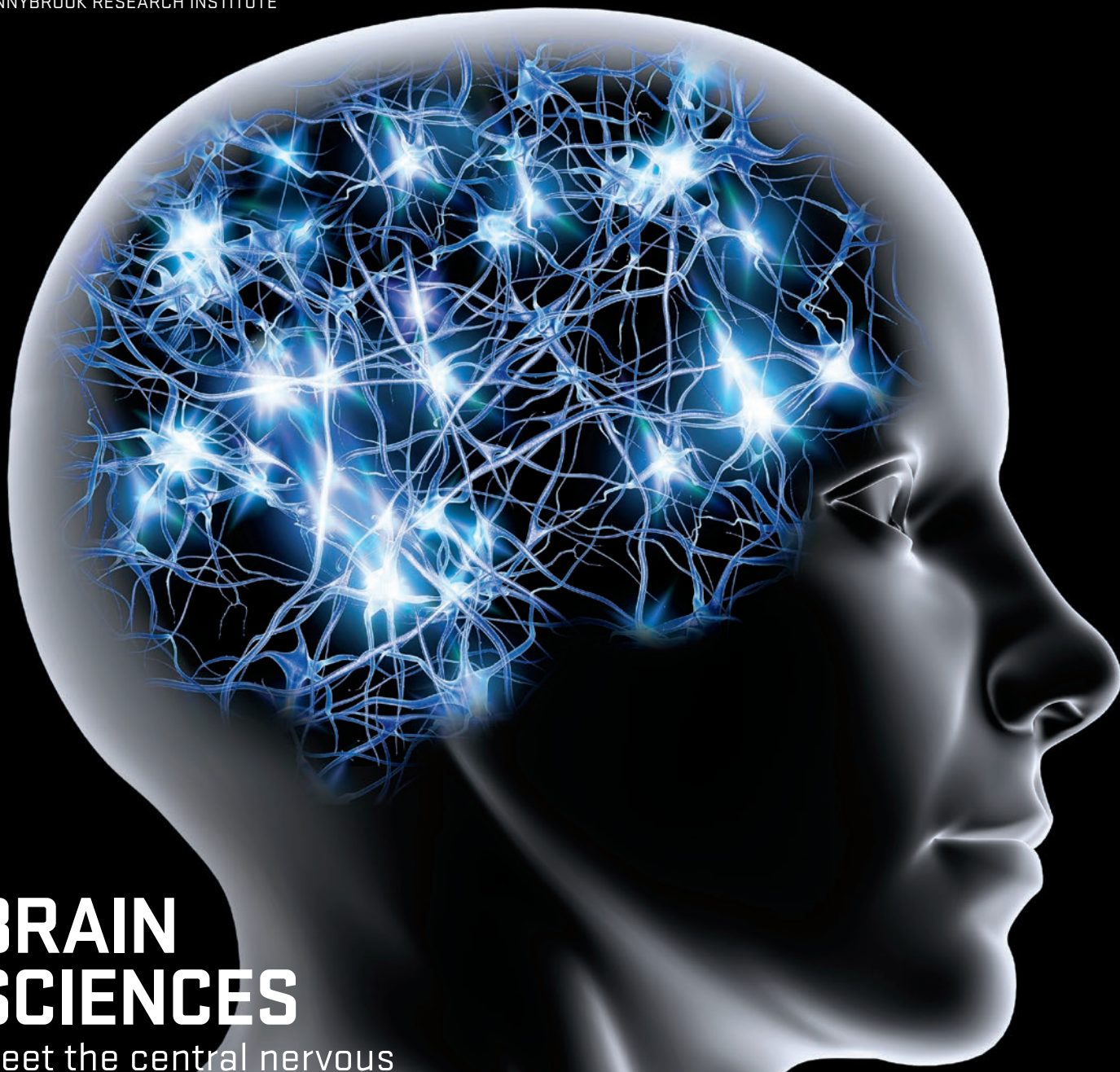


SRI MAGAZINE

SUNNYBROOK RESEARCH INSTITUTE



BRAIN SCIENCES

Meet the central nervous system

C STANDS FOR CARE

What's best for lower-body cancers?

A TALE OF TWO HEART PROCEDURES

Surgery vs. angioplasty: research settles the great debate

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



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Messages



FROM THE PRESIDENT AND CEO, AND CHAIR OF THE BOARD, SUNNYBROOK HEALTH SCIENCES CENTRE

Sunnybrook has an ambitious vision: we will invent the future of health care. To achieve this, we have developed a culture of discovery and innovation that permeates every corner of the organization.

From our roots as a hospital for Canadian veterans, Sunnybrook, which is fully affiliated with the University of Toronto, has evolved into one of Canada's premier academic health sciences centres.

Care across our eight clinical programs is outstanding. This care derives in part from its grounding in research. Our practitioners always strive to do better, motivated by the challenges they encounter daily. In this magazine you will find a few of the many examples of how we are achieving our vision.

For example, researchers in our Brain Sciences Program have shown that exercise-based cardiac rehab programs help to maintain the size of the hippocampus, a region of the brain responsible for memory, which can become damaged in patients with heart disease. These are encouraging findings for those patients, who are at increased risk of stroke and dementia. Researchers are also examining the link between changes to the brain's blood vessels and brain disorders, to develop interventions that may stave off disease. These are but two of many such examples.

Such discoveries wouldn't be possible without the support of our funding, government and community partners, and the ingenuity and dedication of our staff and volunteers. Thank you for helping us to invent the future of health care.

David Agnew
Chair, Board of Directors

Barry A. McLellan
President and CEO



FROM THE VICE-PRESIDENT, RESEARCH, SUNNYBROOK RESEARCH INSTITUTE, SUNNYBROOK HEALTH SCIENCES CENTRE

Discovery to clinical impact via the medical marketplace—that's the "business" that Sunnybrook Research Institute (SRI) is in, and over the last year we've made significant headway.

As with every successful hospital-based research enterprise, our scientists are our most precious assets. We have created an ethos of innovation at SRI, an environment that has some of the best minds in the world who are enabling the most social of activities: discovery.

Our vision of creating an international hub for life sciences is supported by providing space without disciplinary boundaries. Physicists, engineers, geneticists, molecular and cellular biologists, and health services researchers, along with a growing family of business partners, work shoulder-to-shoulder with practitioners and patients toward solving the most challenging problems in medical science.

At first blush, it might seem out of place to have private sector partners walking the hallways of SRI. Their presence, partnership and investment, however, are fundamental to our success. Translating ideas into products that will help our patients is a high-cost, high-risk endeavor.

The result of such partnership is an "end-to-end" solution—from discovery to the uptake of innovative and disruptive technology into the health care system.

Welcome to this year's *SRI Magazine*, with its special focus on brain sciences—an area in which we lead. We hope that you enjoy the captivating stories. In-between each line, know that we have implemented a commercialization speedway, one that ensures our patients will benefit from our breakthroughs faster than ever.

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

Digest

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

DYNAMIC DUOS

Spinal metastasis, or cancer that has spread to the spine, occurs in 30% to 50% of all cancer patients, and puts them at increased risk of spinal fracture. Photodynamic therapy (PDT) is a minimally invasive procedure that has been shown to destroy tumours and improve the structure and strength of the spine in the short term. It uses a drug called a photosensitizer that is activated by light. When the drug is exposed to a certain wavelength of light, it makes an oxygen molecule that kills nearby cells.

Dr. Cari Whyne, director of the Holland Musculoskeletal Research Program at Sunnybrook

Research Institute, led a study aimed at assessing the effect of PDT after a longer time period, alone and combined with prior bisphosphonate or radiation treatment. She found preclinical models treated with a combination of PDT and bisphosphonates (drugs that prevent loss of bone mass) showed enhanced bone formation and structural integrity six weeks after treatment, compared with untreated controls and those who received one type of therapy. Radiation combined with PDT yielded the next best improvement in bone architecture. The findings highlight the promise of PDT as an adjunct treatment for spinal metastasis.

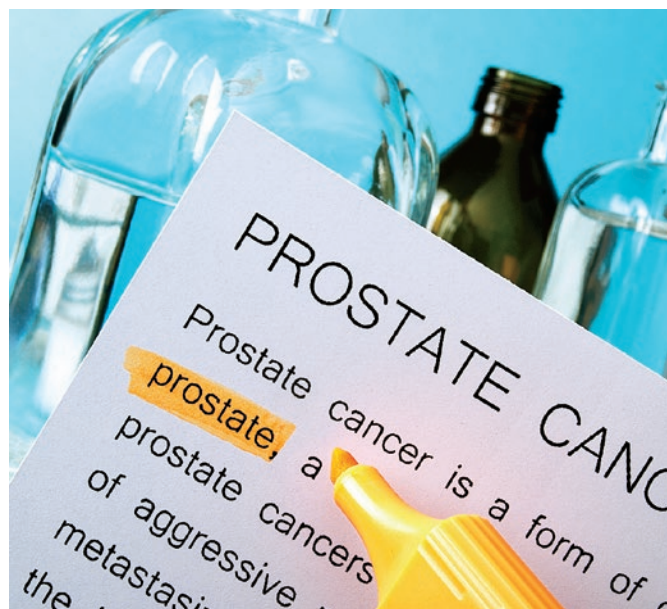
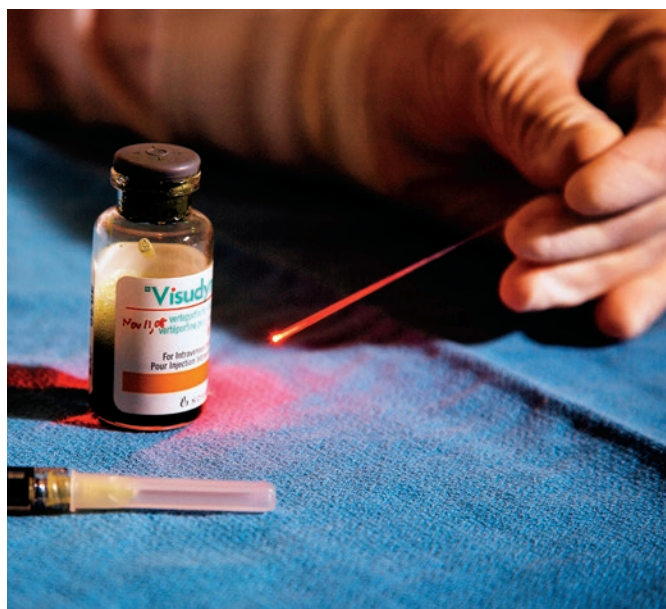
Choosing a Prostate Cancer Treatment? Know All of the Risks

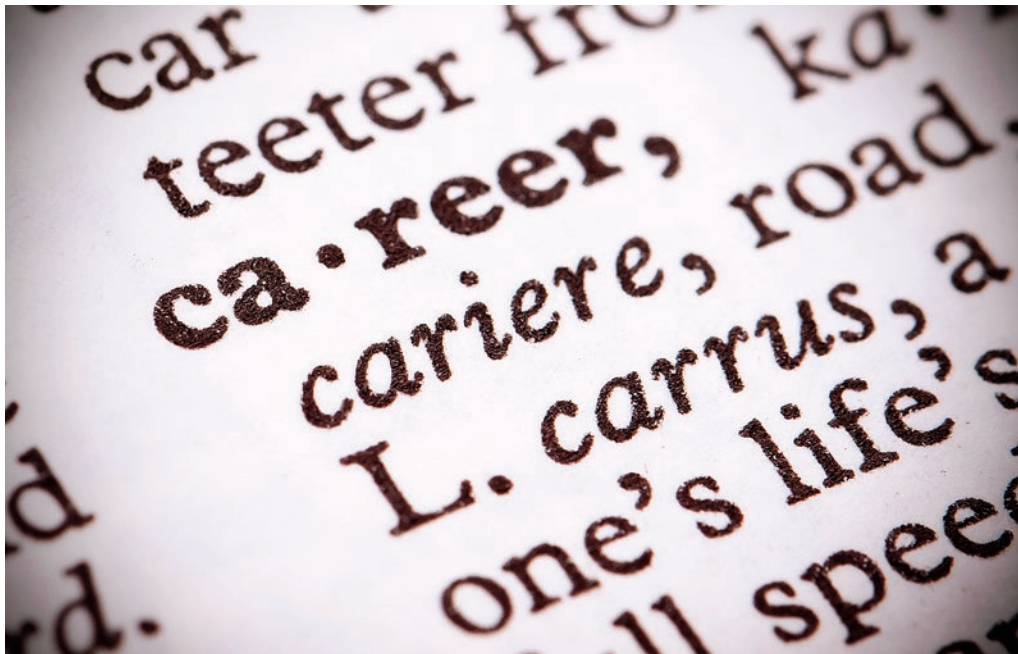
Incontinence and erectile dysfunction are two well-studied adverse effects of prostate cancer treatment, but there are other potential problems to consider.

Dr. Robert Nam, a researcher in the Odette Cancer Research Program at Sunnybrook Research Institute, led the first study to turn the spotlight on other complications after radiotherapy and surgery for prostate cancer.

The study, published in *Lancet Oncology*, looked at data of more than 32,000 men in Ontario who underwent treatment for prostate cancer between 2002 and 2009. Nam and colleagues found the five-year cumulative risk of complications, including hospital admission, urological procedures, rectal or anal procedures, open surgeries and secondary cancers, was significantly higher among those who had treatment compared with matched controls with no history of prostate cancer. They also found radiation was associated with higher incidence of all complications except urological procedures, compared with those who had surgery.

These findings can help doctors bring to bear the complications of therapy—all of them—on their discussions with patients about treatment options.





Going Back to Work After a Burn Injury

Research shows most burn injuries occur in people aged 20 to 44 years—prime working years. Although returning to work is an important goal for these individuals, there are significant challenges to doing so, including pain, disruption in sleep patterns and emotional distress. Moreover, an inability to return to work following a burn has been shown to worsen anxiety, resulting in poorer quality of life.

Clinical guidelines for initial recovery and rehabilitation after a burn injury do not address issues regarding work re-entry. To fill this gap, **Dr. Manuel Gomez**, director of

the St. John's Rehab Research Program at Sunnybrook Research Institute, and colleagues developed the first clinical practice guideline aimed at helping health care teams, patients and employers to assess a person's ability to return to work after a severe burn.

The purpose of the guideline, published in *Burns*, is to improve burn survivors' employment outcomes by promoting a systematic approach to vocational evaluation. The authors note the target population is people aged 20 to 65 years; the target users includes these people, along with health and vocational professionals, and employers. The guidelines might also be of use to educators, insurers, family members and policy makers.

Sight Line

The optic nerve delivers information from the retina to the brain via electrical impulses. Many people don't realize this nerve is part of the central nervous system. It contains more than one million nerve fibres, protected by myelin sheaths that help speed impulses to the brain.

Injury to the optic nerve causes loss of vision, which can be lasting. Glaucoma is a group of diseases, and the most common condition that affects this nerve. High intraocular pressure from fluid buildup is usually, although not always, the culprit. Early detection can minimize damage.

Optic neuritis is another, albeit rare, condition. It generally happens when the immune system erroneously attacks the myelin that covers the nerve, causing inflammation and damaging myelin. Pain and loss of vision, sometimes permanent, result.

Neuro-ophthalmologists specialize in diagnosing and treating diseases of the optic nerve. There is no way to transplant an entire eyeball, because the optic nerve is too complex to reconstruct.

LANDMARK GIFT ESTABLISHES UNIQUE BRAIN RESEARCH CENTRE

The Slight Family Foundation will invest \$10 million to establish the Slight Centre for Image-Guided Brain Therapy and Repair at Sunnybrook Research Institute (SRI).

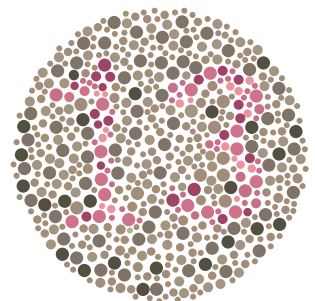
The centre will be the site of the world's first clinical trials evaluating the use of focused ultrasound to deliver therapy through the blood-brain barrier to treat brain disorders,

including dementia and stroke.

At its core will be a fully integrated positron emission tomography-magnetic resonance imaging scanner. It will be modified to incorporate transcranial focused ultrasound technology developed by SRI's **Dr. Kullervo Hynynen**, in collaboration with industry. The resultant system will be unique.

With Hynynen, the lead scientists for this centre are **Drs. Isabelle Aubert, Sandra Black and Curtis Caldwell**. The system will enable them to advance promising preclinical research into patient studies. The aim is to deliver therapies safely into the brain to treat disease and, ideally, to repair damage and restore function.

The investment is part of a \$50-million gift from the Slight Family Foundation to five health sciences centres in Toronto.



PEOPLE WITH OPTIC NEURITIS CAN LOSE some of their ability to perceive colour, especially red. As such, tests using colour plates with "hidden" numbers are used to support a diagnosis.

HOTTEST SCIENCE UNDERGRAD PRIZE IN THE COUNTRY

The Sunnybrook Prize is attracting dozens of undergraduate students eager to showcase their projects in biomedical research at Sunnybrook Research Institute's (SRI) annual competition.

The national award comes with \$10,000 cash. It was established in 2011 by faculty within SRI's Physical Sciences platform using royalties generated by their technology development. They wanted to acknowledge students for their hard work and contributions to research, and promote

careers in biomedical science.

Ben Ouyang, a fourth-year biomedical engineering student at the University of Toronto, won the 2013 Sunnybrook Prize. His outstanding project focused on tissue engineering and developing an elastic, biodegradable material that has the unique ability to be tunable to mechanical properties.

The competition is open to undergraduates in the physical sciences and engineering disciplines who are in their final two years of study at a Canadian university. For more on the Sunnybrook Prize, visit sunnybrook.ca/research.

FLU WORSE THAN FLU SHOT

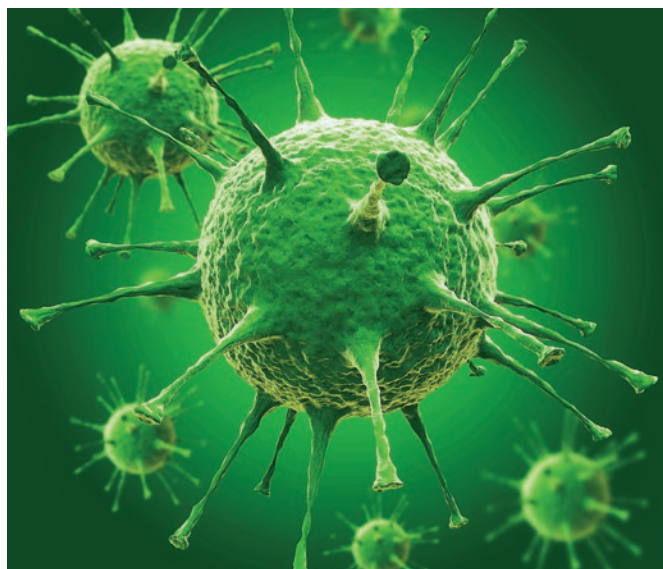
Each year, the urging: get your flu shot! It sits against a wall of statistics: seasonal influenza causes 3 to 5 million cases of severe illness and 250,000 to 500,000 deaths worldwide—every year. In Canada, between 2,000 and 8,000 Canadians die of flu and its complications annually. Research shows that in healthy adults, vaccination cuts infection risk by upwards of 60%.

Research also shows that Guillain-Barré syndrome, an acute autoimmune disorder whose effects can be life-threatening, has been linked to flu vaccination, which may be a barrier to achieving high vaccination coverage. It has also, however, been linked to influenza infection itself.

Dr. Jeff Kwong, a clinician-scientist in the Veterans & Community Research Program at Sunnybrook Research Institute, led a study to get some clarity on the matter. The study found that the syndrome is associated with exposure to the vaccine and the flu illness. Critically, it found that the risk of Guillain-Barré syndrome after influenza illness was greater than after flu vaccination. The authors noted it is important that patients be informed of the risks, in context, of Guillain-Barré syndrome from both the flu vaccine and the flu.



Dr. Martin Yaffe (right) explains his research to last year's contenders. In 2013, Ben Ouyang, standing next to Yaffe, won.



A FAIR COMPARISON

Computerized tomography (CT) uses X-rays to make cross-sectional pictures of the body. It is a useful diagnostic tool; however, scans are costly. As with all health care resources, practitioners must balance prudent use of finite means against provision of the best care possible.

Dr. Michael Schull, a clinician-scientist in the Trauma, Emergency & Critical Care Research Program at

Sunnybrook Research Institute, and colleagues compared use of CT in emergency departments in the U.S. and Ontario, Canada between 2003 and 2008. They focused on four common conditions: abdominal pain, complex abdominal pain, headache, and chest pain or shortness of breath. The researchers found that in these cases, American emergency department clinicians used CT more often than did those in Ontario. Moreover, rates

of CT use increased in both regions, but they did so faster in the U.S. However, for patients with complex abdominal pain who were admitted to hospital, the proportional use of CT was nearly identical. The authors noted that these findings suggest the availability of CT in Ontario is not so limited that it prevents the most critically ill patients from receiving CT, but that further study is needed before such a conclusion can be made definitively.



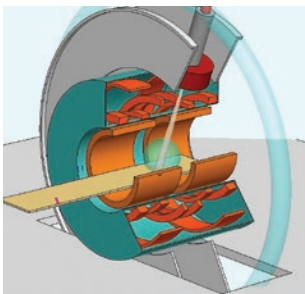
JOINING FORCES ON NEXT-STAGE RADIATION THERAPY

Elekta and Philips Healthcare have partnered with Sunnybrook Research Institute to test a new magnetic resonance imaging (MRI)-guided radiation therapy system.

The system integrates an advanced 1.5 Tesla MRI machine with radiation therapy. The technology was designed to enable physicians to deliver radiation in real time under MR guidance for more precise cancer treatments. Physicists, engineers and clinicians will work together to validate the advantages of MR-guided radiation therapy through technology development and clinical trials.

"We have identified several areas to study the value of this technology for patients," says **Dr. Michael Julius**, vice-president of research at Sunnybrook. "The ultimate goal—acquiring high-resolution MR images of pathology in real time as the radiation is being delivered—could have a dramatic impact on patient outcomes."

The consortium also includes the University Medical Center Utrecht, the University of Texas MD Anderson Cancer Center and The Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital.



THE MR-LINAC SYSTEM INTEGRATES magnetic resonance and radiation therapy into a single system for exquisitely precise, minimally invasive cancer treatment.

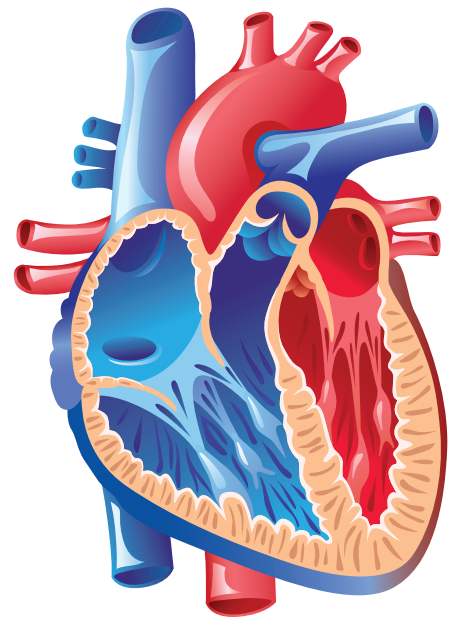
Scalpel-Free, But Not Risk-Free

Aortic stenosis is narrowing of the aortic valve, which blocks blood flow from the heart to the body. Symptoms include chest pain, shortness of breath and fainting.

Transcatheter aortic valve implantation (TAVI) is a nonsurgical procedure in which doctors use catheters to implant a new valve over the existing one. It is offered to people who, due to other medical conditions or age, cannot tolerate surgery.

While uptake of TAVI has been rapid, the procedure is not without risk. **Dr. Dennis Ko**, a clinician-scientist at Sunnybrook Research Institute, led a study to quantify the adverse effects associated with TAVI, and to evaluate whether the type of valve used and the route of implantation are linked to differences in adverse outcomes.

The most common negative outcome was a problem with the heart's electrical system, which requires a permanent pacemaker. Vascular complications and acute kidney failure requiring replacement therapy followed. The authors noted that the type of valve and route of implantation also

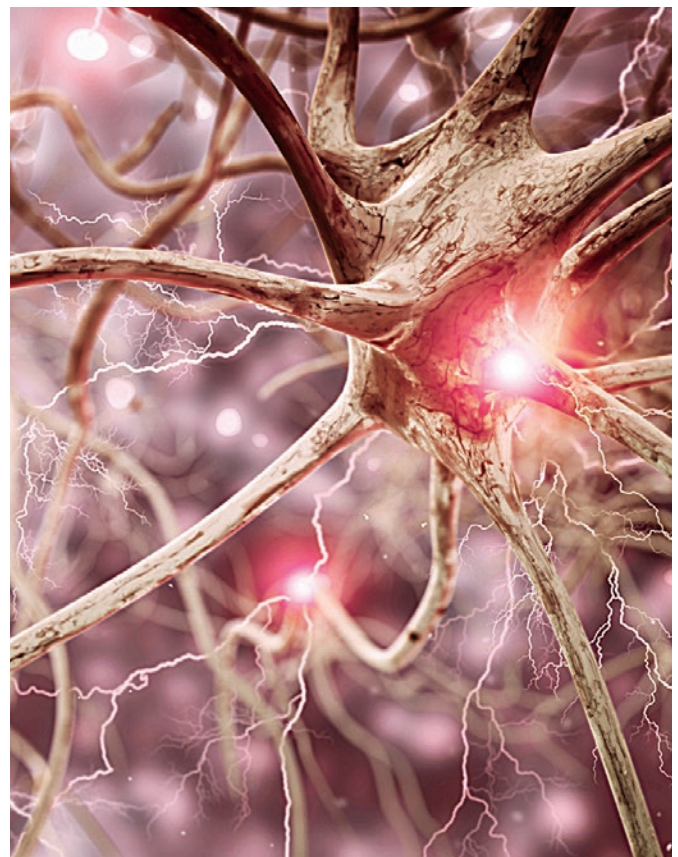


affected the rates of complications.

Results of the review, published in the *Annals of Internal Medicine*, may help clinicians and policy makers to understand better the risk-benefit profile associated with the procedure.

IT TAKES A LOT OF NERVE

The central nervous system contains two kinds of cells: glial cells and nerve cells, or neurons. Nerve cells conduct electrical and chemical impulses to communicate with each other, muscle cells and gland cells. Each neuron is connected to about 1,000 other neurons, which make up extensive communication networks responsible for everything we feel, think and do. Visible only under a microscope, most neurons have a cell body, or soma; dendrites, which branch out from the soma; and an axon, which can be short or long. Dendrites receive and axons transmit information. Most axons in the central nervous system are swathed in myelin, which helps transmit signals smoothly; without it, one cannot function.



OVATION

We salute some notable achievements of scientists at Sunnybrook Research Institute (SRI) announced during 2013

NATIONAL AND INTERNATIONAL AWARDS

The Heart and Stroke Foundation recognized **Dr. Clare Atzema** with a New Investigator Award and appointed **Dr. Harindra Wijeyesundera** a Distinguished Clinician-Scientist. These awards provide salary support to Canada's best young researchers.

Dr. Benjamin Goldstein and **Wijeyesundera** each received a New Investigator Award from the Canadian Institutes of Health Research (CIHR), designed to support high-calibre researchers early in their careers. The agency also presented **Dr. Andrew Lim** the Maud Menten New Principal Investigator Prize, which recognizes the merit of Canadian investigators

working within the mandate of the CIHR Institute of Genetics.

The Canada Foundation for Innovation awarded **Dr. George Mochizuki** a Leaders Opportunity Fund grant. This award pays for infrastructure to help institutions attract and keep the brightest scientists, toward strengthening the country's position as a leader in research and development.

The Government of Canada renewed **Dr. Jack Tu's** Tier 1 Canada Research Chair in Health Services Research. The award is the most august academic honour the government bestows. Ten scientists at SRI hold Canada Research Chairs.

PROVINCIAL AWARDS

Dr. David Alter and **Dr. Robert Fowler** each received a Mid-Career Investigator Award from the Heart and Stroke Foundation (Ontario). The award is given to individuals who have demonstrated research excellence and productivity. The foundation also

presented **Dr. Peter Austin** with a Career Investigator Award and appointed **Dr. Dennis Ko** a Phase 2 Clinician Scientist. These awards recognize established researchers in the field of cardiovascular medicine.

FELLOWSHIPS AND OTHER HONOURS

Dr. Peter Burns was given the 2012 Aixplorer Achievement Award from SuperSonic Imagine. The award recognizes individuals for their accomplishment and leadership in advancing cancer knowledge and awareness.

Dr. Anthony Feinstein, was awarded a 2012 Peabody Award for his documentary *Under Fire: Journalists in Combat*. The Peabody Awards are the most prestigious and selective prizes in electronic media.

The Physicians' Services Incorporated Foundation named **Dr. Andrea Gershon** the 2013 Fellow in Translational Health Research. The fellowship provides clinicians with protected research time to undertake high-impact translational research.

Goldstein received the 2012 Gerald L. Klerman Young Investigator Award from the Depression and Bipolar Support Alliance in the U.S. The award recognizes his role in advancing understanding of the causes, diagnosis and treatment of depression and bipolar disorder.

The Electrical Safety Authority awarded **Dr. Manuel Gomez** the 2013 Chief Public Safety Officer's Special Recognition Award for his role in furthering electrical safety and the care of survivors of electrical injuries.

Dr. Bob Kerbel was presented with the Colin Thomson Memorial Medal at the Beatson International Cancer Conference in Glasgow, Scotland. The medal is awarded annually to recognize those who have had a major impact on cancer research.

The American Academy of Neurology bestowed on **Lim** the Wayne A. Hening Sleep Medicine Investigator Award. This honour recognizes young investigators for their scientific expertise in deciphering the role of neurology in sleep medicine.

The Society for Medical Decision Making awarded **Dr. Don Redelmeier** the 2013 Career Achievement Award, which recognizes distinguished senior investigators who have made major contributions to the field of medical-decision making.

FOR MORE ABOUT THESE

awards or the scientists who have received them, visit the Sunnybrook Research Institute website: sunnybrook.ca/research.



"I have the MRI scan of your brain. The right hemisphere is clogged with computer passwords."

NON SEQUITUR

Recent research puts the number of champagne bubbles in a glass at one million, bursting previous estimates of 10 to 15 million.

A Delicate Balance

Clinical trial seeks to define optimal oxygen levels for premature babies

Oxxygen is the most commonly used therapy in the neonatal intensive care unit: about 90% of infants will need oxygen at some point during their stay.

For decades, clinicians have debated how much oxygen should be given to preterm infants to avoid delivering too much in treating lung disease and other respiratory illnesses, which could cause long-term vision and neurological impairment.

“Oxygen is a drug, and like any drug, you need to know the risks and benefits of any intervention that you provide a patient, especially a preterm infant. Optimal oxygen saturation ensures that any risks of extra oxygen being given to the baby are outweighed by the benefits, which would be promoting growth, minimizing the impact of morbidity and, consequently, having a positive impact on the neurodevelopmental outcomes of these children,” says Dr. Elizabeth Asztalos, a clinician-scientist in the Women & Babies Research Program at Sunnybrook Research Institute (SRI). “We’re trying to balance those risks and benefits, so that the benefits outweigh the risks.”

Asztalos and colleagues conducted the Canadian Oxygen Trial, led by Dr. Barbara Schmidt of the University of Pennsylvania, and published the results in *The Journal of the American Medical Association* in 2013. They compared the effects of targeting oxygen saturations at a lower level of 85% to 89% compared with a higher level of 91% to 95% in extremely preterm infants. The aim was to determine the rate of death or disability at 18 months’ corrected age, the child’s



KELSIE COTE IN THE NEONATAL INTENSIVE CARE UNIT (NICU) AT SUNNYBROOK. ABOUT 90% OF BABIES IN THE NICU WILL need oxygen therapy during their stay.

age from the expected date of delivery, calculated by subtracting the number of weeks born before 40 weeks’ gestation from chronological age. The trial enrolled 1,201 infants aged 23 to 27 weeks’ gestation at 25 hospitals in Canada, the U.S., Argentina, Finland, Germany and Israel over four years. The babies were monitored until a postmenstrual age of 36 to 40 weeks (gestational plus chronological age).

Results found no significant effect of oxygen level on the rate of death or disability between the two saturation groups. “What surprised me was that we didn’t see a difference in cognition and motor skills, and we didn’t see the same impact on mortality as seen in the U.S. and other trials,” says Asztalos, who is also director of the Centre for Mother, Infant and Child Research at SRI and an associate professor at the University of Toronto. The other trials found the rate of

death greater among the lower-target group versus the higher-target group.

Despite the controversy around the results of these trials, she says the study may still help guide clinicians in setting parameters for preterm infants.

Asztalos also notes that the Canadian study was able to meet its full sample size as planned and to continue with assessment to 18 to 21 months’ corrected age. Sunnybrook monitored 103 infants: 93 from Sunnybrook, and 10 from other Canadian sites, for the trial and the neurodevelopmental follow-up. “As a member of the steering committee, we can take pride in how we did the trial, and that we were very strong from a methodological perspective.”

ELENI KANAVAS

The Canadian Institutes of Health Research funded this research.

Shouldering the Burden

Research supports an extended role for physiotherapists in the treatment of damaged deltoids

In a health care environment fraught with long wait times, the results of a study from the Holland Musculoskeletal Research Program at Sunnybrook Research Institute (SRI) are welcome news.

For patients with shoulder problems, the wait time for surgical consultation in Ontario is as long as two years. Through visiting with an advanced practice physiotherapist (APP) first, however, these wait times are reduced significantly. The responsibilities of an APP include triaging referrals, providing assessment and ordering investigations (including magnetic resonance imaging and computed tomography scans, ultrasounds and X-rays).

About 50% of shoulder-related referrals do not require surgical intervention, and APPs are able to provide management for these patients within four to six weeks. For potential surgical candidates, investigations ordered prior to seeing the surgeon can speed operative care decisions. In addition, postsurgical patients without complications can be managed by APPs.

“Since the launch of the APP shoulder program in 2009, our senior shoulder specialist, Dr. Richard Holtby, has been able to focus more on surgical candidates,” says Dr. Helen Razmjou, an APP at Sunnybrook and associate scientist at SRI, who led the study.

Through the study, “Evaluation of an advanced practice physical therapist in a specialty shoulder clinic: diagnostic agreement and effect on wait times,” Razmjou and colleagues found that 53% of the clinic’s shoulder patients could be treated by physiotherapists independently.

“We wanted to scientifically prove that our program was effective in reducing wait times while maintaining optimal care and patient satisfaction,” says Razmjou, who says she wasn’t surprised by the findings. “Science usually confirms what a good clinician already knows.”

Because the program is relatively new in Canada, Razmjou says that some patients can be initially reticent to see a physiotherapist instead of a surgeon. Following the examination and discussion of management of their care, however, these patients typically express satisfaction in how their care was facilitated.

“We still see occasional patients who say, ‘I don’t need to see a physiotherapist. I’m here because I need surgery,’” says Razmjou, who sees about 250 new patients and 300 follow-up patients every year. She notes that the conceptual model of APPs as independent examiners is becoming more accepted by family physicians and patients suffering from complex shoulder conditions.

Razmjou and her team are now studying the efficacy of the clinical decision-making process in regards to APPs ordering costly investigations. They are also developing risk factor and management assessment tools, which will help in estimating disease probability. With an aging population and a shortage of surgeons, Razmjou says that these studies could have greater implications, as they will enhance the ability of extended-role care providers across Canada to manage shoulder conditions using validated strategies.

“We need to maximize the use of our existing human resources. Using APPs will improve access and quality of health care at a reduced cost to the system,” she says.

JESSICA WYNNE LOCKHART

Funding for both studies has been provided by practice-based research funds through Sunnybrook Health Sciences Centre.



DR. HELEN RAZMJOU IS LEAD AUTHOR OF A STUDY SHOWING THAT USING ADVANCED PRACTICE PHYSIOTHERAPISTS TO manage patients with shoulder conditions can improve treatment and health care efficiency.

Pandemic Readiness

The MERS-CoV and H7N9 bird flu virus have emerged in humans and caused severe illness, death and fear of an outbreak. Experts caution we need to be prepared—not only as doctors, but also as researchers

Critical care physician Dr. Robert Fowler is at the frontlines of medical research when new life-threatening infectious diseases strike around the world. In the spring of 2009 when the H1N1 influenza pandemic emerged

globally, Fowler and his research team at Sunnybrook Research Institute (SRI) led the first studies to describe what the virus looked like, and help doctors and hospitals to prepare better for future outbreaks.

“Being prepared ahead of time for pandemics and epidemics is critical, because otherwise a lot of real-time research can’t happen, as it takes too long to get regulatory startup procedures done,” says Fowler, who is a senior scientist in the Trauma, Emergency & Critical Care Research Program at SRI and an associate professor at the University of Toronto.

This past year, Fowler has been working with a group of researchers on a combination of emerging severe acute respiratory infection etiologies at the World Health Organization’s department of pandemic and epidemic diseases in Geneva, Switzerland. The department provides clinicians with guidance in the diagnosis and treatment of infected patients using standard protocols and research guidelines. The purpose is to enable better global pandemic preparedness to reduce the impact of infectious diseases on affected populations and limit their spread internationally.

Fowler and colleagues are looking at two infections that emerged only in the last one-and-a-half years: avian influenza A (H7N9) virus, which broke out mainly in eastern China; and the



DR. ROB FOWLER (SECOND FROM THE RIGHT) IS WORKING WITH RESEARCHERS AT THE WORLD HEALTH ORGANIZATION TO analyze two severe acute respiratory viruses. Their aim is to improve global pandemic preparedness and reduce the impact of infectious diseases.

Middle East respiratory syndrome coronavirus (MERS-CoV), which was found in Saudi Arabia and surrounding regions, as well as some European countries and Tunisia, North Africa. Both viruses have caused severe human illness and admission of patients to intensive care units.

Unlike the common cold or seasonal influenza, which infect 10% to 20% of the population each year and have relatively low death rates, the H7N9 virus has a 35% to 40% risk of death. Most cases are male with a median age of 60 years. Researchers have found the virus is transmissible to humans from direct contact with infected poultry or indirect contact with contaminated environments, such as poultry markets. Common symptoms

include fever, cough and shortness of breath, but most patients experience rapid progression to severe pneumonia. Patients are treated with anti-influenza drugs known as neuraminidase inhibitors, such as Tamiflu. Although human-to-human spread has not been a prominent aspect of this outbreak, that is the big worry, says Fowler.

“A virus like H7N9 mutates a bit, develops a better ability to be transmitted, [and] then you have the workings of something that is a real problem because it kills a lot of people even with the best therapy we have,” says Fowler.

He notes that if the virus develops resistance to the usual drugs prescribed, then, unsurprisingly, the case fatality rate will be higher. Fowler and his team are collaborating with groups in China



VIRUS FACTS

H7N9 is one subgroup among the larger group of H7 avian influenza viruses (H7N2, H7N3, and H7N7) that normally circulate among birds.

MERS-CoV is a coronavirus from the same large family of viruses that includes SARS.

This is the first time infection with viruses H7N9 and MERS-CoV have been found in humans.

There are no travel restrictions to China and Middle Eastern countries.

Hand and respiratory hygiene are prudent to prevent infection of H7N9 and MERS-CoV.

Sources: the Public Health Agency of Canada and the World Health Organization

to understand the illness better and encourage research support to conduct observational studies and clinical trials with people infected with the H7N9 virus to improve treatment.

In the Middle East, MERS-CoV is a coronavirus similar to SARS, a severe acute respiratory syndrome that struck globally in 2003 and infected more than 8,000 people, with 774 reported deaths. The case fatality rate of MERS-CoV carries a similar risk of death as the H7N9 virus: 40%. Researchers have found that camels are the most common host of MERS-CoV due to the large camel trade in the region; this could have a substantial financial impact on the industry, Fowler notes, as happened with bovine spongiform encephalopathy, or “mad cow disease,” which caused stocks of cattle to be recalled worldwide.

There is no vaccine or antiviral drug for MERS-CoV, says Fowler; treatment is limited to supportive care in the intensive care unit. His team also established a collaborative research program among affected countries to determine which institutions in surrounding areas could facilitate observational and experimental research for patients who are critically ill. The aim is to identify and then provide patients with a more targeted treatment for the illness.

Researchers are looking at convalescent plasma therapy as the most promising potential treatment. This technique involves extracting antibodies either from survivors who have been exposed to MERS-CoV or from animals that have been inoculated with MERS-CoV, and making a concentrated antibody formulation that is delivered to infected patients.

“Our goal is to develop a randomized controlled trial of this therapy for

Camels are the most common host of MERS-CoV.

viruses like MERS-CoV amid all the challenges that go along with the science and the culture of research in different areas,” Fowler says. “This is research at the front end, trying to establish the capacity to do research in clinical trials in resource-challenged areas.”

Domestically, Fowler is working with the Public Health Agency of Canada to become “research-ready” with pre-vetted protocols so that Canada can lead the global charge when needed, he says. Fowler aims to expedite studies by having research ethics board preapprovals in place at hospitals across the country, along with signed data-sharing agreements between hospitals and organizations like SRI leading this research. If regulatory procedures that normally take up to a year to process are completed in advance, then doctors could begin to describe the illness and conduct clinical trials on antiviral drugs and other respiratory therapies immediately.

“We need to evolve much better ways to do research quickly, and to have observational studies and clinical trial protocols that might be focused on the most common interventions all ready to go before they happen. If we don’t adopt that model, we will not be able to respond effectively—if you are not

ready to do research, then you will have disastrous consequences,” says Fowler.

When asked if Canada is prepared, he says doctors and health care professionals are equipped better than before because of their experience with SARS and H1N1.

“From a perspective of surveillance and epidemiology, infection prevention control and clinical response, we are better prepared,” Fowler says.

“However, from a research perspective, are we better prepared to undertake things in real time? No, we’re not. That’s what I’m trying to promote and advocate, so that we’re ready when things do happen because they will, probably with increased frequency.”

ELENI KANAVAS

Fowler’s research is funded by the Canadian Institutes of Health Research, the Heart and Stroke Foundation of Ontario and the Public Health Agency of Canada, and is being done in collaboration with the World Health Organization.



THE MIDDLE EAST RESPIRATORY SYNDROME CORONAVIRUS has no antiviral drug or vaccine, hence the urgent need for research in affected regions.

Photos: Courtesy of Dr. Robert Fowler

Meet the central nervous system— the marrow of our existence, at the core of which is the brain.

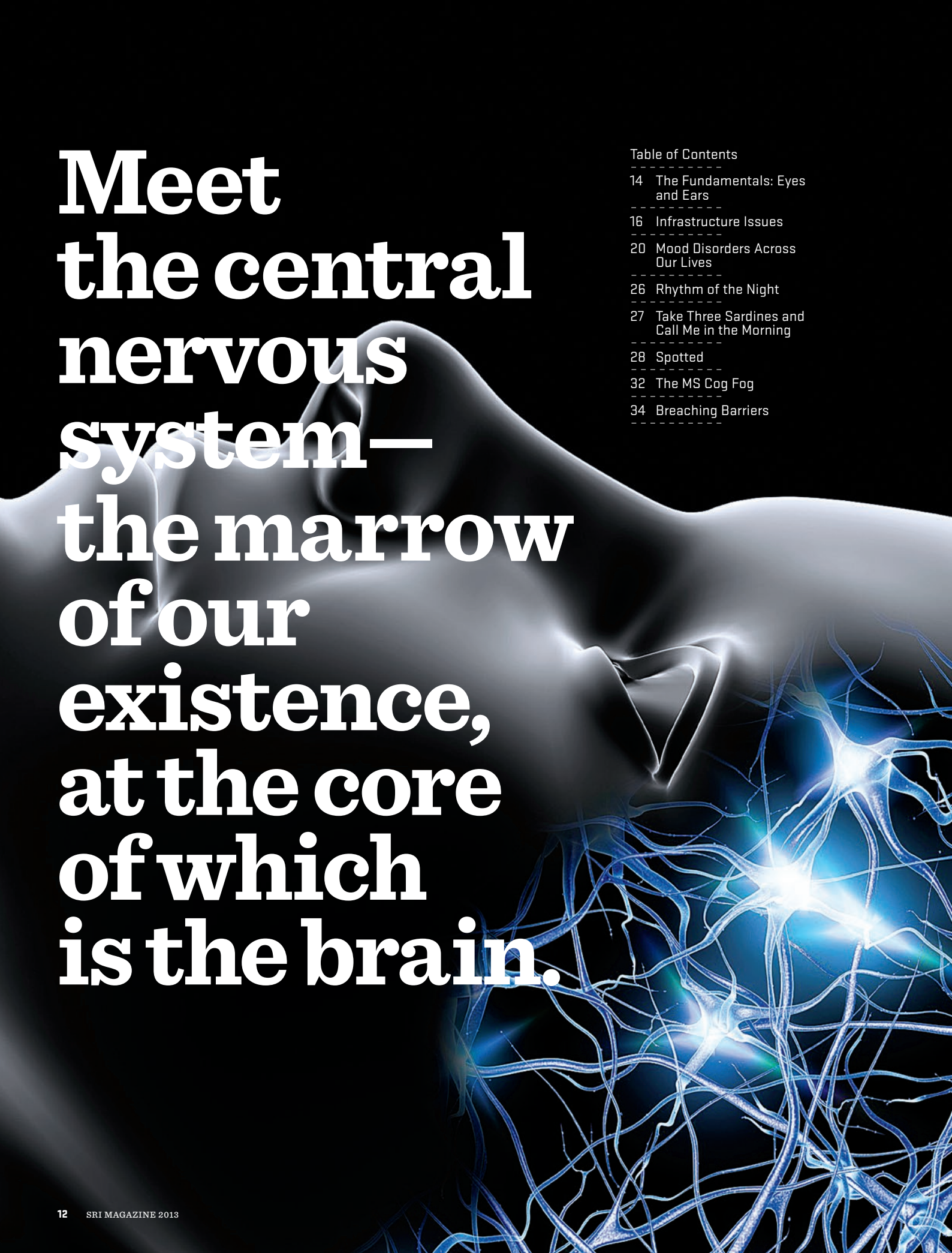
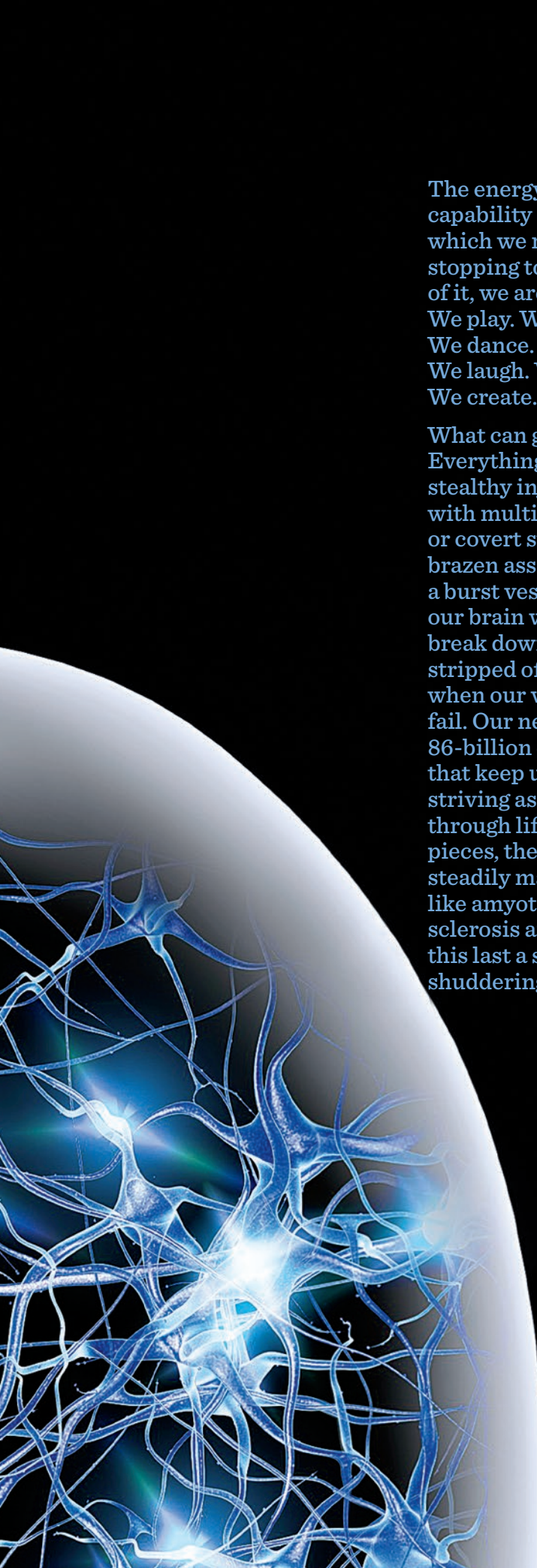


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The energy, power and capability of this system on which we rely is breath-stopping to consider. Because of it, we are and we do: We play. We walk. We work. We dance. We dream. We laugh. We learn. We kiss. We create. We imagine.

What can go wrong? Everything. It can suffer stealthy injury, as happens with multiple sclerosis or covert stroke; or endure brazen assault, as with a burst vessel that floods our brain with blood. It can break down. We can be stripped of our known world when our vision and hearing fail. Our neurons, some 86-billion cellular workhorses that keep us pulsing and striving as we move and think through life, can fall to pieces, they can die, as with steadily marching-on diseases like amyotrophic lateral sclerosis and dementia, this last a scourge of shuddering proportions.

Brain is mind. Its might belies its three pounds. Although we don't have a good grasp on why, we do know that our mind can drag us into dark, confusing places. It can enshackle us, blacking out clarity, inflicting only torment.

Ahead, hope: that while everything can go wrong, something can be done. These slices of what our scientists are passionately pursuing show that we are making progress—but that we need to push on, for we are far from there.

Welcome to Brain Sciences at Sunnybrook Research Institute.

THE FUNDAMENTALS

Eyes and Ears

Often overlooked as part of the brain, these portals of perception are essential to living to our full potential

Our eyes and ears absorb information from all directions, converting it into signals that enable us to experience images and sound, and act accordingly. We are often unaware of this process until

something goes wrong, owing to injury or issues that accrue with age or disease. Herein, a glimpse at what three investigators in the Brain Sciences Research Program at Sunnybrook Research Institute (SRI) are doing in the field.

WINDOWS TO THE BRAIN

As scientists uncover more about the link between the brain and the health of the blood vessels that nourish it, being able to study the vasculature of the eye noninvasively presents opportunities to learn more about development of brain diseases.

“The retina is essentially externalized brain,” says Dr. Peter Kertes, a researcher and chief of ophthalmology at Sunnybrook Health Sciences Centre. “We have a real advantage insofar as the retina is the only place where you can look at blood vessels directly just by looking into the eye.”

His research focuses on diseases of the retina, the light-sensitive

tissue at the back of the inner eye, which functions like camera film to record an image of what we are seeing before sending it to the brain for processing.

Kertes, who is also a professor at the University of Toronto, was among the first in Canada to evaluate a drug called ranibizumab to treat diabetic macular edema, a complication of diabetes that leads to vision loss and affects about 60,000 Canadians. Retinal blood vessels leak fluid, which causes swelling in the macula, a part of the retina responsible for sharp vision. This swelling causes impaired vision.

Ranibizumab works by blocking vascular endothelial growth factor, a molecule that promotes growth of new blood vessels and vessel “leakiness.”

Kertes and his group at Sunnybrook were part of an international clinical trial that showed the drug was superior to laser therapy, which reduces swelling by welding leaky vessels shut. Laser therapy prevents further impairment but rarely improves vision, says Kertes, who notes this and other research on ranibizumab has influenced clinical practice and health policy. In 2008, Ontario approved coverage of the drug for people aged 65 years and older.

“Now we use ranibizumab. When somebody presents with diabetic macular edema, they can expect an improvement in their vision. Patients will gain an average of two ‘lines’ of vision [in an eye test], which is a big difference from laser,” says Kertes.

He’s also peering at the blood vessels of the retina for clues about development of Alzheimer’s disease (AD), for which there is no single diagnostic test. He’s teamed up with Dr. Sandra Black, director of the Brain Sciences



OPHTHALMOLOGIST AND SCIENTIST DR. PETER KERTES IS USING OCULAR IMAGING TO TRY AND DEVELOP A NOVEL TEST for early diagnosis of Alzheimer’s disease.

Research Program at SRI and a cognitive neurologist, to look at the relationship between retinal blood vessel diameter and AD.

The study involves 35 of Black's patients with a clinical diagnosis of AD. The pair are using measurements of retinal vessel diameter and correlating this with other neuroimaging data that show structural and pathological changes in the brains of these patients, as well as results of cognitive testing.

The research is in early stages, but Kertes says he is excited at the prospect of using ocular imaging to gain insight into how AD begins. "It gives us the potential to diagnose problems noninvasively. As treatments come online, it allows patients to be treated earlier and more successfully."

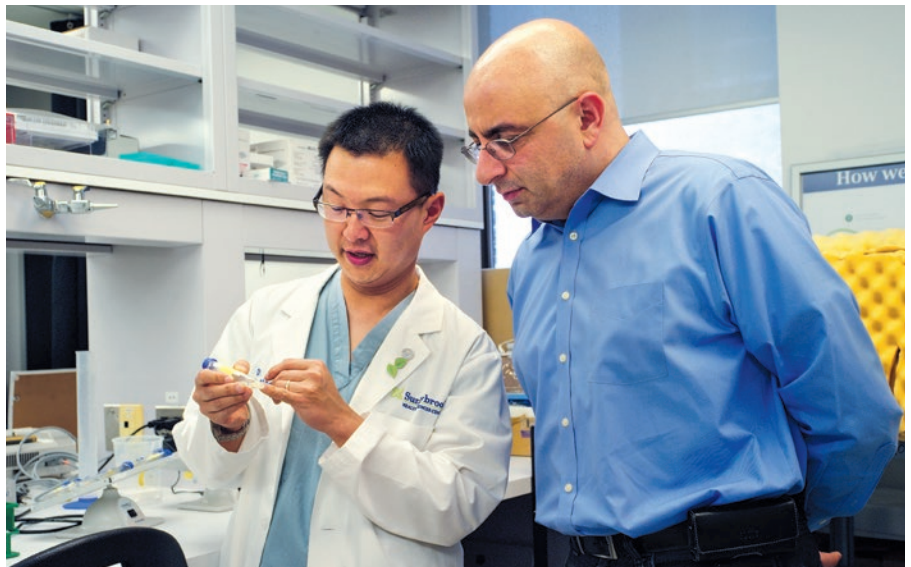
WHAT WAS THAT?

Biological scientist Dr. Alain Dabdoub is uncovering the developmental processes unfolding in a less accessible sense organ: the ear. Dabdoub directs the Sonja N. Koerner Hearing Regeneration Laboratory at SRI, where he and his colleagues are working toward biological solutions for hearing loss. It is the only lab in Canada doing such research.

Hearing impairment, estimated to affect about three million Canadians, results from loss of hair cells, which translate sound vibrations into electrical signals; and auditory nerve cells, which transmit these signals to the brain. Birds and other non-mammals can regenerate these cells spontaneously. We are not so lucky; once lost—to disease, noise or injury—they are gone for good.

Dabdoub is studying how these cells form in development for leads on how they can be restored. "We are learning how these neurons develop and what genes we can use to regenerate them," says Dabdoub, who is also an assistant professor at U of T.

He has shown he can grow these cells in vitro by injecting a gene to induce the formation of hair cells and auditory neurons. "The great thing about the cochlea is you can harvest it at embryonic stages, before any of these cells have developed, and you can manipulate them in your incubator as time goes by. Within a week you can have a nice organ formed," says Dabdoub.



DRS. VINCENT LIN (LEFT) AND ALAIN DABDOUB ARE SEARCHING FOR BIOLOGICAL SOLUTIONS FOR HEARING LOSS, a condition that affects three million Canadians.

He is zeroing in on the Wnt signalling pathway, which is important in ear development because it regulates the division and differentiation of cells. Dabdoub is trying to identify which of the Wnt family of proteins are responsible for signalling in the cochlea, which could serve as targets for drugs and gene therapy.

Dr. Vincent Lin, a clinician-scientist at SRI who specializes in hearing regeneration, collaborates with Dabdoub. They are analyzing differences in how the Wnt pathway is modulated in embryonic versus adult tissue, specifically, changes in Wnt signalling molecules. "Studying inner ear development provides important insights into regeneration, which in many ways is like development recapitulated in an older animal. As we do more analysis of cochlear tissue from many age ranges, from embryonic to adult, we're going to

identify more molecules of interest," says Lin, who is an otolaryngologist and cochlear implant surgeon at Sunnybrook, and an assistant professor at U of T.

Their work has been mainly in cell culture, but they are moving their experiments to preclinical models that mimic the human hearing system. As they learn more about the mechanisms that trigger regeneration of the cells that enable hearing, their goal is to develop therapies that will cause the organ to restore itself to a functional, natural state.

Are we close?

Lin is cautiously optimistic. "We're only a few breakthroughs away from moving forward with that. Those could happen tomorrow, or they could take years. Science doesn't work in a linear fashion; there are often big jumps. When it happens is anybody's guess."

Their goal is to develop therapies that will cause the organ to restore itself.

Dabdoub's research is supported by the Canada Foundation for Innovation, National Institutes of Health, and Ontario Ministry of Research and Innovation.

Kertes' research is supported by the Canadian Retina Foundation, Physicians' Services Incorporated Foundation and industry.

The study to validate an eye test to help early detection of dementia is led by Dr. Sandra Black, and funded by Brain Canada and the W. Garfield Weston Foundation.

Lin's research is supported by the Canadian Institutes of Health Research, Hearing Foundation of Canada and industry.



Dr. Sandra Black and Dr. Brad MacIntosh discuss their joint research on white matter hyperintensities—bright patches in the brain detectable using magnetic resonance imaging—found in people with and without dementia.

Infrastruct



CONGESTION AND CHAOS ON THE BRAIN'S HIGHWAYS: THIS IS NEURODEGENERATION

The human brain is magnificently elaborate. It is thought to contain 86 billion neurons interconnected by several trillions of synapses that process and transmit information about pleasure, pain, emotion and movement, and form memories. When neurons fail, as they do in neurodegenerative diseases like Alzheimer's disease and amyotrophic lateral sclerosis (ALS), those connections collapse and information-processing stops. For the most part, these diseases progress slowly and remain hidden for years. By diagnosis, they have taken hold of the neurons and begun dismantling them.

Clinicians would prefer to diagnose neurodegenerative diseases before they wreak havoc, but much of their neurobiological basis remains unknown. To that end, scientists at Sunnybrook Research Institute (SRI) are pulling at the threads of neurodegenerative diseases to understand their origins and progression, and uncover ways of changing their course.

The signature of many neurodegenerative diseases is the accumulation of abnormal proteins in the brain. Healthy neurons produce lots of beta-amyloid,

but clearing this toxic protein becomes troublesome with age. In the early stages of Alzheimer's disease these proteins form clumps, contributing to the demise of nearby neurons. In ALS, which has beset notable figures including the physicist Stephen Hawking and New York Yankees Hall of Famer Lou Gehrig, misfolded proteins accumulate in the brain and spinal cord.

Dementia comes in several forms; Alzheimer's disease is the most common. Short-term memory loss is frequent in its earliest stages. As it advances, people become disoriented and experience mood changes. They have trouble planning and organizing, and may struggle to find words. The *World Alzheimer Report 2010* predicts the number of people with dementia will double every 20 years, rising to 65.7 million in 2030.

Plaques and tangled neurons are the hallmarks of Alzheimer's disease, but there are also almost always flaws in the brain's blood vessels. These failings occur in the small vessels in the cortex, the brain's outermost layer, also called the grey matter, and in those vessels that plunge from the surface into the white matter to nourish the

Photo: Curtis Lentinga

ure

Issues

deepest areas of the brain. The blood vessels feed the brain with oxygen, glucose and other nutrients; channels along the vessel walls gather up and dispose of waste and debris. The brain's vasculature has thus become a priority for scientists interested in the origins and progression of Alzheimer's disease.

TRAFFIC SNARLS

Dr. Bojana Stefanovic, a biomedical engineer in the Brain Sciences Research Program at SRI, wanted to understand the relationship between beta-amyloid accumulation and the brain's blood vessels in Alzheimer's disease. In collaboration with Dr. JoAnne McLaurin at the University of Toronto, she used a preclinical model of the disease, a genetically engineered mouse with an aggressive and early onset of amyloid deposition in the cortex. Working with a microscope that uses a laser to illuminate fluorescent dyes injected into the mouse, they were able to watch the changes in the individual blood vessels as they failed.

In 2012, Stefanovic and her colleagues published the results of their study in the journal *Brain*. They found that as the beta-amyloid accumulates around the neurons and blood vessels, the arterioles traversing the cortex become misshapen—twisting and coiling within the tissue. The more beta-amyloid on a vessel, the more tortuous and narrow it becomes. Stefanovic also found that these changes to the arterioles undermined their function. They didn't react to carbon dioxide, a potent vasodilator, as normal arterioles do by widening and increasing blood flow to the tissue.

"You used to have this straight highway through the brain, and now you're left with a curvy country road," says Stefanovic. "The delivery of nutrients and the dumping of debris, or metabolic waste, becomes less efficient." The findings offer evidence of the disease's early stages and how vascular changes might prime the brain for neurodegeneration.

Beneath the cortex lies white matter, containing glial cells that provide support and protection for the brain's neurons, and myelinated axons that transmit signals from one part of the brain to another. Dr. Sandra Black,

director of the Brain Sciences Research Program at SRI, and Dr. Brad MacIntosh, a medical biophysicist in the program, have been using imaging technologies to probe the brain's white matter for clues about the early signs of dementia.

Bright spots and patches sometimes show up within the white matter on certain types of magnetic resonance imaging (MRI) brain scans called T2-weighted MRI images. The spots, called white matter hyperintensities (WMH), can be little holes in the brain resulting from blockage due to twisting or hardening of artery walls. The patches develop from leakage of blood plasma into the brain due to hardening of the deep veins. They are seen in normal aging brains, but can also be associated with a higher risk of stroke, dementia and death. They are like dry patches in a lawn that doesn't get enough water. "It's not a specific sign, but it's telling of an overarching problem and a sign of future risk," MacIntosh says.

In 2013, he and Black, along with Ilia Makedonov, a graduate student at U of T, published a study in the *European Journal of Neurology* comparing the blood flow near WMH in older adults with and without Alzheimer's disease. They found that blood didn't flow through these regions as readily as it did in the normal-appearing white matter, and that adults with Alzheimer's disease were more likely to have WMH in the tissue near the ventricles, the large

cavities deep in the brain that produce cerebrospinal fluid.

Blood pulses through the brain in synch with the heartbeat. As it does, it sends vibrations through the brain tissue like the ripples that radiate outward after a stone is dropped into water. "Your brain is like Jell-O—every heartbeat, it jiggles around a little bit, but not a lot. Too much is not a good thing," says MacIntosh.

Recently, scientists have found that changes in the brain's pulsatility can be a useful marker for some diseases. In a study published in *PLOS One*, Black, MacIntosh and Makedonov used a brain imaging technique called BOLD functional MRI that measures blood flow and oxygen uptake by brain tissue to show that the pulsatility of normal-looking white matter was dramatically higher in people with damaged cerebral blood vessels (a condition called small vessel disease) compared with age-matched healthy controls. They think the brain's deep veins may harden in response to lower oxygen levels, causing plasma leakage and difficulty clearing amyloid from the brain.

"The work we're doing is opening the world's eyes to the venous side of the brain's circulation, and how changes that go on with aging can contribute to the acceleration of Alzheimer's disease," says Black. A brain with scarred blood vessels or clogged spaces around the vessels can have trouble clearing debris and waste, including accumulated proteins. "There's an important system in the brain to get rid of garbage, but this has only come to light recently," says Black. "The garbage truck can't go into a neighbourhood if a whole lot of streets are blocked."

The research shows there are strong links between cerebrovascular disease and Alzheimer's disease. The risk factors associated with white matter disease include hypertension, high cholesterol, smoking, unhealthy diet and lack of exercise, so intervention may be possible. For MacIntosh the next step is to see if exercise can benefit people at risk of developing WMH. "Exercise may not impact directly the hypoxic zone, but it may help everything else around it and buy people time," he says.

THE MORE BETA-AMYLOID ON A VESSEL, THE MORE TORTUOUS AND NARROW IT BECOMES.



Neurologist Dr. Lorne Zinman talks with his patient Lucia Corapi, who has amyotrophic lateral sclerosis, a progressive neuromuscular condition that kills the motor neurons of the central nervous system.

MOTOR TROUBLE

Amyotrophic lateral sclerosis is another age-related neurodegenerative disease. It is marked by the death of motor neurons in the central nervous system. The first signs are often muscle weakness and atrophy, usually in the legs and arms. People with it may suddenly feel awkward when they run or walk, or trip or stumble. They might find buttoning a shirt or turning a key in a lock challenging.

"It's a devastating disease. People have total insight and just watch themselves become weaker and weaker," says Dr. Lorne Zinman, a neurologist and the director of the ALS Clinic at Sunnybrook. On average, two new cases are diagnosed for every 100,000 people per year. About 3,000 Canadians live with the disease. With no cure, most people with ALS survive two to five years after they begin to show symptoms.

Sometimes to decipher a disease you need to start from scratch. When Zinman began his academic career about a decade ago, he was disappointed by the lack of clinical trials to test promising therapies available to Canadians with ALS. "I used to tell my patients that they would have to go to New York or Boston to get into a clinical trial," he says.

In 2008, he founded the Canadian

ALS Research Network to link the 15 academic ALS clinics across Canada. The network promotes multicentre ALS studies in Canada with the help of a patient registry, established in late 2010. The registry allows researchers to identify Canadian ALS trends, and Canadian ALS patients to participate in clinical trials, by logging information about people's genetics, symptoms, risk factors and medications. "A principal barrier to doing a trial is recruitment," says Zinman. When the registry launched, researchers submitted the details of more than 1,700 individuals, 25% more cases than expected.

The registry will help researchers share blood and tissue samples from people with ALS so that they can better understand the disease and find genetic mutations associated with its inherited form. About 10% of ALS cases have a familial link. Recently, an international group of researchers, including Zinman, published a study in *Nature Neuroscience* detailing the discovery of mutations in a newly identified gene called *Matrin 3* that causes an inherited form of ALS. In 2011, Zinman's research team had helped identify a mutation on chromosome 9 that is found in one-third of people with familial ALS. Mapping these genes gives scientists a better understanding of the biological

pathways that cause ALS and provide novel targets for intervention.

"This is information we need to have so that we can start designing treatments to test in patients," says Zinman.

The registry has already helped Canadian ALS patients enrol in large, international clinical trials. Two additional industry trials are underway in Canada, and the network will lead a Phase 2 trial in late 2014 to test a plant extract compound that has slowed ALS progression in preclinical studies. "We're aiming to enrol 100 patients across Canada to determine if this compound can also slow disease progression in our patients," says Zinman. "It's something we're really excited about."

Research Funding & Other Information

Black: Alzheimer Society of Canada, Canada Foundation for Innovation (CFI), Canadian Institutes of Health Research (CIHR), Heart and Stroke Foundation Canadian Partnership for Stroke Recovery (CPSR), LC Campbell Foundation, and the Ontario Ministry of Research and Innovation (MRI). **MacIntosh:** CIHR, CPSR, and Natural Sciences and Engineering Research Council. **Stefanovic:** CFI, CIHR and MRI. **Zinman:** ALS Society of Canada, CIHR and Temerty Family Foundation. Black and Zinman are faculty within the department of medicine (neurology) at the University of Toronto; MacIntosh and Stefanovic, the department of medical biophysics.

Dr. Benjamin Goldstein is searching for biomarkers in the blood to optimize diagnosis and treatment of youth with bipolar disorder.

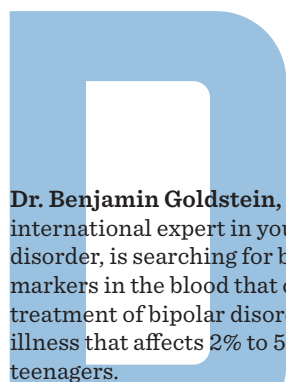
MOOD DISORDERS ACROSS OUR LIVES



Photo: Curtis Lantinga



THE HEALTH OF OUR MIND, WHICH IS LINKED INTRICATELY TO THAT OF OUR PHYSICAL BEING, FACES CHALLENGES AT ALL AGES AND STAGES OF LIFE. AS THESE VIGNETTES SHOW, PSYCHIATRISTS AND RESEARCHERS AT SUNNYBROOK ARE DIVING DEEP INTO THESE CHALLENGES TO STEER THE COURSE OF CARE



Dr. Benjamin Goldstein, an international expert in youth bipolar disorder, is searching for biological markers in the blood that can guide treatment of bipolar disorder, a chronic illness that affects 2% to 5% of teenagers.

Bipolar disorder is characterized by alternating episodes of mania, pathological elation accompanied by high energy and other symptoms, and depression. These disturbances can impair work or school performance, damage relationships, and lead to suicide or substance abuse. It is the fourth most disabling medical condition among adolescents.

Goldstein is studying whether increased markers of inflammation and decreased levels of a protein called brain-derived neurotrophic factor coincide with acute depression or mania. “We’re trying to parse out how people look biologically when they’re well versus when they’re symptomatic,” he says.

Bipolar disorder is associated with reduced life expectancy. Although people with this illness have a relatively high risk of suicide, the leading cause of death is heart disease, which occurs at higher rates and earlier ages than among people without the disorder.

Goldstein notes that there are no biological tests that clinicians can use to guide their decisions; psychiatrists rely on patients’ recollections and their observations of patients during a session.

“You’re asking someone affected by their mood disorder to comment on their mood symptoms,” he says, noting the limitations of that. “We’re not looking to replace the clinical interaction, but to augment it—to have some biological validation that can add to our understanding of the activity of the illness,” he says.

Goldstein hopes the markers he is examining, like C-reactive protein (CRP), will shed light on the link between bipolar disease and heart disease. C-reactive protein, which is used clinically to assess risk of future cardiovascular disease in adults, has been shown to rise during bouts of mania and depression. “If you have high CRP when depressed or manic, you can see how over a period of months or years that this is not healthy.”

Detailing the biology of the disorder would not only validate patients’ self-reports, but could also help doctors tailor therapies to individuals. Perhaps most promising is the potential use of biomarkers to predict and treat an episode of illness proactively.

“[Now] we wait for symptoms to happen, then name them as symptoms and treat them. We’d like to be able to get ahead of the puck,” says Goldstein. “Teens with bipolar disorder spend more than 50% of the time with symptoms that negatively affect quality of life. Being able to shift that by 10%—making it 60/40 or 70/30 in favour of wellness—would have a meaningful effect.”

TEENS: A PRIMARY FOCUS

Like those of Goldstein, Dr. Amy Cheung’s patients are young—teens, and some younger than that. Against a backdrop of research showing people aged under 20 years have the highest rate of depression, Cheung wants to get more teens the help they need, and faster.

She notes about 20% of teens will have had an episode of depression by the time they finish high school. Depressed youth struggle academically and may abuse drugs or alcohol, or engage in reckless behaviour.

Family doctors are well positioned to screen for depression because they see patients regularly and, in general,



DR. SOPHIE GRIGORIADIS IS LEAD AUTHOR OF A STUDY that analyzes the risks of antidepressant use during pregnancy.

patients feel comfortable with them. Unfortunately, it’s not standard practice, says Cheung. “We screen for all sorts of things in primary care, and yet there’s no standardized mental health screening when we know one in five kids has a mental health problem in Canada. It’s a lost opportunity.”

Barriers to mental health screening are considerable. Family doctors receive minimal mental health training and may feel unequipped to treat depression. Moreover, their practices can be unsuited to managing psychiatric illness because patients are booked back-to-back for short appointments. “How do you assess a child with depression in three minutes?” asks Cheung.

Through interviews with family doctors, Cheung uncovered that one obstacle to screening for depression is concern about mental health support. If a problem is discovered, then the family doctors are unsure what to do and to whom referrals should be made. To address the matter, she helped create an online resource that contains screening tools, educational material for families and information on medication.

As a next step, Cheung, newly bestowed with the Bell Canada Chair in Adolescent Mood & Anxiety Disorders, is evaluating whether a tool to help

family doctors perform mental health check-ups enables earlier identification of depression. Through earlier diagnosis, she hopes to lessen the impact of illness on teenagers' lives. "It's such a significant disruption in their development. The quicker we catch it, the better."

THE PREGNANCY BLUES

For a pregnant woman, depression takes a different cast. For starters, it's often overlooked, says Dr. Sophie Grigoriadis, head of the women's mood and anxiety clinic at Sunnybrook. Her research tackles a controversial topic: antidepressants during pregnancy.

She notes pregnant women are often told symptoms, including fatigue, and changes in sleep, appetite and sex drive, are part and parcel of having a baby. "The diagnosis is easily missed," says Grigoriadis.

Between 8% and 15% of pregnant women experience depression. Left untreated, the risks are serious. These women are less likely to eat and sleep well, or seek prenatal care; they are more likely to smoke and drink alcohol, and may be at risk of suicide.

Advisories issued by Health Canada and the U.S. Food and Drug Administration warning of adverse effects of antidepressant use in pregnancy has generated worry on the part of women and confusion among clinicians, says Grigoriadis.

Seeking clarity, she and her team analyzed the evidence surrounding use of antidepressants in pregnancy. They led the first meta-analysis of outcomes after antidepressant exposure in utero, which looked at gestational age, birth weight, Apgar scores (rating of a newborn's health after birth) and spontaneous abortion.

The results were intriguing: there were statistically significant increased risks of *some* adverse effects, but the differences found in the exposed group were small and typically within normal ranges.

For example, on average, the birth weight of babies whose mothers took antidepressants during pregnancy was 75 grams lighter. "When dealing with a 3,500-gram baby, what is 75 grams—clinically?" says Grigoriadis, who notes

that although the effects weren't large, they are worthy of consideration.

Results also showed the gestational age of babies exposed to antidepressants during pregnancy was about three days shorter, and their Apgar scores were within the range signifying normal to excellent health.

She has also studied the effects of untreated maternal depression and found it is associated with premature delivery and less breastfeeding initiation. "Untreated depression is not without its consequences. You have to weigh the risks and benefits and do what's best for mom and baby," she says.

Grigoriadis and her colleagues have created a guide that includes the results of this research for obstetricians, family doctors and psychiatrists. They are doing a pilot study to evaluate the usefulness of the tool in practice, and hope to make it available across Canada.

WORRY KNOT

As adults, we all fret—there's the mortgage, children, aging parents, career—but there's anxiety, and then there's Anxiety. Obsessive-compulsive disorder (OCD) is a chronic illness

Perhaps most promising is the potential use of biomarkers to predict and treat an episode of illness proactively.

that affects 2% of the population and is characterized by unwanted and intrusive thoughts that produce fear or worry. People with OCD perform repetitive acts to reduce obsession-related anxiety.

Although OCD has a strong genetic basis, its mechanisms are unclear. If you're looking for a causal gene, you won't find one, says Dr. Peggy Richter, head of the Frederick W. Thompson Anxiety Disorders Centre at Sunnybrook. "Psychiatric illnesses are complex. They're thought to be related to a number of small genes of small effect that contribute to risk in interactive ways."



Drs. Peggy Richter and Neil Rector are studying how to improve outcomes in obsessive-compulsive disorder.



DR. MARK SINYOR IS MINING CORONER'S DATA TO IDENTIFY PATTERNS OF SUICIDE IN TORONTO. HIS AIM IS TO DEVELOP targeted suicide prevention strategies.

Richter is exploring the biology of OCD. Her approach is to study the genes—specifically, those that encode for liver enzymes that break down psychiatric medicines—of people who respond well to a class of antidepressants. The aim is to shed light on mechanisms of the disease, and predict drug response and tolerance.

Medication is a first-line treatment for OCD, but its effectiveness is limited. Antidepressants work—partially—in roughly 60% of patients. Richter puts it into perspective: “If your rituals take four to six hours a day, you might be on a drug treatment, be deemed a ‘responder,’ and your rituals still take two-and-a-half to three hours a day.”

She led the first study showing the CYP (“sip”) family of genes, known to

play a role in antidepressant response generally, may play a role in OCD.

Richter found that patients with OCD who have extra copies of the CYP2D6 gene had to try more antidepressants before finding the right one. These people tried, on average, five drugs, versus patients with OCD who had two normal copies of the gene, who tried two.

Her goal is to be able to personalize treatment so that it works better. She imagines a scenario in which a doctor adjusts dosing or switches drugs based on a patient’s genetic make-up: “Wouldn’t it be lovely if we could do that, and your odds of response go up from 60% to maybe 80% or 90%?”

Richter, along with psychologist Dr. Neil Rector, head of research at the Thompson Anxiety Disorders Centre, is also investigating disgust processes in OCD. “We’re learning that disgust processes may be related to the development and maintenance of OCD for some. We also think the emotion of disgust may have important treatment implications, requiring more targeting than in the past,” says Rector.

In a study looking at facial recognition of disgust, they found people with OCD had impaired ability to identify the emotion compared with people who had other anxiety disorders. They also found that patients with OCD who responded well to cognitive-

behavioural therapy (CBT) were much better at identifying expressions of disgust than were untreated patients; their ability was on par with that of people without an anxiety disorder. That, says Rector, is encouraging: “If this deficit exists, it appears to be something that can change in the context of treatment.”

This study is the first to look at whether facial recognition of disgust can improve among people with OCD. It provides evidence that successful CBT may lead to more accurate identification of disgust, which may have implications for the commonly observed exaggerated disgust reactions in OCD.

They plan to conduct a larger study to analyze changes in disgust in relation to ameliorating symptoms. “Does improvement of facial recognition of disgust correlate with symptom improvement?” asks Rector. “It’s the next step in this line of research.”

THE AGING MIND NEEDS A STEADY HAND

Later in life, a plethora of medical conditions can emerge, including those that affect the brain. “You have to be able to differentiate between a mood disorder like depression and the beginning of a dementia. That’s why careful assessment of elderly people needs to be conducted,” says Dr. Ken Shulman, a geriatric psychiatrist and head of the Brain Sciences Program at Sunnybrook.

Although depression is common among people aged 65 and older, experts warn it shouldn’t be viewed as a natural consequence of aging. It is estimated that symptoms, including persistent sadness and hopelessness, affect 15% of older adults in the community. Among seniors in long-term care facilities, the rate swells to about 40%, although this may be associated with the development of dementia and other medical conditions.

Mood stabilizers are a first-line therapy prescribed to stave off depression and mania. One of these, lithium, is a mainstay of treatment for bipolar disorder—and a double-edged sword, says Shulman. “It’s a very effective treatment, but it can also be toxic and cause significant side effects.”

“Psychiatric illnesses are complex. They’re thought to be related to a number of small genes of small effect that contribute to risk in interactive ways.”

One of his interests is lithium use and risk of kidney disease. Lithium is the only mood stabilizer that is removed solely by the kidney. With age, kidney function decreases, resulting in increased blood levels of the drug. “We need to make sure doctors are aware that as people age on lithium maintenance, the dosage needs to be lowered accordingly,” says Shulman.

Drug interaction is also a problem. Lithium poisoning can occur when used with medication commonly prescribed to older adults, including water pills, blood pressure medicine and anti-inflammatory drugs. Family doctors and specialists should therefore work together and be familiar with a patient’s medical conditions and the drugs she is taking, says Shulman, who adds it’s what they aim to do at Sunnybrook.

The goal of his research is to provide clinicians with greater knowledge of the risks associated with lithium, which, he says, “when used at the appropriate levels, is a drug that can keep people stable and well, and their quality of life is much improved.”

He is also looking at ways of improving guidelines for laboratory analysis of lithium levels in the blood. Establishing a therapeutic range specific to older adults could help prevent lithium intoxication. “An elderly person in their late 70s or 80s cannot tolerate the same lithium level that a 20- or 30-year-old can, but the labs don’t differentiate between a geriatric lithium level and a young adult lithium level,” says Shulman.

At play is a larger public health concern, he adds: “It’s one of the biggest problems we face in medicine: the effects drugs have on older adults. That’s not to say we can’t and shouldn’t use drugs in older adults; it [just] calls for a more careful approach.”

SUICIDE: AGELESS, STAGELESS

Mood disorders present different challenges across the lifespan, but common across ages is that they increase the risk of suicide. Dr. Mark Sinyor is combing through coroners’ data to probe that risk.

“We want to understand who dies from suicide and the situations that

surround it. How do specific health or psychiatric conditions change the risk of suicide? Do the events just prior to death give us a window into the minds of people thinking about suicide, and could they give us clues about how to stop it? We’re hoping this will be the start of a larger conversation on how to prevent suicide,” he says.

There are about 4,000 suicides in Canada annually. Although it is the 10th-leading cause of death overall, suicide is the second-leading cause of death among people aged 10 to 50 years, notes Sinyor.

In one study, Sinyor examined thousands of suicides that happened in Toronto between 1998 and 2010. Using statistical analysis, he identified five distinct clusters. The study, the largest of its kind in Canada, provides a clear snapshot of patterns of suicide in Toronto based on age, sex, mental illness and stressors such as bereavement and financial troubles.

Understanding these details is important, says Sinyor. For example, one group he uncovered was middle-aged men with depression and substance abuse problems. “That’s a very particular set of circumstances. If we know those people at that phase of life are at high risk, [then] we can target a strategy toward them.”

He also found that while suicide occurs at all ages, those at highest risk are elderly males. Targeted, thorough interventions, including education geared to specific groups, are therefore critical, says Sinyor, whose prior work showed erecting a bridge barrier at Toronto’s Bloor Street Viaduct didn’t change suicide rates.

“One of the lessons of [that study] is that you can’t think of an object, like a barrier, in and of itself being a suicide prevention strategy. It’s one component, but the strategy has to be comprehensive. We need to educate people about mental illness, suicide and the risks of suicide.”

Research Funding & Other Information

Cheung: Bell Canada, Canadian Institutes of Health Research (CIHR) and Ontario Mental Health Foundation (OMHF). **Goldstein:** CIHR, The Depressive and Bipolar Disorder Alternative Treatment Foundation, Heart and Stroke Foundation (Ontario), National Institute of Mental Health (NIMH) and OMHF. **Grigoriadis:** CIHR, OMHF, Ontario Ministry of Health and Long-Term Care (MOHLTC), Ontario Women’s Health Council and C. R. Younger Foundation. **Rector:** CIHR and Frederick W. Thompson. **Richter:** CIHR, International OCD Foundation, NIMH, OMHF and Frederick W. Thompson. **Shulman:** MOHLTC. **Sinyor:** Dr. Brenda Smith Bipolar Research Fund and Physicians’ Services Incorporated Foundation. Each holds an appointment within Sunnybrook Research Institute, and is a member of the department of psychiatry at the University of Toronto.



DR. KEN SHULMAN IS INVESTIGATING THE RISKS ASSOCIATED WITH LITHIUM, A DRUG THAT STABILIZES MOOD, BUT CAN have toxic side effects.

Rhythm of the Night

Want a healthy brain? Get a good night's sleep

**Sleep that knits up the ravell'd sleeve of care,
The death of each day's life, sore labour's bath,
Balm of hurt minds, great nature's second
course, Chief nourisher in life's feast.**

William Shakespeare, *Macbeth*

The Bard understood the importance of sleep.

Although research shows sleep plays a critical role in learning and memory, metabolism and mood, there is a tendency in our culture to equate a hefty amount of shut-eye with laziness.

"I think there's a bit of negative social pressure against sleep and, on top of that, an under-appreciation of how important sleep is," says Dr. Andrew Lim, a scientist in the Brain Sciences Research Program at Sunnybrook Research Institute and a neurologist at Sunnybrook Health Sciences Centre. Lim's research into the link between sleep disruption and development of neurological disease calls into question this bias against the heavy-sleeping set.

In 2013, his research, published in the journal *Sleep*, was the first clinical study to connect sleep fragmentation with a higher risk of developing Alzheimer's disease (AD). Lim measured the sleep of 737 older adults, and, over several years, found those with highly fragmented sleep were one-and-a-half times more likely to develop AD compared to sound sleepers. He also found a correlation between deficient sleep and a faster rate of cognitive decline.

Lim has also shown sound sleep can counteract the most common genetic risk factor for AD and the development of neurofibrillary tangles, a key brain change underlying the disease. His research is important because the number of people with dementia is projected to soar—from an estimated 44 million people worldwide in 2013 to 75 million by 2030. As Lim notes, age and genetic predisposition—the main risk factors for dementia—cannot be changed; poor sleep, however, can be addressed.

"A lot of sleep disruption happens because of social factors and choices—we get sleep-deprived because of work, school or family obligations. These are things that can potentially be changed through social interventions. Sleep is a potentially modifiable risk factor. If we're able to intervene to get people to choose to sleep longer, or more regularly, or to have sleep disorders treated, we may have an impact on the incidence of dementia," says Lim.

He is also studying whether sleep is tied to other neurological diseases, including Parkinson's disease and stroke.

He is leading the Ontario Sleep Health Study, which will examine the sleep patterns of thousands of Ontario residents to determine whether poor sleep is related to development of these and other brain disorders.

His landmark research into the biology of circadian rhythms (the internal 24-hour sleep-and-wake cycle) also has potential for clinical impact. He's found a gene variant associated with patterns of human sleep and activity that also influences the time of day someone is most likely to die. "We want to get a good understanding of the genes and proteins that account for important sleep traits with the goal of designing therapies and tests to identify people's biological tendencies and sleep needs," says Lim.

Sleuthing for genetic differences underlying circadian rhythms could lead to drugs designed to offset the effects of shift work or jet lag, for example. Identifying individual sleep needs based on biological preferences could also lead to tailoring of schedules based on those needs, he says. Could this give rise to a simple blood test indicating whether someone requires more or less sack time?

Possibly. We'll have to sleep on it.

Lim's research is supported by the Canadian Institutes of Health Research and the Heart and Stroke Foundation of Ontario.



DR. ANDREW LIM USES ACTIGRAPHS (WRISTWATCH-LIKE DEVICES THAT TRACK PEOPLE'S movements) to study whether poor sleep is linked to brain disorders, including Parkinson's disease and stroke.

Photo: Doug Nicholson

Take Three Sardines and Call Me in the Morning

Could fish oil help treat cognitive impairment?

N

Nutrition guidelines suggest that a diet rich in omega-3 fatty acids, as found in salmon, flaxseed and nut oils, helps maintain a healthy brain and heart. Supplements are popular for people who do not eat fish or other omega-3 fatty acid-rich foods. Although research indicates that these polyunsaturated fatty acids play a crucial role in brain function, findings from clinical trials of supplements have been inconsistent.

Seeking to understand better the effects of omega-3 fatty acids on cognitive performance, researchers in the Brain Sciences Research Program at Sunnybrook Research Institute (SRI) conducted a meta-analysis—a method that compiles and analyzes findings from many clinical trials—to assess the evidence.

Graham Mazereeuw, a PhD student supervised by scientist Dr. Krista Lancôt and clinician-scientist Dr. Nathan Herrmann, who co-direct the neuropsychopharmacology research group at SRI, led the study. After sifting through the literature, they examined the neuropsychological benefits of omega-3 fatty acid treatment in 10 randomized controlled trials of elderly patients.

“We looked at three groups: normal controls; mild cognitive impairment, that pre-Alzheimer’s stage; and Alzheimer’s disease. Interestingly, this study showed that the positive [effect] was in the mild cognitive impairment group. That’s a very important group from a prevention point of view, because we know that a good proportion of them—about 12% to 15% per year—convert to Alzheimer’s disease,” says Lancôt, who is also a professor at the University of Toronto.

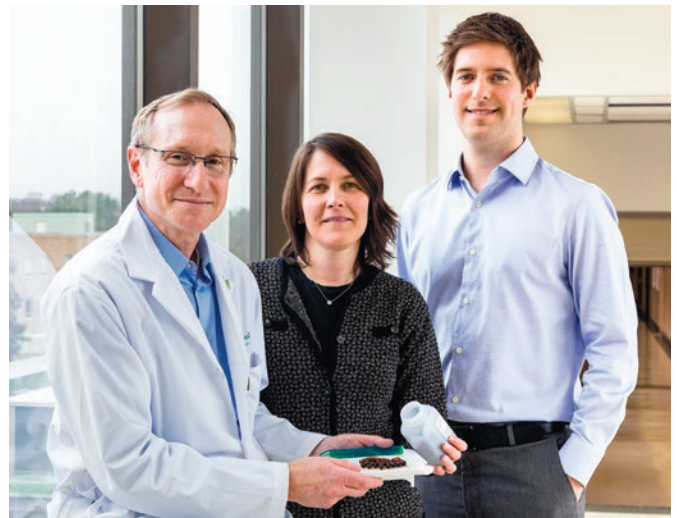
Omega-3 fatty acid treatment was associated with a small but significant benefit in immediate recall and attention, and processing speed in patients with mild cognitive impairment, but not in healthy patients or those with Alzheimer’s disease.

“If there’s anything we can do in that middle at-risk group, it’s very important, especially if it’s going to have low side effects. Right now there are no treatments for mild cognitive impairment,” says Lancôt.

On how omega-3 fatty acids work, Mazereeuw cites research suggesting they reduce inflammation. “It is thought that they work by having an overall anti-inflammatory and antioxidant effect, potentially reducing neuroinflammation, not only in the body, but also in the brain,” he says.

The group is now leading a randomized controlled trial investigating if treating depression in patients with heart disease with omega-3 fatty acids will improve symptoms and quality of life.

The trial is built in part on the back of their previous research. In 2010, Herrmann and Lancôt published the



DR. NATHAN HERRMANN (LEFT), DR. KRISTA LANCÔT AND PHD STUDENT GRAHAM MAZEREEUW are studying the effects of omega-3 fatty acid supplements on brain health.

second-highest cited paper since 2009 in *Biological Psychiatry*: a meta-analysis looking at the role of inflammatory markers in depression.

“One of the consistent findings was that two inflammatory measures, cytokines IL-6 and tumour necrosis factor alpha, had elevations in them that appeared to be consistently associated with depression,” says Herrmann, who is also a professor at U of T.

This underscores the importance of picking which patients are most likely to gain from omega-3 treatment. Mazereeuw says they are looking at blood lipid biomarkers that interact with the inflammatory system and may be related to omega-3 fatty acids. The idea is to predict which groups of patients will respond.

“If there’s a consistent signal there, with one or two different biomarkers, then we might be able to anticipate who is most likely to benefit,” says Mazereeuw.

“It matters because if there was to be an effect with the omega-3 fatty supplements, then it’s something that you can take with a high degree of tolerability and low side effects, and it’s a good preventative step that you can take from early life,” he adds.

This research was funded by the Canadian Institutes of Health Research and the Ontario Mental Health Foundation.



IMAGING AND THE INJURED BRAIN: DETECTING THE OBVIOUS AND THE INSIDIOUS

PHOTOGRAPHY BY CURTIS LANTINGA

“Stroke is a cataclysmic event,” says Dr. Richard Aviv, a neuroradiologist in the Brain Sciences Research Program at Sunnybrook Research Institute (SRI). The symptoms come on without warning: sudden limb weakness, nausea, slurred speech and loss of vision, among others.

There are several types of stroke, but all disrupt blood flow in the brain and rob its tissues of oxygen, causing neurons to die. Hemorrhagic stroke, or a brain bleed, occurs when a blood vessel suddenly leaks or bursts inside the brain. It is the deadliest type of stroke: about 40% of people who have a hemorrhagic stroke die in hospital, and most survivors are left with disability, which can include paralysis, loss of speech, blindness and dementia.

No effective, targeted therapy to stop the bleeding in a hemorrhagic stroke exists. Hypertension is the most common culprit, and in those cases, blood pressure control can help reduce bleeding risk. With aging, amyloid deposits in the walls of the blood vessels can also give rise to bleeding in the brain. “Alzheimer’s disease, which is associated with amyloid deposits, is becoming a more common cause of cerebral hemorrhage,” says Dr. Sandra

Black, director of the Brain Sciences Research Program at SRI. Surgery is only suitable for a few patients.

“There is a huge, unmet need for a safe and effective treatment for brain hemorrhage,” says Dr. David Gladstone, a stroke neurologist in the Brain Sciences Research Program at SRI and director of the Sunnybrook Regional Stroke Prevention Clinic.

The first few hours after an intracerebral hemorrhage occurs are critical. Although some brain bleeds stop quickly and spontaneously, aided by natural pressure within the brain and blood-clotting factors, others continue to bleed, and become fatal or leave a person permanently disabled.

“We see some patients arriving at the emergency room while the brain hemorrhage is still at a small size—they’re awake, talking and moving, and stroke symptoms are relatively mild. However, minutes or hours later, many will be in a coma and in critical condition because of an enlarging hemorrhage,” says Gladstone. “We desperately need a treatment to prevent this catastrophic progression,” he adds.

Until recently, clinicians had no way to predict which hemorrhages would worsen. Then, in 2007, Aviv and



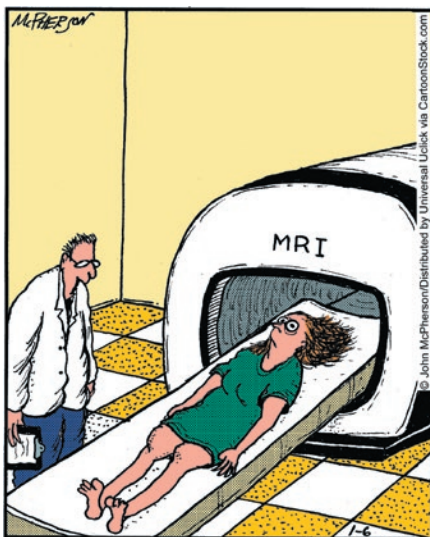
Intracerebral hemorrhage, when a blood vessel inside the brain bursts, either spontaneously or because of trauma, is especially dangerous when it expands further into the brain. Dr. Richard Aviv has discovered the "spot sign," a marker seen with brain imaging that can predict which hemorrhages are likely to expand.

colleagues developed the “spot sign,” a noninvasive imaging sign that can identify patients with an intracerebral hemorrhage that will likely grow. It uses an imaging test called a computerized tomography (CT) angiogram to look at blood vessels in the brain. The test relies on a contrast dye to highlight the vessels on the image; the dye will leak out of ruptured vessels and pool nearby, forming a bright white spot in the middle of the hemorrhage on the image.

The spot sign is a mark of active bleeding in the brain. Between 25% and 33% of patients with an intracerebral hemorrhage have one or more spot signs. Because the CT angiogram scan takes only two minutes, the spot sign has enabled clinicians in the emergency department to predict quickly and accurately which patients are likely to get worse.

The more spots there are, the greater the chance the hematoma will expand. “The bottom line is that one is too many,” says Aviv. “There is a lot of optimism amongst neurologists that finding a spot sign may eventually mean a treatment for intracerebral hemorrhage. It’s an orphan disease without a cure, and we hope that we’ve discovered the sign that will allow at least the testing of potential candidates for a cure.”

One such drug has shown promise.



“OK, Mrs. Dunn. We’ll slide you in there, scan your brain, and see if we can find out why you’ve been having these spells of claustrophobia.”

This is the first preclinical model of the spot sign for acute intracerebral hemorrhage.

Recombinant activated factor VIIa, a blood-clotting drug used in hemophilia, is known to stop bleeding quickly. Gladstone and his colleagues wanted to test it in a subgroup of patients with a spot sign who could benefit most from the drug. Previous studies had not been done with any image-guided techniques to target the therapy to these highest-risk patients.

“We know the spot sign is a marker of bad outcomes, including prolonged hospital stay, death and morbidity,” says Aviv. “Now we want to know: can we intervene when we see this marker to prevent the poor outcome?”

STOPPING THE LEAKS

In 2011, Gladstone, Aviv and their colleagues launched SPOTLIGHT, a first-of-its-kind clinical trial of an image-guided emergency treatment protocol for intracerebral hemorrhage. This trial aims to stop brain bleeds from growing bigger by identifying patients with a spot sign and treating them in the emergency room with an injection of factor VIIa. The spot-sign-positive patients—the active bleeders—identified by the imaging scan are thought to be the ones who will respond best. The patients who don’t have a spot sign are unlikely to worsen and therefore are not enrolled.

The study is headquartered at Sunnybrook and involves 12 stroke centres across Canada. They expect it will take about five years. “The hope is that this treatment, if administered quickly enough and to the right patients, might save lives and reduce disability in survivors,” says Gladstone.

Outside the clinic, Aviv is tackling the biology of intracerebral hemorrhage. As is often the case in medicine, researchers and clinicians need to learn

more about how a condition, in this case intracerebral stroke, begins and develops. “We don’t know enough about how hematomas grow,” says Aviv. “We wanted to see how hematomas expand, and whether there’s a cascade effect where one vessel ruptures, followed by another, et cetera.”

Dissatisfied with existing models that aimed to approximate intracerebral hemorrhage, Aviv created a model that more closely mimics acute human hemorrhagic stroke. He worked with Dr. Kullervo Hynynen, director of Physical Sciences at SRI and a pioneer in the development of focused ultrasound, to design a way to rupture the blood vessels in the basal ganglia, a frequent site of hemorrhagic strokes. Using magnetic resonance imaging (MRI) to guide a high-intensity ultrasound wave to the right spot in the brain, they were able to cause a more localized brain bleed than could be done with other models.

This is the first preclinical model of the spot sign for acute intracerebral hemorrhage. Its creation opens up myriad possibilities.

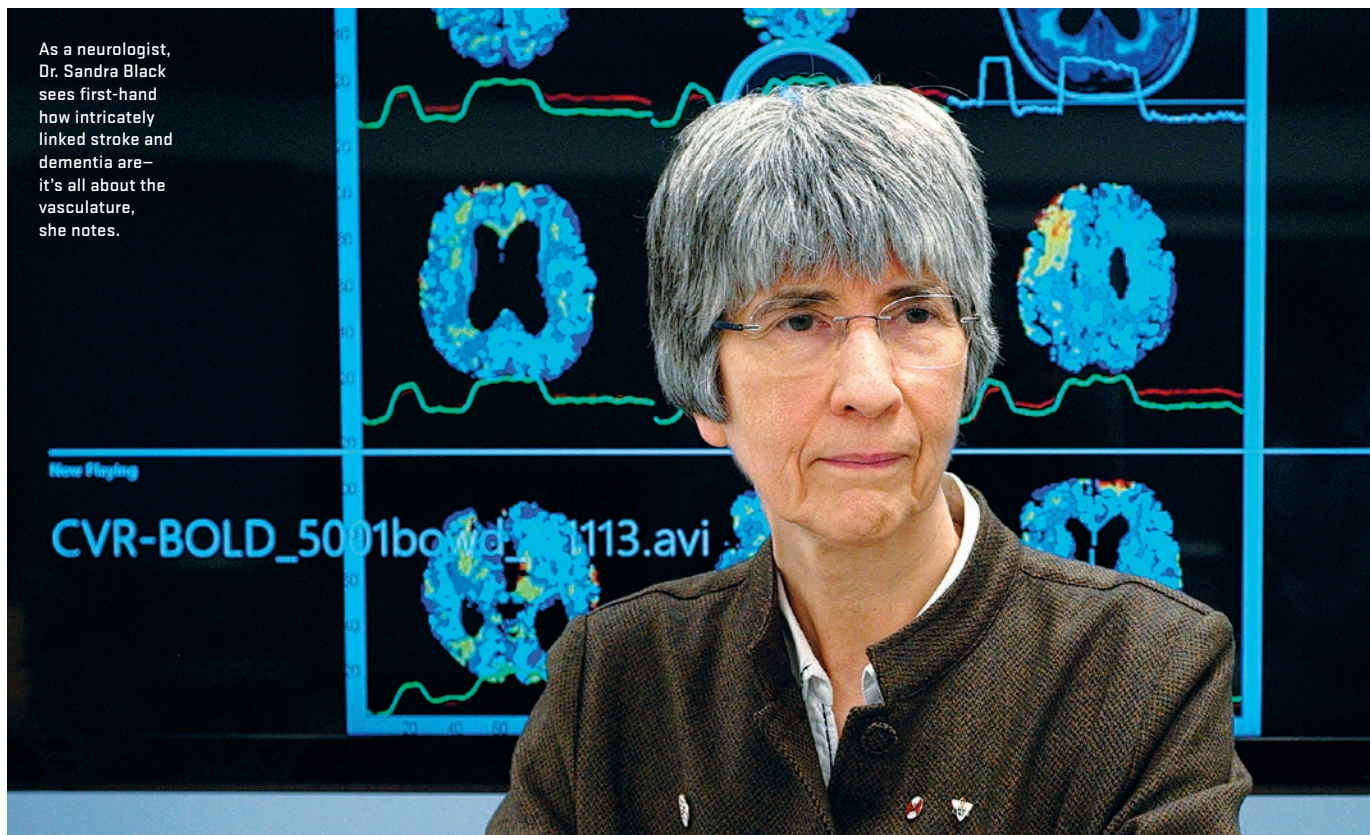
Aviv says they are now able to understand the different phases of hematoma growth, and have a model they can use to study therapies to treat people with an ongoing brain hemorrhage. “We totally think this simulates the human condition,” says Aviv.

COVERT ATTACKS

Not all strokes are so evident. Silent strokes lack the obvious symptoms associated with stroke, but still cause damage. They often happen in the brain’s white matter—its inner core. This layer is more vulnerable to disruptions in blood flow because fewer blood vessels traverse it than the cerebral cortex (grey matter). Silent strokes can be hemorrhagic (bleeding) in nature, but they are mainly due to a blockage of the small arterioles that plunge into the white matter.

Black, who sees patients with stroke and dementia, says that many patients come to the clinic because they have a memory complaint, or they don’t seem

As a neurologist, Dr. Sandra Black sees first-hand how intricately linked stroke and dementia are—it's all about the vasculature, she notes.



to be functioning as they normally do. Often the family is worried. “The main effect of the small strokes is that they may interfere with the flow of information between the front and the back part of the brain—you get executive dysfunction,” says Black. “With respect to memory, you can encode the information, but you have trouble retrieving it.”

Silent strokes are more common in older people and linked to future problems. A study of 3,660 people with an average age of 75 years revealed that 28% of seniors had silent strokes. Another study that followed-up participants for four years found that those with evidence of past silent strokes were more likely to experience problems with memory and thinking, and develop dementia and stroke.

Black, along with Dr. Brad MacIntosh, a medical biophysicist at SRI, and their colleagues are finding links between silent stroke, white matter disease and dementia. (See Infrastructure Issues on page 16.) They’ve used a functional MRI technique to uncover evidence of silent strokes and white matter disease, and understand their origins and

impact on the brain and its function. The technique shows bright white spots where silent strokes have occurred and diffuse white areas, called white matter hyperintensities.

The common factor between the three—silent stroke, white matter disease and dementia—is the vasculature that feeds the brain and removes its waste. The white spots and larger areas are signs of reduced blood flow, which can have knock-on effects. For example, if pathways along the vasculature can’t clear out dangerous proteins like beta-amyloid, which damages cells, then amyloid deposits may form within the brain, and the person may develop dementia. “The vasculature is intimately related to the development of Alzheimer’s disease. But it also works in the other direction: Amyloid deposits can cause blockages and hemorrhagic stroke,” says Black.

Black and MacIntosh expect that by understanding the early changes to the brain’s blood vessels, intervention before people succumb to stroke, cognitive decline or dementia might be possible. People at risk can try to reduce their vascular risk factors by keeping

hypertension under control with diet, exercise and medications prescribed by their physicians. “You need to do activities that increase brain blood flow and make it healthier,” says Black.

“Some people say that having silent strokes is a part of getting old, and that we should just move on,” says MacIntosh. “I think that’s a pessimistic point of view. We should be chipping away at this attitude, so that we can age as best as we can by preserving our brain’s health.”

Research Funding & Other Information

Aviv (excluding SPOTLIGHT trial): Canadian Stroke Consortium, Heart and Stroke Foundation of Ontario and NovoNordisk Canada. **Black**: Alzheimer Society of Canada, Canada Foundation for Innovation (CFI), Canadian Institutes of Health Research (CIHR), Heart and Stroke Foundation Canadian Partnership for Stroke Recovery (CPSR), LC Campbell Foundation, and the Ontario Ministry of Research and Innovation (MRI). **MacIntosh**: CIHR, CPSR, and Natural Sciences and Engineering Research Council. **SPOTLIGHT trial** [Aviv and Gladstone]: CIHR, MRI and Ontario Stroke Network. Aviv is a faculty member within the department of medical imaging at the University of Toronto; Black and Gladstone, medicine (neurology); MacIntosh, medical biophysics.

The MS Cog Fog

Neuropsychiatrist aims to detect and decipher dysfunctional cognition in this demyelinating disease of the brain and spinal cord

Multiple sclerosis (MS) is an unpredictable disease of the central nervous system and the most common cause of neurological disability in young to middle-aged adults. Canada has the highest prevalence in the world: about 100,000 Canadians have MS.* Although symptoms can be physical, including blurred vision, muscle weakness and difficulty with balance, MS can also affect cognition: 40% to 70% of people with MS will have some form of impairment—cloudy thinking, poor recall and high distractibility, for example.

Dr. Anthony Feinstein is a neuropsychiatrist at Sunnybrook and scientist at Sunnybrook Research Institute who sees about 500 patients in his MS clinic. In his experience, people with MS want to know if and how their brains are affected. “You want to know about your disease,” he says. “If you have cognitive difficulties, it’s not just an abstract finding. It will predict difficulties with work, with relationships, with recreational activities—it’s got practical implications for how individuals lead their lives.”

It is estimated 20% to 30% of patients show early signs of cognitive impairment. Wait times for neuropsychological testing can take many months. Full cognitive testing is limited by the cost of resources and a shortage of neuropsychologists to administer the lengthy tests in a busy medical setting. To address this, Feinstein and colleagues developed a short, computerized battery of tests for MS patients to complete in the clinic.

“The tests detect the speed with which you think, and they look at your working memory. We focus on these



DR. ANTHONY FEINSTEIN'S FINDINGS THAT PEOPLE WITH MS HAVE LESS INATTENTIONAL BLINDNESS COULD BE A real-world measure of distractibility in these people.

two aspects of cognition because we know that they are commonly affected in MS,” he says.

Feinstein and colleagues enrolled 138 patients aged 18 to 63 years from MS clinics at Sunnybrook and St. Michael's Hospital. Patients were organized into one of four groups based on their disease subtype: clinically isolated syndrome (an individual's first neurological episode); relapsing-remitting (unpredictable

episodes when new symptoms appear or existing ones get worse, interchanged with a relative absence of symptoms); primary progressive (a slow increase in disability, without relapses); and secondary progressive (often follows relapsing-remitting MS; the disease begins to worsen steadily). They had to complete three computer-generated problem-solving tests. The total test time was 10 minutes.

* Multiple Sclerosis International Federation Atlas of MS: <http://www.atlasofms.org>

His team evaluated the degree to which patients were able to achieve particular aims and how quickly they could do it. Immediately after the tests were completed, a neurologist reviewed the results.

They found that the battery was able to identify cognitive differences among the four groups of patients that spanned the range of MS subtypes, including those with clinically isolated syndrome.

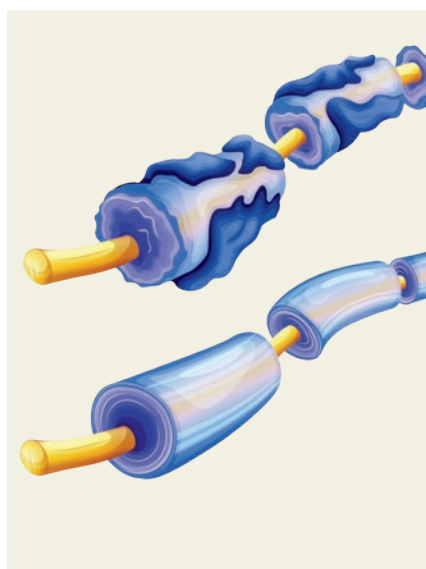
“So you get a very quick assessment there in the clinic. That was the aim behind developing this study,” he says.

With results published in the *European Journal of Neurology* in 2014, Feinstein and colleagues now propose to use the computer-generated test in the MS clinics at Sunnybrook and St. Mike’s, which together see more than 7,000 patients. He says the next step in this research is to incorporate real-life distractions—a ringing telephone, for example—to do the same test in a busy clinical setting.

MONKEY? WHAT MONKEY?

In another study led by Feinstein, published in the journal *Neurology*, researchers looked at “inattentive blindness,” a phenomenon whereby individuals fail to notice an object in plain sight. Although researchers have studied selective attention in individuals with no identified cognitive problems using the ‘Gorilla in the Room Test,’ Feinstein was the first to apply the paradigm to people with MS, who, in general, have difficulty paying attention, to measure their distractibility.

His group examined 68 people with MS aged 18 to 59 years at Sunnybrook’s and St. Mike’s MS clinics.



WITHIN A NERVE CELL, A HEALTHY FIBER, OR AXON, is protected by intact myelin (bottom). This “insulation” helps to conduct electrical impulses smoothly and quickly, so that the brain and body can communicate and function properly.

In multiple sclerosis, myelin is damaged (top), it is thought because the immune system attacks its own brain, spinal cord and optic nerve. These attacks strip myelin from the axon, leaving small scars—scleroses—also called plaques or lesions. These demyelinated areas disrupt brain-body communication. Problems then develop, like muscle weakness, fuzzy thinking or blurred vision, depending on where the damage is.

His group examined 68 people with MS aged 18 to 59 years at Sunnybrook’s and St. Mike’s MS clinics. Patients were shown a 30-second video in which three people wearing white shirts passed a basketball to one another, while another three people in black shirts passed a different basketball to each other. Patients were instructed to count the number of passes made by the players wearing white only. Halfway through the test, a person wearing a gorilla suit wanders into the scene waving his hands, and then leaves.

“We came up with this really interesting finding that if you have attentional problems, then paradoxically you have less inattentive blindness because you are just so distractible. Patients are seeing the gorilla that [more than 50% of] healthy people are missing, but they are not counting the passes accurately,” he says. “The implication is really quite significant, and it’s a further marker of how their cognition is impaired.

“What might be interesting is that a test like this may help explain why individuals with high premorbid intelligence, who do well on conventional cognitive tests, still end up struggling when at work.”

Of course, not everyone with MS will have cognitive issues, he notes: “If your disease is primarily in the spinal cord, for example, then you may have no cognitive difficulties. If you have a light lesion load in the brain, or your brain hasn’t atrophied, then you may be one of those individuals who escape cognitive difficulties.”

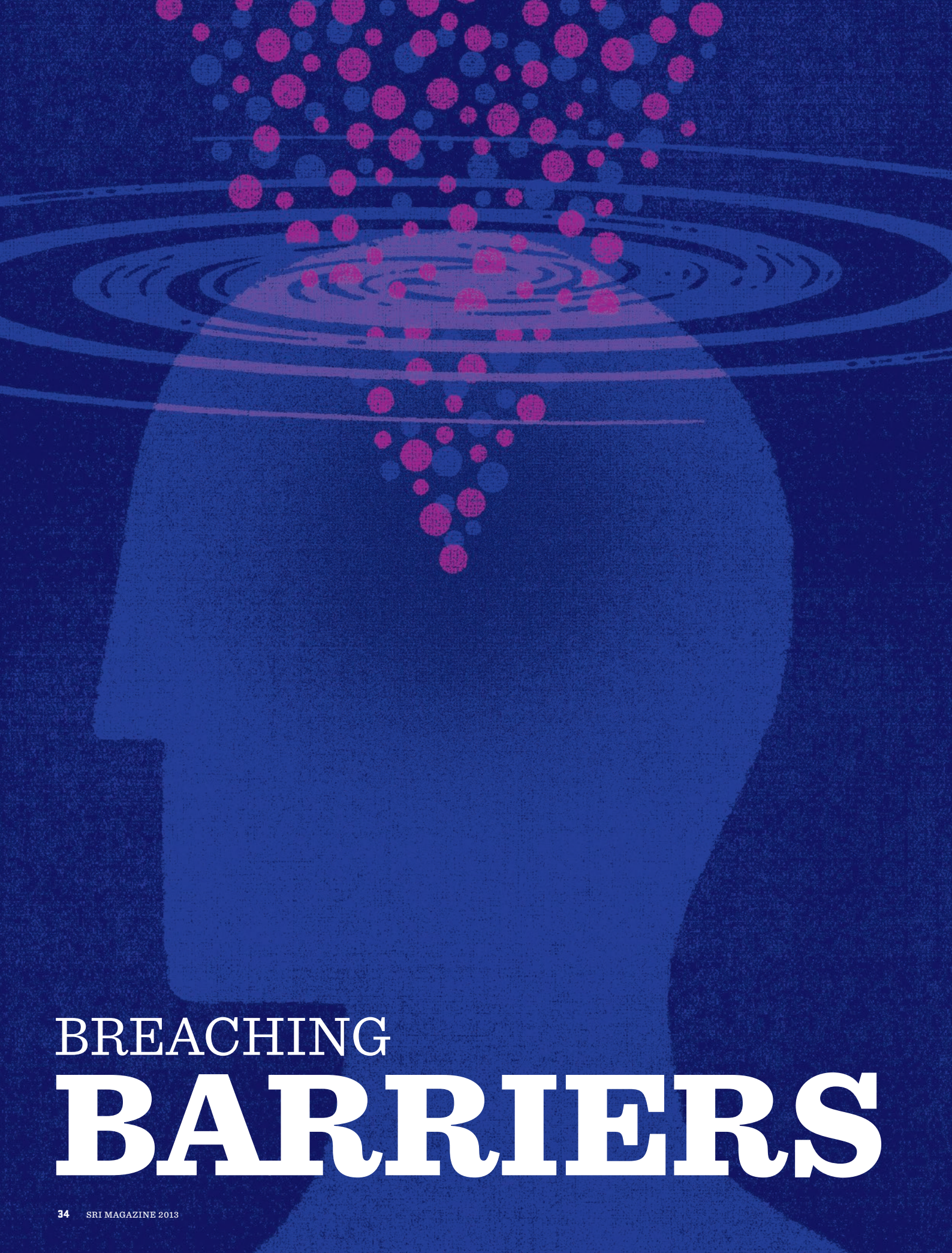
Feinstein is now running a study of 40 people with MS using functional magnetic resonance imaging to capture what is happening in the brain during inattentive blindness.

“We hope to get a better understanding of an interesting cognitive phenomenon. That’s what brain imaging can do—help you understand how the brain functions,” he says, adding, “There are unfortunately no immediate clinical benefits for patients from a study like this, but it does help us understand how the MS brain works.”

He acknowledges that therapy for cognitive difficulties lags behind research. “It’s one thing to detect the problem, it’s another to provide the treatment.” Feinstein notes that medications generally don’t work, with the possible exception of amphetamines, and that in many cases teaching people how to compensate for their cognitive problems is the best they can do. “We teach the patients to maximize their strengths, while working around their limitations.”

For the field of MS more generally, Feinstein expresses hope. “When I did my PhD 22 years ago there were no treatments for MS apart from steroids. Now patients with relapsing-remitting disease have a choice of disease-modifying drugs that can help them. The whole therapeutic landscape for some patients has changed dramatically, and there are multiple new drugs and some in the pipeline that offer promise. There’s an enormous amount of energy and interest in MS research now.”

Feinstein’s research is supported by the funding agencies the Canadian Institutes of Health Research and the Multiple Sclerosis Society of Canada, and the company Biogen Idec.



BREACHING **BARRIERS**

A look at the promise of focused ultrasound to outsmart the brain's natural defenses and smuggle therapies into deep-brain territory to treat intractable disorders of the central nervous system

R

esearchers know more about the biology of neurological disorders than ever before. They have identified genetic mutations and defects in cell signalling pathways linked to disease that may serve as therapeutic targets. Moreover,

pharmaceutical companies have spent billions developing drugs for brain disorders—ones that might promote growth of brain cells, repair damage or slow progress of tumours, something not possible now. Obstacles to effective therapy delivery remain, however, most notably, the blood-brain barrier (BBB).

“The blood-brain barrier is the interface between the blood vessels and the brain,” says Dr. Isabelle Aubert, a senior scientist in brain biology at Sunnybrook Research Institute (SRI) and a professor at the University of Toronto. “The barrier is lined with brain endothelial cells sealed together by tight junctions and maintained through cellular and molecular interactions.”

The BBB protects brain chemistry by maintaining a constant environment. Unlike elsewhere in the body where gaps between endothelial cells allow fluid to pass through vessel walls, endothelial cells lining the brain's blood vessels are tightly knit; this cohesiveness excludes large molecules, like antibodies, and 98% of small molecules, including most drugs, from the brain. There are exceptions; for example, proteins like insulin, needed to regulate eating, are ushered through cell membranes to neurons via transporter proteins. Caffeine and active components of sleeping pills are other examples.

While protecting the brain from toxins, the BBB also prohibits agents that could help heal it—a not unsizeable problem that needs to be solved before biologists and drug companies can capitalize fully on the advances they are making.

Dr. Kullervo Hynynen, director of Physical Sciences at SRI, first used ultrasound to disrupt the BBB in the 1980s. He developed technology showing he could pass ultrasound beams through the skull safely, something thought impossible. Over the next two decades he worked with industry to refine and commercialize the technology.



DR. ISABELLE AUBERT IS WORKING WITH DR. KULLERVO HYNYNEN ON EVALUATING THE use of imaging-guided focused ultrasound to sneak therapeutics past the blood-brain barrier.



DR. TODD MAINPRIZE (LEFT) OPERATES ON A PATIENT. HE IS LEADING THE WORLD'S FIRST CLINICAL TRIAL ASSESSING magnetic resonance imaging-guided focused ultrasound for targeted delivery of anti-cancer drugs to the brain.

The device works by emitting therapeutic ultrasound at high and low frequencies. Application of acoustic power changes properties of biological tissue: high-intensity focused ultrasound generates heat to destroy tissue, such as a lesion, either in the body or deeper in the brain, away from bone, which can overheat.

In 2001, Hynynen was the first to show that low-power ultrasound could open the BBB focally and reversibly without damaging surrounding brain tissue. His lab has worked since then on advancing the technology, taking it from theory to where it is now: showing strong preclinical results and the potential to transform clinical care.

The technique combines ultrasound with tiny gas bubbles that are injected into the bloodstream. Guided by magnetic resonance imaging (MRI), low-frequency ultrasound is applied when bubbles reach the target area. As the bubbles expand and shrink, the tight junctions between endothelial cells loosen, which allows molecules to cross over into brain tissue temporarily. "We don't disrupt the blood-brain barrier permanently. We just increase permeability for about six hours. It reseals by itself after," says Aubert.

Hynynen says the biggest challenge was controlling acoustic power such that the barrier is opened enough

to let therapeutics through. His group developed controllers with microphones that "listen" to how the bubbles behave. "By listening at different locations we can pinpoint where the bubbles are active. We can see how they are expanding and contracting, and use that information to control the power at that location," says Hynynen, who is also a professor at U of T.

Hynynen and Aubert's preclinical studies have led to pioneering publications detailing how MRI-guided low-intensity focused ultrasound can be used to deliver immunotherapy, and gene and cell therapies across the BBB.

In 2010, they published the first experiment using the technique to deliver immunotherapy to mouse models of Alzheimer's disease (AD), for which there is neither a cure nor a treatment that will halt disease progression. Their results showed antibodies cleared amyloid-beta, a protein found in the plaques that are a hallmark of AD, in four days—much faster than injecting antibodies into the bloodstream, which can take up to 18 months to get rid of the protein. "The big breakthrough here was that we were able to reduce the pathology much faster in a localized manner," says Aubert.

Compared with other options, delivering immunotherapy using

focused ultrasound is noninvasive, more precise and safer. For example, administering antibodies intravenously works by pulling amyloid-beta from the brain into the circulation; much higher doses are needed compared with direct delivery to the brain; moreover, drawing amyloid-beta into the bloodstream can harm the circulatory system and sometimes causes brain swelling. Another method, convection-enhanced delivery, is a newer, aggressive treatment for brain tumours that have not responded to other treatments. Doctors drill a hole in the skull and insert a tiny catheter into the brain to dispense chemotherapeutic drugs. In addition to being invasive, it lacks precision; the medication can follow uncontrolled pathways.

Hynynen and Aubert have also shown they can direct gene therapy to specific brain regions, including the hippocampus, which is important for memory and learning. Gene therapy, which holds out hope of being able to treat disease without drugs or surgery, involves delivery of a vector containing genetic coding to make proteins that may be restorative. "By modifying brain cells with therapeutic genes, we allow them to use their own cell machinery to produce the proteins required to rescue neuronal function, in effect creating a 'mini pump' of therapeutic factors produced by brain cells," says Aubert.



DR. KULLERVO HYNYNEN IS WORKING WITH DR. ISABELLE Aubert on evaluating the use of this technology to deliver therapies into the brain.

The next challenge was transporting stem cells, which are even bigger than vectors, across the barrier. They administered stem cells into the blood and delivered them to certain areas of the brain in healthy preclinical models. They confirmed the cells' entry by labeling them with markers. The stem cells not only survived after transplantation, but they were also able to differentiate into neurons, a feat that gives rise to the possibility that a damaged brain could be supplemented by healthy new cells, including neurons.

They've also demonstrated that areas of the brain treated with only ultrasound reduced plaque in models of AD—another first. While the mechanism is unknown, they surmise the effect might be owing to entry of natural antibodies in the circulation into the brain, or activation of glial cells, which are supportive cells that sweep away debris, including amyloid-beta. In recent studies, they found ultrasound alone rescued memory, thereby restoring function, and stimulated production and development of new brain cells.

The pair is pushing the boundary of what is known about the technology's potential. They are not the only ones working in this field (most others are Hynynen's former trainees), but they are at its forefront. "I think we'll probably be the first ones to do clinical work. Once we do the first phase, everybody will be doing it," says Hynynen.

As a start, neurosurgeons at Sunnybrook recently launched the world's first clinical trial evaluating focused ultrasound for targeted delivery of chemotherapeutics to the brain. The outlook for patients with glioblastoma, the most common malignant brain tumour, is grim: average survival is 14 months from diagnosis. There is, however, cautious cause for hope.

Hynynen and Dr. Todd Mainprize, a clinician-scientist who heads neurosurgery at Sunnybrook, are leading the Phase 1 trial to see whether low-frequency ultrasound safely increases delivery of doxycycline, a drug with known anti-tumour effects. Subsequent trials will evaluate efficacy. They will use the technique to open the BBB only where they want the drug to go, making it safer than osmotic disruption, which

opens the barrier everywhere.

"There's going to be very little drug delivered to healthy tissues. The drug concentrations will only be high where we are delivering the ultrasound treatment. It should theoretically be extremely safe and very effective," says Mainprize.

Health Canada approved use of Hynynen's focused ultrasound brain device for the trial, which involves six to eight of Mainprize's patients. (They are also using the device to conduct a Phase 1 clinical trial to ablate tumours nested deeply in the brain, which permits use of high-frequency ultrasound to destroy lesions.)

The trial is a gateway to treatment of other brain disorders, says Mainprize. "Once we show we can do it, there'll be opportunities to try and treat various conditions [including] Parkinson's disease and psychiatric illnesses—to open up selective areas of the brain where we think the problems are, and get drugs we think will be helpful into the areas where they can help."

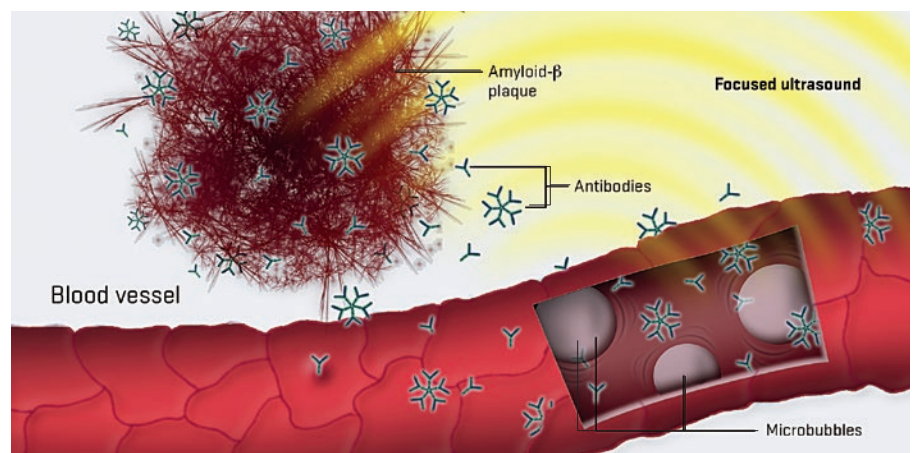
The establishment of the Slaughter Centre for Image-Guided Brain Therapy and Repair will also accelerate translation. At its core will be a unique molecular imaging system that will fuse positron emission tomography, MRI and Hynynen's focused ultrasound device. This will enable them to map brain anatomy and pathological changes simultaneously during therapy, thus tracking delivery and outcome in real time. The technology, combined

with Aubert's expertise in brain biology and the leadership of clinical expert Dr. Sandra Black, head of the Brain Sciences Research Program at SRI and an authority in neurodegenerative disorders, will give rise to trials in patients with Alzheimer's disease and stroke.

Translation is still some years away. While his goal is for the technology to be used routinely to treat patients, Hynynen says getting there will take time. "Clinical trials are a significant amount of work. That's where you really learn how to do things. The idea is that we do multiple Phase 1 trials and see what can be done with the device."

As one case in point, before moving forward to human trials they have to ensure the treatment doesn't just get in, but also improves function, as Aubert emphasizes: "We need to show much greater improvement in cognitive function, learning, memory, mood-related behaviour—everything that AD can present with, and that we can reproduce in preclinical models. We need to be more successful at curing all of this compared with other treatments before we can move forward."

This research is supported by the Alzheimer Society of Canada, Canada Foundation for Innovation, Canadian Institutes of Health Research, National Institutes of Health, Ontario Mental Health Foundation, Ontario Ministry of Research and Innovation, Slaughter Family Foundation and W. Garfield Weston Foundation. Hynynen holds the Canada Research Chair in Imaging Systems and Image-Guided Therapy.




DELIVERING THERAPIES ACROSS THE BLOOD-BRAIN BARRIER: FOCUSED ULTRASOUND IS APPLIED THROUGH THE SKULL to the brain region of interest. Microbubbles are injected into the bloodstream. When the bubbles reach the ultrasound field, they vibrate. This changes the property of the blood vessel wall, making it more permeable. This temporary effect allows therapeutic molecules like antibodies to move from the blood to the brain. Here, the aim is clearance of amyloid plaques, the telltale signs of Alzheimer's disease.

Dr. Stephen Femes is lead author of an influential study comparing coronary artery bypass graft surgery—CABG, pronounced “cabbage”—with angioplasty for patients with advanced heart disease.



A Tale of Two Heart Procedures



**The trend
in health
care is toward
less invasive
procedures
that seek
to minimize
the risks
of surgery.
When it comes
to treating
advanced
heart disease,
however,
new research
shows that
the scalpel has
the edge—
except when
it doesn't**

BY ALISA KIM

PHOTOGRAPHY BY CURTIS LANTINGA

In 2009, a team of researchers, including U.S. and Egyptian cardiologists, did a study using cross-sectional X-ray pictures of 20 mummies displayed at the Museum of Egyptian Antiquities in Cairo, Egypt.

Among the 16 mummies—some aged as old as 3,500 years—whose arteries and hearts could be identified, nine had calcification in the arteries or in the path of where the arteries should have been. That atherosclerosis (plaque build-up in and on artery walls) was detected in these mummies suggests that heart disease isn't a malady of the modern era.

Today, heart disease is the number one cause of death globally. In Canada, cardiovascular disease, comprising disorders of the heart and blood vessels, is the leading cause of hospitalization.

The most common form of heart disease is coronary artery disease, when the thoroughfares supplying blood to the heart become blocked or narrow. For these patients, medicine is the best way of reducing the chance of heart attack or death, says Dr. Harindra Wijeyesundera, a scientist in the Schulich Heart Research Program at Sunnybrook Research Institute (SRI) and an interventional cardiologist at Sunnybrook Health Sciences Centre.

In addition to drugs, patients can undergo one of two procedures to restore blood flow to the heart. One option is coronary artery bypass graft surgery (CABG, pronounced “cabbage”), in which doctors open a patient's chest and sew a healthy artery from the chest or leg to the diseased vessel, thereby bypassing the blockage and rerouting blood to the heart.

Percutaneous coronary intervention (PCI), or angioplasty, is another option. This is a nonsurgical procedure in which an interventional cardiologist makes a small puncture in the groin or arm, and under X-ray guidance threads a catheter with a balloon at its tip to the blockage. The balloon is inflated to widen the artery; sometimes a small mesh tube called a stent is inserted to prop the vessel open.

The trouble is, it's not clear which is better for certain patients. “It's a question that comes up frequently and something that cardiologists and cardiovascular surgeons discuss often with their patients,” says Wijeyesundera. “Is any form of revascularization needed? What are the benefits of it? And if it is needed, which of the two—PCI or



DR. HARINDRA WIJEYSUNDERA (RIGHT), IN THE CATHETERIZATION LAB AT SUNNYBROOK, TRIES TO CLEAR A BLOCKED artery in a patient with heart disease, working with fellow interventional cardiologist Dr. Brad Strauss.

CABG—is most appropriate? For patients who are having a heart attack or have blockages in only one artery, PCI is recommended. However, in advanced coronary disease, there is debate.”

Advanced heart disease includes unprotected left main disease, where there is more than 50% narrowing of the left main coronary artery; narrowing of two or more coronary arteries; blocked arteries and diabetes; and coronary artery disease and left ventricular dysfunction, a sign of heart failure. Historically, surgery was the main treatment. Over time, however, PCI gained traction and was used to treat advanced coronary disease, says Dr. Stephen Fremes, a scientist in the Schulich Heart Research Program at SRI, cardiovascular surgeon at Sunnybrook and professor at the University of Toronto.

To provide evidence-based recommendations on which therapy is better for specific patients, Fremes, Wijesundera and clinical colleagues did a study comparing the effectiveness of CABG surgery with angioplasty.

It was published in the *Journal of the American Medical Association* in November 2013.

The study summarizes results of research published in the last six years that compared the two procedures in patients with advanced heart disease. The researchers looked at which treatment was associated with adverse events.

They found clear benefits to surgery. “The end points we looked at were hard end points: mortality, myocardial infarction [heart attack], stroke and secondary revascularization. In terms of hard clinical outcomes, surgery is better but much more invasive than angioplasty,” says Fremes, the study’s lead author. They noted, however, that where severity of disease is less complex, or there is a high surgical risk due to advanced age or other health conditions, PCI should be considered.

Percutaneous coronary interventions have evolved since the first coronary angioplasty was performed in 1977. [See sidebar.] In the decades since the inception of PCI, the devices it uses have become smaller and more

maneuverable. Success rates have risen, as has the number of procedures carried out. In 1980, 1,000 angioplasties were done worldwide; in 1997, this figure soared to one million, making it one of the most common interventions.

Although PCI is less invasive, it is not without risk. A small percentage of people with stents in their arteries develop a blood clot, which can cause a heart attack or stroke. For this reason, angioplasty candidates must take blood thinners, says Wijesundera, who performs between 250 and 300 angioplasties annually. Other risks include bleeding, heart attack and stroke; the risk of the last two is low, occurring in less than 1% of procedures. “The biggest drawback, and what our review showed is there’s a higher likelihood of [patients] needing more procedures down the road compared to bypass surgery,” he says.

In the study, the researchers also emphasized a collaborative model of care in which cardiologists, interventionalists and surgeons discuss the patient’s complexity of disease, overall health and treatment preference. “When the surgical risk gets to be too high, the relative advantage of CABG versus PCI changes. That’s part of the ‘heart team’ approach—to try and determine what the surgical risk is,” says Fremes.

At Sunnybrook, many of the angioplasties performed are on patients who have just had a heart attack. In such cases PCI is the best option, notes Wijesundera, who is also a professor at U of T: “There’s really no debate in the literature about what they should get, because it’s an emergency situation and they have disease that is focal to one artery that’s caused their problem.”

In treating patients for whom either surgery or PCI is viable, the heart team approach comes into play. This is important because once patients are given all of the pertinent information, the decision of which treatment to choose is up to them, says Wijesundera.

John Russ Smith chose to have bypass graft surgery in December 2005 at the age of 71. A lifelong athlete, Smith enjoyed good health and played in a workplace baseball league for 25 years.

Due to high blood pressure, Smith was referred to a cardiologist. During an angiogram (an imaging test that uses

X-rays and a dye to let doctors see inside blood vessels) Smith learned he had heart disease. “I’ve never had chest pain. I’m watching this black ink go through the arteries, and two of them stopped completely, and the other was 50%,” he recalls.

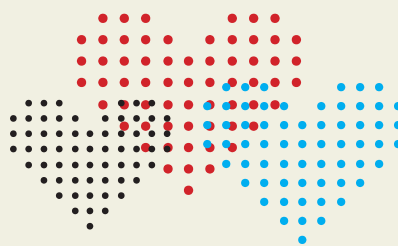
He was shocked to learn he had had two “silent” heart attacks, where blood flow to the heart is partially blocked and symptoms—if any—are few. He was referred to Froles, who, along with Smith’s cardiologist, recommended bypass surgery as he was at risk of a potentially fatal heart attack. Froles performed the surgery.

“He did a miraculous job. It’s a very invasive solution. You wouldn’t know it if you looked at me now. I’m forever grateful,” says Smith. He had no complications, and his recovery was quick. A few days after the operation, he could walk around. At his three-month follow-up there was one thing on his mind: could he play baseball?

Froles reluctantly gave the green light but cautioned him to be careful. Smith, who covers third base or “the hot corner,” played all 42 games of the 2006 season, which was his last. “I went out in a blaze of glory because we won a championship,” he says. Now 80 years old, Smith has slowed down—a little. He works part-time in the insurance industry and has six grandchildren.

Although this study’s findings were clear, Froles says research comparing the two procedures should be revisited every five years owing to new developments in the fields. He is participating in a large study evaluating a new PCI technology against surgery. The EXCEL clinical trial, slated for completion in 2021, will recruit 2,600 patients from centres across North America, of which Sunnybrook is one. In the meantime, Froles wants their research to have broad clinical impact. “Hopefully there will be more interest [on the part of] those who refer [patients] to the cardiologists. That may affect the opinions of the original referring doctor to consider surgery rather than angioplasty more liberally.”

This research was supported by the Bernard S. Goldman Chair in Cardiovascular Surgery at Sunnybrook, Canadian Institutes of Health Research, and the Heart and Stroke Foundation of Canada.



THE BAD NEWS

More people die of diseases of the heart and blood vessels each year than from any other cause.

THE GOOD NEWS

The number of people dying from cardiovascular disease has declined steadily since the 1960s, thanks to advances in research.

FOLLOWING ARE SOME LIFE-SAVING BREAKTHROUGHS IN CARDIOVASCULAR SCIENCE FROM THE 20TH CENTURY.

Electrocardiography

In the early 1900s, Willem Einthoven, a Dutch doctor and physiologist, invented the electrocardiograph, the first practical device to record the heart’s electrical activity. He went on to describe early stages of heart failure, arrhythmia (abnormal heart beat) and other cardiac disorders.

Coronary angiography

This technique uses X-rays and a dye to let doctors see inside coronary blood vessels. In 1941, André Cournand and Dickinson Richards, researchers at Columbia University in New York City, New York, used the catheter as a diagnostic tool for the first time to measure cardiac output.

Preventive cardiology

The Framingham study, published in 1961, looked at development of heart disease in thousands of residents of Framingham, Massachusetts. It set the concept of risk factors, such as high blood pressure, smoking and high cholesterol, providing clinicians with profiles for cardiovascular disease and identifying people who might benefit from preventive measures.

Coronary artery bypass graft surgery

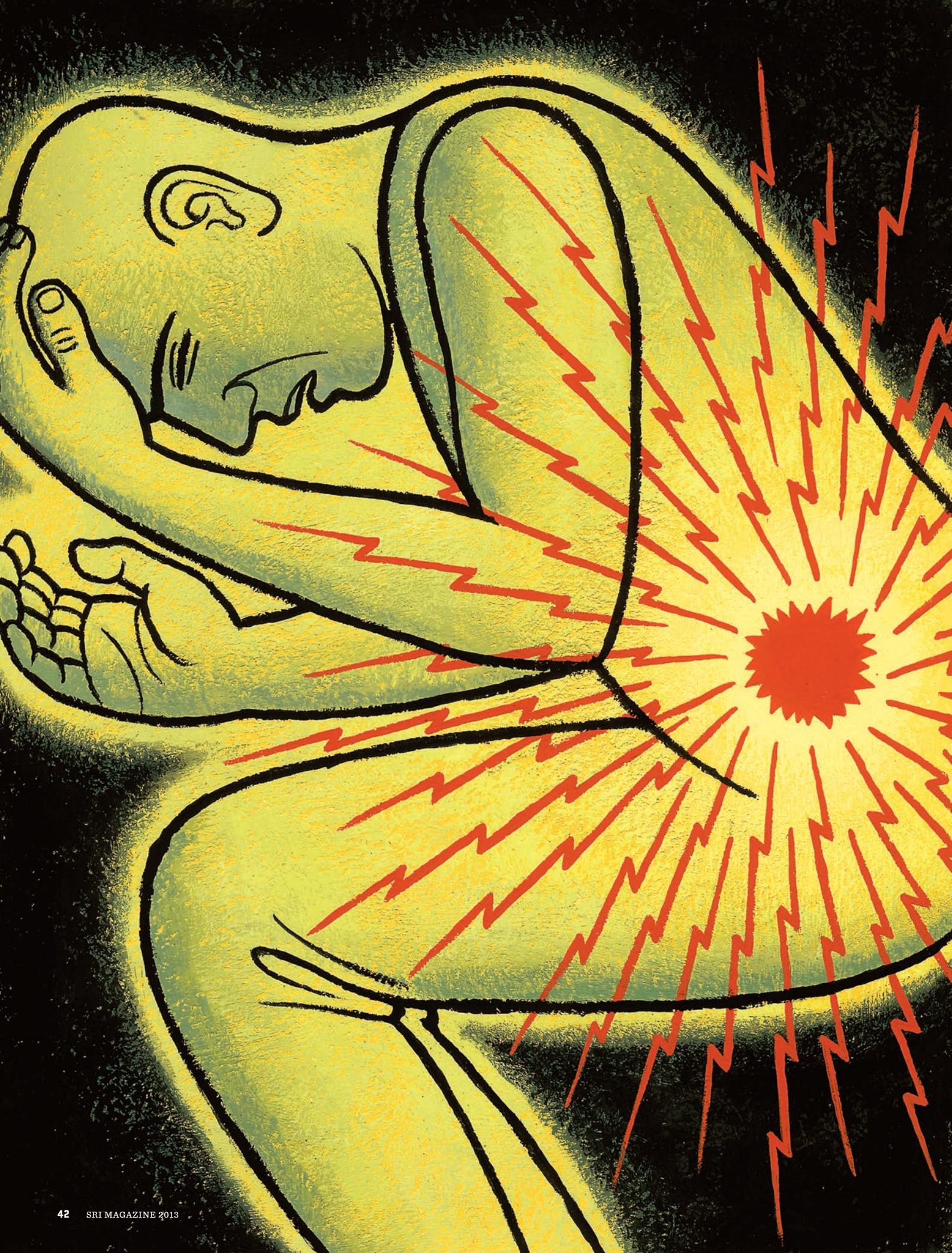
In May 1967, René Favaloro, an Argentine surgeon, used part of the saphenous vein, which runs along the length of the leg, to replace a blocked segment of the right coronary artery. Later that year, he used the saphenous vein to reroute blood around obstructions. Coronary artery bypass graft surgery is one of the most common major surgeries in the U.S. and Canada.

Automatic implantable cardiac defibrillator

This device is placed in the chest to monitor heart rhythms. It uses electric shocks to treat dangerous arrhythmias, especially those that can cause the heart to stop beating suddenly. A team of researchers at Sinai Hospital in Baltimore, Maryland, began working on the device in 1969. Eleven years later the first patient was treated with it.

Coronary angioplasty

On Sept. 16, 1977, German cardiologist Andreas Gruentzig performed the first balloon angioplasty on the human heart. His patient, a 37-year-old man, remained awake. It was a success: Gruentzig opened the narrowed artery in two quick balloon inflations. In Canada, the rate at which doctors performed angioplasties doubled between 1995 and 2005, from 25,000 to 50,000.



STOMACH AND COLORECTAL CANCER THAT HAS SPREAD TO THE LIVER ARE COMPLEX, CHALLENGING ILLNESSES. SURGICAL SPECIALISTS ARE LEADING RESEARCH TO REDEFINE “BEST” IN THE PROVISION OF CARE FOR PATIENTS WITH THESE AND RELATED DISEASES

BY JANE DOUCET / PHOTOGRAPHY BY DOUG NICHOLSON

C Stands for Care

Each year, Canadians walk, bike, run or hold other activities and events to raise money to fund research into common cancers such as breast and prostate. While these are important pursuits that garner a great deal of public attention and support, many researchers are working under the radar to study lower-profile, but potentially more deadly, forms of cancer. Colorectal cancer that has progressed to the liver, for example, is an advanced-stage and serious form of cancer, and while stomach cancer rates are lower in Canada than in many other countries, a high percentage of patients diagnosed with it will die.

Two surgeon-scientists at Sunnybrook Research Institute's Odette Cancer Research Program, Dr. Paul Karanicolas and Dr. Natalie Coburn, are part of teams studying these cancers of the gastrointestinal tract. Karanicolas allocates about 75% of his time to conducting research and 25% to treating patients. "Although much of my work is spent on research, I'm a surgeon and clinician first," he says. "That means my first dedication is to my patients." That dedication helped Karanicolas identify a need in the patients on whom he was performing liver surgery, often for colorectal cancer that had spread there. He noticed that a number of them who

were treated for pain control after surgery were suffering unpleasant side effects that were slowing their recovery. "That moved me to want to find a better way to administer pain control," he says.

There are two methods of relieving pain following liver surgery. The first is intravenous (IV) medication such as morphine, the amount of which the patient controls; the second is an epidural catheter that is put into the patient's back before the operation to freeze from the lower rib cage downward, then removed three or four days post-surgery. Both methods have drawbacks that delay recovery. With the IV, they include trouble breathing,

slowed bowel function and drowsiness, which makes it harder for patients to get out of bed. Those who receive the epidural may experience discomfort when the catheter is inserted, limited mobility after the operation, lowered blood pressure causing dizziness and, although it's rare, bleeding around the spinal cord that can cause leg paralysis.

Karanicolas and a team of surgeons, anesthesiologists, nurses and others at Sunnybrook Health Sciences Centre and Toronto General Hospital have developed a technique to improve pain-medication delivery called MOTAP catheter placement. (MOTAP stands for medial open transversus abdominis plane.) With MOTAP, the surgeon places one or two catheters that deliver pain medication directly through the open surgical site where pain nerves are found. "The catheters are inserted in less than five minutes at the end of an operation without any discomfort to patients and are easy to remove," says Karanicolas. "And they carry no risk of bleeding or spinal cord injury."



SURGEON-SCIENTIST DR. PAUL KARANICOLAS IS LEADING MULTISITE CLINICAL TRIALS TO ADVANCE THE CARE OF PEOPLE who undergo liver surgery, often for colorectal cancer that has spread to this vital organ.

Karanicolas is the study's co-leader and the site leader of the blinded, randomized controlled trial to assess the MOTAP catheters, which began in the fall of 2013. By the end of 2014, about 60 patients will have been enrolled at each site, and the team plans to submit its findings in the spring of 2015.

If that wasn't enough to keep Karanicolas busy, he's also the study and site leader for a clinical trial that will evaluate the impact of tranexamic acid (TXA) on blood transfusions in patients undergoing major liver resection, during which part of the liver is removed. Blood loss is a major risk during this type of surgery. Tranexamic acid is a drug that stops the breakdown of blood clots during or after surgery; it's often used in other medical situations, but rarely in liver surgery, because there is no strong evidence that it reduces bleeding.

"That's what this trial will aim to find out," says Karanicolas, who is also an assistant professor at the University of Toronto. "If we were able to demonstrate that tranexamic acid used in major liver resections resulted in a significant decrease in blood transfusions, clinical practice worldwide would be likely to change." In Canada alone, more than 2,000 patients undergo liver resection every year, about one-third of whom require blood transfusions during or after surgery.

The transfusions are scarce and expensive, plus they can increase the chance of infections, heart complications and breathing problems. There's also a higher risk of the cancer returning in patients who have received blood transfusions.

The TXA trial will be done in two phases. The results of the first phase, which is monitoring 20 liver-resection patients, should be ready by the end of 2014; the second phase will begin in September and assess another 1,000 patients across Canada.

In addition to researchers from Sunnybrook, the multidisciplinary team hails from McGill University Health Centre in Montreal, Foothills Medical Centre in Calgary, University Health Network in Toronto and Queen Elizabeth Health Sciences Centre in Halifax.

Karanicolas enjoys the collaborative nature of the research. "It's a unique opportunity within both Toronto and Canada to work with different organizations and disciplines to help our patients," he says. "Everyone's role is instrumental. As for me, I've always wanted to treat patients and advance knowledge—it's the optimal combination. I'm most passionate about using research to answer medical questions. It's about taking information from the bedside to the bench, and then back to the bedside."

A GUT FEELING, GROUNDED IN SCIENCE

Coburn is also doing groundbreaking work. She leads a team studying the best treatment options for patients with gastric cancer. Although this disease is fairly rare in North America compared to other countries, it's responsible for 10% of all cancer deaths worldwide. Despite five-year survival rates of 40% to 60% in advanced gastric cancer patients in Asia and Europe, the five-year survival rate for similar cases in North America is around 30%. Although the theory has been that improving the treatment these patients receive would improve survival rates, few studies had examined the effect of care processes in the outcomes of patients with gastric cancer.

Coburn, who is head of the division of general surgery at Sunnybrook, developed an interest in this area of research when she was a resident at an American hospital. "I was concerned about the quality of surgery that gastric cancer patients received in a few cases I observed there," she says. In earlier work, she found that despite the evidence of an improved chance of survival when gastric cancer patients have surgery combined with either chemotherapy or chemotherapy and radiation, many patients don't receive appropriate treatment, with up to 43% having surgery alone, and less than one-third having appropriate staging of lymph nodes. Because surgeons in Western countries like Canada and the United States treat so few patients with gastric cancer, lack of experience may contribute to deciding on the best treatment plans.

To address this, Coburn, who is also an associate professor at U of T, led a RAND/UCLA appropriateness study to help establish the highest quality processes of care for these patients. This is a method that, as the RAND manual says, pools the "best available scientific evidence with the collective judgment of experts to yield a statement regarding the appropriateness of performing a procedure at the level of patient-specific symptoms, medical history and test results."

A panel of 16 physicians with gastric cancer expertise was assembled from six countries; they met in Toronto in October 2010. One thing they agreed

on was that the best care for patients is in the setting of a multidisciplinary team, including surgeons, medical oncologists, radiation oncologists and nutritionists. They also felt strongly that those with metastatic gastric cancer and no symptoms are likely not helped by surgery—in those patients, who all have a short life expectancy, chemotherapy might offer a better quality of life.

Coburn says the importance of the expert panel was the influence of those outside North America. “We need to respect the work that has been performed in Japan, Korea and other Asian countries, where gastric cancer is more prevalent.”

Coburn treats complex gastrointestinal cancers, including those of the stomach, pancreas and liver. “My theory is that if you do all the small steps well, you end up with better outcomes,” she says. Those small steps include removing tumours with appropriately large margins of cancer-free tissue and removing enough lymph nodes to

examine them for more cancer, then deciding with the patient’s input on the best course of treatment.

“With most cancers, surgery isn’t enough to kill the cancer unless it’s caught at an early stage,” says Coburn. “When the cancer is more advanced, patients typically need surgery plus treatment following the surgery. But some patients, especially elderly ones, may decline the additional treatment because the chemotherapy drugs are toxic and hard to tolerate. Each treatment needs to be tailored to the patient.”

Further study into optimal treatment, as well as new chemotherapies, is required. “Gastric cancer is a disease that desperately needs better drugs,” says Coburn. The study team has been awarded a Canadian Institutes of Health Research grant to allow the researchers to determine how much it will cost to provide optimal treatments to patients. Next steps include working with Cancer Care Ontario to translate the research findings into treatment


guidelines; if all goes well, the guidelines should be ready to roll out by the end of 2014.

In the meantime, Coburn will continue striving to offer the best possible care to her own gastric cancer patients.

“Patients need a team of doctors and other health care providers, not just the surgeon, to help take care of them through what is a difficult, complex cancer,” says Coburn. “For surgeons, treating one or two of these cases a year isn’t enough to learn about the nuances of care. You want to know that everything possible has been done, and done appropriately, for each patient—then we’ve done the best we can.”

The Canadian Cancer Society, and the Ontario Ministry of Health and Long-Term Care provided support for Coburn’s work on the RAND/UCLA study.

For Karanickolas, the Canadian Institutes of Health Research is funding the TXA trial; the provincial AFP Innovation Fund is funding the MOTAP catheter trial.



Dr. Natalie Coburn operates on a patient with gastric cancer, a disease that was responsible for 2,000 deaths in Canada last year. Her research seeks to improve outcomes for these patients.



COMING TO AN OPERATING THEATRE NEAR YOU: 7D SURGICAL NAVIGATION

Starring a light-based system that uses surface imaging to map a patient's anatomy for faster, more efficient surgery

BY ALISA KIM

The global positioning system (GPS) is a network of satellites that orbits the earth twice daily, transmitting signal information to anyone on earth with a GPS receiver.

When locked onto the signal of four or more satellites, the receiver computes the user's location and time. Owned and operated by the U.S. government, GPS was originally developed for military purposes.

In September 1983, a Korean passenger jet on its way to Seoul from New York City was shot down after veering hundreds of miles off course into Russian airspace. All 269 people aboard the flight died. The incident led the Reagan administration to make GPS available for civilian use to avoid further tragedies owing to navigational errors. From there, the technology took off. Although many people associate GPS with route-finding devices used in cars, the technology is everywhere, including in cell phones, wristwatches, shipping crates and bank machines.

Dr. Victor Yang, an engineer, neurosurgeon and senior scientist in the Brain Sciences Research Program at Sunnybrook Research Institute (SRI), wants to provide surgeons in the operating room with the same kind of navigation offered by GPS. While working at his biophotonics and bioengineering lab at Ryerson University and completing his neurosurgery residency, he invented a surgical guidance system that improves the flow of work and provides doctors with a detailed, 3-D "map" of a patient's anatomy before an incision is made. The map is used to guide them as they operate. Surgeons can use this tool to operate with greater efficiency than when using current navigation devices.

Yang and his research team, including Dr. Beau Standish, Dr. Adrian Mariampillai, Michael Leung and Dr. Peter Siegler, formed a company, 7D Surgical, to fabricate the system and commercialize the technology. Dr. David Cadotte contributed many after-work hours to the project and provided input to refine, optimize and test the system. The "7D" refers to the principle that an object in three-dimensional space has six degrees of motion: forward and backward; up and down;

left and right; and rotations around each of these axes. The seventh dimension is time.

The technology, which is light-based, aims to minimize use of intraoperative X-rays. It is the first surgical guidance system to use surface or topographical imaging to "map" a patient's anatomy.

The system uses a structured light scanner and camera system to measure the three-dimensional shape (that is, the surface points, including curves) of the patient all at once. "Imagine you're trying to measure the shape of a mountain. [With] existing technology, you'd send someone to a [particular] position of the hill and measure its location. You'd have to do this multiple times until you create the surface of the mountain. What we do is look at the entire mountain in one go," says Yang, who is cross-appointed to Ryerson University and the University of Toronto.

The system projects a series of binary patterns (imagine the stripes of a barcode) onto the patient and records these images using cameras. The projection of the stripes is blended within the surgical lighting and is barely visible to clinicians. When the pattern is projected onto the patient, the system's software analyzes deformations of the pattern and mathematically reconstructs the surface of the patient's anatomy, creating a 3-D "map" of the anatomy. When combined with preoperative imaging data, this surface map can be used to guide surgeons as they work.

It's not only novel, it's also fast. The key to its speed is the way in which it matches preoperative imaging to the patient's anatomy, a process called co-registration. With existing systems, surgeons match points on magnetic resonance imaging or computed tomography scans taken beforehand to points on the patient's body, one by one. This process is slow and can introduce inaccuracies when there are slight differences between the two sets of points, says Yang.

Time saved in the operating room translates into savings for the health care system.

In contrast, 7D Surgical's software quickly matches the collected surface imaging data with preoperative imaging data. A tap on a foot pedal yields hundreds of co-registered points almost instantly.

Manually picking dozens of matched points is laborious. Imagine losing those points and having to start over. "With existing systems, if you lose your tracking, it's a big headache because now you have to reacquire [the points]; you need to 'relock' on. That process takes a long time. With 7D Surgical navigation, if you lose your tracking, it's not a big deal because in less than a second you're back on lock," says Yang, who notes the system is 10 to 100 times faster than other guidance systems.

The technology also improves the flow of work by doing its job—providing fast navigation—without getting in the way. "A navigation system needs to function as if it's not there. Any additional equipment that you bring into the operating room, depending on how intrusive it is, adds complexity and time," says Yang.

Unlike other navigation systems, 7D

Surgical's lighting and detection hardware maintains the surgeon's line of sight. "Typically, tracking cameras are off to the side within the surgical operating theatre and the surgeon's back can obstruct the line of sight of that tracking device. Our system has been developed to image from the top down, minimizing line-of-sight difficulties," says Standish, the company's chief executive officer.

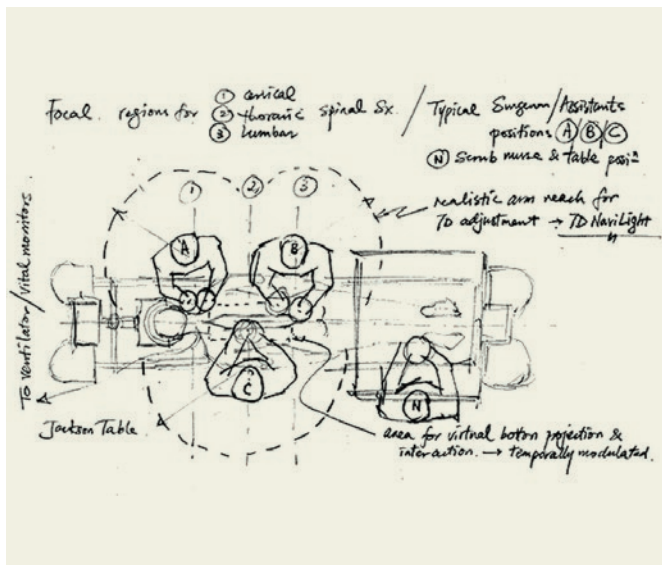
Improved efficiency in the operating room spares frustration—and dollars. While costs vary according to the type of procedure, no surgery is cheap. Time saved in the operating room translates into savings for the health care system.

The technology will be adapted for diverse applications, says Yang. As a first step, it is tailored to spinal instrumentation procedures, during which a surgeon inserts implants such as pedicle screws and rods to stabilize

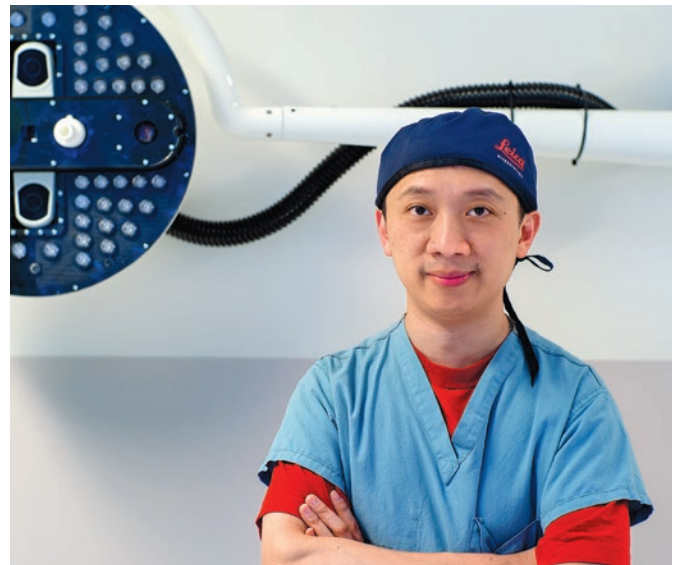
the backbone and encourage bones to join after spinal fusion surgery. The team began with this application because it is an established market, says Standish. These procedures are performed for various conditions, including spinal fractures, herniated discs, spinal tumours and scoliosis. Moreover, research shows using guidance systems during these procedures improves outcomes.

"With an established foothold in the spinal fusion market, our product focus will be extended to neurosurgical procedures. The benefit of our technology is that the core hardware navigation can be used in multiple anatomical locations, where site-specific software packages will become add-ons to the system. This allows for a versatile navigation product that has clinical utility for multiple surgical procedures," says Standish.

Yang and his team began working on the technology in 2009, during his surgical training. He was experiencing difficulties with existing guidance systems. He realized his colleagues were having similar troubles and recognized an opportunity.



DR. VICTOR YANG DREW MANY SKETCHES IN DESIGNING THE SURGICAL NAVIGATION SYSTEM. Here, a schematic drawing of a patient on an operating table. Another diagram is seen in the opening image.



DR. VICTOR YANG STANDS IN FRONT OF THE LIGHTING HARDWARE THAT IS PART OF THE surgical image-guidance technology he has commercialized and spun off into a company, 7D Surgical.



Dr. Victor Yang (right), tests the surgical navigation system he invented on one of the first patients in a clinical feasibility study of the device at Sunnybrook.

This is another element that separates 7D Surgical from other medical device startup companies: its approach. Rather than invent a technology and figure out where it can be used, 7D Surgical developed its product around a bona fide problem. “We know we have a fantastic application,” says Yang. “There’s a clinical demand for it. We know where all the difficulties are. One of our earliest meetings was to map the [surgical] workflow and technological requirements of that workflow to make a product. These designs address a clinical problem.”

Yang realized the technology was commercially viable once he learned he could use components from consumer electronics, such as computer projectors and cameras, in the system’s hardware. That these parts are widely used and fairly inexpensive means the company can keep manufacturing costs low.

The system has generated buzz among Yang’s clinical colleagues. Years ago, Dr. Todd Mainprize, who heads neurosurgery at Sunnybrook, heard of Yang’s technology and was so intrigued that he visited Yang’s lab at Ryerson for a peek. Even at that early stage of development what he saw impressed

him. Since then, Yang has been recruited to SRI, and is using the device development lab in SRI’s Centre for Research in Image-Guided Therapeutics to assemble the system.

Mainprize has used the device in SRI’s preclinical operating room. He says it’s a big improvement over existing technologies. “I have not had much success with spinal 3-D navigation over the years. You spend an hour trying to set it up, and you end up abandoning it because it doesn’t work. Anatomically, you know where the screw goes, and the navigational unit is saying it should go two centimetres lower—right in the middle of the spinal cord. I’ve used [the 7D system]. It’s seamless, [takes] 10 seconds and has been accurate every time I have used it. It will be a big step forward,” he says. Yang, along with neurosurgeons and orthopedic spinal surgeons at Sunnybrook, is leading initial clinical feasibility studies of the device.

The goal is to have the system available for sale by 2016. While the price is to be determined, Standish says it will be comparable to existing products—in the range of \$250,000 to \$400,000.

The team at 7D Surgical is confident that users will find the technology intuitive and user-friendly. In addition to Mainprize, Dr. Ashish Kumar, a neurosurgeon from India, has used the system with ease. “With [other] surgical navigation systems, surgeons are invited for an entire weekend to learn how to use them. This gentleman, who hadn’t used our system before, was using it to its full capability within three minutes,” says Standish.

Noting SRI’s track record of commercializing research, Yang sees similarities between 7D Surgical and companies that were spun out of technologies invented by SRI researchers. “I think we’re following the same path—finding the clinical application first, having a good conceptual design, surveying a lot of technologies before settling on [something] manufacturable and commercializable, and then having a dedicated team to make the sacrifices to do it.”

Yang’s research is funded by Brain Canada, Canada Foundation for Innovation, Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada and the Ontario Ministry of Research and Innovation. He holds the Canada Research Chair in Bioengineering and Biophotonics.

The World Is Their Oyster

These bright young grads and postgrads from across the globe surveyed the research training landscape—and landed on Sunnybrook Research Institute

Some human resources experts believe people don't quit their jobs, they quit their bosses. On the flip side, people don't just choose where, but for whom, they wish to work. In searching for the right opportunity, smart and focused trainees—who typically have the freedom to go anywhere they want to go—look for an advisor whose work fits with their interests, as well as a prospective supervisor's personality and management style. The faculty and facilities at Sunnybrook Research Institute (SRI) attract people at all stages of their careers from all over the world. Following are snapshots of four researchers-in-training who are furthering their know-how at SRI.

As a high-school student, Cristina Gallego Ortiz contemplated studying music in university. In the end, she decided to keep music as a hobby and majored in biomedical engineering at the Antioquia School of Engineering in Medellín, Colombia.

These days, she has little time for her flute, but has no regrets. "I am passionate about building systems that can learn from data," says Gallego Ortiz, a second-year PhD student in the lab of Dr. Anne Martel, a senior scientist in Physical Sciences at SRI.

Near the end of 2007 she searched online for faculty working on computer-aided diagnosis, which led her to Martel, who is also a professor at the University of Toronto. For her master's project, Gallego Ortiz developed an automated algorithm to segment the breast using magnetic resonance imaging (MRI), which can be used to assess breast density.

Her thesis is on the use of machine-learning approaches to improve characterization and early detection of breast cancer in high-risk women.

Gallego Ortiz is looking for new imaging markers or descriptors that can be used to characterize lesions better.

She is developing software that extracts information from a breast MRI scan to "train" a computer to identify a tumour. The software selects features such as the shape and appearance of a lesion; an algorithm "learns" from these characteristics to diagnose a new case. "A malignant mass is likely to be irregular in shape," says Gallego Ortiz. "So if a new case presents with the same features, the algorithm is able to highlight that characteristic, and it's able to say within a certain probability whether the lesion is malignant."

In 2013, Gallego Ortiz received a three-year fellowship worth more than \$100,000 from the Canadian Breast Cancer Foundation. "It's good to have that guarantee of support, and I like that you become part of a network of researchers," she says.

Outside the lab, she has complemented her science education with business activities. To wit, she and Martel filed a patent based on her master's research.

She is considering a career in industry once she completes her PhD, and says she feels privileged to do translational research. "I'm inspired to improve the specificity of MRI screening through computer-aided diagnosis technology and aid radiologists in making more informed clinical decisions."

CHEMISTRY CALLING

Growing up, Dr. Marzena Cydzik was a good student all around, but there was one subject for which she had an affinity. "I was always good at chemistry. It was really easy for me.

Chemistry 'spoke my language,'" she says.

She took her PhD at the University of Wrocław in Poland, one of the oldest universities in Europe. Once done, she didn't linger. Cydzik is now a postdoctoral fellow in the lab of Dr. Jean Gariépy, a senior scientist in Physical Sciences at SRI and a professor at U of T. In 2011, Gariépy, whose lab engineers biomolecules for imaging and targeted therapy of cancer and other diseases, hired Cydzik for her expertise in a specialized area of biochemistry.

As a freshly minted PhD, she sought a position that would enable her to apply her skills in a new field; the postdoc role in Gariépy's lab fit the bill. "I was looking for a place where I could improve my skills by learning new techniques and having access to the newest technologies, a place where I could change my field of study and look at the science from a different perspective. That's why I joined Dr. Gariépy's lab. Now, after two years, I am slowly becoming a molecular biologist," says Cydzik, smiling.

In developing novel therapeutics, the lab defines the influence of the therapeutics on cellular processes, including migration, proliferation and adhesion. The position has given Cydzik a crash course in cell biology. "I'd never done tissue culture. Now I'm working with cells. Everything I'm doing here is new. I am evolving every day, and I know I can learn so much more," she says.

Cydzik is developing chemical compounds aimed at blocking the growth of tumour-nourishing blood vessels as a potential therapy for ovarian cancer. She is also helping develop therapeutics that weaken

inflammatory responses to treat conditions like allergies and rheumatoid arthritis.

Cydzik gets much satisfaction from using her expertise to further the group's research. Gariépy tasked her with prolonging the blood-circulating time of therapeutics designed by the lab. She met the challenge by using a chemical commonly found in personal care products and drugs, and developing a protocol that helps the team study interactions between its drug-like compounds and specific receptors or proteins.

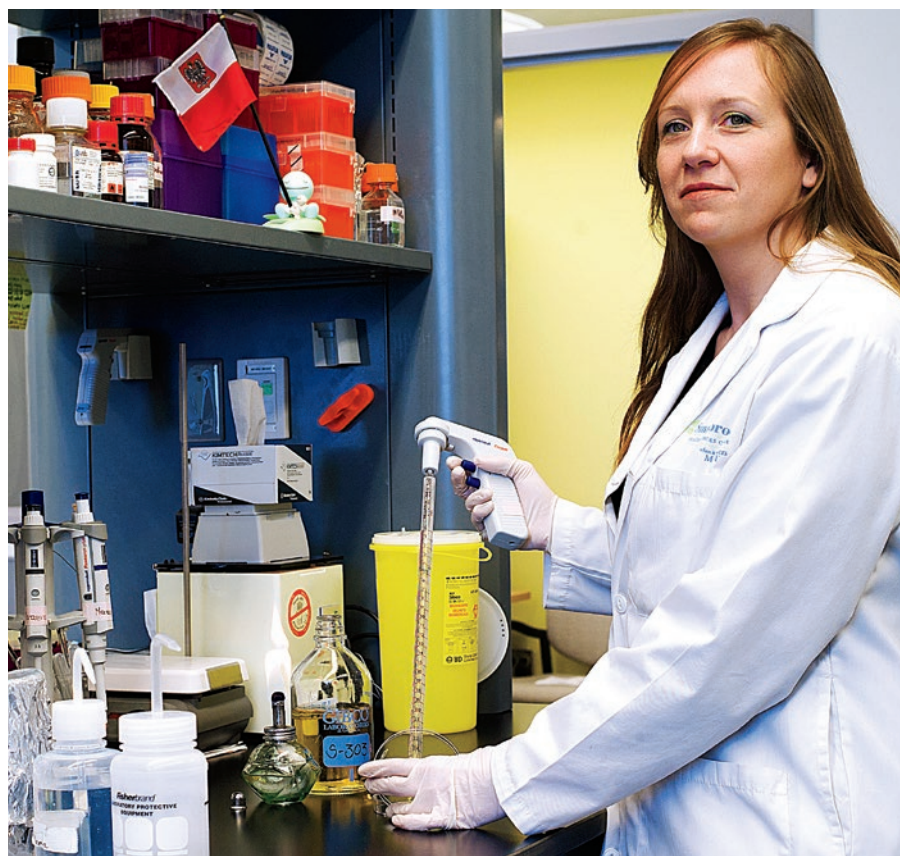
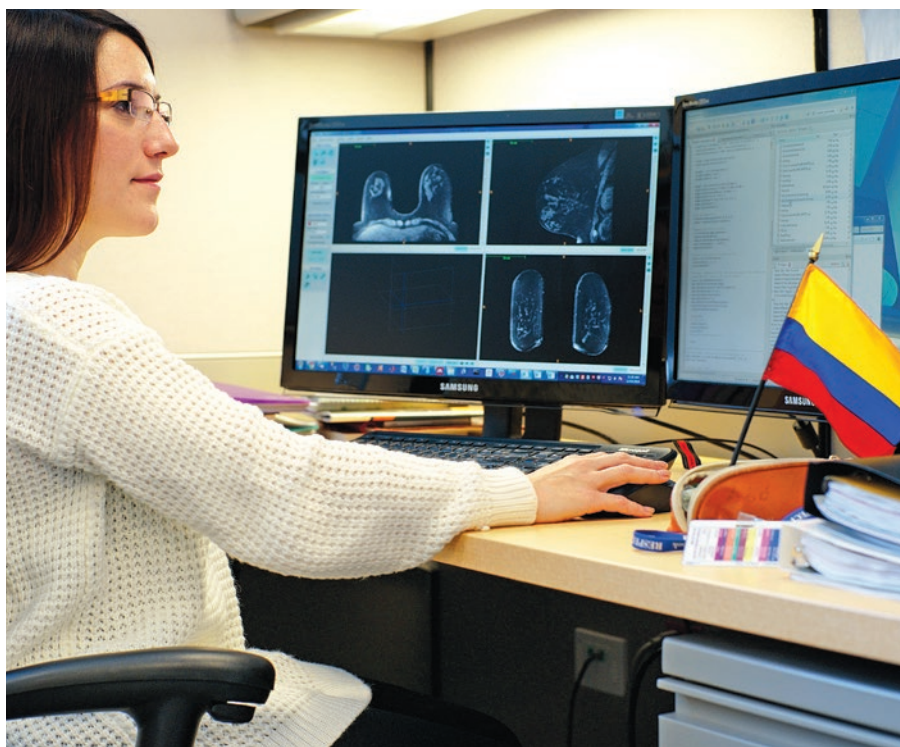
She's also become proficient with state-of-the-art techniques, including surface plasmon resonance, which enables the study of binding kinetics of molecules in real time—know-how sought by industry. Like Gallego Ortiz, she is contemplating a career in the private sector after her training, but is not ready to trade in her lab coat. "I really love working at the bench. I don't see myself at a desk."

TARGET PRACTICE

Access to cutting-edge equipment also prompted Xiaoke Chi to do his research training abroad. Born and raised in the province of Shanxi in mainland China, Chi studied biochemistry at Tsinghua University, in Beijing. Like his classmates, Chi wanted to do graduate studies outside China because he felt it would advance his knowledge in the field. In 2009 he immigrated to Canada to do his PhD with Dr. David Andrews, SRI's director of Biological Sciences.

He came to the right place.

Andrews, who is also a professor at U of T, not only has the world's first automated, high-content screening microscope that can measure



TOP: CRISTINA GALLEGO ORTIZ, A SECOND-YEAR PHD student from Colombia, is developing software to improve early detection of breast cancer in high-risk women.

BOTTOM: DR. MARZENA CYDZIK, WHO EMIGRATED FROM POLAND to do her postdoctoral fellowship at Sunnybrook Research Institute, is developing therapeutics for ovarian cancer, allergies and rheumatoid arthritis.

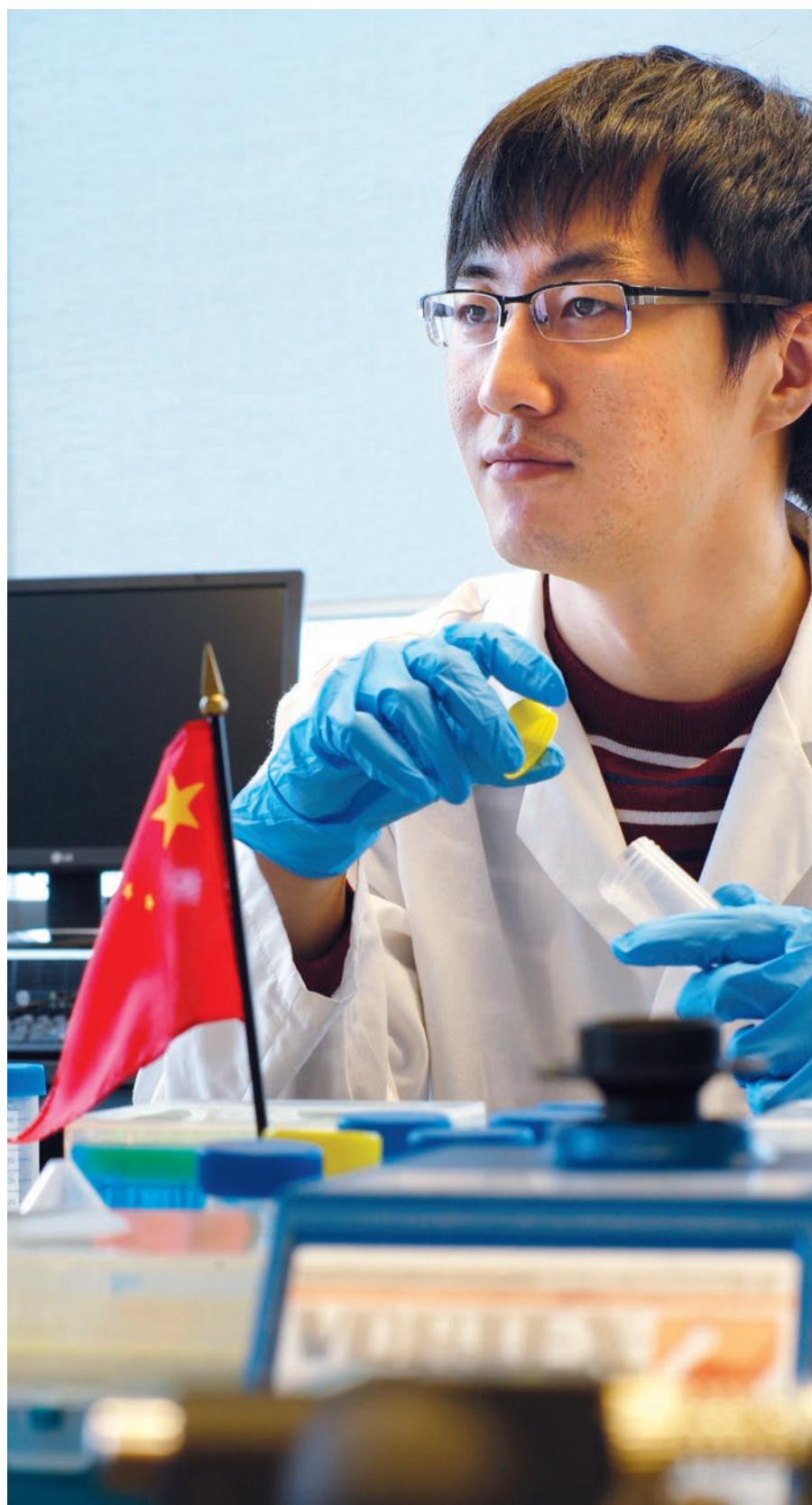
protein-protein interactions in live cells, but he also helped build it. This instrument—of which there are only four in the world—is of interest to drug companies because it can identify new therapeutic targets for cancer, stroke and other diseases.

Chi wanted to work with Andrews because of his leading research in apoptosis, or programmed cell death. Apoptosis is crucial for health, because it gets rid of abnormal or unneeded cells, but is compromised in some diseases. In cancer, for example, a faulty mechanism allows rogue cells that should self-destruct to proliferate uncontrollably. Andrews' lab is trying to manipulate apoptosis—not only to kill malignant cells, as in cancer, but also to halt the death of healthy brain cells, as in stroke and other brain disorders.

Chi's thesis is on the role of Bim, a protein that is implicated in apoptosis. He is trying to purify this protein for study outside its biological environment, which will allow him to analyze its function in detail. Studying Bim in the cell is problematic because of the numerous proteins at work, says the third-year doctoral student. "If you see an effect, it's hard to know if it's due to the interaction of the protein you're looking at."

He says he admires his supervisor's breadth of knowledge. "He knows a lot of stuff—not just about apoptosis. He knows about imaging, data analysis, computers, microscopes and lasers. He looks at all these fields and uses whatever he can find in one field to help the research. He's like a [symphony] conductor. He has that view."

Chi says the guidance he's received from Andrews has shaped how he works. "He's taught us to think smart and design experiments that give a lot of information. He trains us to think like a scientist."



XIAOKE CHI, A THIRD-YEAR PHD STUDENT FROM CHINA, IS STUDYING THE MECHANISMS OF PROGRAMMED CELL DEATH, a biological process that is compromised in diseases like cancer and stroke.

Photo: Curtis Lantinga

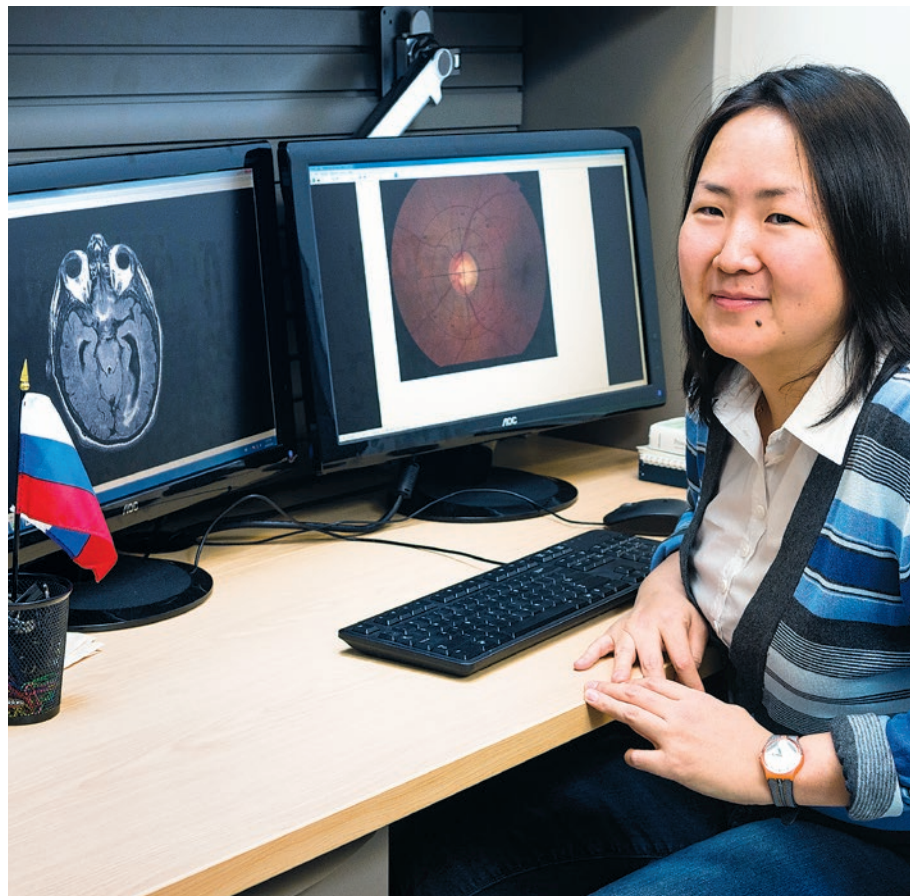
“She was interested in meeting with me and knowing more about me. We met, had a very nice conversation, and I started my fellowship a year later.”

MAKING THE CONNECTION

Near the end of her clinical fellowship at Western University, in London, Ontario, Dr. Alexandra Kim attended a lecture on cognitive impairment and stroke. The lecture was given by Dr. Sandra Black, a cognitive neurologist, director of the Brain Sciences Research Program at SRI and a professor at U of T. The talk would help shape the direction of her career.

“I was fascinated by her lecture. It was just so interesting,” says Kim, who began her postdoc with Black in July 2010. Although she had seen Black’s name in journals, this was the first time she had heard her speak. Kim felt compelled to reach out; she sent Black an email, inquiring about training opportunities.

“She was interested in meeting with me and knowing more about me. We met, had a very nice conversation, and I started my fellowship a year later,” she recalls.



DR. ALEXANDRA “SASHA” KIM, WHO HAILS FROM RUSSIA, DID HER POSTDOCTORAL TRAINING AT SUNNYBROOK RESEARCH Institute. She is examining the link between abnormalities in retinal blood vessels and white matter changes in Alzheimer’s disease.

Kim, a permanent Canadian resident whose ancestral roots in Russia go back generations, did her medical degree at Moscow State University of Medicine and Dentistry, and her PhD at the Research Centre of Neurology, which is affiliated with the Russian Academy of Medical Sciences.

Her postdoc finished in June 2012. Her research looked at retinal blood vessels in patients with Alzheimer’s disease and white matter hyperintensities. The aim of the project, a collaboration with Sunnybrook’s department of ophthalmology and vision sciences, was to see if there was a link between vascular abnormalities and white matter changes, which show up as white spots and patches of bright signal on MRI brain scans.

Kim says clinical input from the hospital’s ophthalmologists in interpreting the retinal images was a big help. Moreover, the project enabled her to become familiar with neuroimaging techniques.

“Dr. Black’s lab is huge. There’s the neuroimaging part and the clinical psychometry part. I learned a lot from both teams. Neuroimaging analysis is very interesting. I learned how to do assessment of white matter changes using a rating scale, and vessel measurement using special software,” says Kim.

She is wrapping up the project, doing statistical analysis and writing a paper on the findings. She describes her former supervisor as a “great mentor and teacher.” In particular, she says she appreciated how Black tailored advice to her strengths and weaknesses. She notes the fellowship gave insight into the busy life of a clinician-scientist, a career she hopes to have in Canada. “Nobody understands how she handles all of this with only 24 hours in a day. I’m learning how to balance things.”

ALISA KIM

Lighting the Way

Research can have an impact in many ways. The creation of clinical guidelines, while not as obvious as the introduction of a new drug or device, is one such way; herein, an illuminating success story

Psychiatrist
Dr. Anthony Levitt
co-penned
the definitive
guidelines
on how to
treat seasonal
affective disorder.



Since the early 1980s researchers have been investigating how disorders of one's biological clock and the processing of light affect psychiatric illnesses. They have found that seasonal affective disorder (SAD), or winter depression, is a distinct subtype of clinical depression and that light therapy—daily exposure to bright, artificial light—is an effective treatment.

Although a growing number of papers were being published on SAD two decades ago, there were no summary guidelines to provide health care professionals with a “go-to” resource when diagnosing and treating patients.

Starting in 1994, Dr. Raymond Lam and Dr. Anthony Levitt, experts in mood disorders and SAD, organized the Canadian Consensus Group. It comprised the country's top researchers in the field and sought to answer commonly asked questions about SAD. The members of the group reviewed the scientific literature, and from this formulated evidence-based recommendations for the diagnosis and treatment of SAD.

The result was the *Canadian Consensus Guidelines for the Treatment of Seasonal Affective Disorder*. The book was published in 1999 in a question-and-answer format for use by family doctors, psychiatrists, psychologists, nurses and other health care professionals.

“We felt it was important to bring experts together because we figured it's going to be decades, if ever, before we can conduct the research needed to answer all the clinical questions that would form the basis of best-practice guidelines,” says Levitt, who is a psychiatrist at Sunnybrook and scientist in the Brain Sciences Research Program at Sunnybrook Research Institute (SRI).

“The guidelines have had an impact internationally, and there have not been any published since,” he adds.

Fifteen years later the guidelines are still relevant—and needed more than ever. The prevalence of SAD is about 2.6% of the Canadian population, and about 50% of Canadians say they have difficulty with their mood or energy after autumn's end. “It's an interesting public health issue: people

“The guidelines have educated a whole generation of consumers and patients.”

are reporting a significant change in their mood and energy in the winter time, resulting in noticeable problems with their life and function, even though they are not clinically depressed,” says Levitt.

The guidelines have had an impact on practice and policy. Levitt says family doctors and psychiatrists are making use of them for educational purposes. For example, he notes universities are using them to teach residents about the treatment of SAD, and some family doctors are lending the book to patients to help them understand the condition.

“The guidelines have educated a whole generation of consumers and patients for whom this information was not available in one spot. We get lots of feedback from patients who like that we’ve written a book on guidelines that is also a self-help book,” says Levitt, who is also a professor at the University of Toronto. Many physicians across Canada also requested—and received at no cost—copies of the book, making its true impact hard to quantify.

Insurance companies were also persuaded to cover light therapy as a result of the guidelines, supported by other research. “In terms of policy, we’ve been able to convince insurance companies that it’s reasonable for them to cover the cost of light therapy units because, in the end, it’s less costly than medications,” he says.

Levitt says that perhaps the biggest impact of the guidelines has been that they led to the development of other such tools for managing mental illness. One example is the *Guidelines for Adolescent Depression in Primary Care* developed by Levitt’s colleague, Dr. Amy Cheung, a clinician-scientist in the Brain Sciences Research Program at SRI.

Cheung, together with pediatricians, family doctors and scientists, created the publication to address the lack of research-based evidence and recommendations for the management of depression in youth. “Her guidelines have precipitated further research and the development of programs internationally—it’s been a really valuable exercise,” Levitt says.

The SAD guidelines not only addressed questions about diagnosis and treatment, but they also helped identify knowledge gaps and promote research. “When we published the guidelines, the rate of increase in the number of publications in seasonal depression was astronomical,” says Levitt.

Guidelines are often updated as new knowledge surfaces, and Levitt says he can see this happening here, too. “It would be worth looking back and saying, ‘How have things changed, and what’s important?’ It wouldn’t require a whole book, but more likely a review of progress.”

Light therapy has become a widely accepted treatment for SAD, followed by antidepressants and psychotherapy. Relatively new to the arena are two types of devices: head-mounted light units, which sit on the head at a fixed distance from the eye; and dawn-simulation units, a technique that uses a digital clock and gradually increases lighting in the bedroom hours before awakening. The use of LED lights, as opposed to fluorescent lights, has also changed treatment, making therapy units more compact and portable.

As for the direction the field is going, Levitt points to neuromodulation, a process that involves direct stimulation of brain structures to adjust disrupted brain circuitry. Neuromodulation alters nerve activity by delivering physical stimulation directly to an area of interest in the brain; this stimulation may be electrical, magnetic, ultrasound or other; indeed, as Levitt notes, light therapy is photic stimulation of the retina, which is actually part of the brain.

Scientists at SRI are at the forefront of this kind of neuromodulation research, preclinically and with patients for certain conditions—though not yet in depression. (See page 34.) Levitt says he’s optimistic that the first human trials with new forms of neuromodulation are just around the corner.

“The new phase of therapeutics for mental illness is about neuromodulation, and we already have evidence that neuromodulation using light therapy works in seasonal depression. This kind of treatment represents an amazing opportunity for our patients to feel better and stay well,” he says.

Still, treatment of psychiatric illness is one thing; stopping it from happening is another. “The field has been focused on treating people when they get sick, but where the field needs to go is prevention. Seasonal affective disorder is one condition that you can look carefully at prevention because you know when it’s going to start. I think the field is now moving toward prevention.”

ELENI KANAVAS

This research was funded by the Canadian Institutes of Health Research, Ontario Mental Health Foundation and Physicians’ Services Incorporated Foundation.



“Whenever I walk in a room, everyone ignores me.”

Collaboration + Expertise = Impact

National network is a powerful engine for brain tumour research

In the late 1990s, global biotech and drug companies were seeking to partner with Canadian hospitals and research institutes to support clinical trials of treatments for brain tumours. With no national organization in this arena, an opportunity emerged.

Established in 1998, the Canadian Brain Tumour Consortium is a not-for-profit corporation. It comprises 150 clinicians and investigators who treat pediatric and adult patients with brain tumours at 25 sites across the country.

Dr. James Perry, a neuro-oncologist at Sunnybrook's Odette Cancer Centre and researcher at Sunnybrook Research Institute (SRI), is the chair of the consortium. His idea to form a network came to life with seed funding from a donor, Tony Crolla, after Perry pitched the idea to him.

"We created the network so that every brain tumour group interested in clinical trials had an opportunity to hear about, participate in and lead these trials," he says.

The consortium develops and promotes multicentre research in collaboration with public and private sector partners. It evaluates and executes clinical trials of promising agents quickly and cost-effectively. It also holds scientific meetings.

Over the past 16 years, the consortium has conducted many high-impact trials. Its capacity to accrue vast patient pools allows the network to carry out large-scale, independent research studies not easily conducted by a single centre.

Perry notes Canada's productivity in this area is high. "We always punch way above our weight. Given the population of Canada, we do way more than our expected share of the heavy



THE CANADIAN BRAIN TUMOUR CONSORTIUM ORGANIZES MULTI-SITE CLINICAL TRIALS FOR PATIENTS WITH BRAIN tumours; at the helm is neurologist Dr. James Perry.

lifting for metrics like the number of patients in a clinical trial," says Perry, who is also an associate professor at the University of Toronto.

One notable success story is that of RESCUE, which generated new global standards of care.

The RESCUE study had its origins in an idea of Perry and his colleagues at the Odette Cancer Centre and SRI. They decided to treat a patient whose tumour had recurred using metronomic chemotherapy, the daily, low-dose administration of a drug. "We treated one patient with a daily dose of temozolomide and her brain tumour disappeared," he says. "She had complete response to the treatment, and we said, 'This doesn't happen very often.'"

Perry and colleagues then did a small trial of about 80 patients at Sunnybrook, and found the drug appeared to be safe and effective.

"We were able to take that idea and write the protocol for the RESCUE trial, and we ran it through the consortium centres," he says. The trial's results

showed it had the highest clinical response rate of any drug used for recurrent brain tumours at that time.

"The so-called 'RESCUE regimen' is used worldwide as a standard of care. It's in many of the national guidelines in different countries as a treatment option, and has become a standard option in Canadian centres," he says.

Perry highlights as one of the network's strengths its quality of data, which is population-based—but notes it owes its success to a superlative team effort.

"The quality of our data is fantastic, and our performance is simply the best in the world," he says. "Because we had the vehicle to drive, everyone could get onboard. We have financial partnerships to put in the gas, and we load it up with patients and investigators—it's a virtual bus that we drive for global impact."

ELENI KANAVAS

Perry holds the Tony Crolla Chair in Brain Tumour Research.

What Is the Hardest Part About Your Research To Communicate to Someone Without a Scientific Background?

Three scientists at Sunnybrook Research Institute talk about how they talk about their work outside of their natural habitat

EDITED BY STEPHANIE ROBERTS



DR. NICK DANEMAN

My research program uses clinical epidemiology and health services research methods to help prevent and treat health care-associated infections. None of this is easy to convey. It's hard to explain that clinical epidemiology research happens at a desk, and in meetings, and on computers, without the Bunsen burners, pipettes and microscopes of wet lab research. It's tough to convey how crucial health services research can be when it is not targeting new discovery, but rather, improved use of already available scientific knowledge. The hardest part of all, though, is explaining that the infections I study are not all infectious, that many evolve from a patient's own bacterial tenants, and that many infections are caused by the very treatments designed to improve health and well-being. So I find it's better just to call myself an internist. Nobody knows what that means either, but at least they're not worried I'm contagious.

Dr. Daneman uses hospital- and provincial-level data to optimize prediction, prevention and treatment of hospital-acquired infections. Among his interests are *C. difficile*, infections of critical care and antibiotic resistance. One recent project entails defining the optimal duration of antibiotic therapy for bloodstream infections.



DR. SIMON GRAHAM

I find that it isn't the scientific details that are hard to discuss—over time I have developed examples and analogies to discuss my research, and I am enthusiastic about my job. The difficulty has more to do with the social context of the discussion. Speaking to charities, such as the Canadian Cancer Society and the Heart and Stroke Foundation, the environment is very supportive. Typically there aren't tight time constraints, so communicating is relatively easy. However, I find talking to news media rather nerve-wracking, as it takes a lot of my concentration to deliver a good 'sound bite.' I also worry that my words will get taken out of context. Perhaps surprisingly, I find discussing my job at social gatherings to be the most difficult. In some cases, indicating that you are a scientist shuts down the conversation, rather than opening it up. So I take a low-key approach.

Dr. Graham is a neuroimaging scientist exploring the use of functional magnetic resonance imaging (fMRI) for mapping the activity of neurons within the brain. This technology enables noninvasive visualization of how neurons respond in a brain region of interest when doing certain tasks, like thinking or drawing. One project involves studying how to improve fMRI for presurgical planning of brain tumour removal.



DR. JONATHAN RAST

I recently spent time with some non-scientist, college friends who I had not seen for some time, and tried to explain to them what I do. The immediate practical aspects of the work are easy enough to explain. What excites us the most, however, is more subtle. It lies in what we still don't understand about immunity. We have really just begun to grasp the breadth of animal immune function, and it is increasingly evident that it is about much more than protection from pathogens. Our immune system mediates a half-billion-year-old conversation with the microbes that themselves are part of us. Buried in this wider view of immune function is a universe of unexplored medical possibilities. Our excitement about this less-defined aspect of our work can be difficult to convey, and I'm not sure how well I explained it to my friends. More than ever, though, I think that it is important to keep trying.

Dr. Rast is using purple sea urchin larvae as a simple model in which to study interactions among genes involved in immune response. These interactions are critical in disease, but are difficult to study in humans with their trillions of cells. Using sea urchins is a way to get around that, because they are close relatives of the vertebrates and thus share many genetic traits with humans, but are less complex in terms of morphology.

Supporting Excellence

Sonja and Michael Koerner establish Canada's premier hearing regeneration lab

About three million Canadians have a hearing disability. Hearing loss is the fastest growing, and one of the most common chronic conditions facing older adults. In support of exploring new frontiers in hearing, Sonja and Michael Koerner established the Sonja N. Koerner Hearing Regeneration Laboratory at Sunnybrook Research Institute (SRI). As Canada's only research lab in hearing regeneration, it has become the most important initiative in inner ear research in the country, and among the best in North America.

"The point of giving the gift was that someone helped me when I needed help, and we were able to return the gesture," says Sonja, who lost her balance due to a viral infection in her left inner ear a few years ago. "I couldn't walk in a straight line, and Dr. Julian Nedzelski was most helpful." Nedzelski is part of Sunnybrook's otolaryngology team, led by Dr. Joseph Chen. Nedzelski specializes in cochlear implantations, and treating dizziness and imbalance.

Dr. Alain Dabdoub, a scientist in the Brain Sciences Research Program at SRI and an assistant professor at the University of Toronto, moved from the University of California, San Diego, to Toronto to become the research director of the Koerner Laboratory. His team aims to understand and discover how to regenerate hair cells of the inner ear in humans. Hair cells are essential for balance and help convert acoustic energy into electrical signals that travel through the auditory nerve to the brain, where sound is interpreted. Studies have shown non-mammals, such as birds and fish, can regenerate lost hair cells.

In November 2013, Sonja and Michael met with Dabdoub to learn more about his research and work with Dr. Vincent Lin, a clinician-scientist in the Brain Sciences Research Program and assistant professor at U of T. The two are collaborating to discover what happens inside the ear during development and aging, and how drugs and gene therapy can be used to reverse hearing loss. Lin's lab focuses on the cellular and molecular pathways related to regeneration and age-related hearing disability, and ways to develop therapeutic interventions. (Read more on page 14.)

"I was very encouraged by the progress, and I think Dr. Dabdoub is making a huge difference," Michael says. "What he's doing at Sunnybrook is leading-edge work."

When asked why they chose to give to Sunnybrook, Sonja responds, laughing, "Well, it's across the street." Lightheartedness aside, as residents of the community, they are

committed volunteers and members of the Sunnybrook Foundation Governing Council. Sonja joined Sunnybrook's Board of Trustees in 1988 and served until 2002, when she retired as vice-chair. "It was fascinating to learn about all the problems that were brought up," Sonja says.

The Koerner Foundation, established 30 years ago, is perhaps best known for its support of the Art Gallery of Ontario, Royal Conservatory of Music and the Museum of Anthropology at the University of British Columbia, but its mandate to support excellence goes beyond the arts. "When I wrote the purposes of the foundation, one was to alleviate suffering," Michael says. "That's exactly what this [gift] is. It's tough not to have your balance, and we felt there must be some sort of solution."

Sonja and Michael say they will continue to support Canadian scientists and their projects (including two other programs in brain research in Toronto and Vancouver). "Equipment and knowledge are evolving very fast, and the strides that could be made in medical research over the next decade could be immense," Michael says. "That's the excitement and hope that I have."

ELENI KANAVAS



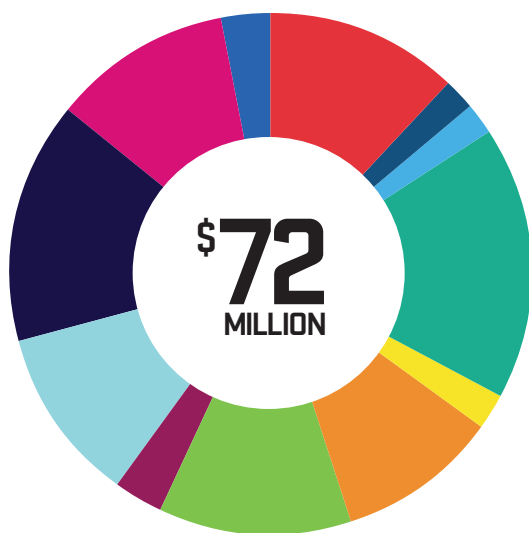
SONJA AND MICHAEL KOERNER ESTABLISHED THE SONJA N. KOERNER HEARING Regeneration Laboratory at Sunnybrook Research Institute, the only scientific lab in Canada doing this work.

Photo: Doug Nicholson

Quick Statistics

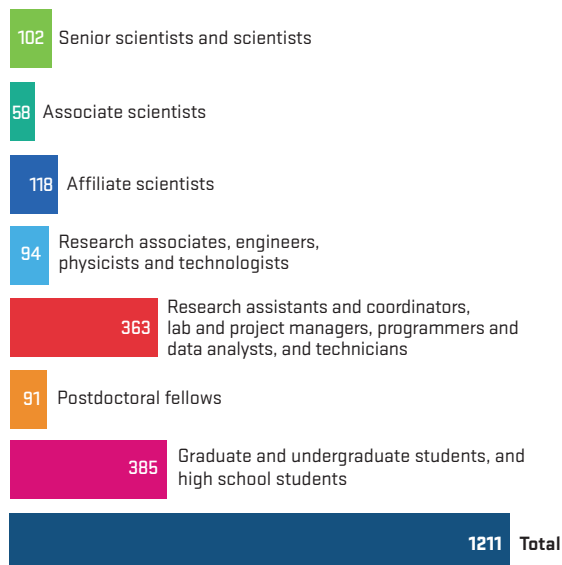
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MAJOR SOURCES OF EXTERNAL FUNDING 2012-2013

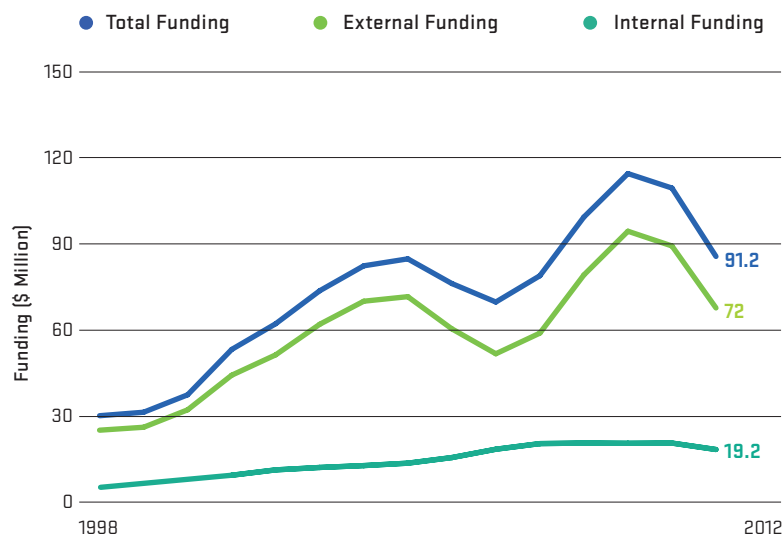


Sources	\$(M)	%
Canada Foundation for Innovation	8.5	12
Canada Research Chairs Program	1.7	2
Canadian Cancer Society Research Institute	1.4	2
Tricouncil Funding: Canadian Institutes of Health Research, and Natural Sciences and Engineering Research Council	12.1	17
Donations and Trust Income	1.8	2
Foundations	7.1	10
Industry	8.9	12
Ministry of Health and Long-Term Care	2	3
Ministry of Research and Innovation	7.6	11
Other Funding Sources	11	15
Other Government Sources	7.6	11
U.S. and International Sources	2.3	3
Total	72	100

RESEARCH STAFF



HISTORY OF RESEARCH EXPENDITURES AT SUNNYBROOK RESEARCH INSTITUTE



Q&A

Dr. Arjun Sahgal is a scientist in the Odette Cancer Research Program at Sunnybrook Research Institute (SRI), associate professor at the University of Toronto and radiation oncologist at Sunnybrook Health Sciences Centre, where he is also the deputy chief of the department of radiation oncology. He spoke with Alisa Kim about his research.



FACTS ABOUT RADIATION THERAPY IN CANADA

- About 50% of all patients with cancer receive radiation therapy.
- Radiation therapy is the main treatment for various skin cancers; cancers of the mouth, nose, pharynx and larynx; brain tumours; and gynecological, lung and prostate cancers.
- More than 100,000 radiation therapy courses are prescribed annually.

What's your research focus?

My focus is treatment and response assessment of brain metastasis (cancer that has spread to the brain from elsewhere in the body) with stereotactic radiosurgery. This entails using high-precision radiation focused on the brain tumour and delivering an ablative dose of radiation such that we maximize local control and minimize the dose to normal brain tissue. The aim is to avoid whole brain radiation, a more archaic form of therapy.

How does radiosurgery differ from conventional radiation therapy?

Conventional radiation involves low-dose radiation. It blankets all the tissue with radiotherapy, and therefore is not as targeted as radiosurgery. When you do target [the tumour] with precision radiation, there's still a bit of low-dose exposure in normal brain tissue, but it's clinically negligible. With radiosurgery, we're using the most precise image-guided radiation technology to maximize the dose in the tumour and minimize the dose to surrounding normal tissue. We're therefore allowed to deliver much higher doses than with conventional radiation—anywhere from two to six times higher. This means a transition from treating patients with locally palliative intent to locally curative intent.

How does stereotactic radiosurgery work for planning and delivery?

It's complex and time-sensitive, as treatment is focused on the tumour we see on magnetic resonance imaging. We need to make sure we have the radiation planned on the target before it changes [and] any tumour growth or bleeding occurs. It's stressful because we need to image, plan and treat at the right time—from the same day for brain radiosurgery, to within five to seven days for spine. It's a major undertaking—the clock is ticking and the pressure is on. Delivery involves multidirectional beams of radiation concentrating on the target,

image guidance with cone-beam computed tomography, robotic couch-top technology and complex head immobilization devices. Radiosurgery requires medical physicists, therapists, radiation oncologists and dosimetrists to work together closely.

What has been your most interesting finding?

Thus far, the survival benefit of radiosurgery for younger patients. These data were presented at the [meeting of the] American Society for Radiation Oncology [in September 2013]. We're completing the manuscript, which shows for the first time that by sparing the brain from radiotherapy and maximizing the dose to the tumour itself, patients may live longer because they're not getting the toxicities associated with whole brain radiation. This could be practice-changing.

What are the next steps in your research?

One is treatment of multiple brain metastases with radiosurgery alone. It's a new area and challenging because we're dealing with 10, 15 or 20 [tumours] using a single treatment of radiation directed to each tumour simultaneously. That's not an easy undertaking. We need to understand how to do it safely to minimize the risk of radionecrosis (tissue death due to ionizing radiation). We need a dedicated radiosurgery system that incorporates image guidance to figure out how to treat these patients efficiently, and to develop software to track the multiple tumours treated to monitor response and overall brain control. In addition, we want to incorporate novel sequences like those from the lab [of SRI scientist] Dr. Greg Stanisz, aimed at characterizing response right after radiation with respect to tumour cell death. That's where development of software and imaging [technology] is going to come into play, in collaboration with SRI and the Odette Cancer Centre.

Sahgal's research was funded by the Brain Tumour Foundation of Canada. For more on his research, visit sunnybrook.ca/research



Through the Wormhole

Journey into a different
time in medical science

In

November 1906, German physician Alois Alzheimer gave a talk outlining the psychiatric symptoms and postmortem results of his late female patient, Auguste Deter. It was the first time the clinical and pathological findings of dementia were presented together.

Five years earlier, in 1901, Deter's husband had admitted her to the Frankfurt psychiatric hospital where Alzheimer worked.

Alzheimer's detailed notes of interviews with Deter show she displayed progressive memory loss, hallucinations and erratic behaviour. Her condition worsened, and Deter passed away in 1906, at the age of 55.

Alzheimer, who was by this time working in Munich at the Royal Psychiatric Clinic, received permission from Deter's family to do an autopsy of her brain.

Under a microscope, Alzheimer observed shrinkage of Deter's cerebral cortex and the presence of unidentified plaques, tangles and hardened arteries in the brain. Her brain displayed what are now considered the hallmarks of this disease: loss of neurons and accumulation of neurofibrillary tangles and amyloid plaques.

Emil Kraepelin, Alois's colleague and a pioneering figure in psychiatry—he is considered by many to be the founder of modern psychiatry—used the term "Alzheimer's disease" in a textbook he wrote. This led to widespread adoption of the disorder's eponymous name.

COVER SLIP

In the brain, amyloid plaques are a hallmark of Alzheimer's disease. When focused ultrasound is delivered through the skull, the activation of astrocytes (star-shaped red cells) and microglia (blue) could contribute to reducing the number and size of amyloid plaques (green). Biologists and physicists at Sunnybrook Research Institute have joined forces to investigate these processes.

Image: taken with a Zeiss LSM510 confocal microscope. Labelling of the brain sections was done by Lillian Weng; imaging by Dr. Emmanuel Thévenot; selection, Jonathan Oore. Dr. Isabelle Aubert did the post-processing.

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