular membranes.

*See photos online: **sunnybrook.ca/research**

JEAN GARIÉPY

ANTICIPATING RESULTS FOR grant competitions or manuscript submissions represent a constant source of stress that is in part linked to the ever-changing mood of academic research. This 'intangible' issue has been more recently accentuated by a major shift in the way research is being evaluated and funded in Canada. For instance, projects are now being ranked by CIHR reviewers who typically lack the overall level of expertise of past expert panels.

One coping mechanism is to ensure that your research program remains exciting, since new concepts and ideas are what attract new recruits and, to some extent, are what appeal to panel members that are less familiar with our research areas. Finding talented, dedicated scientists is probably the single most important task that I need to focus on. It dictates the overall success of the laboratory, makes for a great working environment and reduces my stress level.

Gariépy is a senior scientist in Physical Sciences at SRI. He is midway through a five-year CIHR grant of close to $600,000 for his work in designing novel anti-inflammatory agents. He is generating synthetic, targeted biomolecules to block or dampen uncontrolled immune responses.

THÉRÈSE STUKEL

THIS IS AN interesting question since it's what I coach my graduate students and junior faculty on. My first major research setback was as a PhD student when I spent four months proving a theorem that turned out to be wrong, because the second line of the proof was wrong! It took me four months to recover confidence, so I lost eight months' worth of time.

After a setback, I wake up the next morning and just get back to work. I now anticipate that there will be regular setbacks so these have become part of the ebb and flow of doing research. In fact, they often spur me on to greater heights, to ideas I hadn't originally thought of. Research is a destination, but its pursuit is a journey all of whose disparate aspects must be embraced in order to be a good scientist.

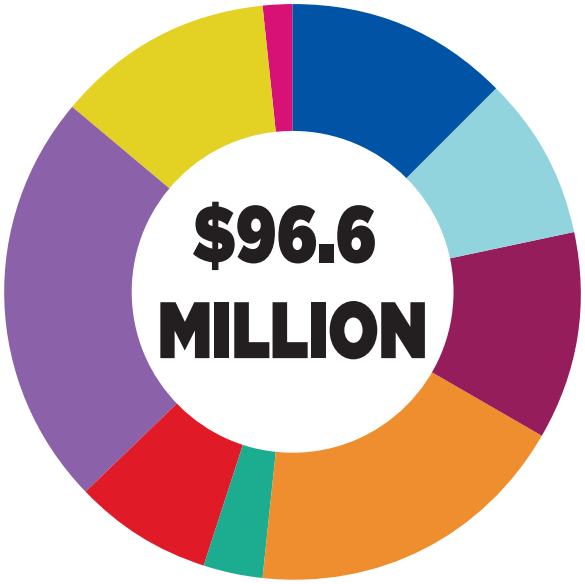
Stukel is a scientist in Evaluative Clinical Sciences at SRI. She was awarded more than $1.8 million over seven years through the same CIHR Foundation Scheme pilot as Andrews. She is measuring and evaluating the performance of integrated health systems for patients with complex chronic disease.

Photos: (Left) **Curtis Lantinga** / (Centre) **Nation Wong** / (Right) **Doug Nicholson**

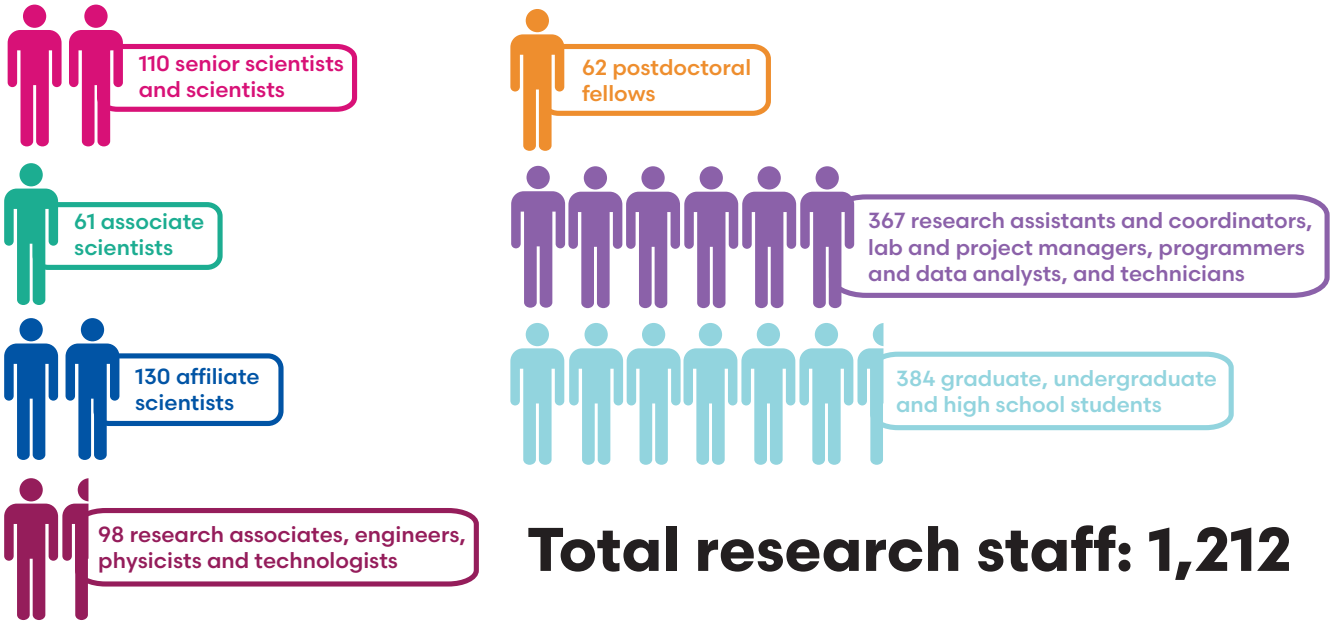
Quick Statistics

Each dollar we receive is invested in high-impact discovery and innovation

MAJOR SOURCES OF FUNDING 2014–2015



Sources	$(M)	%
Canada Foundation for Innovation	12.2	12.7
Contracts With Other Private/Public Organizations	8.9	9.2
Industry	11.2	11.6
Internal Funding	17.7	18.3
Ontario Ministry of Research and Innovation	3.2	3.3
Other Government Sources Within Canada	7.5	7.8
Private Sector Funding From Philanthropic Organizations	22.6	23.4
Tricouncil Funding: CIHR, NSERC and SSHRC; also includes Canada Research Chairs Program	11.9	12.3
U.S. Government	1.4	1.4
Total	**96.6**	**100**



Total research staff: 1,212

Q&A

DR. MEAGHAN O'REILLY is a recently appointed scientist in the Physical Sciences platform and the Holland Musculoskeletal Research Program at Sunnybrook Research Institute (SRI). She is also an assistant professor in the department of medical biophysics at the University of Toronto. She spoke with Alisa Kim about her research.

What excites you most about therapeutic ultrasound?

If we're creative about it, we can focus ultrasound deep into the body, which we can't do with most other wave energy. For example, you can have an ultrasound ablation or a radiofrequency (RF) ablation. In RF ablation, you have to insert an electrode somewhere to deliver the energy, but with the ultrasound ablation [which uses sound waves], we can apply it outside the body and direct it. If you look at trials where they're doing ablation of these very small structures in the brain, instead of having to open the skull, treatment can be delivered through an intact skull so patients can go home the same or next day.

Why is it challenging to treat cancers of the central nervous system?

Right now, drug therapies don't work well, if at all. Radiation in the spine is limited because dose limits are hit fairly quickly. Also, in the brain and spinal cord, we have the barriers of the central nervous system that prevent drugs from getting out of the vasculature and into the tissue.

How are you using focused ultrasound in the spine?

One of the studies I'm working on with [SRI scientist] Dr. Arjun Sahgal is to treat leptomeningeal (lep-TOE-men-IN-gee-al) tumours. This is late-stage, metastatic disease where tumour cells get into the cerebrospinal fluid and circulate in the fluid around the linings of the brain and spinal cord. They deposit on these linings and form long coatings of tumour. They're thin, but large-surface-area tumours that compress the spinal cord and brain, so patients develop neurological complications very quickly and survival is short.

FACTS ABOUT LEPTOMENINGEAL (LEP-TOE-MEN-IN-GEE-AL) CANCER

- It occurs in the cerebrospinal fluid and the membranes covering the brain and spinal cord.
- It usually arises from cancers of the breast, lung and gastrointestinal tract; and leukemia, lymphoma and melanoma.
- It occurs in 5% of people with cancer.
- Symptoms include seizures, pain, difficulty thinking and headaches.
- Median survival is two to three months.

There's no good treatment. We've been looking at whether we can use ultrasound to enhance drug delivery to these tumours.

Why is focused ultrasound a promising way to treat cancer that has spread to the spine?

It's noninvasive and nonionizing, which is important because that's the limitation with radiation. One way to get drugs in is by direct injection. That can work for local tumours, but when you're talking about something that can stretch for lengths of the spinal cord, you can't imagine injecting at all these sites. Because focused ultrasound is nonionizing and noninvasive, we would be able to repeat treatments. Our preliminary preclinical work suggests there's no issue with repeat treatments. If there's a recurrence, patients could come back and have it treated again. It's also the only technology that allows us to facilitate drug delivery without scarring the tissue from an injection site or other invasive procedure.

What do you look forward to in developing your research program at SRI?

I look forward to getting to know what the clinical research interests are. I've aligned with one of the programs [Holland Musculoskeletal], but my research is in image-guided therapy, so that can be applied to cancer, musculoskeletal or brain. What I'm interested in, from an engineering and physics perspective, is how can we tailor these technologies for hard-to-treat conditions and hard-to-reach places?

O'Reilly's research is funded by the Natural Sciences and Engineering Research Council of Canada. For more on her research, visit **sunnybrook.ca/research**.

Illustration: **Antony Hare**

Through the Wormhole

Journey into a different time in medical science

Illustration: **Ernest Board (public domain) via Wikimedia Commons**

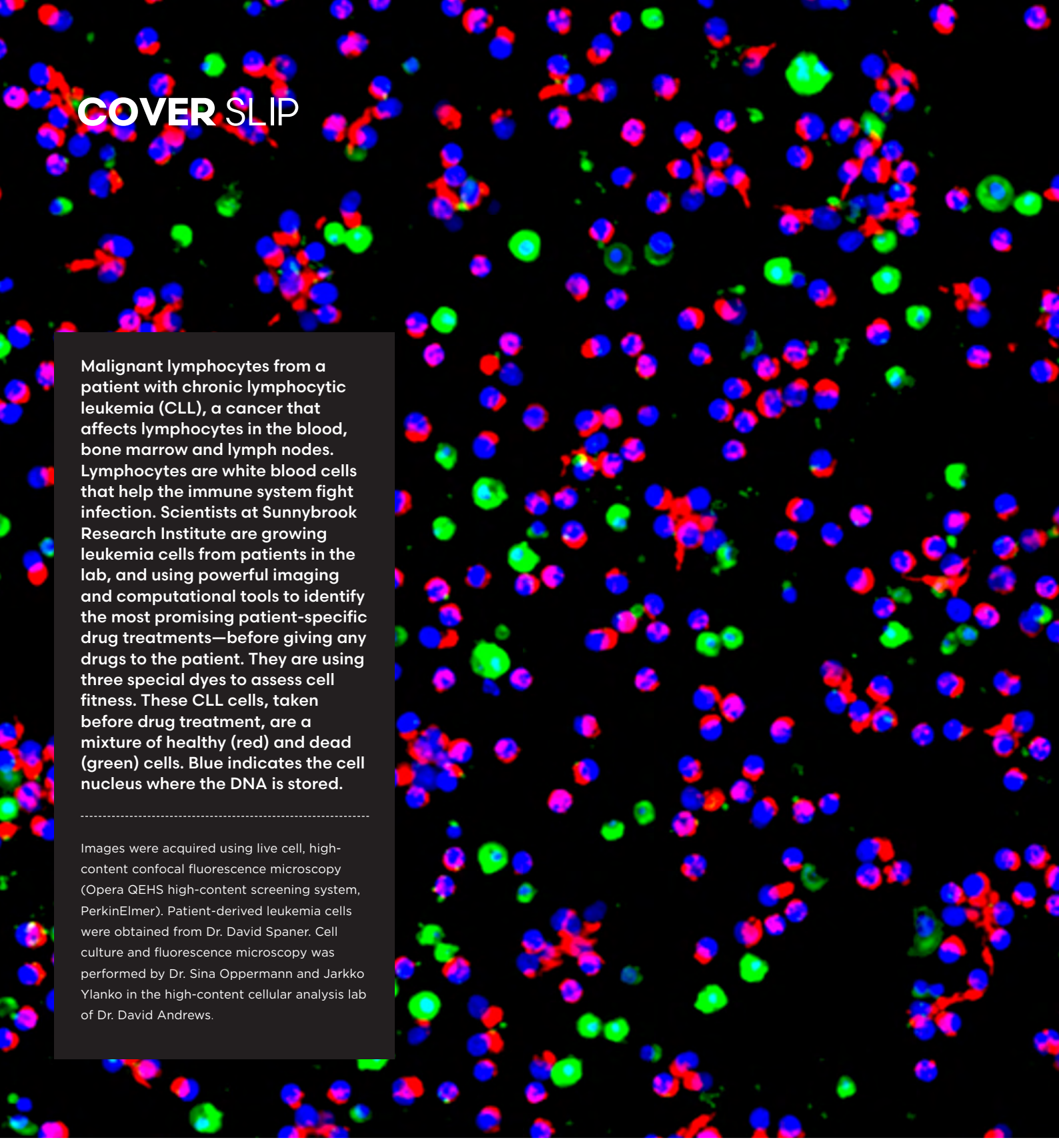
THE WORD "ANESTHESIA" comes from the Greek an- ("without") and *aesthēsis* ("sensation"). Before the discovery of anesthesia, having surgery was considered a terrifying prospect due to the extreme pain suffered by patients. The only strategy to numb pain was to administer alcohol, marijuana or opium to knock patients out. Some doctors even went so far as giving patients a blow to the head to render them unconscious.

The first successful public demonstration of general anesthesia was at Massachusetts General Hospital in Boston, on October 16, 1846. Dr. William Morton, a dentist, used inhaled diethyl ether to anesthetize Edward Gilbert Abbott, a patient with a tumour in his neck. Morton named his compound Letheon, inspired by the Lethe River from Greek mythology. According to the ancients, drinking its waters wiped out painful memories.

The operation was uncharacteristically quiet; until this point surgery was filled with the screams and moans of agonized patients. Dr. John Warren removed the tumour, with no pain to the patient, after which he reportedly declared, "Gentlemen, this is no humbug!" to awestruck onlookers. The operating theatre in which the procedure took place is now known as the Ether Dome.

This was a landmark discovery that made possible painless surgery. AK

COVER SLIP



Malignant lymphocytes from a patient with chronic lymphocytic leukemia (CLL), a cancer that affects lymphocytes in the blood, bone marrow and lymph nodes. Lymphocytes are white blood cells that help the immune system fight infection. Scientists at Sunnybrook Research Institute are growing leukemia cells from patients in the lab, and using powerful imaging and computational tools to identify the most promising patient-specific drug treatments—before giving any drugs to the patient. They are using three special dyes to assess cell fitness. These CLL cells, taken before drug treatment, are a mixture of healthy (red) and dead (green) cells. Blue indicates the cell nucleus where the DNA is stored.

Images were acquired using live cell, high-content confocal fluorescence microscopy (Opera QEHS high-content screening system, PerkinElmer). Patient-derived leukemia cells were obtained from Dr. David Spaner. Cell culture and fluorescence microscopy was performed by Dr. Sina Oppermann and Jarkko Ylanko in the high-content cellular analysis lab of Dr. David Andrews.

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