SRI

MAGAZINE

Inventing the Future of Health Care

Sunnybrook Research Institute / 2011

IN DEATH, LIFE

Suicide by cell: the drama and the promise

Boom, Baby, Boom!

Aging, dementia and the cost to family caregivers

Out of the Dark

Scientist invents device to navigate the blackest channels of the heart

ALSO IN THIS ISSUE

Canada's Got (Science) Talent

Helping Burn Patients Heal

Sunnybrook
HEALTH SCIENCES CENTRE

Inventing the Future of Health Care
Sunnybrook Research Institute
2011

Editor Stephanie Roberts
Design HM&E Design Communications
Writers Eleni Kanavas, Alisa Kim and Stephanie Roberts

Inventing the Future of Health Care is published annually by the vice-president, research, Sunnybrook Health Sciences Centre. Queries, address changes and requests for permission to copy or reprint material in this magazine should be directed to the editor at stephanie.roberts@sri.utoronto.ca or 416-480-4071.

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

DEPARTMENTS

Pictured opposite: In this image, five biomarkers are co-localized, or imaged at the same time, on one breast tissue section. A biomarker is a substance used as an indicator of a biological state. The following markers are shown: estrogen receptor (green), progesterone receptor (blue), Ki67 (a marker for cell proliferation; yellow), cytokeratin 8/18 (a cell membrane marker; red) and DAPI (a nuclear marker, cyan). The image was acquired with an experimental microfluidic system developed by collaborators at GE Global Research. This fully automated instrument can produce immunofluorescence images of up to 22 markers on a single section. Sunnybrook Research Institute alone in Canada has this system. The biomarker imaging research laboratory, working with colleagues in the department of anatomic pathology, is using this technique to learn how we can best "fingerprint" breast tumours, so that we can move from "one size fits all" therapy to more individualized treatment.

IMAGE COURTESY OF DAN WANG, BIOMARKER IMAGING RESEARCH LAB

Cover: A cell undergoes apoptosis, or programmed cell death. Apoptosis is essential for health. Find out why in the cover story on page 18.

ILLUSTRATION BY MARC DRYER

FEATURES

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

Sunnybrook Health Sciences Centre

For a hospital-based research enterprise like Sunnybrook Research Institute (SRI), we can measure success in several ways. Perhaps the most important of these is how well SRI achieves its mission of making discoveries and getting them to people in the real world. There were a few such achievements over the last year, including one that is having impact now. Our brain scientists have found that many seniors are having small, "silent" strokes that are going undetected, and that are putting them at higher risk for dementia. Their findings underscore the need for more research to understand why this is, and they offer evidence-based help for people right now: the researchers noted that lifestyle actions, like stopping smoking, losing weight and exercising can help prevent stroke and dementia.

If we evaluate success by how well we perform compared with our peers, we can again be proud. We ranked fifth in Canada's Top 40 Research Hospitals List 2011. Our standing was based on our 2010 research income of $106 million, a 26% jump from 2009, and the highest year-over-year growth among the top five research hospitals. Of these top five, Sunnybrook is the only general hospital in Ontario with a single research institute.

The success of SRI depends not only on the dedication and excellence of our scientists, but also on the support of our communities, support for which we are grateful. We will continue to work hard to deserve your support as we strive to invent the future of health care.

David A. Leslie
Chair, Board of Directors

Barry A. McLellan
President and CEO

Message From the Vice-President, Research

Sunnybrook Research Institute
Sunnybrook Health Sciences Centre

How to summarize the past year for Sunnybrook Research Institute (SRI)?

Renewal. Renaissance. Reaffirmation.

We renewed the structure of SRI, paring five disciplines into three platforms, areas of expertise that organize our pursuit of excellence. These are biological sciences, evaluative clinical sciences and physical sciences. Together, they bring into relief those areas of leadership where we most make a difference.

With this restructuring, the stage is set for a renaissance in biological sciences. Advances in understanding how biological systems work are yielding insights that are leading to better methods of diagnosis, treatment and even prevention, on a person-by-person, rather than disease-by-disease, basis. We are at the forefront of this work.

Our new structure reaffirms our leadership position and will help propel our growth. We are home to trailblazers not only in biology, but also in imaging. Our scientists are inventing devices that can visualize disease at ever earlier stages, and deliver therapies noninvasively. Clinically minded researchers provide the critical link between lab and bedside. Never have the research and clinical domains at SRI been more closely tethered.

None of this could happen without the support of funding agencies, private sector partners and community allies, especially during these fiscally challenging times. Nor could it happen without the support of our CEO, Dr. Barry McLellan, and Chair of the Board, David Leslie, who understand that today's research is tomorrow's care. I hope you enjoy the stories in this magazine that give you a glimpse of our research and that care.

Michael Julius
Vice-President, Research
Professor, Departments of Immunology and Medical Biophysics
Faculty of Medicine, University of Toronto

DAVID LESLIE AND DR. BARRY MCLELLAN

DR. MICHAEL JULIUS

PHOTOGRAPHY: DOUG NICHOLSON

OCCUPY SRI

Mass migration to the Centre for Research in Image-Guided Therapeutics begins

As of this magazine's press date, 100,000 square feet of pristine space that is the nucleus of the Centre for Research in Image-Guided Therapeutics (CeRIGT, pronounced see-right) at Sunnybrook Research Institute was welcoming the first of its 250 new inhabitants onto the top two floors of the hospital's main wing. No squatters, these—CeRIGT's lawful denizens comprise a dozen teams in the fields of biology, imaging and clinical research, plus support and administrative staff.

"We're thrilled that CeRIGT is ready for occupancy. An incredible amount of work has gone into achieving this milestone," said Dr. Michael Julius, vice-president of Sunnybrook Health Sciences Centre and Sunnybrook Research Institute.

The centre was designed to enable scientists and clinicians to work together without the barriers found at many other institutes. Labs for biology and imaging research are located on the top floor, while clinical research facilities are just steps away, for a synergistic environment that will see the groups working on better ways to diagnose, treat and prevent complex health conditions, like cancer, heart disease, stroke, bone disorders and dementia.

Altogether, CeRIGT comprises 150,000 square feet, two-thirds of which is on M wing. The remaining space is located throughout the hospital; it includes the focused ultrasound surgery centre, which opened in October 2010; the biomarker imaging research lab, which opened in June 2011 and the biomedical imaging research suite, which opened in November 2011.

The $160-million centre—the only one of its kind in the world—was established by a $75-million investment from the Canada Foundation for Innovation. —Stephanie Roberts

OVATION

We applaud some notable achievements of scientists at Sunnybrook Research Institute (SRI) from 2010 to 2011.

National and International Awards

The Government of Canada renewed **Dr. Ross Upshur's** Tier 2 Canada Research Chair in Primary Care Research. The award is the highest academic honour granted by the federal government. Ten scientists at SRI now hold Canada Research Chairs.

The Canada Foundation for Innovation awarded **Dr. Jean Gariépy, Dr. Marc Jeschke, Dr. Samira Mubareka, Dr. Jonathan Rast** and **Dr. Bojana Stefanovic** each a Leaders Opportunity Fund grant. This award pays for infrastructure to help attract the brightest scientists to Canadian institutions, and then keep them there.

The Canadian Institutes of Health Research (CIHR) awarded **Dr. Baiju Shah** a New Investigator Salary Award, designed to give a boost to excellent researchers early in their careers. The agency also recognized **Dr. Mario Masellis** with a Clinician Scientist Award, which helps highly qualified researchers develop their programs.

Dr. Steven Brooks received a Jump Start Resuscitation Research Scholarship from the Heart and Stroke Foundation of Canada and CIHR. This initiative supports new researchers in improving the quality of patient care through resuscitation research.

Dr. Bradley MacIntosh received a Dr. Tony Hakim Innovative Stroke Research Award from the Heart and Stroke Foundation Centre for Stroke Recovery. The prize recognizes innovation in the field of cerebrovascular science and stroke recovery.

The Canadian Cancer Society presented **Dr. Margaret Fitch** with the Award for Excellence in Medicine and Health for her outstanding activity in supportive cancer care and research.

The Israel Cancer Research Fund recognized **Dr. Robert Kerbel** with a 2011 Man of Distinction award, bestowed on individuals who show notable leadership in the fields of business, science and humanitarian causes. The 2010 Man of Distinction award went to **Dr. Michael Julius**.

Dr. Stanley Liu received a Clinician Scientist Award from Prostate Cancer Canada, which rewards early-stage clinician-investigators who are doing prostate cancer research.

The Canadian Society of Internal Medicine presented **Dr. Jack Tu** with the 2010 Dr. David Sackett Senior Investigator Award for excellence in research.

The Canadian Society for Immunology gave **Dr. James Carlyle** a New Investigator Award in support of his research. The organization also recognized **Dr. Michael Ratcliffe** with the John D. Reynolds Award, presented to a long-term member for remarkable service.

The Consortium of Canadian Centres for Clinical Cognitive Research presented **Dr. Sandra Black** with the Irma M. Parhad Award for Excellence 2011. The award commends her research in the field, as well as her work in treating people with cognitive disorders.

Provincial Awards

The Ministry of Economic Development and Innovation (MEDI) awarded **Gariépy, Jeschke, Mubareka, Rast** and **Stefanovic** Ontario Research Fund-Research Infrastructure awards. This program matches the awards given through the Leaders Opportunity Fund by the Canada Foundation for Innovation.

Also from MEDI, **Dr. David Gladstone** received an Early Researcher Award. The prestigious prize supports bright researchers early in their careers.

The Heart and Stroke Foundation of Ontario awarded **Dr. George Mochizuki** the Kevin Duffy Rehabilitation Scientist Award, given to researchers developing new rehabilitation treatments for stroke patients.

Fellowships and Other Honours

Dr. Robert Maggisano was named the first Chair in Vascular Surgery at Sunnybrook Health Sciences Centre. This endowment will support the development and evaluation of new endovascular devices.

The Commonwealth Fund appointed **Dr. Rob Fowler** a Harkness Fellow in Health Care Policy and Practice. This fellowship enables health services scientists and practitioners to do research with leading U.S. health policy experts.

The International Society for Therapeutic Ultrasound recognized **Dr. Kullervo Hynynen** with a William and Francis Fry Honorary Fellowship for Contributions to Therapeutic Ultrasound. This lifetime achievement award recognizes his accomplishments in the field.

Dr. Stephen Fremes was appointed the first Dr. Bernard S. Goldman Chair in Cardiovascular Surgery at Sunnybrook's Schulich Heart Centre. This endowment will support clinical research in the surgical treatment of heart disease.

Dr. Eileen Rakovitch was named the Campbell Chair in Breast Cancer Research in the LC Campbell cognitive neurology research group at SRI.

Dr. Stuart Foster received the 2010 Rayleigh Award from the IEEE (Institute of Electrical and Electronic Engineers) Ultrasonics, Ferroelectrics and Frequency Control Society for outstanding technical contributions to the field of high-frequency ultrasound.

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

ABSTRACTS

Out of Hospital, but Still in the Woods

Infections of surgical sites occur in up to 500,000 surgeries in the U.S., and come with a two- to 11-fold-higher risk of death, longer hospital stays and billions of dollars in health costs. Research suggests these numbers might even be too modest, given that tracking of surgical site infections, or SSIs, stops once a patient leaves hospital. **Drs. Nick Daneman** and **Don Redelmeier**, researchers in the Trauma, Emergency & Critical Care Research Program at Sunnybrook Research Institute, led a study looking at the frequency, severity and prediction of post-discharge SSIs in patients who had elective surgery in Ontario.

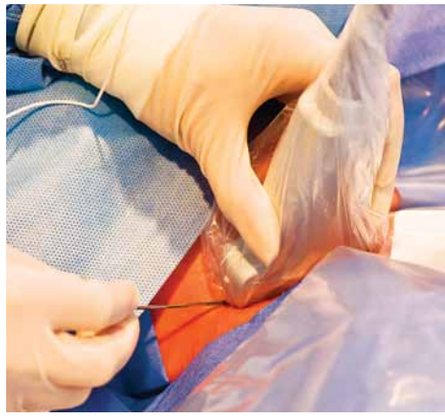
Results were published in the *Journal of Hospital Infection*. Of the more than 600,000 patients in the analysis, 13.5% were diagnosed with an SSI within 30 days of having surgery. Of these, 58% were diagnosed after discharge. Post-discharge SSIs were associated with a higher risk of reoperation, return emergency room visits, readmissions and death.

The authors noted these results support the idea that the frequency of post-discharge SSIs, and thus their burden, is underestimated. They also noted that predicting who will get an SSI isn't easy, though they marked a few categories as being higher risk. Among these: patients who have surgeries of the breast and skin; patients with a shorter in-hospital stay; patients with morbid obesity; and patients with diabetes, alcoholism or a muscle disease. Rural residence and low income were also risk factors. The researchers cautioned, however, that most post-discharge SSIs happened outside these categories; therefore, all patients should be alert to the risk.

Unsettling Claims

Rotator cuff damage is a common work-related injury among manual labourers. It is second only to back pain and causes substantial loss of work. People injured at work have a high incidence of poor recovery after surgery. Psychological issues and receipt of financial benefits without having to work could help explain this poor recovery, but many patients struggle with chronic symptoms regardless of compensation status.

Dr. Helen Razmjou, a researcher in the Holland Musculoskeletal Research Program at Sunnybrook Research Institute, and **Dr. Richard Holtby**, an orthopaedic surgeon at the Holland Orthopaedic & Arthritic Centre, co-authored a study on the impact of an active compensation claim on patients who experienced a work-related shoulder injury. The researchers looked at data from consecutive patients who had completed a one-year follow-up after having rotator cuff surgery and had a compensation claim, and compared them to a group of control patients who had had surgery, but who did not have a compensation claim. They found that more patients on compensation were still off work one year later owing to shoulder problems, but that both groups showed marked improvement after surgery. Although the compensation group had a significantly lower level of improvement than did the control group, they still benefited from surgery. The study, published in the *Journal of Shoulder and Elbow Surgery*, sheds light on the recovery pattern of injured workers.



TOP: DR. NICK DANEMAN
BOTTOM: DR. DON REDELMEIER

PHOTOGRAPHY: DOUG NICHOLSON

Prescription for Danger

Opioid drugs are widely prescribed to relieve pain. Research shows that prescriptions for opioids at doses of 200 mg of morphine or its equivalent per day—a "watchful dose," according to clinical guidelines—are becoming more common. In 2008, 27% of Ontario residents who received social assistance and were treated with long-acting opioids received daily doses over this amount.

Studies on the link between opioid dose and serious adverse outcomes are few. **Dr. David Juurlink**, a scientist in the Schulich Heart Research Program at Sunnybrook Research Institute, investigated the relationship between opioid dose and opioid-related death in patients with pain unrelated to cancer. The study involved Ontario residents aged 15 to 64 years who were given at least one prescription for an opioid over a nine-year period, as identified using a database of publicly funded drug benefits. Among 607,000 identified patients were 498 whose deaths the province's chief coroner ruled opioid-related. Juurlink found that an average daily dose of 200 mg of morphine or its equivalent was linked with a nearly threefold increase in the risk of opioid-related death, compared with daily doses of less than 20 mg. These results, published in the *Archives of Internal Medicine*, provide evidence that there is a major increase in the risk of harm with very high daily doses of opioids, and may be used to guide physicians' practice.

Do Corticosteroids Benefit Preterm Infants?

Pregnant women at high risk of giving birth too early are often given one course of prenatal corticosteroids to reduce the risk to babies of respiratory distress syndrome, bleeding into the brain and death. Researchers at Sunnybrook Research Institute's Centre for Mother, Infant and Child Research, led by **Dr. Elizabeth Asztalos**, studied the effect of repeated courses of prenatal corticosteroids in a clinical trial called the Multiple Courses of Antenatal Corticosteroids for Preterm Birth Study (MACS). Results published in 2008 showed multiple courses of corticosteroids given every 14 days until 33 weeks or delivery did not reduce the risk of infant death or complications, compared with a single course.

Asztalos and her colleagues recently published a two-year follow-up study on the MACS trial, published in *Pediatrics*. They compared the effects of repeated courses of corticosteroids with a placebo. The study followed 1,858 high-risk women from the previous study who were between 25 and 32 weeks of gestation and who remained pregnant 14 to 21 days after the first course of corticosteroids. More than 2,100 infants were monitored, 1,069 in the corticosteroid therapy group and 1,035 in the placebo (no therapy) group. Results showed that there was no significant difference in babies' survival rates or the presence of neurological impairment at 18 to 24 months of age with multiple courses of prenatal corticosteroids. The researchers will continue to monitor these children.

TOP: DR. DAVID JUURLINK
BOTTOM: DR. ELIZABETH ASZTALOS (R) AND DR. SHARYN GIBBINS

The Right Regimen for Gynecologic Tumours

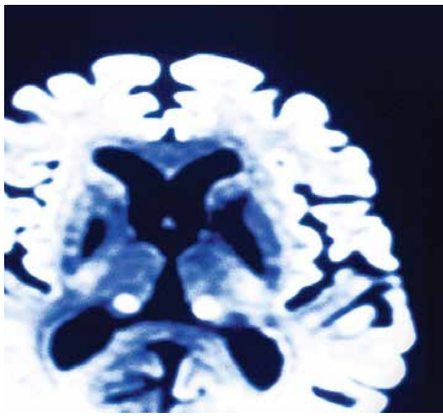
Low-risk gestational trophoblastic neoplasia, a disease in which tumours grow inside a woman's uterus, is curable, but response rates can vary widely, and there is no agreement among institutions as to the best treatment strategy. A randomized controlled trial led by **Dr. Ray Osborne**, a researcher in the Odette Cancer Research Program with the Gynecologic Oncology Group, compared two commonly used chemotherapeutic drug regimens among 216 women who met the criteria for inclusion in this international trial.

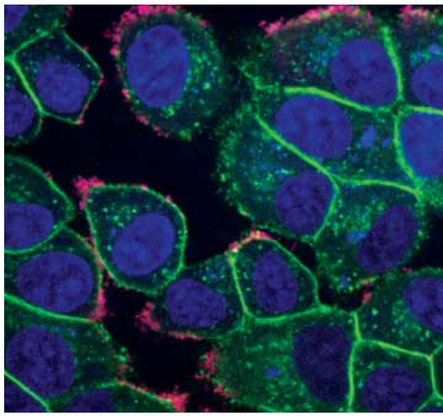
Results, published in the *Journal of Clinical Oncology*, showed that biweekly dactinomycin was more effective than weekly methotrexate. Both drugs were less effective when a woman's World Health Organization risk score was five or six, or if she had choriocarcinoma, a fast-growing type of gestational trophoblastic neoplasia. The authors noted that dactinomycin is easy to administer with a two-week schedule and has a low toxicity profile; therefore, they called for a randomized controlled trial comparing it to other commonly used methotrexate regimens.

An Inside Look

Imaging of the arteries within the brain suggests that intracranial atherosclerosis (hardening of the arteries) is associated with irregular thickening of the vessel wall. Although studies show that 3T high-resolution magnetic resonance imaging (MRI) is useful in studying the wall of intracranial arteries, it remains unknown if high-resolution MRI can distinguish the difference between active and stable carotid plaques in patients presumed to have intracranial atherosclerosis.

Dr. Richard Swartz, a scientist in the Brain Sciences Research Program at Sunnybrook Research Institute, published a study in *Archives of Neurology* that examined the wall imaging patterns of the middle cerebral arteries of patients with atherosclerotic disease who recently had an ischemic stroke (one caused by a blocked artery) in the affected artery. Researchers identified eight patients aged between 50 and 76 years who underwent 3T contrast-enhanced high-resolution MRI. Results suggested that patients with presumed intracranial atherosclerosis of the middle cerebral arteries have eccentric plaques that enhance after a contrast agent is administered when imaging is performed within weeks to months of a stroke. The researchers suggested that this enhancement might represent an unstable plaque, which in turn could lead to stroke. They concluded that prospective studies are needed to investigate which wall imaging characteristics best predict a higher risk of stroke.





MIDDLE: DR. RICHARD SWARTZ

SCREEN THIS

Research mounts that magnetic resonance imaging is the best way to detect breast cancer in women at high risk of the disease

For years, mammography has been the standard screening method for tumours in the breast. However, this technique may be failing young women with a family history of breast cancer, many of whom carry the BRCA1 or BRCA2 gene mutation. This is partly due to denser breast tissue common among young women, which makes it harder for mammograms to find cancers early. By the time a tumour is detected, it is highly likely that the cancer has advanced. Therefore, these women, who have a lifetime risk of up to 75% of developing breast cancer, often face a difficult choice: continue annual screening with an ineffective technique, or surgically remove both breasts.

"You're 35 years old and find out that you have a gene mutation. One of the factors that goes into that [decision] is if I don't remove my breasts and just do screening, what's my chance of dying of breast cancer?" says Dr. Ellen Warner, a researcher at Sunnybrook Research Institute (SRI) and an oncologist at the Odette Cancer Centre at Sunnybrook Health Sciences Centre.

An estimated one in nine Canadian women will be diagnosed with breast cancer. Most of these cancers will be diagnosed after age 60, detected by mammography. However, women with a BRCA mutation or who have close relatives who developed breast cancer at an early age, often develop breast cancer before age 50.

In an effort to detect this disease at the earliest possible stage in these high-risk women, researchers at SRI have spent more than a decade comparing the use of magnetic resonance imaging (MRI) with the "traditional" screening methods of mammography and clinical breast examination, and with ultrasound, a modality shown to have greater sensitivity (the ability to detect a disease when it is there) than mammography in women with dense breasts.

Since 1997, Warner and her team have been exploring the role of MRI in screening women with a BRCA1 or BRCA2 mutation. In 2004, she authored a landmark study published in *The Journal of the American Medical Association* that analyzed five years of data on 236 Canadian women aged 25 to 65 years with the BRCA gene mutations. The study compared the sensitivity and specificity (the rate of detecting suspicious abnormalities that turn out not to be cancer, known as false positives) of four imaging methods—mammography, ultrasound, MRI and clinical breast exam—for detecting breast cancer in these high-risk women. The researchers found MRI detected lesions with much higher sensitivity than did mammography, ultrasound or clinical breast exam. There were more false positives with MRI, but the rate was acceptable, and there were far fewer after the first year of screening.

It was the largest such single-centre study. Results showed MRI detected breast cancer tumours with 77% sensitivity, compared to 36% for mammography, 33% for ultrasound and 9% for clinical breast exam. When all four methods were combined, sensitivity increased to 95%.

"We found all these small cancers with MRI that mammography missed, and it was incredibly exciting," says Warner, who is also a professor in the department of medicine at the University of Toronto. "MRI is the best method we have for high-risk women and the most sensitive to pick up cancers at a very early stage."

It was logical to believe that had the women not been screened with MRI, their cancers would have eventually been detected, but at a significantly more advanced stage. However, this remained to be proven. Building on her earlier research, Warner and colleagues published a cohort study in 2011 in the *Journal of Clinical Oncology*. They followed 1,275 women (including those from the previous study) aged 25 to 65 years with the BRCA1 and BRCA2 mutations. Of these, 445 received MRI screening in Toronto, and 830 had conventional screening

DR. ELLEN WARNER

PHOTOGRAPHY: DOUG NICHOLSON

"So far, the results are very reassuring, as there hasn't been a single breast cancer death in women getting yearly MRI screening," says Warner.

elsewhere in Canada and the U.S. Researchers compared the incidence of early- and late-stage breast cancer between the two groups. At the end of the three-year trial, there were 41 cases of breast cancer in the MRI-screened cohort and 76 cases in the comparison group.

The researchers found there was a 70% reduction in the risk of advanced breast cancer in the MRI group. They concluded that annual MRI screening is associated with reduced rates of advanced-stage breast cancer compared to conventional screening. This was the first study to compare an MRI-screened cohort of BRCA gene mutation carriers with a control group.

Warner and her colleagues aim to follow women in both cohorts to determine whether annual MRI screening reduces mortality rates in high-risk women. "Our results have been quite impressive and successful since we started the first study," she says. "Now, we just have to sit and watch these women long enough to be fairly confident that we're not going to see substantial numbers dying from breast cancer." Warner adds it will take at least 10 more years to see significant survival differences. "So far, the results are very reassuring, as there hasn't been a single breast cancer death in women getting yearly MRI screening," says Warner.

The group's research has also helped make annual MRI screening the standard of care for women at high risk in Ontario.

The Ontario Ministry of Health and Long-Term Care puts the five-year survival rate for breast cancer in the province at 88%. In July 2011, the province expanded the Ontario Breast Screening Program to provide women at high risk for breast cancer aged 30 to 69 years with greater access to specialized screening centres. These sites will provide patients with referrals for genetic testing, and offer breast screening MRI and mammography, plus diagnostic services for any abnormality detected.

The screening program is designed for women aged over 50 years who are at average risk of developing breast cancer. The expansion is part of a $15-million investment over three years to conduct 90,000 more breast cancer tests based on clinical evidence and recommendations from Cancer Care Ontario.

The ministry estimates 34,000 women in Ontario are at high risk of developing breast cancer. By providing women with annual breast MRI and mammography screening, doctors will be able to detect about 17 cancers per year in every 1,000 women screened. The hope is that through this initiative more breast lesions will be detected at earlier stages, thereby increasing women's chance of survival, and, moreover, with less invasive treatments.

In spite of its improved sensitivity, one of the drawbacks of MRI screening is the high number of false positives it detects. For this reason, it is not for everyone, says Warner. "If your chance of having breast cancer in the first place is small, then you're more likely to have a false positive than to have a real cancer, and that's annoying and stressful for the patient."

Although regular mammograms are still a good method for detecting breast cancer in average-risk women, the age at which women should be tested has recently sparked a debate among medical experts.

In November 2011, the Canadian Task Force on Preventive Health Care released new screening guidelines for women who are at average risk of developing breast cancer. They recommend that women aged under 50 years should not have regular mammograms; rather, only those women considered higher risk within this age group should be screened.

"There is a lot of controversy around what age to start, and part of the problem with the new guidelines is how they are expressed and interpreted," Warner says. "Women were told by the task force in 2001 to consider going every year to 18 months for a mammogram between the ages of 40 to 49, and now the task force says don't have your breasts examined."

In response to media coverage on the topic, Warner published a commentary in *The Globe and Mail*. In it, she says the new recommendations are based on data from outdated mammography and that "digital mammography today is better than film mammography and more likely to find cancers in women with dense breasts."

As researchers continue to improve screening techniques and advance breast cancer treatments, prevention is the most important piece of the puzzle.

"We want to find out why so many women are getting breast cancer and learn how to reduce the risk of breast cancer for all women," Warner says. "The ideal thing for women with BRCA mutations and other very high-risk women would be to have excellent prevention methods, other than surgical prevention, and to use MRI screening as a back-up plan."—Eleni Kanavas

Warner's breast MRI study was funded by the Canadian Breast Cancer Research Alliance. Funding for the infrastructure came from the Canada Foundation for Innovation and Ontario Ministry of Economic Development and Innovation.

UNDER PRESSURE

Preeclampsia at any stage of pregnancy is always cause for concern. When it sets in early, however, it can strike at the heart of health for women

Nausea. Fatigue. Bizarre food cravings. These are the symptoms most people associate with pregnancy.

Ranging from mild to severe, these symptoms are generally more of a nuisance than a true harm. A more serious complication of pregnancy is preeclampsia, which occurs in 5% to 7% of all pregnancies, and is characterized by high blood pressure and excess protein in the urine.

Because our bodies rely on the healthy circulation of blood throughout to supply organs and tissues with vital nutrients and oxygen, arteries damaged by high blood pressure lead to a host of serious health problems. Thus, preeclampsia poses threats to both mother and baby. In the former: brain injury, impaired liver and kidney function, blood clots, fluid in the lungs and seizure; in the latter, premature birth, poor growth and even death.

"Preeclampsia is a placental disease, and it's the leading cause of maternal and fetal morbidity and mortality in the developed world," says Dr. Michelle Hladunewich, an associate scientist in the Women & Babies Research Program at Sunnybrook Research Institute. "One of the biggest risk factors is increasing maternal age, and as we keep waiting to have our babies, preeclampsia is becoming more common."

She would know. Hladunewich leads the divisions of obstetrical medicine and nephrology within the department of medicine at Sunnybrook Health Sciences Centre, and treats women in the Greater Toronto Area with any form of kidney disease in pregnancy, including preeclampsia.

Preeclampsia was once thought to be a self-limiting condition that resolved itself after delivery of the placenta, but research, notably, a population-based cohort study published in the *British Medical Journal* in 2001, has shown that women with preeclampsia are at increased risk of death from cardiovascular causes. "When you look at the epidemiological studies, a few patterns emerge: the earlier the onset of preeclampsia, the more severe your preeclampsia, whether your baby lived or died—all indicate that the more sick your placenta was, the worse was your cardiovascular risk later in life," says Hladunewich.

DR. MICHELLE HLADUNEWICH AND ELISA MARTINEZ-REYES

She has taken this important insight even further in a paper published in *Circulation* in October 2010. In it, she and her colleagues showed that among women studied who had placental disease, only those who had early-onset preeclampsia or intrauterine growth restriction without preeclampsia (IUGR, a condition marked by poor fetal growth), showed impaired vascular function, pointing to higher future risk of vascular disease.

In the study, women at one-year postpartum were divided into four groups: those who had early-onset preeclampsia (before 34 weeks gestation), late-onset preeclampsia (after 34 weeks gestation), IUGR without preeclampsia and prior normal pregnancy. Hladunewich found that the women who had early-onset preeclampsia, as well as those with IUGR without preeclampsia, had stiffer arteries than did those in the other two groups.

She also found that these women had reduced flow-mediated dilatation, a test used to detect early vascular disease. The more a blood vessel dilates in response to hyperemic stress—as in the squeeze of a blood pressure cuff—the healthier it is; a vessel that dilates less indicates dysfunction in the endothelium (the inner lining of the blood vessel). Again, there was less dilatation of the main blood vessel of the upper arm only in the women who had early-onset preeclampsia and IUGR without preeclampsia. Moreover, the degree of dilatation in the arteries of the women who had late-onset preeclampsia was similar to that of the healthy control subjects.

Stiff arteries and decreased flow-mediated dilatation are standard measures of vascular dysfunction (damaged blood vessels), which is a precursor to cardiovascular disease. "Our hypothesis that there would be differences depending on the disease was borne out," says Hladunewich. Other researchers have looked at the risks of hypertension during pregnancy; this study is unique in that it differentiated between early- and late-onset preeclampsia. "We were very careful about which women went into which group, which is why we got cleaner, more interesting results than did previous studies," she says.

While she expected to see differences in vascular function among women with early- and late-onset preeclampsia, Hladunewich says that the extent of endothelial dysfunction in the women who had IUGR and normal blood pressure came as a surprise. She reviewed the ultrasound images of the women's placentas from their pregnancies and found that those who had poor blood flow to the placenta were the same women who exhibited endothelial dysfunction. "It's the placenta that can give us predictive value of who's at risk of future vascular disease," she says.

For Hladunewich, the implication of this research for clinical practice is clear: "It's time to pay attention to this complication of pregnancy because we can change women's lives," she says. She wants family doctors and members of the general public, especially women, to know that preeclampsia is as much of a risk factor for heart disease as are age, family history and cholesterol profile.

Educating stakeholders on the relevance of pregnancy history to future cardiovascular disease is a challenge. Primary care doctors contending with massive patient loads find it near impossible to stay abreast of the latest research in all the fields applicable to their practice. Moreover, with the shortage of family doctors in Ontario, many of the patients Hladunewich sees only begin receiving health care during their pregnancies. For these reasons she is passionate about teaching and empowering her patients who have preeclampsia. "[To] every single preeclamptic woman I see in this clinic, I say, 'You need to be an advocate of your health.' These women got an early warning sign, and they need to capitalize on that. If nothing else, we could teach young women early on to eat well, exercise and watch their salt intake—to live healthy-heart lifestyles."

—Alisa Kim

Hladunewich's research was supported by the Physicians' Services Incorporated Foundation and the department of obstetrics and gynaecology at the University of Toronto.

PHOTOGRAPHY: DOUG NICHOLSON

THAT'S A RELIEF

How a new ultrasound-guided technique is helping orthopaedic surgery patients feel less pain and heal faster

The sound of a pulse beating on the heart monitor echoes in a small operating room inside Sunnybrook's Holland Orthopaedic and Arthritic Centre on a cold Monday afternoon in January. Lying in a patient bed is Mrs. Rose Billik, ready to undergo a nerve block procedure before her scheduled surgery.

"How old is your grandson?" asks Dr. Shefali Dave, as the small dose of medication administered by Dr. Colin McCartney minutes earlier sedates Mrs. Billik. Dave is a resident anesthetist at Sunnybrook Health Sciences Centre training with McCartney, an anesthesiologist at Sunnybrook and researcher in the Holland Musculoskeletal Research Program at Sunnybrook Research Institute (SRI).

Dressed in a blue gown and mask, Dave puts on latex gloves and opens a sterilized surgical kit. She carefully unfolds each corner of the package that's filled with large sheets, sponges, and the needle and catheter that will be used to deliver the local anesthetic to Mrs. Billik's brachial plexus nerves—a bundle of fibres that run from her neck down her arm. Dave takes the surgical sheets and covers Mrs. Billik, exposing only the base of her neck and shoulder, and begins to sterilize the area.

Standing across the bed and next to the ultrasound machine is McCartney, who will guide Dave through this minimally invasive procedure, called an interscalene block. As Dave applies some gel to the exposed skin, McCartney passes her the ultrasound probe and explains which nerves to look for. With a steady hand, Dave slides the probe up and down Mrs. Billik's neck, keeping a close eye on the images that appear in front of her on the ultrasound screen. In her other hand, she holds the needle with an attached catheter and slowly inserts it toward the nerves that begin to twitch from a small electric current McCartney sends through the needle. This allows Dave to place the needle very close to the visualized nerves. Using a syringe, McCartney injects a small dose of local anesthetic into the catheter to block temporarily any pain signals from Mrs. Billik's upper arm and shoulder. Together, they watch the ultrasound screen and see the anesthetic spread around the nerves. The procedure is complete.

Severe acute pain is a common problem among patients who have orthopaedic surgery. Researchers at SRI are pioneering a new pain relief technique: low-volume, ultrasound-guided interscalene block. It pairs ultrasound guidance with a small dose of local anesthetic. McCartney helped develop the technique to reduce the amount of local anesthetic injected around the brachial plexus nerves. Studies show that patients benefit from this method; they have less pain, fewer respiratory complications and improved mobility of their upper arm and shoulder. This technique is being used clinically worldwide.

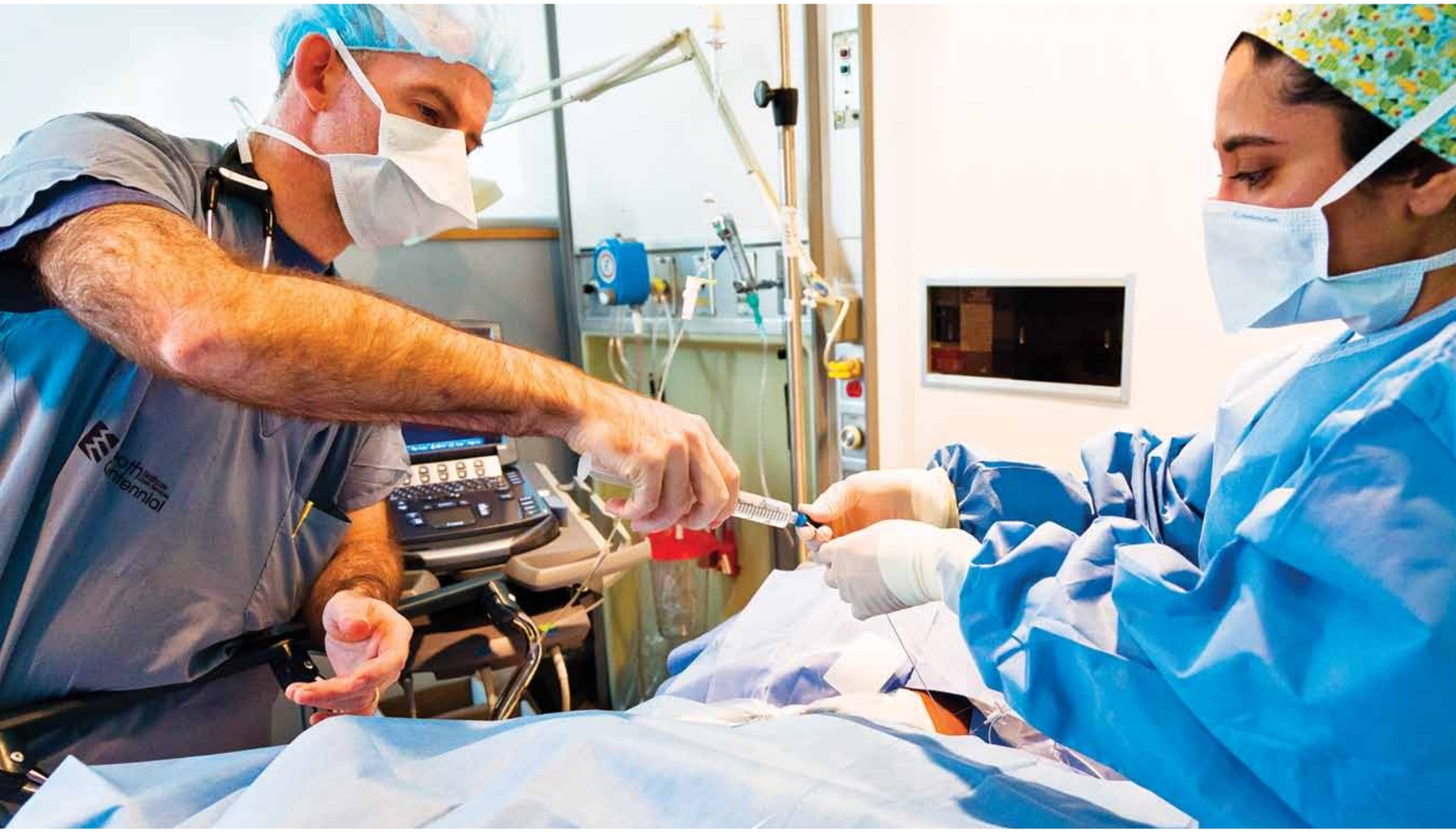
"We use local anesthetic techniques in about 90% of patients having orthopaedic surgery at the Holland Centre because it's one of the most effective ways of reducing severe acute pain after surgery," says McCartney, who is also an associate professor in the department of anesthesia at the University of Toronto.

In 2008, McCartney and his colleagues published a paper in the *British Journal of Anaesthesia* that looked at a lower volume technique by using ultrasound to guide administration of 5 millilitres (ml) of the local anesthetic ropivacaine for interscalene block. The standard volume used for this nerve block is 20 ml or more of local anesthetic. The study showed that the low-volume technique provided the same pain relief as did the standard volume method, but with fewer adverse effects and less risk of respiratory problems. Patients who received the standard-volume block experienced difficulty breathing, voice hoarseness and Horner's syndrome, a temporary eye condition caused by accidental spread of the anesthetic to the sympathetic nervous system. This was the first study to show the benefits of this low-volume technique.

McCartney authored a follow-up study in 2011 published in the same journal that compared a low volume of local anesthetic with two techniques: ultrasound guidance and peripheral nerve stimulation. The latter involves the use of a small electrical current to cause motor impulses, and has commonly been used to isolate and place local anesthetic around nerves. The aim of the study was to determine whether the new technique, ultrasound guidance, would reduce the amount of local anesthetic needed to perform a successful block. The researchers randomly assigned 40 patients aged 18 to 80 years undergoing shoulder surgery to either the ultrasound or nerve stimulation technique.

They found that the ultrasound group received on average one needle pass to locate the brachial plexus nerves, compared with three passes in the nerve stimulation group. In addition, volumes were significantly lower, and a successful block could be created with as little as 1 ml of

"A lot of people were shocked by the results of this paper, that you do actually get a successful block with a surprisingly low amount—around 1 ml of local anesthetic." Dr. Colin McCartney



DR. COLIN MCCARTNEY AND DR. SHEFALI DAVE

local anesthetic. Moreover, pain scores measured 0 out of 10 when patients were in the recovery room 30 minutes after surgery.

"The major advantage of ultrasound compared to nerve stimulation is you can see the target in front of you on the screen, and you only need to make one needle pass, which allows us to be more precise in the way that we're placing the local anesthetic in order to reduce the volume that we're using," McCartney says.

"A lot of people were shocked by the results of this paper, that you do actually get a successful block with a surprisingly low amount—around 1 ml of local anesthetic."

He also notes that it is more difficult to find the target and place the needle with nerve stimulation because there is decreased sensitivity and specificity, which causes a high number of false positive or false negative responses (either when stimulation is obtained but needle tip placement is not ideal, or no nerve stimulation is possible despite needle contact with the nerve). As a result, many needle passes are required to place the needle correctly, which McCartney notes may cause harm. Several patients in the study in the nerve stimulation group required more than 10 needle passes, and were switched to the ultrasound group to complete the procedure.

In addition, the practice of placing larger volumes of local anesthetic without ultrasound guidance may pose a risk to some patients. A higher volume could block nerves in the neck aside from the brachial plexus, therefore causing adverse effects, for example, by blocking the phrenic nerve, a nerve in the neck that supplies movement to the diaphragm. Although the procedure is well tolerated in most patients, in elderly or obese patients, or patients with respiratory disease, it can cause much discomfort or even respiratory failure. The low-volume technique spares respiratory function without impairing the benefits of the interscalene block on pain control, says McCartney.

Mrs. Billik, aged 76, says she greatly benefited from the nerve block procedure. "It was beautiful. I felt great with no pain the Monday and Tuesday after my surgery. I was very pleased with the [nerve block] and would definitely have it again, if needed."

Dr. Richard Holtby, an orthopaedic surgeon and surgical lead in the research team at the Holland Orthopaedic and Arthritic Centre, performed Mrs. Billik's shoulder replacement surgery. He says a major advantage of using the low-volume, ultrasound-guided nerve block with arthroscopic surgery is the quick recovery time, which allows patients to get back to their lives pain-free. "Some of our patients will have to be in a sling for a few weeks, but for those who need to start moving right away, obviously this is an advantage," Holtby says. "The value of the research is to prove that patients are getting as much pain relief without the neurological symptoms such as numbness and paralysis."

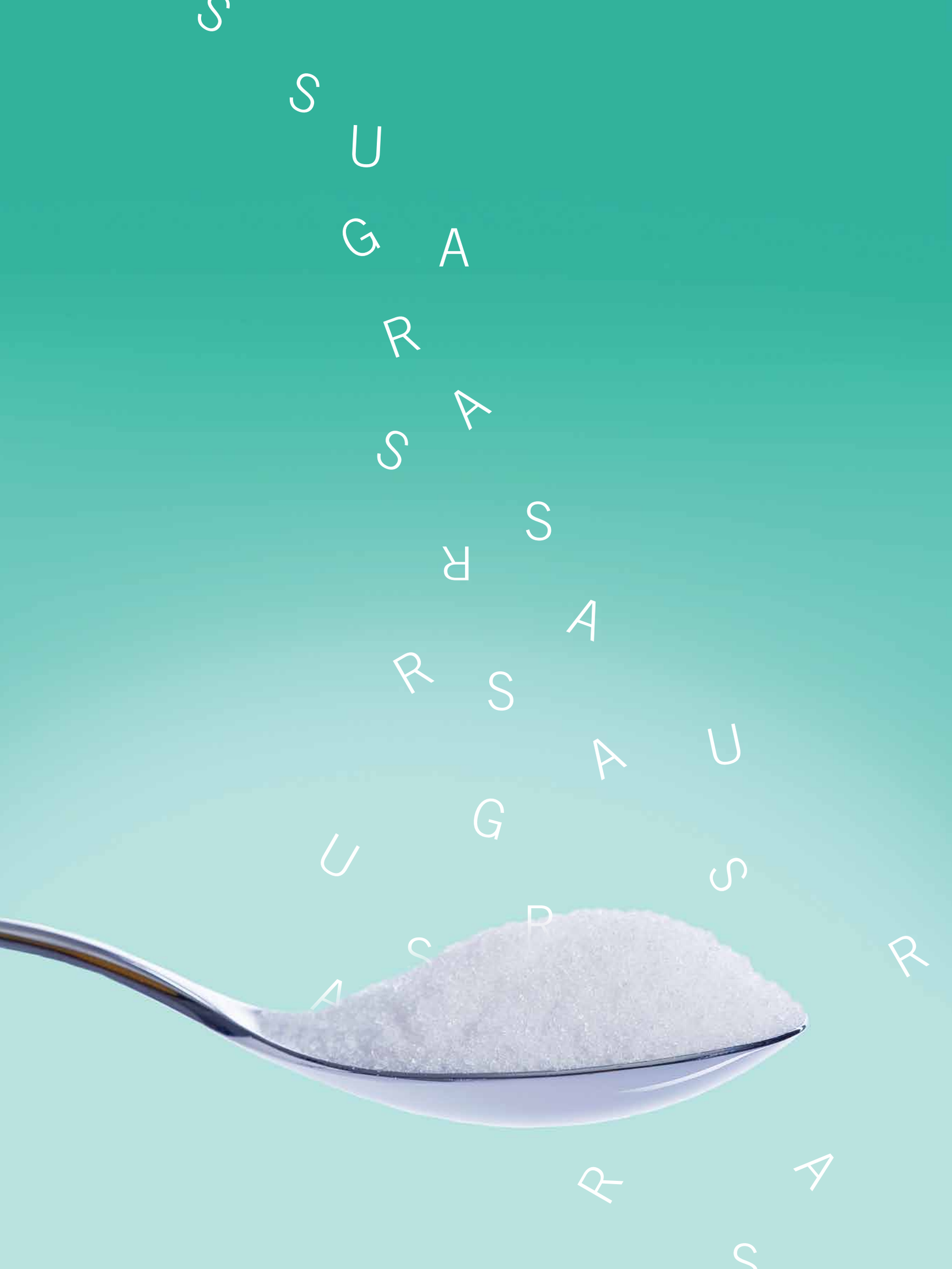
Five days after the surgery, with her left arm in a sling, Mrs. Billik returned to her Toronto home that she shares with her husband of 57 years. She says she still feels a bit of pain that she manages by applying ice packs to her shoulder. She does arm exercises three times a day to gain a greater range of motion and get back to her daily activities and spending time with her family and seven grandchildren.

McCartney and colleagues will next evaluate if it is possible to use a much lower volume of local anesthetic in patients and if this affects overall duration of the nerve block.

"The future is bright," he says. "Research into anesthesia and postoperative pain-control methods continues to improve practice, allowing patients earlier discharge and faster recovery after increasingly more extensive surgery." —Eleni Kanavas

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

PHOTOGRAPHY: DOUG NICHOLSON


SUGAR

A SPOONFUL OF SUGAR

Insulin is given to severely burned patients

to help regulate their blood sugar levels, but disastrous consequences can result when too little or too much is given. How, then, to determine that delicate, "just right" balance? BY ALISA KIM

A severe burn takes a devastating toll on the mind and body. Burn patients endure excruciating pain and undergo a lengthy recovery. Treating these injuries is complicated by the ensuing metabolic disturbances that can last up to one year. The stress response to a burn causes profound changes in the endocrine and immune systems, and an overall hypermetabolic state characterized by increased energy expenditure and body temperature and muscle wasting.

"The greatest metabolic need that you can have is burns," says Dr. Marc Jeschke, a scientist in the Trauma, Emergency & Critical Care Research Program at Sunnybrook Research Institute and director of the Ross Tilley Burn Centre at Sunnybrook Health Sciences Centre. "It beats any critical illness, any surgery, any trauma. Your metabolic demands are the equivalent of running marathon after marathon without any break."

Nutrition is a vital part of the treatment of burns, as the energy requirements of thermal injuries are immense. A patient with a burn covering 40% of his total body surface area can lose one-quarter of his weight by the third week after injury, even with substantial oral nutrition. Moreover, because protein is lost through the wounds, burn patients have increased caloric needs for healing. Burn injuries cause protein and muscle catabolism, whereby the body ravages its own protein stores for fuel, resulting in the loss of lean body mass. Without adequate nutrition these patients suffer from poor wound-healing, weight loss and weakened immunity.

Severe burns also damage the liver, preventing patients from properly metabolizing fats. Thus, carbohydrates, which are broken down into glucose, provide burn patients with most of their caloric needs. Due to the stress of frequent interventions and high-carbohydrate feeds, however, these patients are prone to hyperglycemia, or high blood sugar.

Hyperglycemia, which is common in intensive care unit (ICU) patients—even among those who do not have diabetes—is a much-studied phenomenon. It is associated with higher rates of infection, organ failure and even death. Burn patients with high blood sugar experience a prolonged hypermetabolic state, putting them at risk of infection and muscle wasting. When blood sugar levels rise above 160 milligrams (mg) per decilitre of blood, there is protein glycosylation. This occurs when a sugar molecule binds to a protein in an uncontrolled way and the protein is altered. Protein glycosylation can lead to multi-organ failure.

The paradigm of glycemic control in critical care medicine was introduced in 2001 through a practice-changing study published in the *New England Journal of Medicine* by researchers from the Catholic University of Leuven. Dr. Greet Van den Berghe and colleagues showed insulin given to postoperative surgical patients to keep glucose levels between 80 and 110 mg per decilitre of blood decreased rates of mortality and the incidence of infection, sepsis and organ failure.

Soon after the study's publication, critical care units worldwide began adopting protocols to keep patients within this tightly controlled range. Within a few years, ICUs and trauma centres reported that intensive insulin therapy targeting glucose levels of 80 to 110 mg per decilitre posed risks of hypoglycemia (low blood sugar), which is just as dangerous as hyperglycemia, if not more so. In the decade following the release of the Leuven study, glycemic control in the care of critically ill patients has been the topic of much controversy.

Not as well documented, hypoglycemia is thought to be lethal for critically ill patients. Burn patients are at risk of low blood sugar as nutrition, which is delivered via a feeding tube, is interrupted due to operations, dressing changes and daily showers to keep wounds clean. Severe hypoglycemia (blood sugar levels under 40 mg per decilitre) is believed to cause brain damage, immune impairment and organ failure, says Jeschke, who is studying the outcomes associated with it in collaboration with researchers from Texas and Germany.

"We know glucose is the main energy source for the body, but too much is not good and too little is not good," says Jeschke, who is responsible for the care of about 250 burn patients annually, and sees firsthand the dangers of hyperglycemia and hypoglycemia in burn patients.

In 2009, researchers from Australia, New Zealand and Canada (including two from Sunnybrook Research Institute) published a study titled "Normoglycemia in Intensive Care Evaluation–Survival Using Glucose

DR. MARC JESCHKE

PHOTOGRAPHY: CURTIS LANTINGA

Algorithm Regulation (NICE–SUGAR). They conducted a multicentre trial with more than 6,000 critically ill patients to compare the effects of tight glucose control to conventional glucose control therapy (keeping blood sugar levels at or less than 180 mg per decilitre). After 90 days, there were 829 deaths among patients who received insulin to keep glucose levels within the range from the Leuven study, compared with 751 deaths among those who received conventional therapy.

The conflicting evidence from the scientific literature raises the question: in critically ill patients, how much glucose is too much?

The answer, it turns out, may depend on the patients themselves. Research suggests postoperative surgery patients benefit from tight glucose control, while critically ill medical patients, including burn patients, do not respond as well to it. The trauma of burns differs in severity and length from that of other critically ill patients; burn patients have longer hospital stays, more complications and are more likely to die compared with general ICU patients. The NICE-SUGAR study showed the only patients who benefited from intensive insulin therapy were trauma patients and those who needed corticosteroids to treat septic shock and other serious conditions.

Given that burns are an extreme form of trauma, and a high degree of sickness and death is associated with hyperglycemia in burn patients, glycemic control makes sense—but how tight should this control be?

Finding no answers to this question in the literature, Jeschke, who is also a professor of surgery at the University of Toronto, entered the debate. "We took all this data that are saying different things, and asked what is a good range?" he says.

Specifically, his aim was to determine which glucose levels were associated with improved outcomes in burn patients. The study involved 208 pediatric patients with burns to over 30% of their total body surface area. Based on 6:00 a.m. glucose level measurements, patients were divided into groups based on good glucose control and poor glucose control. The former were those patients whose glucose levels were 130 mg per decilitre or less for at least 75% of their hospital stay; the latter were those whose glucose levels were higher than 130 mg per decilitre.

Jeschke found that patients with good glucose control had a lower incidence of infection, sepsis and death compared with patients with poor glucose control. He also found that patients with good glucose control had milder inflammatory and hypermetabolic responses. "We found that 130 mg per decilitre is one of the ranges burn patients should be in. This is in line with critical care guidelines and sepsis guidelines, which are in the 130 to 150 [mg per decilitre] range," says Jeschke.

The results of his inquiry were published in the *Annals of Surgery* in 2010.

"Our data demonstrate that the ideal glucose target is around 130 to 140 mg per decilitre, and that the glucose curve has a U-form shape, meaning that very low glucose levels are as detrimental as very high glucose levels," says Jeschke.

With no other published research on target glucose ranges to guide clinicians in the treatment of burns, Jeschke's work is all the more valuable.

"Prior to Marc's research, everybody was trying to get to 80 to 110 [mg of glucose per decilitre]," says Dr. Steven Wolf, vice-chair of research and the burn section chief at the University of Texas Southwestern Medical Center. "There was a lot of resistance, but the only data we had was [the] Van den Berghe [study]. People were trying to do that and noticing that we're seeing more hypoglycemia than we normally do. That's when backing off of the range seemed to be a prudent goal, and that's what Marc showed."

Wolf, who is editor of the journal *Burns*, says that he and his colleagues at other burn centres are using more moderate glucose ranges as therapeutic targets and that this practice is guided by empirical evidence. "Other than a few reports—one of them being Marc's—people aren't really talking too much about it; they're just kind of doing it," he says. "The question is: is not-so-tight [glucose] control as effective? Marc is showing that maybe it is. We can get less risk and the same benefit, which is the optimal solution."

Jeschke is using the findings from this research in a clinical trial he is leading at Sunnybrook. He will study the effects of glucose levels between 130 to 140 mg per decilitre in severely burned patients to see whether improved outcomes through glycemic control are due to insulin-specific responses.

As the only study thus far to zero in on an optimal glucose range for burn patients, Jeschke's research has attracted a lot of attention. In a letter to the editor of the *Annals of Surgery*, Drs. Hanazaki, Munekage and Okabayashi from the department of surgery at Kochi Medical School in Japan write: "We believe this is a crucial article in our understanding of the efficacy of tight glycemic control for critical surgical patients." Others apparently think so, too: "Most burn centres and critical care units are now using a 110 to 130 mg per decilitre range," says Jeschke.

But what excites him most about the study's findings is the potential to do better by patients. "We finally have an idea what glucose range is on one hand beneficial for survival, but on the other hand safe for burn patients. By identifying the exact range, patient care is safer."

Jeschke's research was supported by the American Surgical Association Foundation, Shriners Hospitals for Children and the National Institutes of Health. At Sunnybrook Research Institute, he is supported by the Canada Foundation for Innovation, Ontario Ministry of Economic Development and Innovation, and Physicians' Services Incorporated Foundation.

"The greatest metabolic need that you can have is burns," says Dr. Marc Jeschke.

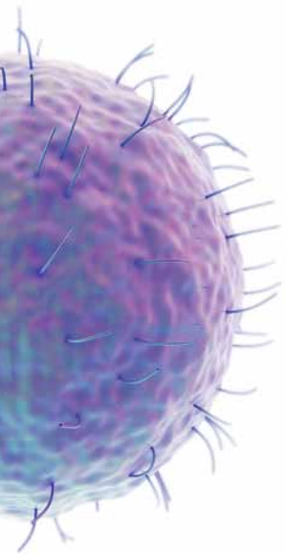
DR. DAVID ANDREWS

IN DEATH, life

One scientist's quest to reveal and master the body's most complex processes, in aid of developing more effective treatments for cancer and other diseases

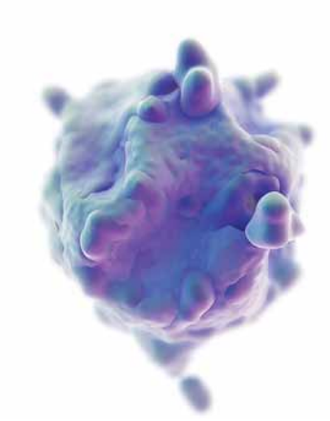
BY STEPHANIE ROBERTS

ILLUSTRATION: MARC DRYER; PHOTOGRAPHY: CURTIS LANTINGA



This

new capacity to study protein-protein interactions where they take place, in the membranes of live cells, opens up myriad possibilities for identifying drug candidates.



He calls himself a cancer researcher. Some might call him a masochist.

"I tell people who want to come and work in my lab that it's not good enough to be able to tolerate banging your head against the wall. You have to like it."

Like it with the same eagerness as he does: to be captivated by the shock of a setback, enraptured by a riddle. "One of my favourite things is when somebody brings me data and you look at it and think, 'What the heck is this? What's going on? This is completely not what I expected!' That's fantastic, 'cause now you know there's something really interesting to find out. I love working on those kinds of puzzles."

Dr. David Andrews is the newly appointed director of biological sciences at Sunnybrook Research Institute. The objects responsible for his happy suffering are proteins: he is in thrall to understanding how proteins interact to control the behaviour of cells, especially during apoptosis, or programmed cell death.

What is apoptosis, and why study it?

First, let's deal with pronunciation. The second p is silent. That's the point on which most agree. Sparking more lively discussion, however, is how to pronounce the "a": long or short? Ape or app? In general, south of the border, it's ape. In Europe, it's app. Here in Canada, as usual, we play it both ways. Andrews, however, goes short, backed by an authoritative source: a footnote in the publication that first described apoptosis. "These Scottish guys went to the classics department in a university in Scotland and asked them for a word that would be kind of like mitosis, but would have to do with cell death," he explains. After giving it some thought, professor James Cormack coined apoptosis, which in the original Greek means "the falling of petals from flowers, or of leaves from trees," and which, the authors noted, is pronounced with a short a, and a silent second p, with the stress on the second syllable; thus, we have: apo-*ptosis.*

Apoptosis refers to the biological process by which cells are genetically programmed to commit suicide. It is critical for healthy functioning. It tells cells to kill themselves if they are no longer needed, for example, during tissue development to get rid of unwanted bits, like webbing between our fingers, or if they are damaged, as in precancerous cells. It differs from necrosis, the other kind of cell death, in that with necrosis cells die owing to an acute, usually traumatic, injury.

It was first described in 1972 by scientists from the University of Aberdeen in Scotland, in the *British Journal of Cancer*, in an 18-page article that has been cited more than 11,000 times.[1] In that article, the features and function of this newly characterized process were laid out in as much detail as could be had with the technology of the time. The authors speculated that decreased apoptosis might be responsible for the runaway growth of tumour cells, and not increased mitosis (cell reproduction), as was the prevailing opinion, but noted, "We know of no definitive studies to support such a hypothesis."[2] They concluded that more research remained to be done to understand the phenomenon.

Four decades later, more work certainly has been done, most within the last 20 years. At last count, 1.6 million articles on apoptosis have been published.[3] Do researchers now understand it? Sort of. It is now known, as the Scottish team posited, that too little apoptosis does indeed cause tumour cells to proliferate and cancer to dig in—and not only cancer. It also is implicated in other diseases, such as autoimmune and viral diseases. Moreover, the problem can swing the other way, as in when apoptosis runs amok and kills too many cells, which can cause tissue damage, human immunodeficiency virus, and brain-wrecking disorders like dementia and stroke.

Harnessing this process, therefore, holds untold promise in designing pro- and anti-cell-death therapies.

KA-BOOM!

During apoptosis the suicidal cell appears to pull into itself, a function of its shrinking cytoskeleton, which lives in the cytoplasm, the jelly-like environment inside the two-layered plasma membrane where much of cell life takes place. Then, the chromatin, which comprises the proteins and DNA that make up the cell's nucleus, condenses. The nucleus cracks under the pressure and fragments. The shrinking cytoplasm causes the membrane to bulge, forming stubby finger-like objects called blebs. The blebs grow rounder and fall away from the membrane to form bubble-shaped apoptotic bodies. I imagine this is what a planet exploding in slow motion would resemble. At this point, phagocytes, white blood cells that help protect the body, engulf

the debris. The process takes hours to days, but once done, it cannot be undone.

The powerhouses behind this dramatic process are protein-protein interactions that take place in the outer mitochondrial membrane. Signals to and from proteins direct every aspect of cell function. Proteins enable the cell to receive and respond to messages about what to do and how to do it. Without them, the cell might as well exist in a blacker-than-night, soundproof box. Understanding how proteins interact, therefore, is the key to mastering the life-and-death processes they control. This, as one might imagine, is no easy feat—apart from proteins' complexity, the number of them staggers: a database of proteins has catalogued almost 24,000 proteins, and more than 73,000 interactions.

Andrews has honed in on a family of membrane proteins called the Bcl-2 family, which is made up of proteins that activate cell death and those that block it. As a class, membrane proteins, which comprise about 30% of the body's proteins, are hot drug targets. That's because most drugs that work do so because they target membrane proteins.

"The beauty of the Bcl-2 family, from my point of view, is that there are two proteins, Bax and Bak, that are the ultimate decision-makers, and then lots of other proteins funnel down to those two. That gives the cell a way to monitor many different events, and integrate a whole bunch of signals to make a decision. From the point of view of somebody like me who's a biochemist or [someone] in the pharmaceutical sciences, it means that is the point you can regulate and have the most effect, because it's as close to that decision point as possible," he says.

Bax and Bak are the executioner proteins. Think of them as akin to the Queen of Hearts, without the nasty temper. They control the final decision as to whether a cell that should die, like a precancerous cell, does so. They take their cue from other family members, which sense when a cell is damaged and needs to be snuffed out. Sometimes, though, their activation is blocked by yet another branch of the family, the anti-cell-death relatives, like Bcl-2 and Bcl-xl. This blocking effect not only allows cancerous cells to grow; it also helps them resist chemotherapy. While there is much jockeying for dominance within the family, the essential event in apoptosis is the binding of the executioner proteins to the membrane. Here, they make it porous, and in doing so launch the irreversible chain of events that commits a cell to self-destruction.

"My interest in those proteins is that they regulate the response of cancer cells to chemotherapy. The ultimate goal is to be able to make chemotherapy more effective and more selective, and these proteins, most of the time, they are the decision-makers as to whether or not the cells will die," says Andrews.

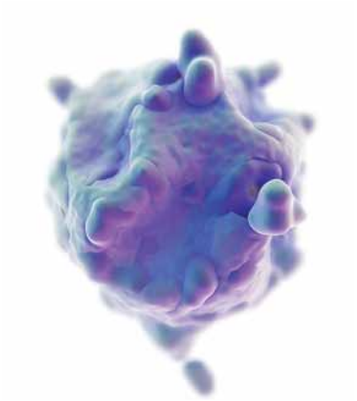
Ensuring that Bax and Bak can do their job, either by making sure they get activated, or that nothing blocks them, is thus the focus of scientists looking to design anticancer drugs that would target Bcl family members. Of course, the anti-cell-death proteins are not always a menace; activating them could offer a way to treat diseases like stroke or heart attack, in which too many cells die, by halting the process long enough to minimize damage or enhance the effects of treatment. As one might imagine, the precise mechanisms by which this warring family of proteins achieves its ends are complex and a matter of much study.

A TALE OF DISCOVERY

Back when this family of proteins was first discovered, in the mid-1980s, Andrews was a graduate student in medical biophysics at the Ontario Cancer Institute in Toronto. It would be a good few years before he would fall under their spell, but the work he was doing would prove to be instrumental to his later research.

His attention then was held by trying to solve the "oil and water" conundrum of membrane proteins. "All proteins get made in the cytoplasm, which is essentially a water-type environment," he explains. "The cytoplasm is hydrophilic [water-loving]. It's a different environment from the membrane, which is lipid." The lipid environment is the opposite of the cytoplasm milieu, in that it's hydrophobic, or water-repelling. "The easiest way to think

DR. DAVID ANDREWS



of it is as oil and water. Oil and water don't mix—but you can only make proteins in the water. So if you can only make proteins in the water, what kind of machinery do you need to keep them from aggregating in the water and still be able to put them into oil?"

While wrapping up his postdoctoral degree in cell physiology at the University of California, San Francisco, in the late '80s, he made a discovery that not only solved this mystery, but was to help solve another puzzle he would face when he turned his mind to apoptosis a few years later. "I rediscovered something that people already had known about, but at this time were conveniently forgetting, because it didn't fit anything [that was known]: that some proteins have only one hydrophobic piece on the protein and that's right at the c terminus, right at the end of the protein."

It was this "rediscovery" that enabled him to figure out how some proteins could get targeted to the membrane: basically (an abridged explanation), via a series of signals and with the help of a "tail anchor" that allowed it to bind to the membrane. His finding of the unexpected role of this tail-anchored protein made the oil-and-water issue moot, and was critical at a time when almost nothing was known about membrane protein targeting.

A few years on, now an associate professor in biochemistry at McMaster University, he and his colleagues were working on the newly discovered Bcl-2 protein when he had another brainwave. "I realized many of the Bcl-2 family proteins have that hydrophobic sequence at the extreme c terminus," he says. Turns out, they, too, were tail-anchored proteins—which explained how they got targeted to the membrane. The realization hit him with a gratifying thud. "The original paper on Bcl-2 was all wrong—everything about the membrane targeting and assembly of the protein was wrong. It was a full article in *Nature*. So I thought, there's an opportunity here," he says, his glee evident.

He seized the opportunity—despite hostile reaction from the scientific community that delayed publication of these findings for three years—and hasn't let go since. Some 15 years later, he and others studying apoptosis have made real headway in understanding how it works. He says his eye now is trained on making that knowledge clinically useful. "The most important thing is that it impacts the patient. As my career has progressed, it's become more and more important.

"When you're intellectually curious about a certain biological phenomenon and you figure that out, the next logical thing is, 'OK. What can I do with it?'"

He is not saying that all the puzzle pieces for protein-protein interactions and cell death are in place—far from it; it's clear that the table holding them is as big as one's imagination can build—but he is saying there is enough knowledge to be working toward getting it to patients, while continuing to study the fundamentals.

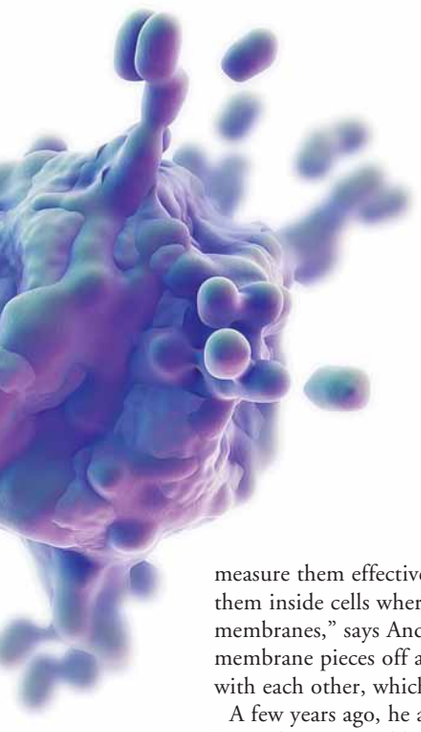
JOURNEY TO THE MEMBRANE

Drug discovery: high risk; high stakes. There are many steps that go into identifying a potential drug target and taking it all the way to where it gets the regulatory thumbs up. Once a drug is discovered, it will be 10 to 15 years before a patient can benefit from it—if it gets past preclinical testing showing that it doesn't have nasty side effects, and then if something doesn't go belly up during the last stage of clinical trials, as happens more often than not, because trials are the only way to know for certain if a drug works in people. It costs about $1.8 billion to develop one drug; with rewards of annual sales in the billions of dollars, however, it's not hard to see why companies make the effort.

As we've already seen, membrane proteins are the most promising and the most difficult of drug targets. One of the greatest challenges is being able to see how the proteins work and interact with each other where the action takes place, in the membrane.

Traditional methods have been inadequate. "Because these protein-protein interactions take place in a membrane, you can't

DR. DAVID ANDREWS



measure them effectively outside of cells. You can only measure them inside cells where you have the normal architecture of the membranes," says Andrews. An early method was to cut all the membrane pieces off and look at the rest of the pieces interacting with each other, which, Andrews notes, "was very unsatisfactory."

A few years ago, he and colleagues devised a better method. It involves reassembling proteins in a sort of artificial membrane using liposomes, which are like soap bubbles, but composed of two layers of lipid molecules, and then using an imaging tool called fluorescence resonance energy transfer, FRET, to observe the proteins interact. This tool, commonly used in drug discovery research, gives information about how molecules associate with each other by measuring the energy transfer between them, which appears as the movement of fluorescent light from one molecule to another. Because the transfer happens only if the molecules are close enough together, it can be used to track where and when molecules interact.

Using this system, Andrews and colleagues undertook to witness the steps by which Bcl-2 family members regulate apoptosis. They inserted purified proteins into the liposomes and used FRET to see what happened next.

They weren't disappointed. They saw precisely how Bcl-2 family members interact, resulting in the executioner protein Bax binding to the membrane, and the membrane becoming permeable and kick-starting apoptosis. They were also able to see how the effects of a meddling relative prevented Bax from binding to the membrane. Perhaps most importantly, they were able to see that another protein interaction reversed the effects of the meddling relative, so that Bax could once again bind to and make porous the membrane. The results were a big deal. They showed that the process was orderly, step-wise and reversible, and that the membrane was not only essential, it was also an active participant. The findings profoundly changed researchers' understanding of how Bcl-2 proteins regulate apoptosis.

"This was a big step forward, which is why it came out in *Cell*, because we could see interactions that people had completely missed, and just recently there was a review article which pointed out that that paper still is the only demonstration that Bid actually binds to Bax directly, and that's in the membrane," he says.

Although a major advance, Andrews is quick to note the technique is a stopgap. "It's in an artificial membrane. To study these things in real membranes, we have to be able to make all those spectroscopic measurements in live cells." Alas, such a highly specialized tool doesn't exist. Correction: it didn't, until Andrews set to thinking about it.

Bax

and Bak are the executioner proteins. Think of them as akin to the Queen of Hearts, without the nasty temper.

PRETTY AS A PICTURE

Spectroscopic tools analyze properties of light to provide information about a molecule. For Andrews, three properties are of interest: intensity, wavelength and something called fluorescence lifetime, which measures how long a molecule that has been stained with fluorescence dye is excited when light hits it. Lifetime is the property in which drug companies are most interested, because it tells them if a drug is working.

Confocal microscopes are a mainstay of the biologist's toolkit. They are miles away from the widefield microscopes of our high-school science classes. There are two kinds of confocals, the raster and the spinning disc. Each excels at measuring the intensity of light, and, with software, produces crisp, high-resolution images that can be reconstructed as 3-D multicoloured structures on a screen.

The raster is typically used for fixed specimens, in part because it takes a while to capture an image. It can deal with very thin slices of specimens, enabling scientists to peer deep inside cells. It may sound complicated, but as Andrews explains, it works much like a regular TV does. "You scan a beam of light across the sample; at each point in the sample you measure the fluorescence that is given off, and that creates your image." The spinning disc is a bit different. It can do time-lapse imaging of live cells and is much faster than the raster, but at the expense of crispness of images. Neither is good at measuring wavelength, and neither can measure fluorescence lifetime.

Confronted by these limitations, Andrews began to think about building a more powerful microscope. "If I need an answer and there isn't any equipment or tool to get the answer, then I make one myself," he says. He had done that before, work that resulted in two patents and the launch of a spinoff company. This would be something else entirely.

It began with the Opera—a type of microscope, not a stage drama headlined by Pavarotti. The Opera is a spinning disc confocal microscope that produces ultra-high-resolution images.

It's unique among confocals in that it is fully automated. "It will take 100,000 pictures a day without you being there," says Andrews. This capacity to do high-content screening was perfect as a starting point for his reinvention of the tool, because he knew that to get the kind of data he wanted he would need truckloads of images.

He brokered a deal with the company that made the Opera, later acquired by PerkinElmer, to modify the system so that it could do fluorescence lifetime imaging microscopy, FLIM, the only way to measure protein-protein interactions in live cells. His first attempts fell short, though not fatally. "It didn't work very well. We realized there were problems with it, but that it showed tremendous promise," he says.

He also realized he needed some way to make sense of what he was seeing.

"You can ask all kinds of physiological questions [with this microscope] that you can't ask with a normal microscope, because you can get huge numbers of images. The problem is that you get huge numbers of images, and so you can't interpret them," he says.

For example, they did one genome screen that produced four million images, which was thrilling—except that no one could look at them. "So we had to write software that would interpret the images," he says.

Others had written software to interpret images automatically, but the programs were "philosophically different" from what Andrews had in mind. "All of that software depends on the observer being as close to perfect as he or she can be," he explains. "So the person whose data it is becomes the gold standard, and they decide, 'These are what I'm looking for, and these are what I'm not looking for.' And then the computer learns how to do that.

"Our approach was to say, 'I don't know what I'm looking for—if I'm going to knock out all the genes in the genome, I don't know what's going to happen—so I'm not the right person to ask which are the ones I'm interested in and which are the ones I'm not interested in. We had to teach the computer to learn for itself to find anything that wasn't normal. And if it found things that were not normal often enough, [then] it would group those together and say, 'When you knock out this gene, a whole bunch of cells all do something abnormal similarly, and here are those cells.'"

Needing to write this software "distracted" him from retooling the microscope, he says, laughing, and would swallow two of the five years he spent working on it. (The effort, still ongoing as his lab refines the program, was not for naught: in addition to giving him the capability he needed, it has led to a provisional patent for diagnosis of primary brain tumours with colleagues at the Sanford-Burnham Medical Research Institute in California.)

Distraction notwithstanding, reimagine the Opera they did, producing the first fully automated high-content screening microscope that can do FLIM. "It works," says Andrews. "And we can get what I was interested in getting all along, which was binding curves, because it's biochemical binding curves that the pharmaceutical industry uses to say whether or not a drug is working, and how well a drug is working and how it works—and we can do that now at high speed."

As significant an advance as the retooling of the Opera is, he notes it's not perfect. It cannot provide the level of detail he wants. And, it's terribly expensive. So, naturally, he's been building another microscope, one that he says will have much higher resolution, but operate at the same high speed and cost much less.

It will enable researchers to shut off genes or proteins associated with a particular disease or process, and see what happens next, snap!, just like that.

His invention is called the multiplexing streak camera. It solves the problem of how to measure the intensity, wavelength and fluorescence lifetime of light at once. Working with collaborators Dr. Qiyin Fang at McMaster University, INO in Quebec and Spectral Applied Research in Ontario (which helped build Canada's first space telescope), he cobbled together a prototype device. The team set up different microscopes using mostly off-the-shelf components and assembled them in such a way that they could take all three measurements by scanning a single beam across the sample. They then amplified the effort so that they could scan 100 beams at once. The next step involves a neat bit of physics that rearranges the data, which come out in a square array, into a tidy line of points.

"Once you have the line of points, you can take them and put them into a glass prism, and now all the colours separate from each other, and you can also put the line of points into something called a streak camera, and then you can measure all the fluorescence lifetimes. We can measure the spectra, the intensity and the lifetime 100 times faster than any other microscope," says Andrews.

They have secured two provisional patents and are setting up a company to commercialize the device. They're building a production prototype, which Andrews predicts will be functional within two years. It won't supplant the retooled Opera, however. He'll use the streak camera to analyze a relatively small number of samples in detail, whereas he'll use the Opera to look at lots of samples in less detail.

ON TARGET

This new capacity to study protein-protein interactions where they take place, in the membranes of live cells, opens up myriad possibilities for identifying drug candidates. It will enable researchers to shut off genes or proteins associated with a particular disease or process, and see what happens next, snap!, just like that. Together, the microscopes are part of a system that uses robots to store a massive library of DNA, pull samples out upon command and organize them in just the way a researcher needs for automated analysis. "It allows anyone who is looking at a disease to find and validate targets for treatment," says Andrews. "You can look at the effect of knocking down hundreds of genes, instead of looking at them one at a time, and then use the robot and the software and the automated microscopy to say, 'Of these hundreds or maybe thousands of genes, which are the ones I really need to go back and look at in detail one at a time?' You can also use the equipment to screen small molecules [drug-like chemicals]."

To wit, he has already identified two small molecules that will shut down the pro-cell-death proteins Bax and Bak in live cells. He plans to use these molecules in a stroke model, where just briefly knocking down these executioners reduces the impact of stroke by preventing the death of oxygen-starved cells, results he hopes will convince a drug company the targets are viable.

Moreover, he's identified 18 new Bcl-xl inhibitors (retrieved with robotic aplomb from a library of 35,000 compounds), an especially relevant finding in light of the promise being shown by other such molecules now in patient trials, including navitoclax, a small molecule in phase 2 clinical trials for chronic lymphocytic leukemia. So far, results show that navitoclax prevents some of the anti-cell-death proteins from thwarting the executioner proteins, thereby permitting cancer cells to fulfil their mandate of self-destruction, boosted by chemotherapy. As Andrews explains, because cancer cells are trying to die, their capacity to deal with stress is lower than is that of healthy cells. "What the Bcl inhibitors do is reduce that reserve capacity even more, so the tumours will start dying of their own accord. Plus, because the Bcl-2 family is already engaged, when you come in with chemotherapy, the cancer cells should have no reserve capacity left, and they should just explode."

The makers of navitoclax, Abbott and Genentech, have worked with Andrews to analyze their drug and sent people to his lab for training.

Andrews is also looking at if activating Bax can selectively kill cancer cells, sleuthing for drug targets within the cell death pathway for hormonally triggered breast cancer, and examining the links between the oncogene myc and apoptosis, all on the basis of early promising results from his lab.

The technologies Andrews and his team have developed are game-changers for the drug discovery process. There are many examples of drug targets that looked intriguing but that couldn't be studied outside their live cell environment. Perhaps more importantly, these devices will be able to impart information about a compound's toxic effects much earlier in the discovery process, saving time and money.

We won't wake up to a headline tomorrow proclaiming that new therapies for cancer based on controlling cell death are here. Although several such therapies are in clinical trials, it could be 10 or more years before we see such reports—if all goes well. But if it does, then the clinical implications are as headline-worthy as it gets. It means doctors would be able to stop giving treatments that poison the whole body, and that may or may not work, determined only by time, to giving those that work selectively by targetting genes and proteins, where the outcome is known, and without harming healthy cells.

THE GREATEST "TRICK" OF ALL

He calls himself a cancer researcher, but the labels biochemist, engineer and medical biophysicist fit as easily, though perhaps not all on one business card. There's one more title that could be added: magician. Not for his science—though one could say that whoever succeeds in revealing these life-and-death mechanisms and designing therapies to control them will in effect become a wizard of apoptosis, able to switch on and off vital cell processes at will, no sleight of hand involved—but for his avid interest in performing stage magic, one he has held for twice as long, 40 years, as he's been studying apoptosis.

It's the psychology that grabs him the most, he says. "There are all the different kinds of people that will come and look at you and watch what you're doing. Some are fun. Some are not. But the people who enjoy it and don't mind suspending disbelief for a few minutes so that we can have fun and interact with each other, that I really like. I like it to be fun."

Fun like running smack into the wall of one science stumper after another, solving only some, but always pressing on, eye on the prize.

"I would desperately like to have enough money so that I would not have to write grants, not have to worry about all that stuff, and take on something high-risk, high-gain, and really plough all of my resources into it for 10 years to see if we can really accomplish something.

"I don't know exactly what it would be, but it would be something in the cancer therapy direction, with the Bcl-2 family of proteins. I would love to be able to map all of the interactions between them in such a way that you could really determine how they're regulating the physiology of the cell. Because if you understood exactly what it is that they're doing, then you would know how to manipulate them to have an impact on patients."

Andrews' research is funded by the Canadian Cancer Society Research Institute, Canadian Institutes of Health Research, Canadian Stroke Network and the Ontario Institute for Cancer Research. Infrastructure support was provided by the Canada Foundation for Innovation, Natural Sciences and Engineering Research Council, and Ontario Ministry of Economic Development and Innovation.

1. Google Scholar. Accessed January 31, 2012.
2. Kerr, J. F. R., Wyllie, A. H., & Currie, A. R. (1972). Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. *British Journal of Cancer*, 26, 239–257.
3. Google Scholar. Accessed January 31, 2012.

Interventional cardiology, where doctors use catheters to open narrowed arteries of the heart, is the gold standard of care for patients with heart disease. To be successful, doctors have to be able to see where they're going, a tough task in the case of stubbornly clogged blood vessels. To beat this problem, a scientist has invented a device that enables doctors to visualize previously invisible corridors of the heart BY ALISA KIM

Out of the Dark

Computer scientist and visual artist John Maeda, widely known for his book *Laws of Simplicity*, argues that "thoughtful reduction" and the skilled application of knowledge are ways to enhance design. Maeda, a technology and design expert, points to the iPod's spare gadgetry as an example of the kind of elegance and functionality that can be achieved through simple, yet carefully considered design. Of the computer giant, Maeda has said, "Apple products aren't simple technologies by any stretch, but there is a beautiful simplicity to them."[1]

Dr. Charles Cunningham, a physicist in the Schulich Heart Research Program at Sunnybrook Research Institute (SRI), has invented a medical device with a simple design to tackle a complex health issue. Over the last four years, Cunningham has developed a technology for use in the treatment of blocked coronary arteries, the most common form of heart disease in the western world.

The heart is the body's most important muscle. Always at work, it moves over 11,000 litres of oxygen- and nutrient-rich blood around the body each day. Vital to this circulation are healthy coronary arteries. As we age, lipids floating in the bloodstream, coupled with an inflammatory process, can form a plaque that protrudes from the inner walls of the blood vessels. The buildup of this plaque restricts blood flow to the heart. A coronary artery that is completely blocked for longer than three months is called a chronic total occlusion (CTO).

Cunningham's device was designed to improve the success rate of CTO crossings, a procedure in which interventional cardiologists open a narrowed artery by passing a guide wire with an empty balloon at its tip (a balloon catheter) through the middle of the months-old blockage. The guide wire is inserted through a needle puncture made in the upper thigh. Under X-ray guidance, the wire is snaked through the passageway of the affected vessel, into the blockage, where the balloon is inflated to crush the plaque and restore blood flow. Although a CTO crossing is preferable to coronary bypass surgery, because the latter requires hospitalization and longer recovery, it accounts for just 10% of all percutaneous or through-the-skin cardiac treatments.

The main reason that CTO crossings fail is cardiologists' inability to pass the guide wire through the occlusion, a function of the limitations of current imaging practices. The procedure is normally done via X-ray angiography, through which images are obtained using a fluoroscope and an X-ray dye that is injected in the patient's artery to highlight it on X-ray images. In a patient with a CTO, the flow of the dye stops at the blockage, which prevents clinicians from seeing the wire and the vessel past the occlusion—crucial information if they are to perform the procedure safely and effectively.

DR. CHARLES CUNNINGHAM; PHOTOGRAPHY: CURTIS LANTINGA

DR. WILLIAM DOMINGUEZ-VIQUEIRA AND DR. CHARLES CUNNINGHAM

Magnetic resonance imaging (MRI) overcomes this constraint by providing contrast between the blocked part of the vessel and the surrounding tissue, without any dye. "That's the big advantage of MRI: being able to see the path of the occluded vessel, the device and the open vessel all at the same time," says Cunningham, who is also a professor in the department of medical biophysics at the University of Toronto.

The CTO crossing can also be troublesome because many plaque deposits have a hard, fibrous "cap" covering the first segment of the blockage, making the lesion harder to penetrate. Further, while angiography provides images of the open part of the vessel in real-time, MRI reveals the plaque's structure, including calcifications and softer, lipid-rich areas that are easier to treat. Cardiologists need adequate depiction of the vessel wall boundaries and the make-up of the lesion to figure out the proper path of the wire to avoid puncturing the artery.

Electronic tracking devices that work well with MRI can be built, but pose safety risks if used inside patients while they are in the scanner. Moreover, such devices are complex and expensive to manufacture, an unviable option given that in this setting they would be used just once. Needed is a safer and cheaper way to locate the position of a device using MRI during coronary diagnoses and treatments.

Enter Cunningham's catheter tip.

"What our device gives is position and orientation information—how the device is positioned against the occlusion. It will enable visualization of the part of the occlusion where the dye won't go. We're hoping [the interventional cardiologists] will wheel the patient into the MRI scanner and for that step, where they push through the first part of the occlusion—the hard-to-cross part—that it can be done under MRI guidance using our device," he says.

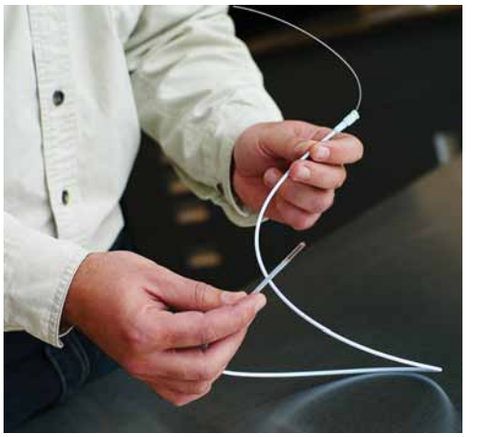
Part of Cunningham's lab is housed within SRI's Imaging Research Centre for Cardiac Intervention, a state-of-the-art facility that contains an integrated X-ray and MRI suite—an appropriate setting for the creation of this device. The technology evolved out of his interest in magnetic susceptibility, the tendency of a material to become magnetized in response to a magnetic field. In particular, he was intrigued by the way in which devices with magnetic material can be detected through the "dark spot" they create in the MRI scan. This dark spot, created by the magnetic-field disturbance from the device, is what's known as an artefact—something that appears in the image, but that doesn't exist in the object itself. The artefacts from devices can be useful in that the dark spots they produce on MR images allow devices to be tracked. Artefacts are also problematic, however, because they prevent images from being taken at the device's tip.

The beauty of Cunningham's catheter tip is that it allows the user to control the appearance of artefacts.

"Say you're looking at the plaque in the artery. You can't image right by the tip [of the catheter] because the artefact is so big," says Dr. William Dominguez-Viqueira, a research associate in Cunningham's lab who helped develop the device. "With this, you can produce a big artefact just to see where you are, then change the position of the device to remove the artefact to do images right at the tip."

The design of the device is clean and minimal. About three centimetres long and only three millimetres in diameter, it is shorter than a standard paperclip, but resembles a much smaller and lighter triple A battery. The device attaches to the end of a catheter and consists of an outer titanium layer, a middle graphite layer and a titanium wire on the inside. Cunningham used these materials because in addition to being inexpensive and plentiful, they have roughly equal and opposite magnetic properties.

Titanium is paramagnetic: it has a positive magnetic susceptibility and is slightly attracted by a magnetic field. Graphite is diamagnetic: it has a negative magnetic susceptibility and is slightly repelled by a magnetic field. In the "off" position, the parts are aligned and the magnetic fields of the materials cancel out one another. A minimal artefact appears on the image, allowing the user to see what is at the tip of the catheter. When the graphite layer within the device is moved using a wire running down the catheter, the effect from the device is "turned on." The resulting magnetic disturbance produces artefacts at both



In particular, he was intrigued by the way in which devices with magnetic material can be detected through the "dark spot" they create in the MRI scan.

ends of the device, allowing the interventional cardiologist to see the exact position of the device and its orientation relative to the occlusion on the MR image.

Cunningham used computer models to study the magnetic fields created by differently shaped parts and how they would work together, which streamlined the design process. "We were able to figure out the thicknesses and geometry of the device in a computer model and use that to have the pieces manufactured. Otherwise you'd have to try and make the device with a whole bunch of test thicknesses and test them all to see which one was better. We did all of that in the computer and just made the one device that worked," he says.

Building the first tip was fairly straightforward. "We made this in a conventional machine shop using a lathe and drill, to drill out the centre," says Cunningham, holding up a clear container with the first prototype suspended in water, to simulate the inside of a blood vessel. "We did the experiment where we had this in the MRI scanner moving the pieces and seeing the effects come and go. We got to that step pretty quickly."

Shrinking it to fit onto a catheter, however, proved to be more challenging. "We began with a really big tip. This was to prove that the materials work. To do the machining for this tiny thing is not easy," says Dominguez-Viqueira, who worked on miniaturizing the device.

He and Cunningham spent a lot of time sussing out a manufacturing facility that could make the components to the appropriate size and thickness. They had to send the parts to a plant in the U.S. that does microelectrical discharge machining, a specialized technique for drilling tiny holes using high-voltage sparks. They are now able to build prototypes more efficiently at SRI, with the recent opening of the device development lab that is part of the research institute's Centre for Research in Image-Guided Therapeutics. "In terms of prototyping, we'll definitely do it here because even if we license it, we'll have something to show that works—something that's the right size and the right feeling for cardiologists to actually use," says Cunningham.

With the scientific research for the project completed, more funding is needed to move the technology further along the innovation pipeline. In the months ahead, Cunningham plans to build a large number of prototypes to send to cardiologists for evaluation. He and Dominguez-Viqueira have already filed an international patent for the device; they now need to decide in which countries they will do national patent applications, which cost about $10,000 each.

Cunningham has partnered with MaRS Innovation, an organization that works with SRI and other Toronto-area research institutes to commercialize promising discoveries. Dr. Fazila Seker is a project manager at MaRS Innovation who is working with Cunningham to advance this process. While researchers look at their breakthroughs from a scientific viewpoint, MaRS Innovation looks at technologies strategically, with a view to translating them into marketable products and services.

Cunningham and Dominguez-Viqueira, along with Seker and other staff from MaRS Innovation, comprise the "deal team." Together, they will decide what the next step will be, whether it is meeting with companies who may be interested in licensing the technology or forming a startup company. "If it's decided that a startup is the way to go, [then] the next step is to raise capital and start looking at hiring the right type of expertise," says Seker.

She says that MaRS Innovation offered its product management and business development services to Cunningham because the technology shows commercial potential. "The device is unique in that it looks at the interventional MRI market opportunity. That's really the way of the future when it comes to imaging. There aren't a lot of devices on the market that would work well with MRI so it's very much a development area," she says.

The technology has been developed as a standalone catheter, but the magnetic tip of the device can be integrated into existing catheters. It is ready for preclinical testing. In addition to making more prototypes to give to cardiologists, Cunningham must obtain government approval to use the device in clinical trials, all of which could take a few more years. Like Seker, he believes MRI research is a field in which there is room for innovation. "Research on devices for use inside the MRI scanner is a really fascinating area that, I think, has yet to reach its potential. Catheters that are available commercially would be a big step forward. That's what we're trying to do: make devices that work and can be sold for a reasonable price."

Cunningham's research on catheters is funded by the Canada Foundation for Innovation, Canadian Institutes of Health Research and Ontario Ministry of Economic Development and Innovation.

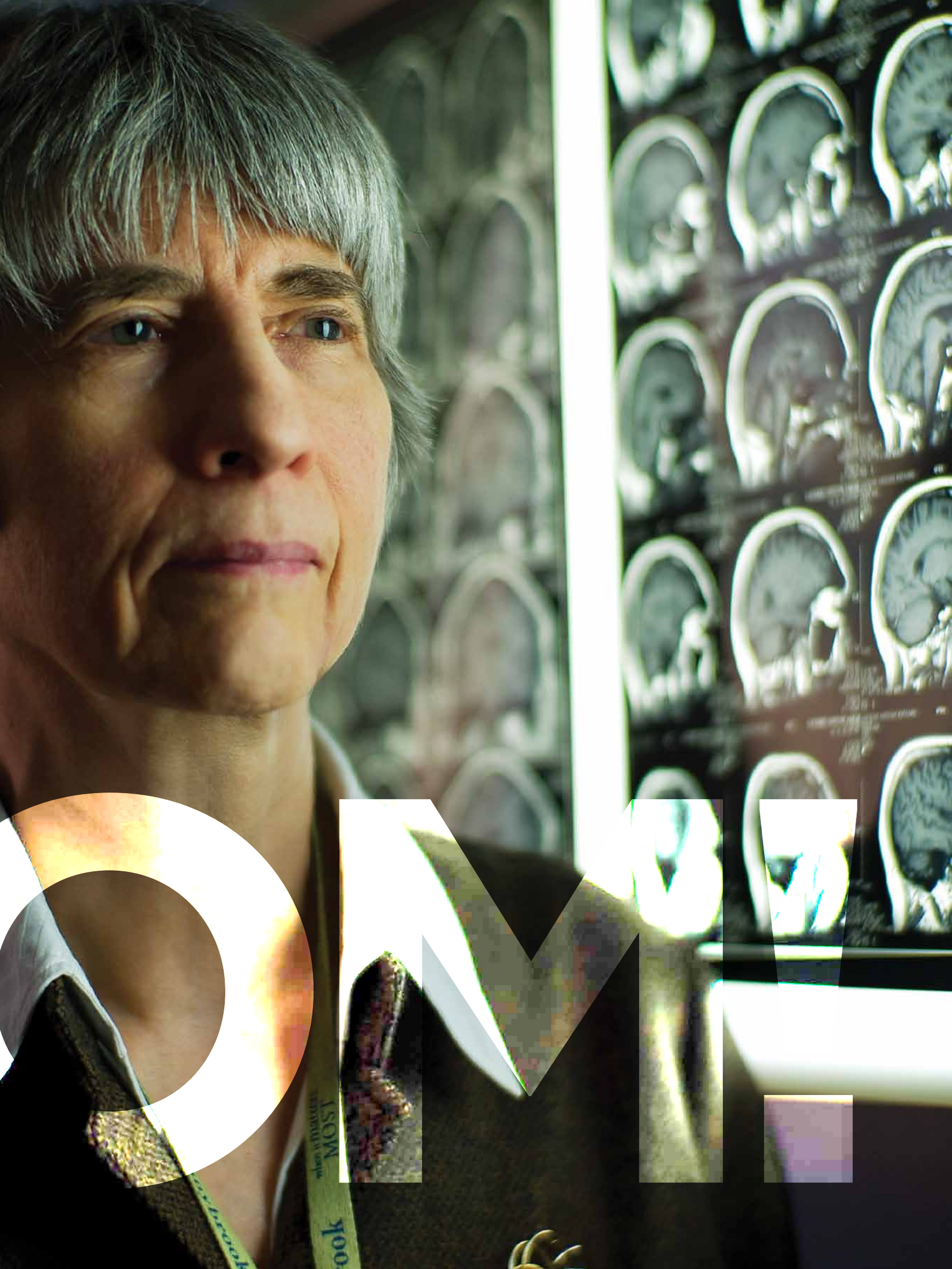
1. John Maeda, "Why Apple Leads the Way in Design," *Huffington Post*, http://www.huffingtonpost.com/john-maeda/technology-design-apple_b_291748.html

As the over-65 set swells, and with it the number of people with dementia, the question arises: at what cost to family caregivers?

BY ALISA KIM

BOOM, BABY, BO

DR. SANDRA BLACK


MOST

"SOMETIMES IT'S VERY HARD," HE SAYS, STRUGGLING TO CONTAIN HIS EMOTIONS. "BUT LIFE GOES ON." Luis Jaramillo

In the early '90s, Scott McMeekin started to see the first signs that his mother's brilliant mind was beginning to slow. During spirited family debates, his mother would become uncharacteristically withdrawn. "She was still bright and articulate, but was starting to find it hard to keep everything sorted out in that kind of conversation," he says.

His mother was in the early stages of Alzheimer's disease (AD).

In 2011, the first of the "baby boomers" (those born between 1946 and 1964) turned 65. In 20 years they all will be seniors. Most will be healthy; some won't. As Canada ages, policy makers, economists and researchers have turned their attention to the sustainability of social programs and the health care system. The cost of caring for this population—dubbed the "silver tsunami"—is not just financial. There is also a significant social, emotional and mental toll on the family caregivers of people with chronic, debilitating conditions like AD and other dementias.

"It may seem like scare tactics, but the numbers are very, very worrisome. When you do the projections, it's clear that there is a very big challenge ahead," says Dr. Sandra Black, director of the Brain Sciences Research Program at Sunnybrook Research Institute and a cognitive neurologist specializing in stroke and dementia.

Overall, people are living longer. In developed countries, life expectancy has increased dramatically. Statistics Canada has predicted that by 2036, the average life expectancy of men and women will be 84 and 87 years, respectively. In the next few decades, seniors will represent a greater share of the population: 25% by 2036, compared with 14% in 2010.

In Canada, health care spending per capita on seniors is more than four times that on adults aged 20 to 64 years. While seniors use proportionally more hospital and physician services, home care and prescription drugs, compared with non-senior adults, researchers are careful to note that the increasing number of chronic conditions, not increasing age, is what drives primary health care use.

The problem is that advanced age is associated with a higher risk of having chronic conditions such as diabetes, cancer and heart disease. "Age is one of the most consistent risk factors for dementia, as it is for stroke. These conditions start to double in prevalence for each decade over 65. Diseases of aging are going to increase, because we're maintaining people into the eighth and ninth decades, almost twice the average lifespan at the turn of the 20th century," says Black, who is also a professor in neurology at the University of Toronto.

Alzheimer's disease is the most common form of dementia. It is marked by progressive cognitive decline. One of its early symptoms is difficulty remembering new information; because it's a degenerative disorder, symptoms worsen over time. Confusion, impaired judgment, difficulty with language, and changes in personality and behaviour are its scourges, gradually robbing people of their ability to live independently. It can also be distressing because of the behavioural and psychological symptoms, which include anxiety, depression, aggression, apathy and delusions.

A 2010 study commissioned by the Alzheimer Society of Canada estimates that the annual economic cost of caring for the half-million Canadians who have AD or a related dementia is $15 billion. This includes the cost of providing care, indirect costs such as lost wages for the person with AD and opportunity costs, the wages that informal caregivers could have earned had they been able to work. Within 25 years, the yearly cost of caring for the estimated one million Canadians who will have dementia could rise to $150 billion.

Drs. Nathan Herrmann and Krista Lanctôt are researchers at Sunnybrook Research Institute who study the social and economic cost of AD. "We know from the demographics that there's going to be huge numbers of patients in the 85-plus age group, and in that age group, 26% of people will have AD. As that demographic expands, the absolute number [of people with AD] is going to become huge," says Lanctôt, who is also a professor of psychiatry and pharmacology at U of T.

In a paper published in the *Canadian Journal of Psychiatry* in late 2010, Herrmann and Lanctôt showed that the cost of caring for community-dwelling AD patients is higher with increased disease severity. Moreover, indirect medical costs, which include home care by caregivers like family and friends, and loss of productivity by patient and caregiver, formed the bulk of the overall costs of AD at most levels of the disease.

"Interventions to treat AD have not paid enough attention to caregiver outcomes," says Herrmann, who is also the head of geriatric psychiatry at Sunnybrook Health Sciences Centre. "There's still not a clear idea of what is the gold standard in terms of an outcome measure for caregivers—whether we should be focusing on caregivers' emotional health, physical care or caregiver cost of care as outcomes for these particular studies."

Black, who not only does extensive research on AD, but also diagnoses and treats symptoms of it, published the results of a survey of Canadian caregivers of persons with AD or other dementias. She found that the impact of caregiving is broad and deep.

"There's huge morbidity in the caregivers. They get more depressed. They end up using more health care dollars for medical illnesses. They're stressed. So this is not a disease of an individual. This is a disease of the caregiving circle," says Black.

Her research showed that live-in caregivers are especially vulnerable. Luis Jaramillo is caring for his wife of 19 years, Tina, aged 59, who has early-stage AD. Last year, the couple moved from Brampton to Guelph to lower their cost of living so that they could live on his income alone. At 61, an age when many consider retirement, Jaramillo has shifted his hours at the manufacturing company where he works full-time in order to care for his wife. "Sometimes it's very hard," he says, struggling to contain his emotions. "But life goes on."

Jennifer, Pam and Susan MacDonald (not their real names) are sisters who are caring for their mother, aged 79 years, who also has early-stage AD. Although their mother is able to live independently—she can cook and run basic errands—she relies on her daughters for more complex tasks, such as managing finances.

The sisters are busy with their careers and families, but one of them sees their mother daily. "We have to give her the medication every day. We've taken over all her finances and all the mail because she doesn't distinguish between what is important and what isn't. She thinks junk mail is important. We have taken over paying the bills. Simple banking like withdrawing cash is fine. Anything beyond that, she needs help," says Susan.

They are fortunate in that they can lean on each other and share the caregiving. "We turn to each other for support a lot. Every time any combination of the three of us talks, it's one of our top topics," says Pam. She says that the toughest part of the situation is missing the parent she grew up with. "[My mother] has always been very wise and had really good advice. Now, sometimes if you have conversations about issues in your life, she kind of listens

"TO ME, IT SEEMS LIKE SHE IS MY CHILD INSTEAD OF ME BEING HER CHILD." Susan MacDonald

and then she's onto, 'I don't have any bread now,' and she's back to her microcosm. That's been hard because it's a real change in her personality."

For Susan, caregiving has involved a reversal in roles. "To me, it seems like she is my child instead of me being her child. It's like having a teenager where they're kind of OK on their own, but you're worried if they're going to get into trouble. [Safety] is a real worry."

The MacDonald sisters say their mother is doing far better than they had expected owing to treatment that has stabilized her symptoms. "A year ago around Mother's Day when she was being diagnosed, I thought, 'A year from now, is she going to even know who we are?' But thankfully, she does. She hasn't declined that much in the last year because of the medication," says Susan.

For McMeekin, who has cared for his mother since 1998 when she was diagnosed with AD at 77 years, medication that helped manage her symptoms also made things easier. "We were lucky in that my mom was on a fairly low-dose antidepressant that worked well," he says. "My mom was generally pretty happy. You'd go in and she'd smile. It would have been a different story if my mom had been miserable."

McMeekin says that although caring for his mother was an added responsibility, he didn't feel burdened by it. "I have a hard time classifying it as a sacrifice. There's always a bit of worry about how they're doing, but that's an issue whether your parent has Alzheimer's or not. When their health starts to fail, you have to be a little bit more involved. It was a privilege to be able to do it," he says.

While progress has been made in managing symptoms of AD, there are no therapies that will change the underlying disease. Treating it early on or delaying it from setting in would buy people more time and result in better quality of life and significant savings. "The good news is that because of the age factor, if we can push back the onset of dementia by five years, we can actually reduce the prevalence [of disease] by 50%," says Herrmann.

More research is needed on earlier detection of the disease and to understand better its progression. Sean Nestor is a medical and doctoral student at U of T who is supervised by Black. He is working to characterize AD better by developing tools that show what is happening in the brain of a person with AD at any given time and over the course of the disease. He has developed software that can be used to measure changes in the hippocampus, a structure in the brain that governs memory and spatial navigation.

"The hippocampus is an area of the brain that's targeted early in the disease and shows a lot of atrophy. Historically, it's been very challenging to make automated tools to segment out this structure. It takes a long time to manually trace, and it's not feasible in the clinic or even in research," says Nestor. He says that loss of volume in the hippocampus may be an indicator of disease that could help clinicians make a diagnosis of AD.

Nestor is also studying whether cerebrovascular disease (conditions that limit or halt blood flow to the brain) worsens cognition in people with AD by comparing the brains of people with both diseases with those with only AD. He has found that even though patients with cerebrovascular disease and AD can show the same cognitive deficits as people with AD alone, there is less hippocampal shrinkage in the patients with both diseases, leading him to believe that the cerebrovascular disease may be damaging patients' brains differently.

"Imaging markers can add value to cognitive test scores because, for instance, they might tell us that a person with AD has a lot of cerebrovascular pathology and less hippocampal volume shrinkage. This suggests that there might be other strategies to treat this person compared to someone with no cerebrovascular disease and AD," he says.

For people with cerebrovascular disease or AD, managing risk factors for heart disease is important, especially early on. "Usually what's good for the heart is good for the brain," says Black. "The risk factors for heart disease and stroke are the risk factors for dementia. There's a lot more we could be doing to control the big ones: hypertension, high cholesterol, diabetes, obesity, smoking, etcetera. We've got to treat those as vigorously as possible because that will keep the brain healthier for longer."

On a macro level, Black says that Canada needs a national action plan for dementia that will bolster research and support for patients and caregivers. For those like Jaramillo, who is the sole caregiver, such help cannot come soon enough. He and Tina were finally able to get government benefits after three years of trying, but they're still waiting on approval of their application for a support worker who would help out twice a week. "It's very hard for her, but I do my best," he says.

As scientists try to come up with disease-modifying therapies and treatments that will delay the onset of AD, McMeekin, whose mother passed away in December 2011, has some encouraging words for caregivers: "You have to focus on what's left and not what's gone. You have to remember it's not about you anymore. For everything that was lost, even to the end there was still an awful lot of my mom there."

Black's research is funded by the Alzheimer Society of Canada, Canada Foundation for Innovation, Canadian Institutes of Health Research (CIHR), Canadian Stroke Network, Heart and Stroke Foundation (HSF), National Institutes of Health (NIH), and Ontario Ministry of Economic Development and Innovation.

Herrmann and Lanctôt's research is funded by the Alzheimer Society of Canada, CIHR, HSF Ontario, NIH and Ontario Mental Health Foundation.

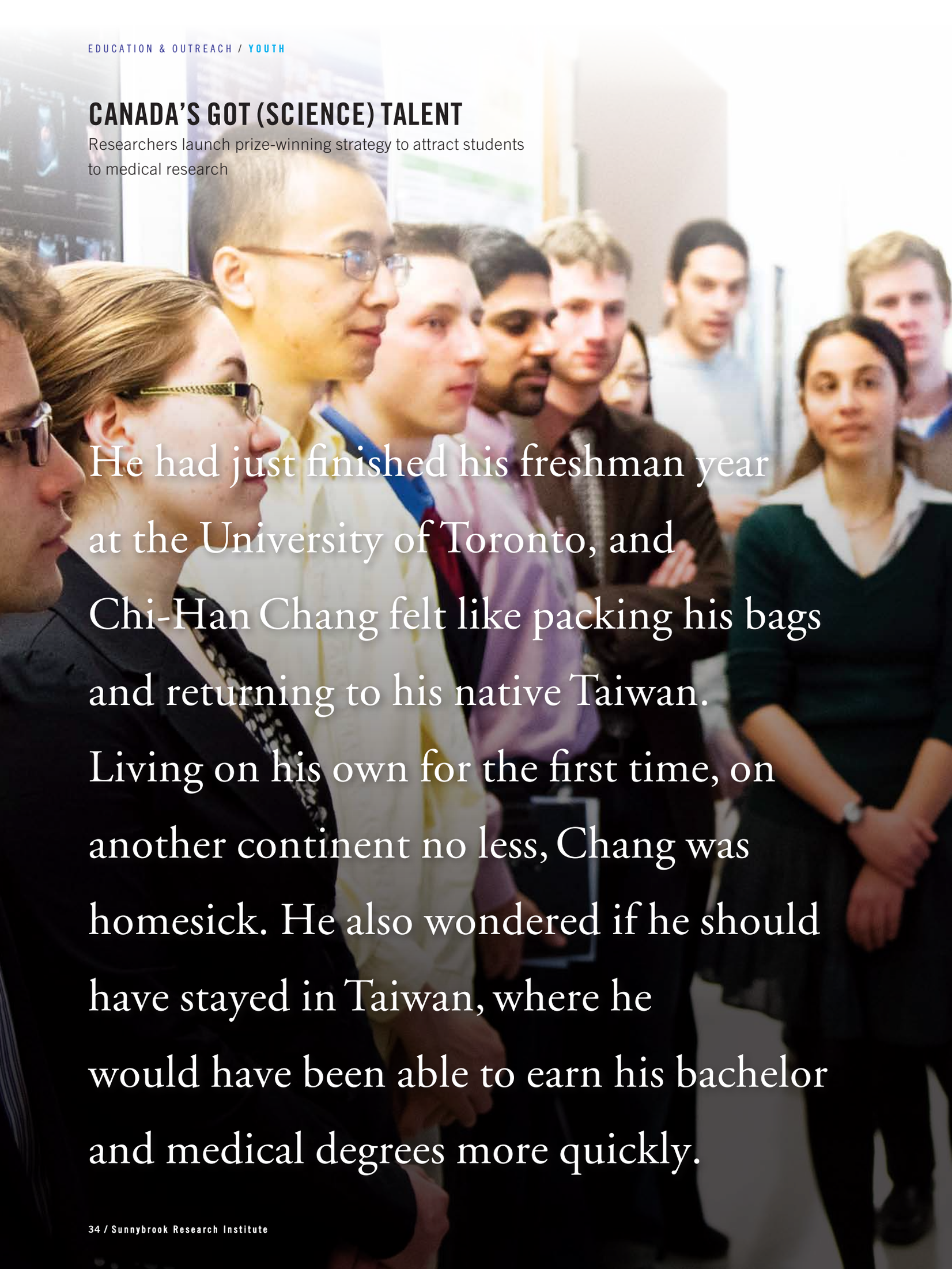
Nestor's research is supported by the CIHR.

DR. SANDRA BLACK AND SEAN NESTOR

PHOTOGRAPHY: CURTIS LANTINGA

CANADA'S GOT (SCIENCE) TALENT

Researchers launch prize-winning strategy to attract students to medical research



He had just finished his freshman year at the University of Toronto, and Chi-Han Chang felt like packing his bags and returning to his native Taiwan. Living on his own for the first time, on another continent no less, Chang was homesick. He also wondered if he should have stayed in Taiwan, where he would have been able to earn his bachelor and medical degrees more quickly.

"It got me more excited about medical physics. I knew I wanted to do research, but it gave me great exposure in terms of medical physics and imaging in particular," Cui says.

"I was unsure whether medicine was a better path for my undergraduate education, or [whether] basic science [was]," says Chang, a fourth-year physics and chemistry student. "I was convinced to stay, because at that time I hadn't done any research, and someone told me that I should do at least one research project before deciding to leave."

The decision to stay in Canada would prove to be a critical one for Chang. He found one of his passions: research. The 22-year-old has spent the last two summers working with professors from U of T thanks to two undergraduate awards he received from the Natural Sciences and Engineering Research Council of Canada. "I'm really excited not just about the results, but the whole process of research," he says.

Stimulating enthusiasm for science and discovery in students such as Chang is a priority for scientists at Sunnybrook Research Institute (SRI), who are mentoring the next generation of problem-solvers. Dr. Kullervo Hynynen, director of the physical sciences platform at SRI, says he thinks it's important to give high-school and undergraduate students hands-on research experience. "When I was an undergraduate, I had no idea of the opportunities in research," he says. To give younger students the opportunity to work in a lab, Hynynen and fellow SRI imaging scientist Dr. Rajiv Chopra offer summer placements to high-school students enrolled in the enriched math and science program at Toronto's Marc Garneau Collegiate Institute, through its TOPS program, which stands for Talented Offerings for Programs in Science.

The physical sciences faculty at SRI last year launched another outreach initiative: the Sunnybrook Prize. This annual, national award recognizes excellence in undergraduate research. The idea for the award came out of staff meetings about a year ago. "The imaging scientists here have lots of students, including summer students, who are undergrads. They do important work, but sometimes it doesn't link to a paper. We wanted to make a prize that would recognize their contribution," says Hynynen, who holds the Canada Research Chair in Imaging Systems and Image-Guided Therapy and is a professor at U of T.

The prize is open to physical sciences and engineering students who are in their final year at a Canadian university, and who have completed a research project. The $10,000 prize is funded by income generated by royalties from technology developed by SRI scientists. Dr. Graham Wright, director of the Schulich Heart Research Program at SRI and one of the competition's judges, thinks the award is a worthwhile investment.

"We think it very important to encourage the top undergraduate students to consider research as a career option," says Wright, who holds the Canada Research Chair in Imaging for Cardiovascular Therapeutics and is also a professor at U of T. "The value of the prize reflects our commitment to building this talent pool. The funding comes from revenues generated through companies spun out from Sunnybrook research. Those spinoffs wouldn't have been possible without the type of students recognized by the prize. Such students were central to the founding of past spinoffs and will be critical to the development of an innovation economy in Ontario and Canada."

In January, Chang and nine other students from universities across Canada were invited to SRI to present their work as part of the first competition. Sunnybrook Research Institute covered the travel and accommodation costs of the finalists who live outside Toronto. There was a diversity of projects that ranged from those tackling problems in basic science to those with an applied research focus. Although the students' backgrounds were different, what they had in common was potential for success, as Hynynen said during his opening remarks at the competition: "Each of you has huge talent. You can be anything you want and make lots of money, but we need you. We hope you will work in science and make the contributions we all need."

Each finalist had 15 minutes to present and answer questions from the judges. "I was a bit nervous, to be honest," says Chang, who was the first presenter of the day. He described his research into the problem of entanglement in photosynthesis, a phenomenon in physics that supports the existence of long-range quantum behaviour in biology.

Cheryl Cui, an engineering student at U of T, showed no signs of fatigue even though she had caught a red-eye flight from Haiti in order to give her talk. Cui, who is interested in point-of-care medicine in developing countries, discussed her role in creating a device that captures and detects cancer cells. She says that taking part in the competition and hearing more about the research of SRI scientists,

PHOTOGRAPHY: DOUG NICHOLSON

LEFT TO RIGHT: DR. KULLERVO HYNYNEN, JONATHAN LIPSITZ, CHERYL CUI, CHI-HAN CHANG AND ERIC MOULT

particularly its translation to the clinic, reinforced her desire to pursue a career in research. "It got me more excited about medical physics. I knew I wanted to do research, but it gave me great exposure in terms of medical physics and imaging in particular," Cui says.

Eric Moult, an electrical engineering student at Queen's University, is also interested in the clinical impact of research in medical imaging. He was a finalist for his research into prostate brachytherapy, a treatment for prostate cancer in which radiation is delivered via radioactive seeds that are implanted in the prostate. For the last two years, Moult has been a member of the Laboratory for Percutaneous Surgery at Queen's University. He has been working on an enhanced X-ray image computing technique that will allow clinicians to see the seeds and the prostate better during brachytherapy.

"It really grew on me," says Moult about the project. "I never took biology in high school. I was more of a math and physics person. I really got into the interdisciplinary interaction between clinicians and engineers and biologists."

The technology is now in clinical trials at Johns Hopkins Hospital in Baltimore, Maryland. "It has the potential to really make a difference. It sounds like things are going really well down there. It's pretty exciting to make contributions to something that can be useful," he says.

Although unrelated to medicine, Karl Ayton's research project also impressed the judges. Ayton is a physics and chemistry student from Grant MacEwan University who travelled from Alberta to discuss his work. He and his supervisor, Dr. Samuel Mugo, have developed plant-based waxes that can be substituted for petroleum products used in gasoline, asphalt and various consumer products. Mugo has filed for a provisional patent for the waxes.

"We don't have a mass-produced product that's ready to go on the shelves, but we have a prototype that we can further develop," says Ayton, over the telephone from Edmonton. "It's a step in the right direction in terms of environmental protection and sustainable, renewable resources."

Following the presentations, Wright, Hynynen and the half-dozen other physical sciences faculty in attendance were charged with the unenviable task of selecting a winner. After a lengthy discussion and a vote to break a three-way tie, the judges reached their decision. "It was difficult choosing a winner. You are all stellar. You will have great futures. There is no doubt about it," Hynynen told the group.

With the students on the edge of their seats awaiting the verdict, Hynynen announced Chang as the winner.

Wright says he was impressed with the quality of Chang's work, as well as his communication skills. "They were all outstanding, but what stood out for me was his capacity to explain the concept. It's very complicated physics, quantum entanglement. He conveyed the challenges and interesting aspects of the idea in a very effective way."

Chang says it took a few days to recover from the shock and excitement of winning the award. "I was really surprised," he says. "My research is related to transbiology, not medicine. I thought another person would win. I think it shows that SRI is open to several different disciplines."

He isn't the only student who thinks this. After touring the facilities, including the newly built Centre for Research in Image-Guided Therapeutics, Cui saw first-hand the interdisciplinary research that happens at an academic teaching hospital. "It's a very unique environment where you have engineers working with clinicians," she says.

Both Ayton and Moult are thinking about becoming clinician-scientists. Ayton says his visit to SRI helped him realize he has many career options. "I think a lot of students think that whatever degree they get, they're locked into that for life. You can do a number of degrees but you can still end up doing what you like if you realize your tastes change. Dr. Wright is certainly proof of that."

Ayton was referring to a talk in which Wright shared his experiences with the finalists, along with some words of advice. An engineer by training, Wright spoke of how much he enjoys medical research and why he finds it meaningful. "You are at a critical stage in your education where you have choices to make about your future. Hopefully that choice is driven by what's going to be satisfying at the end of the day. Health research is not just about coming up with a neat idea, but the opportunity to see that idea used for the benefit of patients."

As for Chang, he hasn't ruled out medical school, but he says his PhD will come first and that winning the Sunnybrook Prize has helped him see he is on the right track. "This is definitely an encouragement to pursue interdisciplinary research—integrating different sciences for useful applications in either biomedical science or other disciplines."

For all of the finalists of this year's prize, the future is wide open. — Alisa Kim

WITH WHOM WOULD YOU MOST LIKE TO HAVE DINNER, AND WHY?

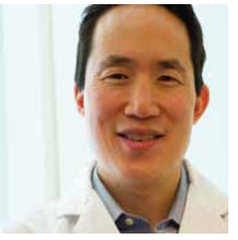
Choosing from among the fascinating, inspiring people in history with whom to break bread is no easy decision. Three researchers at Sunnybrook Research Institute offer their top picks.

Dr. Michele Anderson

Senior Scientist, Sunnybrook Research Institute
Associate Professor, Department of Immunology, University of Toronto

If I were able to have dinner with anyone in history, I would choose Marie Curie. From humble beginnings, she rose above the common belief that women were not intellectually fit to make scientific discoveries to become a two-time Nobel Prize winner, working in close collaboration with her husband, Pierre. It was in part due to her story that I came to believe that, as a woman, being a scientist and a mother and a wife were not incompatible goals. Like her, I am married to a fellow scientist and have two children. Her children were girls, and ours are boys, however, and this is obviously why we have not yet achieved a Nobel Prize! Seriously, though, I would want to hear her story firsthand, with all the struggles, sorrows and triumphs, in hopes of learning something that might guide my own rocky journey through this life I have chosen.

Anderson's research is aimed at understanding the role of transcription factors in T cell development.



Dr. Stanley Liu

Scientist, Sunnybrook Research Institute
Radiologist, Sunnybrook Health Sciences Centre
Assistant Professor, Department of Radiation Oncology, University of Toronto

Time listed Dr. Randy Pausch as one of the top 100 influential people in 2008. He was a pioneer in computer-human interface design who bridged computer science with art, and helped nurture the next generation of computer programmers. But what sets him apart? Why request dinner with Randy? It's because he inspired and moved me, and many others, with his last lecture, Really Achieving Your Childhood Dreams. He was dying from pancreatic cancer, but you wouldn't have known it. He delivered a down-to-earth, inspirational and humorous yet frank lecture about valuable lessons he learned in life. It has been viewed over 14 million times! A book based on his lecture reached the *New York Times* bestseller list. With his limited time, he testified before Congress in support of pancreatic cancer research, and inspired many others during media appearances. To quote Randy, "I mean, I don't know how to not have fun. I'm dying and I'm having fun. And I'm going to keep having fun every day I have left. Because there's no other way to play it."

Liu is working to improve treatment outcomes for cancer patients by researching and integrating novel, molecular, targeted agents with radiotherapy.

Dr. Alan Moody

Associate Scientist, Sunnybrook Research Institute
Radiologist-in-Chief, Sunnybrook Health Sciences Centre
Chair, Department of Medical Imaging, University of Toronto

"Mr. Churchill, you are drunk!" "Yes, madam, and you are ugly. But in the morning, I will be sober, and you will still be ugly." As the wife of a prominent politician learned to her cost, dining with Winston Churchill was a dangerous business—but never dull. A "dunce" at school, Boer War hero and First World War failure, he nearly caused the death of my grandfather at Gallipoli, and his funeral is one of my earliest memories. His life was one of ups and downs, failure and success, but never self-doubt—a life of "luck," self-made and exploited. He would have made a great researcher! He picnicked on the Normandy beaches on D-Day, ate caviar with Stalin, hosted presidents and kings—there's no doubt the menu would match the man. And to finish, coffee, of which Lady Astor said, "Winston, if I were married to you, I'd put poison in your coffee." To which he replied, "Nancy, if you were my wife, I'd drink it."

Moody is developing and assessing imaging techniques to help improve early detection and intervention in vascular disease.

PHOTOGRAPHY: DOUG NICHOLSON; DR. STANLEY LIU: CURTIS LANTINGA

TO A "T"

Not all researchers have a solid partner just outside their lab, but that's exactly what Dr. Juan Carlos Zúñiga-Pflücker has in the Krembil Foundation.

"The relationship I have with the Foundation makes our research much more enjoyable," Zúñiga-Pflücker says. "They are very engaged, very personal and they want to know what's going on. It's phenomenal."

The Krembil Foundation has backed Zúñiga-Pflücker since the early days of his T-cell research—at a stage typically difficult to find funding for. With experiments costly and requiring full support, Zúñiga-Pflücker says his team was lucky to have a partner that understood the long-term goals and didn't push for results prematurely.

"The Foundation's mandate is to look for projects like Dr. Zúñiga-Pflücker's: world-class research that has the potential for major impact," explains Krembil Foundation president Mark Krembil. "Dr. Zúñiga-Pflücker had the additional benefit of being a talented, driven researcher; after our investigation, we shared his belief that this was an area worth investing in."

By partnering with Zúñiga-Pflücker—and both say it truly is a partnership—Krembil says the Foundation helps Zúñiga-Pflücker avoid the funding model Catch 22.

"It is difficult for many researchers to get funding for cutting-edge ideas without supporting data, but they need the funding to generate the supporting data," says Krembil.

"For research that we believe in, we try to fill this gap."

— Michael McKinnon, Sunnybrook Foundation

MARK KREMBIL

Dr. Juan Carlos Zúñiga-Pflücker is a senior scientist in biological sciences at Sunnybrook Research Institute, and a professor in immunology at the University of Toronto. He holds the Canada Research Chair in Developmental Immunology.

Q&A

Dr. Bradley MacIntosh

Dr. Bradley MacIntosh is a scientist at Sunnybrook Research Institute in the Brain Sciences Research Program, a neuroimaging scientist at the Heart and Stroke Foundation Centre for Stroke Recovery at Sunnybrook Health Sciences Centre, and an assistant professor in medical biophysics at the University of Toronto. He spoke with Eleni Kanavas about his research.

What's your main research area?
My research is motivated by stroke, and my expertise is in using functional magnetic resonance imaging (fMRI) to look at brain activation patterns. I work with MRI to study both the large and the small blood vessels in the brain.

Why did you choose to study the brain?
I've always been interested in studying the brain and brain diseases, specifically stroke. I decided to pursue a PhD at Sunnybrook Research Institute (SRI) with Dr. Simon Graham [an imaging scientist at SRI], who is taking the technology to a clinical forefront. At the time, it was uncharted territory, and we were successful in developing tools to make fMRI more useful for clinical populations.

How have imaging techniques improved diagnosis for brain diseases?
One excellent example of our ability to visualize stroke is the discovery of diffusion-weighted imaging, an MRI technique that produces images of preferential water movement. In acute stroke, where the cells are swollen and injured, the water is unable to move around as freely compared to a healthy brain tissue. We refer to this as brain regions showing "restricted diffusion." The diffusion-weighted image is bright where the stroke has occurred, and the effect is very dramatic from a 30-second scan. That's an example of an MRI technique that has totally changed clinical practice. It's the definitive way of finding an acute ischemic stroke in the brain.

What do researchers know about brain diseases today compared to 10 years ago?
There has been a decade of discovery on brain reorganization after injury, motivated by the observation that the brain has regenerative potential and there are ways we can maximize brain health through biological processes that build connections and grow brain regions. At the same time, we're still working on the immense number of brain connections and what each brain region does. Recovery after stroke is one area we know a lot more about, and there is a sense of optimism that we can do more. There is a lot of research attention on Alzheimer's disease, which I think has helped to put the brain on people's radar. In Alzheimer's disease, we are still trying to understand the interventions that are going to have a positive effect, whereas in stroke, there are strategies that we know work. For example, constraint-induced therapy is an intensive physical therapy that has been shown to improve motor function after a stroke.

How do your research projects relate to clinical work?
I'm an imaging scientist, but I'm closely tied to clinical endpoints. My work is still in the discovery phase within a clinical population to try and gain insight into what's going on with brain diseases. I'm leading a project on chronic stroke patients that looks at how exercise can be considered a stimulant and neuroprotective agent and catalyst to brain changes.

DR. BRADLEY MACINTOSH

What does the future of neuroimaging look like?
The neuroimaging field has advanced rapidly in the last little while, as has the field of genetics. The next 10 years will have all kinds of discoveries that come from forming connections between these domains. We can learn a lot by bringing these fields closer together, which means working with people that have different expertise. If we continue to do this in the stroke world, then I think it will really help us advance recovery from brain injury.

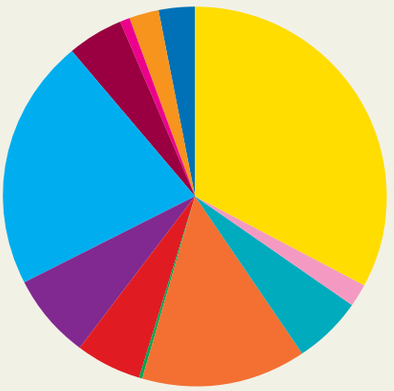
MacIntosh's research is supported by the Canadian Institutes of Health Research, the Heart and Stroke Foundation Centre for Stroke Recovery, and the Natural Sciences and Engineering Research Council of Canada.

PHOTOGRAPHY: DOUG NICHOLSON

QUICK STATISTICS

Major Sources of External Funding

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



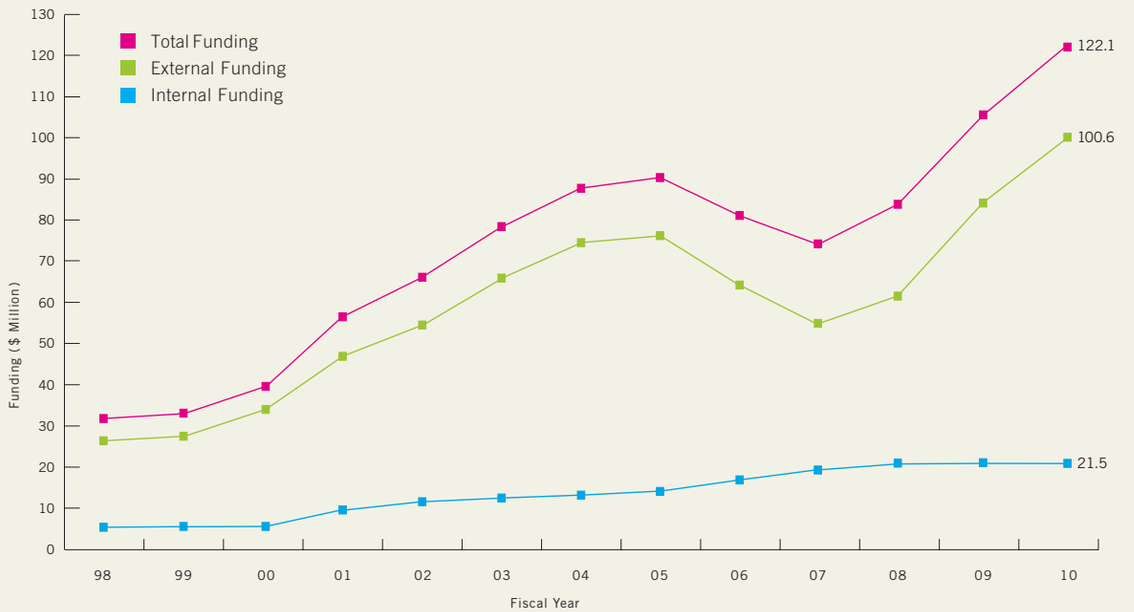
$100.6 MILLION (2010–2011)

- Canada Foundation for Innovation 33%
- Canada Research Chairs Program 2%
- Canadian Cancer Society Research Institute 6%
- Tricouncil Funding: Canadian Institutes of Health Research, and Natural Sciences and Engineering Research Council 14%
- Donations and Trust Income 0.4%
- Foundations 6%
- Industry 7%
- Ministry of Economic Development and Innovation 21%
- Ministry of Health and Long-Term Care 5%
- Other Funding Sources 0.9%
- Other Government Sources 2%
- U.S. and International Sources 3%

Research Staff

History of Research

Expenditures at Sunnybrook Research Institute



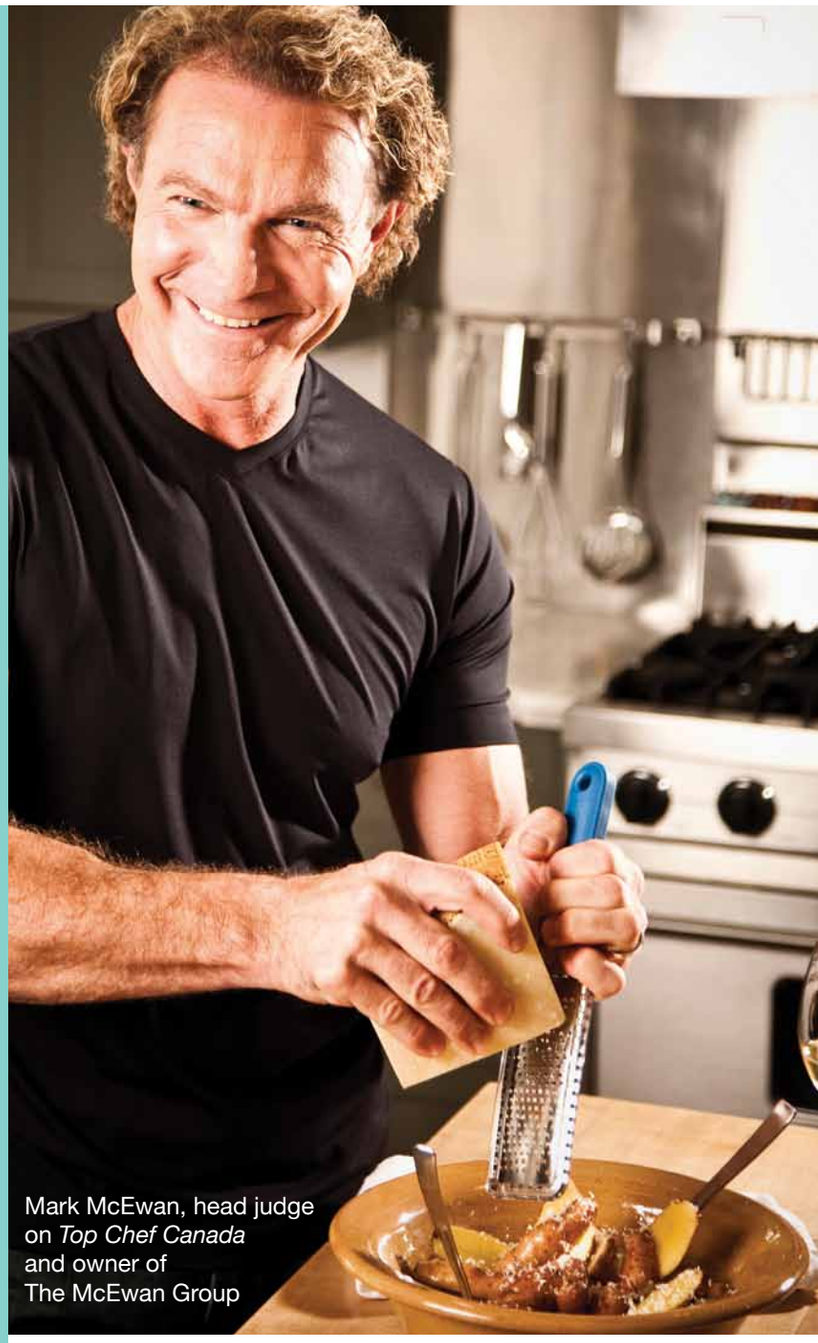
Mark McEwan presents

DINE & DISCOVER

A supper club in support of Sunnybrook research

Host a dinner party like no other.

One that can lead to life-saving discoveries.



Mark McEwan, head judge on *Top Chef Canada* and owner of The McEwan Group

Learn more at
sunnybrook.ca/dinner

Sunnybrook