SRI MAGAZINE

SUNNYBROOK RESEARCH INSTITUTE

ON TARGET?

The promise and challenges of molecular therapies

DO THE MATH
Heart failure + which variables = high risk of death?

THE MEDICAL INNOVATORS
No to the status quo: meet two scientist-clinician-inventors

ALSO IN THIS ISSUE
Why Pay Less?
How Fractures Heal

FIRST, SOME FACTS

Three details underpinning the early science of some of the stories in this issue

FACT

Dr. Sidney Farber, an American pathologist, is considered the father of modern chemotherapy. He was the first to use drugs that block folic acid to induce remission in children with acute lymphoblastic leukemia.

FACT

The first X-ray picture of the human body was taken in November 1895. It is the hand (and ring) of Mrs. Anna Röntgen, wife of Dr. Wilhelm Röntgen, discoverer of X-rays.

FACT

Dutch scientist Antonie van Leeuwenhoek crafted his own microscopes and was the first to describe single-celled organisms. He was also first to record observations of bacteria, spermatozoa and blood flow in capillaries.

INVENTING THE FUTURE OF HEALTH CARE SUNNYBROOK RESEARCH INSTITUTE 2012

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Sunnybrook HEALTH SCIENCES CENTRE

2012

FEATURES

Cover illustration by **GRACIA LAM**

DEPARTMENTS

Messages

From the
PRESIDENT AND CEO,
and
CHAIR OF THE BOARD
Sunnybrook Health Sciences Centre

At Sunnybrook, scientists and their teams need not look far to find inspiration. As they walk through the halls of Canada's largest single-site hospital to get to their labs and offices, they are reminded time and again of the urgent need for solutions to critical health care challenges.

These challenges are many, and we at Sunnybrook see the most complex of them. Such challenges demand innovation and dedication of the highest order.

We are proud that such is emblematic of the work our doctors, allied health professionals, scientists, and research and hospital staff do every day.

One notable example is found within the Centre for Research in Image-Guided Therapeutics, which we opened in 2012. It brings together scientists and researchers working to invent better ways to detect, diagnose and treat cancer, heart disease, musculoskeletal disorders, immune deficiencies, stroke and dementia. The teams are already making advances, such as the completion of Canada's first clinical trial testing focused ultrasound to treat essential tremor.

In another milestone, we opened the Louise Temerty Breast Cancer Centre, the largest of its kind in this country, thanks to a visionary, $10-million donation from Jim and Louise Temerty. It provides expanded areas for specialized clinics, integrated breast imaging research and clinical trials. It will transform breast cancer care.

We celebrate such innovation and dedication thanks not only to the effort of our staff, but also to the support of our funding, government and community partners. As we look back over the last year, we are pleased to share our successes with you, and look forward to achieving many more.

David Agnew
Chair, Board of Directors

Barry A. McLellan
President and CEO

From the
VICE-PRESIDENT, RESEARCH
Sunnybrook Research Institute
Sunnybrook Health Sciences Centre

Our mandate at Sunnybrook Research Institute (SRI) is make discoveries and achieve clinical impact—and we're doing it.

Imagine replacing today's model of generalized therapy for all patients with one that treats disease precisely, guided by knowing how a patient will respond based on his or her genetic makeup and medical history. Add to that being able to tell if a therapy is working within weeks, not months, so that doctors can adjust it as quickly, if needed. This is the future. We're making it happen.

We're doing so by developing gene-screening technologies to identify "druggable" disease targets, and inventing imaging tools able to visualize what was once invisible, guide therapy delivery and monitor outcomes, thereby achieving what was "impossible": incisionless surgery.

Our new structure makes possible this work. Our discovery platforms in biological, evaluative clinical and physical sciences collapse barriers among fields and are tethered to the hospital's clinical programs, ensuring efficient translation of results.

Moving discoveries into the clinic is a high-cost, high-risk endeavour that needs private sector support. Our government funders appreciate this and have created enabling partnership programs. We lead in capitalizing on these programs. Last year, the Federal Economic Development Agency for Southern Ontario made a multimillion-dollar investment, one of its largest, in SRI and our company partners. With it, we are developing and commercializing new technologies—the only way to get results to patients.

Welcome to this year's *SRI Magazine*. We hope you enjoy the stories that aim to share with you our passion for medical science—what we're doing, why it matters and the global impact of SRI discoveries.

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

PHOTOS: (LEFT) **DOUG NICHOLSON**, (RIGHT) **CURTIS LANTINGA**

Digest

A round-up of some of the advances and achievements at Sunnybrook Research Institute from the past year

ABSTRACTS

ATTENTION: THIS DISEASE IS DEADLY

Chronic obstructive pulmonary disease (COPD) is a long-term lung disease that includes chronic bronchitis and emphysema. The World Health Organization predicts it will be the third most common cause of death by 2030, but the general public seems to know little about it. **Dr. Andrea Gershon**, a scientist in the Trauma, Emergency & Critical Care Research Program at Sunnybrook Research Institute and the Institute for Clinical Evaluative Sciences, led the first study to measure an individual's lifetime risk of developing physician-diagnosed COPD in a complete, multicultural, North American population.

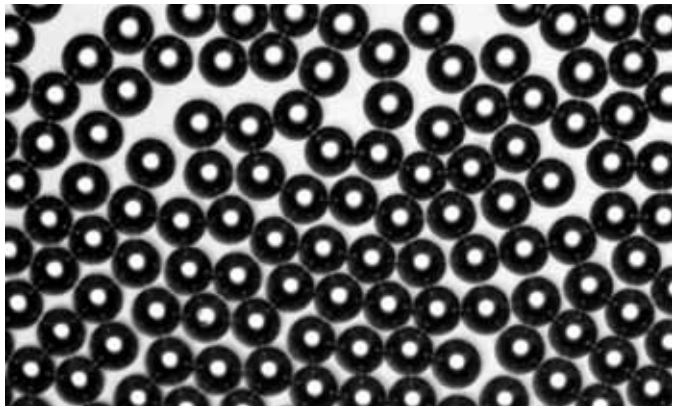
Results, published in *The Lancet*, showed that 27.6% of people aged over 35 years are likely to be diagnosed with COPD in their lifetime—more than are likely to be diagnosed with congestive heart failure, heart attack, and breast, prostate and other cancers. These findings underline the societal burden of COPD, and the need for more resources and public health education to combat it.

POP GOES THE CANCER

Scientists at Sunnybrook Research Institute (SRI) led the world's first preclinical study showing how pairing ultrasound-stimulated microbubbles with radiation enhances the effects of radiotherapy. **Dr. Greg Czarnota**, director of the Odette Cancer Research Program at SRI, led the study, which aimed to make tumours more sensitive to radiation and thus hasten their demise. Right now, an average of up to 35 small radiation treatments are needed to destroy a tumour.

Using ultrasound, the researchers burst microbubbles (tiny lipid-coated spheres of gas that can safely pass through the circulation) to weaken the blood vessels that feed tumours in a preclinical model of prostate cancer. They followed the microbubble treatment with radiation. Czarnota found just a single dose of radiation following ultrasound-stimulated micro-bubbles destroyed up to 50% of the tumour 24 hours after treatment, compared with 5% cell death using either ultrasound and microbubble treatment alone, or only radiotherapy, and thus representing an up to 10-fold greater cell kill.

The study, published in the *Proceedings of the National Academy of Sciences*, shows promise to increase the efficacy of radiation therapy at lower doses, which would mean less toxicity for patients and potentially fewer treatments overall.



CHANCES ARE MORE THAN ONE-QUARTER OF PEOPLE aged over 35 years will be diagnosed with chronic obstructive pulmonary disease in their lifetime.

A DEADLY PAIRING: ULTRASOUND-STIMULATED MICROBUBBLES make tumours more sensitive to radiation. Here, actual microbubbles.

ILLUSTRATION: ©MARYLB/ISTOCKPHOTO. PHOTO: SUNNYBROOK RESEARCH INSTITUTE

RENAISSANCE CELLS

Hearing loss is caused by damage to the auditory hair cells in the cochlea, the organ for sound. Hair cells, which are essential for balance, help convert acoustic energy into electrical signals that travel through the auditory nerve to the brain, where sound is interpreted. It's unclear whether lost hair cells are restored by cellular regeneration or repair, given in part that most damage doesn't result in the loss of all original hair cells. Recent studies have shown that some birds, after going deaf, were able to regenerate hair cells spontaneously and restore hearing.

Dr. Vincent Lin, an associate scientist in the Brain Sciences Research Program at Sunnybrook Research Institute, led a study that examined the regeneration of hair cells in preclinical models. The study's aim was to determine how new hair cells are formed in adult mice treated with an antibiotic that causes hair cell loss. Researchers looked at the rate of renewed hair cells and if manipulating a particular cellular pathway would enhance the growth process. They found that hair cell damage in the mice triggered and controlled supporting cells to regenerate into new hair cells, showing that mature mammals do have a natural capacity for hair cell regeneration. The study, published in *The Journal of Neuroscience*, may provide insight into the development of effective therapies to treat hearing loss.

PREDICTING TROUBLE

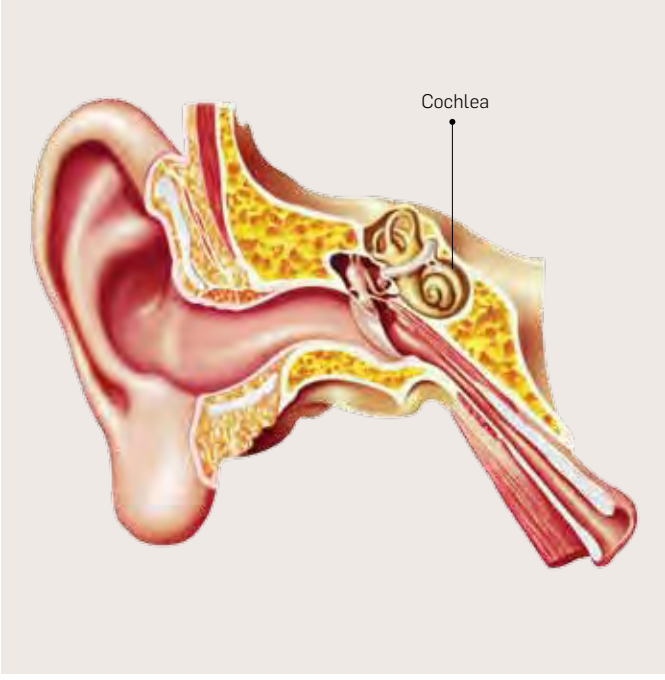
Intracerebral hemorrhage (ICH), when a blood vessel in the brain ruptures or leaks, accounts for up to 15% of all strokes and leads to about 40% of deaths. In patients with ICH, hematoma expansion soon after symptoms start highly predicts poor clinical outcomes, including early neurological deterioration and death. Needed is a way to determine which patients will have a hematoma expansion after ICH, so they can be treated promptly. Research suggests the "spot sign," an imaging marker that appears on a computed tomography angiography (CTA) scan, used to see inside blood vessels, may be one way to do this.

Drs. David Gladstone and **Richard Aviv**, brain scientists at Sunnybrook Research Institute, led the first multicentre, prospective cohort study to validate the CTA spot sign to predict bleeding in the brain in patients who have had a stroke or other ICH.

The study, aptly called PREDICT, enrolled 268 patients in six countries who presented with a brain bleed smaller than 100 ml less than six hours from first symptoms. Of 228 patients included in the primary analysis with a brain bleed, 61 were spot-sign positive and 167 were spot-sign negative. Presence of the spot sign predicted outcome, including hematoma growth, which was significantly more frequent and bigger in the spot-sign positive group. Moreover, clinical outcomes were worse, including mortality at three months: 43% of spot-sign positive patients died, compared with 20% of spot-sign negative patients.

The results, published in *The Lancet Neurology*, validate smaller studies of the utility of the CTA spot sign, and confirm it predicts which patients are at high risk for further bleeding in the brain and poor clinical outcomes.

MATURE MAMMALS HAVE A CAPACITY
for auditory hair cell regeneration, a finding that could spur new treatments for hearing loss.



SPOT THIS: AN IMAGING MARKER
on scans depicting the inside of the brain's blood vessels predicts which patients are at high risk for further bleeding in the brain.

ILLUSTRATIONS: (LEFT) LEONELLO CALVETTI/SHUTTERSTOCK; (RIGHT) SEBASTIAN KAULITZKI/SHUTTERSTOCK

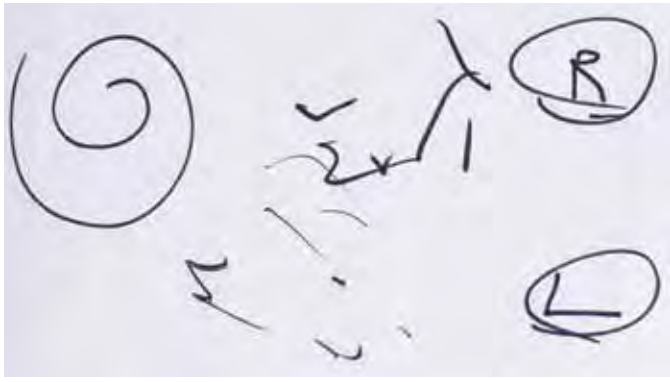
NEWS

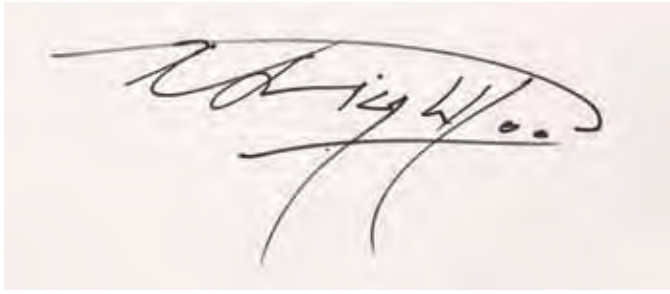
NOTHING SHAKY ABOUT THESE RESULTS

Scientists at Sunnybrook Research Institute (SRI), working with neurosurgeons at Sunnybrook, have completed Canada's first clinical trial to evaluate the use of high-intensity focused ultrasound (HIFU) to treat essential tremor. Results from the study's six patients were excellent. Patients unable to raise a cup to their lips or sign their name legibly have been able to do both these tasks, and many more that were outside their grasp, after treatment.

The noninvasive technology was invented by **Dr. Kullervo Hynynen**, director of Physical Sciences at SRI, and developed in collaboration with InSightec, which commercialized it. The dome-shaped device directs ultrasound beams through the skull to target lesions inside the brain that cause essential tremor. Magnetic resonance imaging guides the procedure. Inside the skull, the beams converge with millimetre precision to heat the lesions, ablating them while sparing healthy tissue.

Essential tremor is the most common movement disorder. It affects about 3% of the population, or 1 million Canadians; of these, 30% don't respond to medication and must have surgery. Compared with other options, HIFU, an outpatient procedure during which the patient needs no anesthesia, has less risk of infection, blood clot formation and damage to surrounding tissue—and no ionizing radiation. The trial, funded by the Focused Ultrasound Surgery Foundation, was led by neurosurgeon **Dr. Michael Schwartz**. Plans for a multi-institutional trial are underway.





TONY LIGHTFOOT IS ONE OF SIX PATIENTS
whose essential tremor was treated successfully in a clinical trial of magnetic resonance-guided focused ultrasound at Sunnybrook Research Institute.

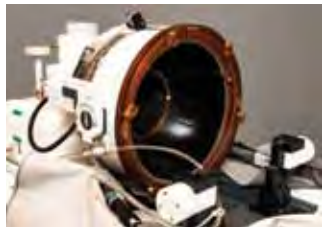
LIGHTFOOT'S ATTEMPT TO WRITE,
by copying the swirl on the left, prior to treatment.

LIGHTFOOT'S SIGNATURE AFTER
the treatment, his first in a decade.

CANADA'S FIRST CENTRE FOR RESEARCH IN IMAGE-GUIDED THERAPEUTICS OPENS

Sunnybrook Research Institute (SRI) officially launched the Centre for Research in Image-Guided Therapeutics, CeRIGT, on Nov. 2, 2012. Governor General **David Johnston** delighted a standing-room-only crowd as the guest of honour.

To celebrate, SRI opened the doors of its $160-million centre, giving invited guests and the public a rare glimpse of its state-of-the-art medical research facilities, some of which can't be found in any other hospital in Canada. At roughly 150,000 square feet, CeRIGT is a two-floor expansion of the hospital's main wing, with additional labs located in other wings.



FOCUSED ULTRASOUND
for the brain is one project within CeRIGT.

More than 50 activities were set up across 16 labs. Visitors interacted with research staff, doing various hands-on tasks, like purifying proteins, taking brain tests and learning about the advances that will become tomorrow's care. Scientists and clinicians at CeRIGT are working together to develop new and better ways to detect, diagnose and treat some of the most complex health conditions, including cancer, heart disease, musculoskeletal disorders, immune deficiencies, stroke and dementia.

PHOTOS: DOUG NICHOLSON

1

DR. DAVID ANDREWS, head of Biological Sciences at Sunnybrook Research Institute, explains how high-content imaging works to Governor General David Johnston; his wife, Mrs. Sharon Johnston and Dr. Gilles Patry, CEO of the Canada Foundation for Innovation.

2

GOVERNOR GENERAL David Johnston walks on the gait track in the brain intervention centre, part of CeRIGT at Sunnybrook Research Institute.

3

DR. KULLERVO HYNYNEN, head of Physical Sciences at Sunnybrook Research Institute, talks to Governor General David Johnston and Mrs. Sharon Johnston about focused ultrasound, a technology he pioneered.

4

GOVERNOR GENERAL David Johnston activates a water jet cutter during the CeRIGT launch at Sunnybrook Research Institute, Nov. 2, 2012. His wife Mrs. Sharon Johnston, right, and research assistant Fedon Orfanidis, left, watch.

PHOTOS: **DOUG NICHOLSON**

In 2008, the Canada Foundation for Innovation announced that SRI was one of only eight institutions in the country to be successful in its bid for a Research Hospital Fund award. **Dr. Barry McLellan**, president and CEO of Sunnybrook, and **Dr. Michael Julius**, vice-president of research at Sunnybrook and SRI, presented a plaque to **Dr. Gilles Patry**, president and CEO of the Canada Foundation for Innovation, to thank the agency for its establishing $75-million investment. Other support comes from federal and provincial funding partners, industry contributions and donations.

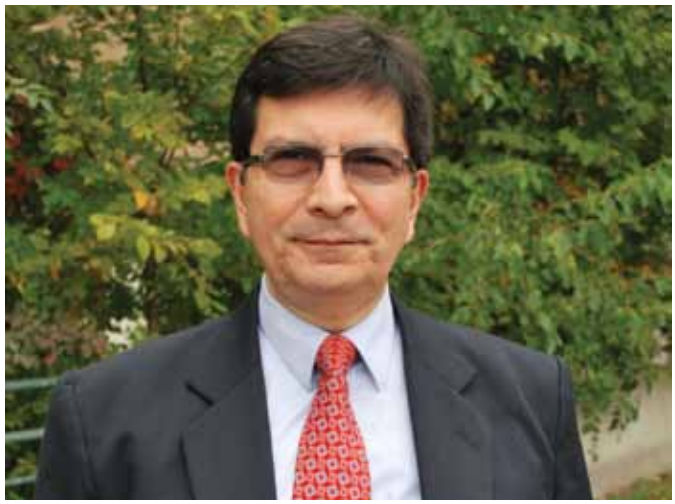
TO LEARN MORE
about CeRIGT, visit
sunnybrook.ca/research/cerigt

UNION WITH REHAB RESEARCH POWERHOUSE

On July 1, 2012, Sunnybrook Health Sciences Centre merged with St. John's Rehab to establish a program that aims to help patients with complex illnesses and injuries. St. John's Rehab became the eighth clinical program at Sunnybrook and, correspondingly, the eighth research program at Sunnybrook Research Institute.

St. John's Rehab provides customized care with a focus on the body, mind and spirit. Each year it helps more than 2,500 people recover. It has five research programs in rehabilitation, which focus on these areas: organ transplantation (Canada's only such); burn injuries (the only one in Ontario); oncology; musculoskeletal injuries arising from motor vehicle accidents, trauma and amputation; and neurology, for example, for people who have Alzheimer's disease or who have had a stroke.

PHOTO: ELENI KANAVAS



DR. MANUEL GOMEZ
directs the St. John's Rehab Research Program at Sunnybrook Research Institute.

OVATION

We salute some notable achievements of scientists at Sunnybrook Research Institute (SRI) during 2012

NATIONAL AND INTERNATIONAL AWARDS

The Government of Canada renewed the Tier 1 Canada Research Chairs of the following SRI scientists: **Dr. Dan Dumont**, in Angiogenic and Lymphangiogenic Signalling; **Dr. Kullervo Hynynen**, in Imaging Systems and Image-Guided Therapy; and **Dr. Juan Carlos Zúñiga-Pflücker**, in Developmental Immunology. The award is the most prestigious academic honour bestowed by the federal government. Ten scientists at SRI hold Canada Research Chairs.

The Canada Foundation for Innovation awarded **Dr. David Andrews**, **Dr. Greg Czarnota**, **Dr. Simon Graham**, **Hynynen**, **Dr. Stanley Liu** and **Zúñiga-Pflücker** each a Leaders Opportunity Fund grant. This award pays for infrastructure to help attract the brightest scientists to Canadian institutions, to strengthen the country's position as a global leader in research and development.

The Canadian Institutes of Health Research recognized **Dr. Nick Daneman** with a phase two Clinician Scientist award, designed to help outstanding clinician scientists develop an independent health research program.

Dr. Lorne Zinman was given the Governor General of Canada Queen Elizabeth II Diamond Jubilee Medal, an award that honours significant achievements by Canadians. He was recognized for his leadership in establishing the Canadian ALS (amyotrophic lateral sclerosis) Research Network.

Dr. Homer Tien was appointed the first Canadian Forces Major Sir Frederick Banting Term Chair in Military Trauma Research. The award will support Tien's research, which aims to improve the care of trauma patients—military personnel and civilians.

PROVINCIAL AWARDS

The Ministry of Research and Innovation (MRI) awarded **Andrews**, **Czarnota**, **Graham**, **Hynynen**, **Liu** and **Zúñiga-Pflücker** Ontario Research Fund-Research Infrastructure awards. This program matches the awards given through the Leaders Opportunity Fund by the Canada Foundation for Innovation.

Also from MRI, **Dr. Mario Masellis** received an Early Researcher Award. The prize supports researchers early in their careers by helping them build a research team.

Dr. Sandra Black was named to the Order of Ontario. It is the province's highest honour and recognizes excellence and achievement in any field.

The Heart and Stroke Foundation of Ontario awarded **Dr. Burton Yang** a Career Investigator award, given to established independent researchers in the field of cardiovascular or cerebrovascular disease.

FELLOWSHIPS AND OTHER HONOURS

Black was elected a Fellow of the Royal Society of Canada. The honour recognizes individuals for outstanding scholarly, scientific and artistic achievement.

The Orthopaedic Research Society presented **Dr. Diane Nam** with the 2012 New Investigator Recognition Award, given to support researchers early in their careers.

Dr. Beverley Orser was named a Fellow of the Canadian Academy of Health Sciences in recognition of her contributions to the promotion of academic health science.

FOR MORE ON AWARDS
given to researchers at Sunnybrook Research Institute, visit the awards section under About SRI on the website:
sunnybrook.ca/research

Walk This Way

It turns out that walking and talking is more complex than one might think

"**Walking is actually a** cognitive activity," says Dr. Sandra Black, neurologist and director of the Brain Sciences Research Program at Sunnybrook Research Institute. "People usually walk for a purpose—to get somewhere or do something."

For people with certain brain disorders, walking is challenging. That's because the brain regions responsible for higher-level thinking and attention are also involved in gait and balance. Given that walking and attention use some of the same neural pathways, Black and colleagues wanted to understand the effects of walking and paying attention at the same time, called "dual tasking." They examined this in healthy seniors and patients with Alzheimer's disease (AD), who had varying degrees of white matter disease, which appears as white spots and patches of bright signal on magnetic resonance imaging brain scans.

They asked healthy seniors and AD patients to perform attention and recall tests while walking on a treadmill. Participants had to keep track of sequences of letters flashed on a screen for one-and-a-half seconds, pressing a buzzer when a letter was the same as the last one or the second-last one seen.

"Participants had to make a trade-off between 'do I get the answer right, or do I try to keep my balance?' We wanted to understand how these trade-offs were made," says Black.

Unlike the healthy people who took more steps to maintain stability, AD patients slowed down while dual-tasking, which meant they spent less time with both feet on the ground, and thus increased their tendency to fall. This effect was even worse in AD patients with white matter disease.

One goal is to help patients become aware of their tendency to fall when distracted, and to train them to improve their balance and awareness.

It's a matter of taking things one step at a time.

- ALISA KIM

This research was funded by the Alzheimer's Association, Alzheimer's Society of Canada, Canada Foundation for Innovation, Canadian Institutes of Health Research, Heart and Stroke Foundation Centre for Stroke Recovery and University of Pittsburgh.

STUDY PARTICIPANT DEIRDRE BRETON WALKS ON A TREADMILL at Sunnybrook Research Institute. The study measured the effects of dual tasking on the brain.

PHOTO: DOUG NICHOLSON

Over the Threshold

Doctors (and the rest of us) know that the bigger the burn, the worse the outcome. Beyond what precise point, however, are patients most at risk of no return?

Over the last 10 years, there have been advances in burn care, mainly stemming from research developments in surgical grafting, wound care and new drugs. As a result, survival rates for burn patients have improved dramatically. Burn care studies published in the 1990s suggest that a burn covering 40% or more of the body results in higher rates of death and serious complications, and thus requires specialist intervention; however, there have been no recent studies quantifying burn size and outcome in light of progress in care.

Dr. Marc Jeschke, a surgeon and scientist in the Trauma, Emergency & Critical Care Research Program at Sunnybrook Research Institute, and colleagues aimed to fill that gap. They did a study to quantify at what point burn size is associated with a higher risk of severe illness and death in children, and thus at what point expert care is required. Results were clear.

"For anyone who sees a child with a burn that is 60% or more, the alarm bell needs to go on," says Jeschke.

Over this value, they found a higher risk of multi-organ failure, wound sepsis (toxic bacteria), infection and death—all of which point to the need for expert care, he says.

"A child should not even be attempted to be treated in some other burn centre that is not experienced. Children have to be sent as soon as possible to a specialized burn centre, because these patients are at high risk for complications," says Jeschke, who also directs the Ross Tilley Burn Centre at Sunnybrook and is an associate professor of surgery at the University of Toronto.

The researchers looked at 952 children with burns covering at least 30% of their bodies who were treated at Shriners Hospitals for Children in Galveston, Texas. Patients were categorized by burn size into groups of 10% increments, from 30% to 100% of their bodies; most had burns covering 40% to 50%. Results were published in *The Lancet* in 2012.

Jeschke and colleagues also correlated outcomes with biochemical markers, and found the presence and concentration of biomarkers in organ function, metabolism and inflammation differed widely in children with a burn size above or below the threshold.

Using biochemical markers confirmed that molecules changed according to burn size, and helped explain survival rates. They also monitored vital signs in liver and kidney function. The study showed that the rate of death was nearly equal in patients with burns covering up to 60% of their bodies, but patients with larger burns were at a much higher risk of dying.

"The beauty of this data is that we not only had demographic data, but we also had biochemical and other markers. That makes the study unique, because we have biochemical approaches backing up the clinical data," says Jeschke.

He says the results of the study can be applied to all burn patients and will enable burn surgeons to identify patients at high risk for poor outcomes and treat them accordingly.

Next, Jeschke will recruit about 1,000 adult burn patients for a similar study at Sunnybrook that will link clinical and biochemical data. For now, though, the message clinically is simple. "Coming to a specialized burn centre is needed; otherwise, patients will not survive," he says.

- ELENI KANAVAS

Jeschke's research was funded by the Canada Foundation for Innovation, Institute for Translational Sciences, National Institutes of Health, National Institute on Disability and Rehabilitation Research, Ontario Ministry of Economic Development and Innovation, Physicians' Services Incorporated Foundation and Shriners Hospitals for Children.

DR. MARC JESCHKE OPERATES ON A PATIENT AT THE ROSS TILLEY BURN CENTRE. Jeschke studies cell survival and organ function in severely burned patients at Sunnybrook Research Institute.

PHOTO: **CURTIS LANTINGA**

How Fractures Heal

A clinician-scientist explores the biological intricacies of how injured bones get better, and guess what? It's all about your immune system

On average, it takes at least six weeks for a fracture to heal in an adult, followed by weeks to months of rehabilitation to regain motion and strength. Moreover, bone injuries that do not heal properly often need surgery to repair the fractured bone.

Dr. Diane Nam, an orthopaedic surgeon and associate scientist in Biological Sciences and the Holland Musculoskeletal Research Program at Sunnybrook Research Institute (SRI), and colleagues conducted a preclinical study to investigate the synergy of two systems: the musculoskeletal system and the immune system. The study looked at how various cytokines (cell-signalling protein molecules) expressed by cells in the immune system altered bone healing. It was the first study to show how a specific immune cell could improve osteogenesis, or the formation of bone.

DR. DIANE NAM EXAMINES John Klotz in the fracture clinic. Nam studies the molecular and cellular aspects of fracture healing at Sunnybrook Research Institute.

PHOTO: **DOUG NICHOLSON**

"Our hypothesis was that the immune system played a critical role during the early phase of fracture repair," says Nam, who is also an assistant professor of surgery at the University of Toronto. "Anytime we have an injury, whether it's a cut on your skin or a broken bone, the immune system is required."

Using a mouse fracture model, the researchers examined the rate, quality and strength of fracture healing in immune-deficient mice lacking the T cells and B cells that are critical to a healthy immune response, and compared them with normal mice.

After careful analysis of the biological processes, the study showed that the fractures of immune-compromised mice did not heal as well as those of normal mice. The researchers found that a lack of T cells delayed fracture healing and decreased bone formation.

Nam also looked at the role of inflammatory cytokines in fracture repair. She found that the cytokine IL-17F (produced by T-helper cells) was crucial to bone healing by causing osteoblasts, bone-forming cells, to mature and stimulate bone formation. These findings were published in the journal *PLoS ONE* in 2012.

"The involvement of IL-17F and osteoblasts in fracture healing is novel, and I think it's a significant finding. Having new insight into the actual mechanism of fracture healing is a huge step in terms of understanding bone repair pathways," Nam says. These results may lead to optimizing fracture repair techniques within the next decade and ultimately improve treatments for patients with impaired bone healing, she says.

Although preclinical fracture modelling is taking place around the world, Nam is the first researcher to do this work at SRI. She says it's tough to find a niche for research in fracture repair and immunology, and is fortunate to have found such a perfect fit at Sunnybrook.

Nam's research is still in the early stages. The next step will be to outline the exact signalling cascade and assess the functional significance of IL-17F to understand better how it is "doing its magic" in fracture healing, she says.

Nam also leads an orthopaedic trauma practice at Sunnybrook Health Sciences Centre. She spends at least two days a week treating patients, and specializes in upper extremity reconstruction and limb fractures. Her goal is to help patients heal and function better, earlier, especially those who have impaired healing, and enable them to get back to their daily activities.

"Most people will have a fracture in their lifetime, and when you have something broken or you've lost function of an arm or a leg, it really limits your mobility and independence," she says. "The collective cost to society from lost productivity is huge and one of the largest health care burdens in Canada, not only with the younger trauma population, but also with the growing elderly population."

Many patients who are elderly have osteoporosis and health issues such as diabetes or cancer, which, in addition to advanced age, contribute to impairment of their immune response. "If you're one of the patients in the 5% to 10% range that show impaired or delayed healing, then you're going to spend more time with doctors and hospitals trying to rectify this problem, and it usually involves some type of surgical intervention," Nam says.

Technology and implants have improved orthopaedic care by helping patients regain some early mobility, but the biological course of fracture healing remains slow. "Surgically we can provide stability internally that allows you to be free from casts, but your ability to weight-bear, to do physical activities like sports, to walk or return to work, is still restricted to a significant degree," she says.

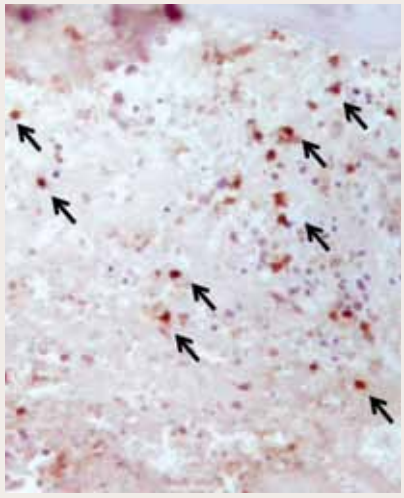
Well-positioned by her joint role as clinician and researcher, Nam is determined to uncover the biological mechanism of how bones heal, and to apply the findings to clinical care.

"We want to make the problems resulting from fractures go away," Nam says. "The connection that's opened up for immunology, bone biology and fracture healing is substantial. In the future, a pharmacological therapy may be possible where you could potentially be able to give someone a drug at the time they break their bone and say, 'Take these for five days and you're good to go.'"

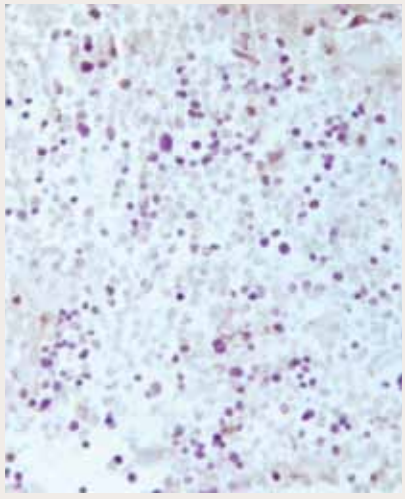
– ELENI KANAVAS

Nam's research was funded by the Canadian Institutes of Health Research, a Roscoe Reid Surgical Science Scholarship Award and the University of Toronto.

FRACTURE REPAIR IN ACTION



A microscopic image of the bone callus tissue three days after a fracture in normal mice shows abundant staining and presence of T cells (black arrows).



In contrast, in mice lacking T cells, this image shows a complete absence of T cell staining, with no recruitment of T cells in the bone callus tissue three days after a fracture.

IMAGES: SUBMITTED BY DR. DIANE NAM

Multiple Options

Globe-spanning trial settles question of which method of delivery is best for twins and expectant moms

Since the early 1990s, the success of in vitro fertilization (IVF) and other assisted reproductive technologies such as intrauterine insemination and ovulation-stimulating drugs has contributed to a dramatic increase in multiple births worldwide. In Canada, there were about 8,000 twin births in 1993; now, that number is about 12,000.

A question that remains unanswered, however, is: which is the safest way to deliver twins—vaginal birth or planned caesarean section (C-section)?

For eight years, Dr. Jon Barrett, director of the Women & Babies Research Program at Sunnybrook Research Institute (SRI), has led the Twin Birth Study, an international, multicentre trial, in a quest to answer this question.

"Studies up to this date have been very unclear as to the best method of delivery for the optimal outcome for the babies and the mother. Many studies were suggesting that caesarean section might be a better option for the second twin, [who] is more at risk," says Barrett, who is also chief of maternal-fetal medicine at Sunnybrook Health Sciences Centre. "But we also have years of history and experience where some studies suggest that a vaginal birth was safer."

Women carrying twins or multiples—triplets, quadruplets and quintuplets—are at increased risk of maternal illnesses such as gestational diabetes and high blood pressure, for which specialized care is required. Each year, 3,800 infants are born at Sunnybrook. Of these, more than 300 are multiple births and considered high-risk deliveries. Twin pregnancies complicate 2% to 3% of all births in many countries. They are also associated with higher rates of premature birth, low birth weight, newborn death and growth abnormalities than are single births.

TWIN BOYS ELIYAHU AND MORDECHAI WERE DELIVERED BY DR. JON BARRETT on Jan. 30, 2013 at Sunnybrook. For more photos of multiples visit sunnybrook.ca/research.

PHOTO: SUBMITTED BY FAMILY

Through an $8.6-million grant, Barrett and researchers at SRI's Centre for Mother, Infant and Child Research coordinated the largest randomized controlled trial for twin births ever done. They looked at 2,804 women who delivered twins at 106 hospitals in 25 countries between 2003 and 2011. Sunnybrook recruited 84 patients, the largest group among all of the centres in Canada.

The trial was designed to determine which method of planned delivery—vaginal birth or C-section—increased the risk of illness and death in women giving birth to twins between 32 and 38 weeks gestation with the first twin positioned head down. Women were randomly allocated to each group; 89.9% delivered twins by C-section, and 56.2% delivered twins vaginally.

Although public perception is that C-section is safer due to reduced risks

IVF

In some parts of the world, the incidence of multiple births is decreasing because of legislative laws controlling the number of embryos that are implanted in the uterus.

This is not so in North America, where multiple births continue to rise, with one exception.

In Canada, Québec is the only province that covers the cost of in vitro fertilization (IVF).

In 2010, the Québec government announced it would fund up to three rounds of IVF per couple. Funding would be contingent, however, on only one embryo being transferred at a time, to help reduce the number of multiple births. Twin births in the province decreased from 27.2% to 5.2% within the first six months of the funding program, according to the Canadian Fertility and Andrology Society.

associated with vaginal birth, such as birth asphyxia and trauma, Barrett found no benefits to justify either method as superior.

"The results show that planned vaginal birth seems to be as safe as a planned caesarean section for the babies," says Barrett, who is also an associate professor in obstetrics and gynecology at the University of Toronto.

He found that the infants were at an equal risk of severe illness or death in either delivery approach. Interestingly, the study showed that women in the planned C-section group delivered slightly earlier—common for twins—compared with those in the vaginal group. Moreover, the risk of death, serious illness or other significant adverse effects was the same for women in each group.

"It seems that whilst planned vaginal birth was not better for the babies, a C-section was not much more dangerous for the mothers, but the babies in the planned C-section delivered earlier, which is not good [either]," Barrett says. "In addition, why would someone [choose to] have surgery if it was not better for the babies, and it would affect her next pregnancy?" It is common for women who have a C-section for the first delivery to not be able to have a vaginal birth for subsequent deliveries.

Barrett says he wasn't surprised by the findings. "I'm delighted with the results because they fit in with my worldview of having babies. It's always been my bias that vaginal birth is safe for twins because if you deliver twins in the right place with the right people, then it's a safe procedure. We were very careful in the trial to make sure that those conditions were met."

There has only been one other randomized controlled trial that compared both delivery methods. It looked at 60 pairs of twins between 35 and 42 weeks gestation. Results of that study were inconclusive due to its small sample size.

DR. JON BARRETT EXAMINES KELLY NEWCOMBE, who is pregnant with twins. Barrett led an international study on twin births.

The study is timely. Barrett points out that with the rise in C-section birth rates for twins, vaginal delivery of twins could have one day become obsolete. "It was important to do this trial now because if we didn't do it, then we would have lost the skills necessary to do vaginal births, and by default it would have gone to caesarean section," he says.

Barrett and colleagues presented the results at the annual meeting of the Society for Maternal Fetal Medicine in February 2013, and have submitted a manuscript for publication in *The New England Journal of Medicine*.

To understand better the immediate and long-term outcomes of the Twin Birth Study, the team is conducting a two-year follow-up of the women and infants. They will look for developmental delay, cerebral palsy and other significant abnormalities in the infants at two years of age, as well as the effect of delivery method on the mother.

"We also want to look at the longer-term impact of vaginal birth on the mother's pelvic floor, [because] that's an area with a lot of interesting risk for incontinence," Barrett says.

The study was a massive effort that involved a large team of people to organize and collect data over the years from all of the centres. It lagged about two years behind schedule, because it was a challenge to recruit pregnant women with twins due to societal pressures surrounding C-section and vaginal deliveries. Barrett describes the journey as a humbling experience he was glad to be a part of as principal investigator. "We are very grateful to all the patients and doctors who participated in the trial," he says with a smile.

The Twin Birth Study is the first of its kind to provide reliable evidence that may change obstetrical practices, says Barrett. He encourages physicians and patients to read the results of the study and reconsider the options available for delivering twins.

His advice to expectant mothers: "[Unless] there is another reason they should have a caesarean section, then they should plan for a vaginal birth because the study shows it's as safe as a C-section without the surgery, and it allows the pregnancy to proceed a little bit longer."

- ELENI KANAVAS

Barrett's research was funded by the Canadian Institutes of Health Research.

PHOTO: **DOUG NICHOLSON**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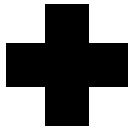
Do the Math

Hospitalize or not? Researchers develop model to help ER docs decide if a patient with heart failure is at risk of death in the near term



BY **ALISA KIM**
ILLUSTRATION BY **YAREK WASZUL**

It's a common scenario in the emergency room: a person anxiously seeks care because of chest pain and difficulty breathing. Upon examination, the physician notes the patient's legs are very swollen. A chest X-ray, blood work and an electrocardiogram, a test that records the heart's electrical activity, point to the cause: heart failure.

In North America, there are one million visits to the emergency department (ED) for heart failure each year. In Canada, heart failure claims more than 4,200 lives annually. While the condition can be tricky to identify—physicians must first rule out other causes of the patient's symptoms—harder still is determining the risk of death in the short term. If the risk is high, then immediate hospitalization is required; if the risk is low, then the patient can be discharged, with close monitoring.

"I think everyone who treats heart failure patients in the emergency room thinks, 'Can I safely send this patient home, or do they need to be admitted?' These days if you can avoid hospitalizing someone, you want to do that—it's better for the patient and for the system," says Dr. Jack Tu, a senior scientist in the Schulich Heart Research Program at Sunnybrook Research Institute (SRI).

Heart failure does not mean the heart has stopped working; in essence, it's a pumping problem: the damaged muscle cannot pump enough blood throughout the body to meet its needs. The condition is sometimes confused with a heart attack, in which an area of heart tissue dies when the flow of oxygen-rich blood is cut off. Heart disease, also called coronary artery disease, refers to the narrowing of the blood vessels to the heart, and contributes to heart failure and heart attacks.

In 2012, Tu and colleagues published a study in the *Annals of Internal Medicine* containing the first model to predict the probability of death in the short term among heart failure patients in the ED. The study is a rare collaboration between clinicians and researchers in cardiac and emergency medicine. It took place at Sunnybrook Health Sciences Centre and the Institute for Clinical Evaluative Sciences.

The Emergency Heart Failure Mortality Risk Grade is an algorithm that calculates the risk of death within seven days among heart failure patients coming to the ED. The model uses

Drs. Michael Schull (left) and Jack Tu in the emergency room (ER) at Sunnybrook are coauthors of a study examining risk of death among heart failure patients in the ER.

OPPOSITE
Dr. Douglas Lee, a scientist at the Institute for Clinical Evaluative Sciences, and lead author of the study.

routinely collected information like age, initial vital signs, clinical features and results from blood work to calculate the risk score; the higher the score, the greater the risk.

The tool is unique in that it can help ED physicians, including cardiologists, internists and emergency room doctors, formulate a patient's prognosis (the course or outcome of a disease) based on measurable data, versus clinical judgment alone.

"Heart failure is one of those conditions where we know some patients probably need to be admitted and some are safe to send home. But we don't know how to distinguish between those groups. I think [the tool] is helpful in saying, 'This patient is low-risk; I'm more comfortable sending them home. Or, this patient is high-risk, and we probably should bring them in," says Dr. Michael Schull, a senior scientist at SRI, emergency physician at Sunnybrook and a co-author of the study.

> "These days if you can avoid hospitalizing someone, you want to do that."

To develop the model, researchers used data from more than 12,500 patients who visited an ED in an Ontario hospital due to heart failure between 2004 and 2007. Patients were divided into two groups: one to come up with the model, the other to validate it. In each of the groups, two-thirds of the patients were hospitalized and one-third were discharged.

The researchers used data from the patients' charts to select the risk variables. The end point was death within seven days of initial presentation to the ED. Of the 30-plus variables they considered, the team narrowed down the model's risk factors to 10, some of which include age, arrival by ambulance, heart rate, oxygen saturation and the presence of cancer (see sidebar for full list).

The model accurately predicted the deaths within seven days of both hospitalized and discharged patients.

What sets this study apart from other prognostic models for heart failure patients is that it included patients discharged from the ED, who were also at risk of short-term death. The risk score thus may be useful to ED physicians because it can be applied to assist with the decision to admit or discharge.

"Prior to this, doctors didn't really have any tools to help them decide which patients needed to be admitted and which patients could be sent home from the ED. We thought this tool would be very useful to help doctors make those decisions," says Tu, who is also a cardiologist at Sunnybrook and a professor of medicine at the University of Toronto.

One of the challenges for ED physicians making this decision is the lack of criteria by which admission can be guided. The decision is left to their discretion as they consider the severity of the patient's symptoms, whether the patient has other illnesses, his or her response to initial treatment, and if the patient has social support.

"There's no standard way of approaching all those different factors, and different physicians do it differently. This is one area where there's a need for standardization in order to try and improve care," says Schull, who is also a professor at U of T.

Moreover, the wrong choice has serious consequences. "Emergency department physicians sometimes do not realize how sick [heart failure] patients are, and are sending them

PHOTO: DOUG NICHOLSON

home. On the other [end of the] spectrum, we've found that some patients who are hospitalized are very low-risk and perhaps may not have even needed an admission to hospital. There are clearly some safety issues with some patients dying at home, and some low-risk patients being admitted to hospital who may not need it," says Dr. Douglas Lee, lead author of the study and a cardiologist at Toronto General Hospital.

The tool could also result in big savings in health care spending. The average length of stay for routine hospitalization due to heart failure is eight days, at a cost of about $10,000, notes Lee. "Hospitalizations are probably the most expensive part of heart failure care. If we can avert hospitalizations in low-risk patients, that would be millions of dollars saved to the health care system," Lee says.

While the researchers say the tool is useful, they note it should not replace a clinician's judgment. "It's important to remember that it's still the physician's decision whether to admit the patient or not. [The risk score] doesn't capture every single factor in the decision to hospitalize someone or not. For example, if you have an elderly patient who doesn't have any family members to look after them, then even if they have a very low risk score you may want to hospitalize them for social reasons," says Tu.

The risk score calculator is available online and has had over 10,000 hits. The researchers are developing smart phone applications so that ED physicians can have the tool at their fingertips. Their plan is to have the "apps" available for users to download later this year.

A related research direction involves establishing concrete values for high- and low-risk heart failure patients. "Figuring out the risk of death is a great place to start," says Schull. "Exactly where the cut-off should be is where we need to do some more work. It would be nice to say these criteria mean admission versus discharge, as opposed to a range of risk."

The tool could also have an impact on health care systems outside Canada. Lee and Tu are working with American emergency physicians who have expressed interest in doing a study to see if the risk calculator works using U.S. patient data. The resource implications are even greater there, where, due to concerns over malpractice suits, an overwhelming majority of heart failure patients are hospitalized.

Lee says that although the tool is relatively simple, it could make a big difference, which speaks to why he got his PhD. "At the outset of my career, I had to make a decision: do I want to be a clinician-scientist or a clinician? I thought I could have more impact by doing research. Seeing patients and treating them is very important, but you treat one patient at a time. If you're doing research, you're helping thousands, maybe hundreds of thousands of people."

This research was funded by the Canadian Institutes of Health Research and the Heart and Stroke Foundation of Ontario. Tu also received support from the Canada Research Chairs program, through which he holds the Canada Research Chair in Health Services Research.

PHOTO: JACQUELINE FORRESTER

CALCULATE THIS

The Emergency Heart Failure Mortality Risk Grade is a tool to help doctors in their decision-making by providing an estimate of risk of death within seven days in patients presenting to the emergency department. Following are the variables used to calculate the risk score:

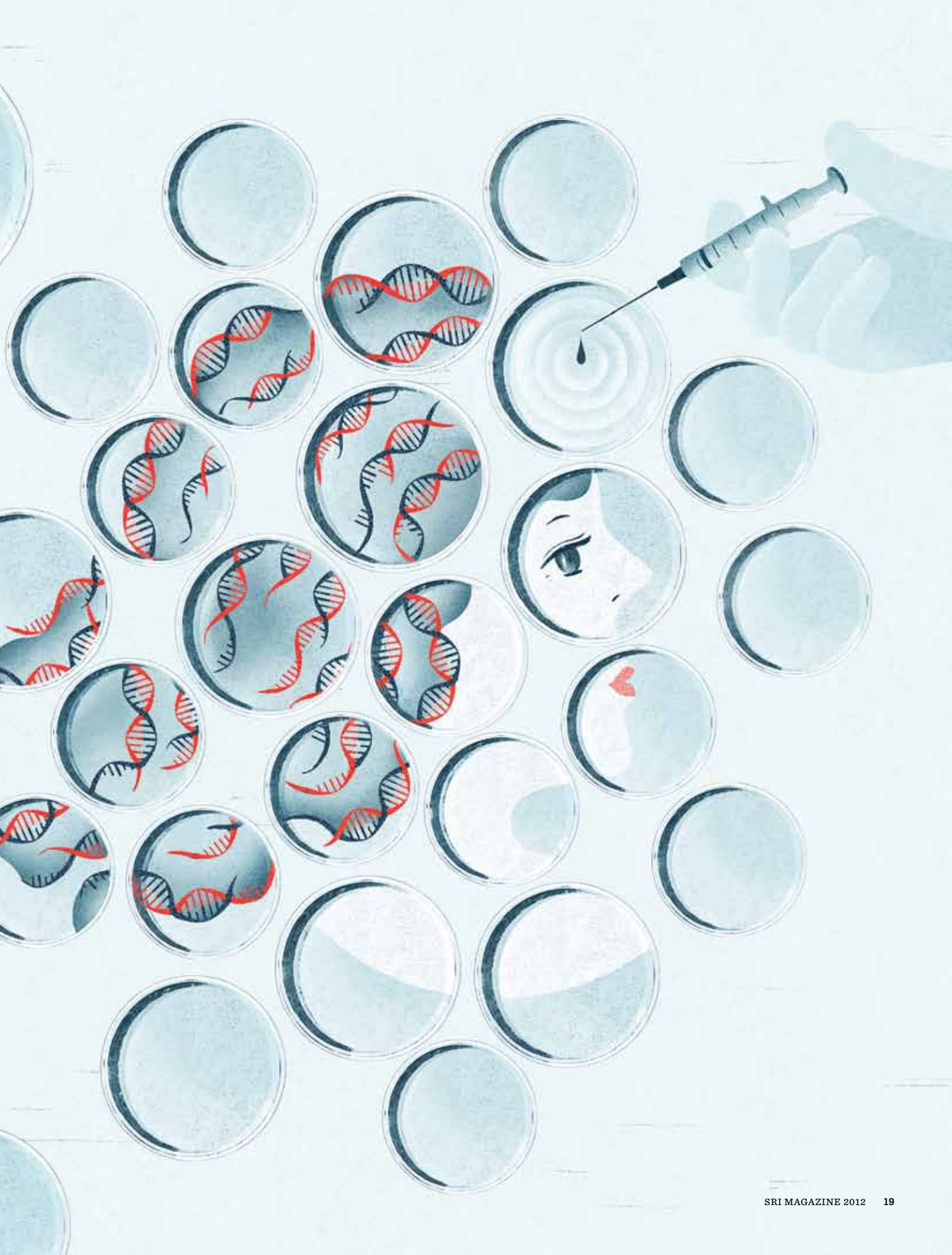
1. **Age**
2. **Arrival by ambulance**
3. **Triage systolic blood pressure**
   (a low number in a heart failure patient could indicate dysfunction of the left ventricle of the heart)
4. **Triage heart rate**
   (in heart failure, the heart beats faster to compensate for weaker pumping power to maintain blood flow around the body)
5. **Triage oxygen saturation**
   (lower saturation reflects breathing problems and build-up of fluid in the lungs)
6. **Potassium concentration**
   (an abnormal blood level can cause irregular heart rhythms; very high or low values can cause the heart to stop beating)
7. **Creatinine concentration**
   (elevated blood levels indicate abnormal kidney function, which is associated with an increased risk of death)
8. **Troponin level**
   (measures proteins released in the blood when the heart muscle is damaged)
9. **Any active cancer**
10. **Use of metolazone at home**
    (a diuretic, or water pill, used to lower blood pressure and prevent excess fluid accumulation in heart failure)

The risk score is online at www.ccort.ca/EHMRGTerms.aspx

ON TARGET?

The promise and challenges of molecular therapies

BY **STEPHANIE ROBERTS**
ILLUSTRATION BY **GRACIA LAM**



Two paintings hang inside the office of Dr. David Andrews. They show patterns of dots. Some look like oversized peppercorns scattered on the canvas; others swirl together in cinnamon bun shapes.

They catch the eye. If that eye is yours or mine, then the patterns probably won't hold any meaning. They're attractive (or not). To the eye of the indigenous artists in Australia who created them, however, they hold bags of meaning. "That pattern goes back about 6,000 years, and it depicts an area in the northwest of Australia where it gives the locations of safe places to camp and places to get water in an area that is inhabited by highly toxic lizards," he says, pointing to the swirliest of the two.

Andrews explains that the dots represent an aerial view of venom-secreting bushes in the desert that kill everything around them. "Because I'm not aboriginal, there's no way I could recognize where that is, but aboriginals know the location from that drawing. They know where that is," says the head of Biological Sciences at Sunnybrook Research Institute (SRI).

The meaning is there, then, for those in the know: the dots provide a kind of map for navigating through dangerous terrain; they mark where to go, if not exactly how to get there. It's a journey beset by pitfalls, but those who reach the destination are rewarded with safety, maybe even life.

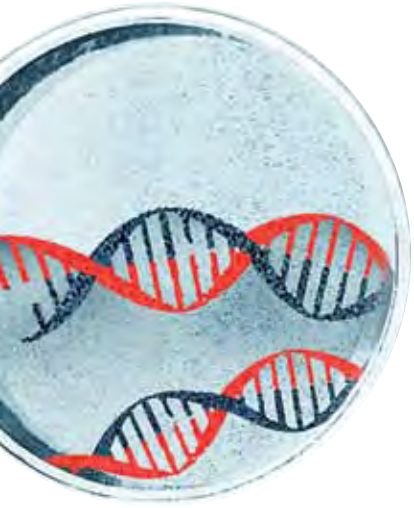
Molecularly targeted therapy is one of the most avidly pursued areas in medicine. At its most basic, it works by attacking a specific molecule or mechanism. This could be a gene mutation or it could be a biological process, like blood vessel growth. This is in contrast to therapies that work nonspecifically, like chemotherapy, which usually attacks DNA or structural components of cells. Targeted therapy seeks to replace today's dominant but variably effective treatments that fecklessly poison healthy as well as diseased cells, and in doing so not only manage disease better, but also banish the effects that are the dark companions of too many therapies.

How are we doing in terms of living up to this potential? We're making progress, but we have a long way to go. Unlike what the paintings in the office of Andrews portray, there is no map. Even if there were, there are no people who know how to read it, in part because the targets, found deep within our genome, are continually shifting (more on that later). And, the genome is a very big place.

Certainly, there are some spectacular successes. Many are in cancer, where the science of genetics is most advanced; we now know that cancer is not one disease defined by its site in the body, but many diseases more usefully defined by gene mutations.

There are also triumphs outside cancer, such as the discovery by Canadian researchers of numerous mutations in schizophrenia, which has jolted people into reimagining this brain affliction as several disorders. Similarly, a U.K.-based group has shown that type 1 diabetes is multifold. On the back of this, they have developed a test for newborns that determines if the babies have a mutation that causes one form of the disease. If they do, then they can be given an oral anti-diabetes drug, rather than insulin—a life-altering benefit.

Within cancer, trastuzumab, trade name Herceptin, is one of the best-known targeted therapies. It works by meddling with the signalling of the HER2 receptor, a protein that is overexpressed in the cancer cells of about 20% of



women with breast cancer. Patients' tumours can be tested for HER2 expression; if positive, then they are candidates for Herceptin, which studies show reduces rates of recurrence, increases odds of survival and helps stop cancer from spreading.

Gleevec (generic name imatinib) is a small molecule inhibitor that has transformed the outlook for patients with chronic myeloid leukemia, a rare cancer that affects white blood cells. Patients given it early in their disease cycle have gone from a state where 30% would die within five years of diagnosis, to 95% living 25 years or more.

Dr. Arun Seth is hoping his research might lead to similar good news. A senior scientist at SRI, he has dedicated his career to untangling the molecular basis of breast and prostate cancer. Twenty years ago, while at the National Institutes of Health in the U.S., he was the first to clone insulin-like growth factor binding protein 7, or IGFBP7, from breast cancer cells, showing that it played a role in this disease. Then about 10 years ago, now at SRI, his lab discovered that the production of IGFBP7 falls as the severity of breast cancer goes up: the more invasive the cancer, the less this protein is expressed. They began to study it even more intently.

This protein is one of the insulin-like growth factor (IGF) binding proteins that occur naturally in our bodies. As a class, binding proteins are part of healthy cell regulation. As their name suggests, they attach to growth factors to keep them away from their receptors, unless otherwise indicated. "They release growth factors only at those times when the receptor needs to be activated, so they are keeping growth factors and receptor signalling in check most of the time," says Seth.

Different growth factors have different specific roles, but as a whole, managing cell growth is their thing. How they do this is known to all biologists: they bind to IGF receptors, which in turn promote cell survival and trigger cell growth. When it's part of normal regulation, it's all good. Sometimes, though, it's not.

PHOTO: **DOUG NICHOLSON**

DR. DAVID ANDREWS, SHOWN WITH GRADUATE STUDENT ELIZABETH OSTERLUND, is working on a small molecule he thinks may have therapeutic potential. To help him and others find and validate such drug targets, he is building an image-based platform at Sunnybrook Research Institute that can knock down hundreds of genes of interest one at a time and analyze what happens—completely robotically.

DR. ARUN SETH HAS DISCOVERED A PROTEIN
that suppresses the formation of tumours in breast cancer cells. The protein, IGFBP7, could be a future targeted therapy, but there are many questions still to answer.

Unchecked cell proliferation is a calling card of cancer, and scientists have long known that activation of the IGF1 receptor spurs growth of breast, prostate and other cancers.

It is against this backdrop that Seth's recent finding on IGFBP7, published by the high-status journal *Science Signaling* in late 2012, was a landmark. "The real function of this protein wasn't known until we published that *Science* paper. We discovered that it directly binds to the IGF1 receptor," says Seth. "It was a totally new, totally unexpected, finding."

In bypassing the growth factor and binding to the receptor, the protein cuts out a step to assert itself at the source, gumming up the receptor and thus stopping cells from growing or even surviving. Pinpointing this mechanism—and upending everything that was known about how it works—was a crucial bit of knowledge. More tangibly, it shows how IGFBP7 could be used as a therapeutic in tumours that need IGF1 to thrive.

In a parallel study to evaluate this protein's therapy potential, Seth's lab grew human breast tumour cell lines, and then put them into mice, where they formed tumours. He injected IGFBP7 into some of the mice; others served as "untreated" controls. A few weeks later, they found the protein had suppressed tumour formation, big time.

"We could see the tumours where we injected the protein were 10 or 20 times smaller than those in the control group. When we analyzed the tumours, we could show that those tiny tumours have huge amounts of IGFBP7 in them—so [the protein] was actually inhibiting tumour cell growth," says Seth. They also determined that it was kick-starting apoptosis, or programmed cell death, and subduing the cells. "When it binds to the cells, the cells just sit there. They don't grow. They senesce. And when you remove IGFBP7, then they grow," he says.

His lab is now doing next-generation sequencing on the cell lines he used in that study. Sequencing gives information about differences in the genetic material of what is being analyzed—a molecular signature of sorts. It has been instrumental in targeted therapy success stories, because it enables people to identify biomarkers that can then help with diagnosis, guide the choice of treatment and predict outcome.

Seth's use of it has led to discovering that not all types of the tumours they're studying respond to the protein. "What we found is that IGFBP7 is not going to cure or inhibit all types of breast cancer, only certain types." One of these is triple-negative breast cancer, so-called because it is driven neither by over-zealous hormones—namely, estrogen or progesterone—nor by the HER2 receptor; thus, it cannot be treated with therapies that target hormone receptors or production, or HER2.

"We got lucky with IGFBP7, and we showed in another paper that the triple-negative cell line is completely inhibited with IGFBP7," says Seth. Given how invasive this tumour type is, it's an exciting discovery.

All of this bolsters the case for IGFBP7 as a future targeted therapy, but although he is hopeful, Seth hasn't uncorked the champagne yet, as he sometimes does when he gets a big grant or publishes a meaningful paper to celebrate with his lab. There are still questions to answer and issues to surmount.

"I would say drug resistance and metastasis are the two biggest things that limit the success we've been able to make in treating advanced disease," says Dr. Bob Kerbel, senior scientist at SRI.

Metastasis is when cancer spreads from its origin to distant places in the body, typically to the lungs, liver, brain and bones. If a primary tumour is "localized," or hasn't spread, then the outlook is often good. "A scalpel blade will cure the patient, so to speak. You remove the tumour and they're sometimes cured," Kerbel says. Or, if there's "minimal residual disease," microscopic tumours left behind after removal of the primary tumour, then treatment usually works. To wit, the five-year survival rate for skin melanoma is 98%. Once it has spread, that rate plummets to 16%. Prostate cancer has similar numbers: a nearly 100% five-year survival rate is smashed to 28% if the cancer has wandered. Metastasis isn't uncommon. In breast cancer alone, about 30% of women will develop it.

Added to this mess is resistance, when drugs stop working. Kerbel explains: "When chemotherapy was initially developed in Boston, for example, for cancer in children, there were some fantastic results right away: tumours would melt that previously had been untreatable. "So that was a breakthrough, but what was then noted is that in a high proportion of cases, even though the children lived longer, the tumours would recur

PHOTO: CURTIS LANTINGA

and no longer be responsive to the same therapy. They became resistant," he says.

Kerbel says that for all their potential, even the newest targeted therapies—65 years from when chemotherapy was first given to those children with leukemia—can't dodge the issue of resistance. It's almost all down to our genome, that massive, complex and evolutionarily canny collection of genetic material that defines us as individuals.

"Cancer cells have this phenomenal, frightening ability to become resistant. Just as you can find so-called 'driver' mutations in a cancer cell that might lead to a new drug targeting the products of such mutations, like the gene being amplified for HER2, which is a good thing, that same process of mutation can do something you don't want: a cancer cell might mutate in such a way that a clone from that cell arises that is no longer sensitive to the drug.

"When you analyze what happened, it turns out that in some cases the mutant protein has mutated again, the mutant gene has mutated again," he says, incredulously. "Now, as a result of that new mutation, the drug is prevented from doing what it was designed to do."

Adds Andrews, "Genomic instability is the hallmark of cancer. By the time you have a tumour large enough to detect, you have millions of phenotypes, so what you're doing isn't necessarily evolving, but selective, so if you kill 99.9% of the tumour, there's still lots and lots left, and if those [cells] are resistant because their genetic makeup is different and doesn't fit the biomarker for the targeted therapy, then you won't kill those [cells]."

This wily capacity of cancer to evade defeat is a formidable challenge and part of the rationale behind a way of delivering therapy that Kerbel has pioneered for almost one-half of his 30 years as a cancer biologist. Called "metronomic chemotherapy," it entails drugs administered in low doses over long periods without prolonged breaks. It works in part by halting new blood vessel growth, a process called angiogenesis. Kerbel is investigating its use alone as maintenance therapy, and paired with drugs that target blood vessel growth, like Avastin (bevacizumab), which works by blocking vascular endothelial growth factor, or VEGF. In both cases, the idea is to sever a tumour's lifeline, its blood supply, over a lengthy, vacation-free period as a way to make drugs less noxious, thwart resistance and, one hopes, improve patient survival.

Avastin is approved for advanced forms of colorectal, kidney, lung and brain cancer in North America. In Europe and Asia, it's also approved for breast and ovarian cancer. A clinical trial of cervical cancer just ended with good results, and hundreds more trials are ongoing. "Avastin is turning out to be one of the most wide-spectrum cancer drugs on the market. If you look at the number of the types of cancers it's been approved for, it's impressive," says Kerbel, though he also notes the drug is expensive and can have undesirable side effects.

"Genomic instability is the hallmark of cancer."

The biggest qualifier? "If there's an overall survival advantage, it might be no longer than two to five months, on average. Now, some patients will do extremely well, living for years longer, and some not at all," says Kerbel.

Again—resistance. "What can happen is VEGF may be the major driver of tumour angiogenesis in a patient's cancer, so you give the drug with chemotherapy, and it works, and the tumour changes, and it says, 'OK; we're going to make something else that drives angiogenesis,' because VEGF is not the only factor that drives angiogenesis. There are likely dozens!"

It also underlines that most targeted therapies need a sidekick, standard chemotherapy, to work. Kerbel calls this "one of the great, ironic things" about targeted therapy. "It was designed with the expectation it would replace bad, old, not-so-targeted chemotherapy. In the main, it has not. There are some exceptions, but a lot of the new targeted drugs, like Avastin and Herceptin, they're normally used initially with chemotherapy, and if you don't use that combination, the targeted drugs don't work well at all," he says—which returns us to the *way* the therapy is delivered and the case for metronomic chemotherapy.

"We're arguing that the nature of the chemotherapy partner, the backbone—what the drugs are and how they are administered—may have an impact on how well the combination of chemotherapy plus the targeted therapy works," says Kerbel. The metronomic chemotherapy concept is being tested in about nine Phase 3 clinical trials. Results from one such trial were announced at the 2013 American Society of Clinical Oncology annual meeting. The Dutch study showed that metastatic colorectal cancer patients benefited from receiving long-term maintenance therapy comprised of continuous, low-dose, daily metronomic therapy plus Avastin after receiving conventional higher-dose chemotherapy and Avastin.

Clinical trials are an integral part of the equation. That they're problematic isn't just because they're expensive—though they are—or because they don't get enough funding—though they don't—but because their design is struggling to keep up with genomics advances.

Science tells us that disease—breast cancer, say—is many diseases. Even triple-negative breast cancer, which accounts for 15% of all breast cancer at most, has at least six genetic subtypes. Thus, the old model of enrolling 5,000 women with breast cancer in a trial to test a targeted drug doesn't cut it. Odds are, the drug won't show an effect, even if one exists.

"Statistically, if all breast cancer patients had been recruited into the

Phase 3 clinical trial of Herceptin, it would have failed, because only 15% have the target, and of those 15%, only half of them respond. That would mean out of 100 patients, in a nonselective trial, roughly 10% would benefit from the drug. The other 90% wouldn't," says Kerbel.

Science also suggests that most targeted therapies will work best in combination, so it makes some sense to test them this way, which is not as simple as it sounds, for a host of reasons. Adding to their complexity won't help trials get cheaper or better funded. Building smarter, more flexible trials is essential, however, to building better therapies. Using biomarkers to enrol patients on the basis of biomarker status, and then tracking them throughout, analyzing who does and does not respond, will help greatly. Sophisticated genomics tools are increasingly enabling researchers to do this.

"You need to develop the biomarker together with the targeted therapy, so that when you do your clinical trial, you're already in a specific subset of patients, and in that case if you have the biomarker, you may be doing the clinical trial with the conventional therapy that they're already getting, and saying, 'Now can we add this to this very specific cohort as opposed to the others and see if we can see a benefit?'," says Andrews.

Better preclinical models are also part of the solution.

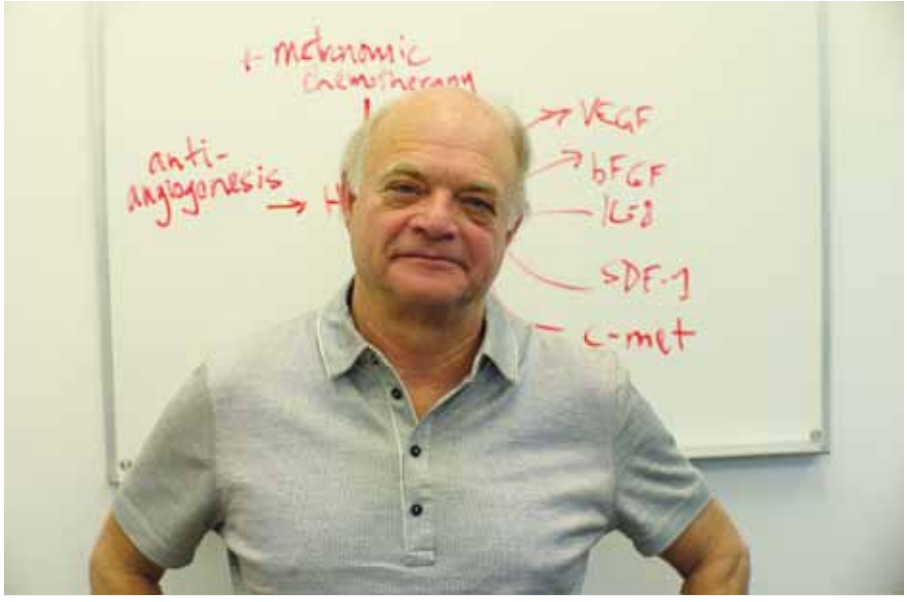
Scientists use animal models to test promising drugs. With these results, companies decide if they will move a drug into patient trials. They are, therefore, vital. The problem is, many drugs shown to work in preclinical or small, early-stage trials fail during larger, later-stage trials, says Kerbel. "How come the mouse models overpredicted what happened in the clinic? And how come the early Phase 2 clinical trials looked like they might be encouraging, and then you go to the large Phase 3 randomized trial and [the drug] bombs?"

Part of the problem, he says, is that much preclinical research is on localized, primary tumours, not metastatic disease, which is far more difficult to treat successfully, and despite that most patient trials enrol people with advanced cancer. He started a program at SRI to develop models with metastatic cancer, and he tests therapies in these, thus mirroring the conditions of clinical trials and real life. He knows most drugs they test won't work, because the disease is so advanced. They look for exceptions, and when they find them, they connect with oncologists at Sunnybrook and elsewhere to begin the process of testing them. He also shares his models with other researchers all over the world.

A recent paper from Kerbel's lab shows the fascinating implications of this focus. In the study, they redid the preclinical experiments of the drug Sutent, an anti-angiogenic small molecule approved for kidney cancer. It was once touted as the next big thing for breast cancer after its preclinical tests showed a robust benefit for it alone or plus standard chemotherapy, which helped convince the drug maker to fast-track it into randomized controlled trials—not one, but four "gold standard" multimillion-dollar trials.

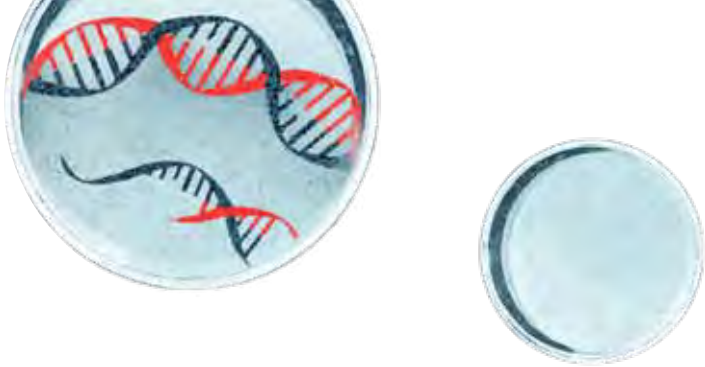
"They all failed. Every trial failed, and the drug has been dropped from clinical development in breast cancer," exclaims Kerbel. "For me, that is an example of one of the most compelling examples of something that worked in mice, but didn't work in the clinic."

Kerbel's lab reproduced the original methods that led to Sutent's clinical testing, but also added a metastatic model of breast cancer. We bow heads over the paper as he explains the graphs depicting the results. The lines show clearly what the original experiments on primary tumours found: the drug seems to work. It shrinks tumour volume, and the mice live longer. It's striking. The graph for the metastatic model, however, tells a different story: the mice don't live longer. The lines drop off. The drug doesn't work. "It bombed," says Kerbel. "Basically, we recapitulated what happened in the clinic.



DR. BOB KERBEL IS A PIONEER OF METRONOMIC CHEMOTHERAPY, the administration of low doses of drugs given over a long period without prolonged breaks. It is here he places his hope, imagining a time when cancer may not be cured, but manageable over the long haul, with good quality of life.

PHOTO: CURTIS LANTINGA



"It's only one model, but if we're right, the implications are huge, because we're saying you'll get a better idea of the effect of targeted therapies or for that matter chemotherapy, or when combining them, when you replicate the circumstance of metastatic disease, because all Phase 1 trials deal with such bad disease, virtually all Phase 2 trials deal with bad disease and most Phase 3 trials are also advanced, metastatic disease trials."

As important as improving preclinical models and trial design are, they don't get to the why of metastasis or resistance, and how to prevent them—or how to find better targets. For that, more precise tools are needed. That's where Andrews

"You need to develop the biomarker together with the targeted therapy."

connects with Kerbel and Seth, as well as other scientists at SRI.

Andrews is building a platform that will enable him and others to identify new targets to treat disease and associated biological processes. At its heart is the most advanced fully automated high-content screening microscope in the world, the FLIM Opera, which Andrews built. It is the only tool that can measure quantitatively in live cells proteins interacting with each other, which gives insights not possible with other technologies, such as if a drug is working.

Paired with this are custom-arrayed RNA-interference lentiviral libraries—basically a massive collection of genomic material. They offer a way to tailor a gene-finding mission, robotically. "For each scientist, we can assemble a custom library to knock down all of the genes that are relevant to the biology that they're studying," explains Andrews. Together with powerful image analysis software that his lab has developed, the platform is as close as one can get to a genome navigation tool for target discovery.

Take Kerbel's research on brain metastasis. As Andrews explains, Kerbel has developed a model of brain metastasis where 150 genes have been found as having changed in morphing from a pre- to post-metastasis state. "The infrastructure will allow us to knock out all of those genes one at a time, or in some limited combinations, and then using a cell culture model ask which ones of those genes have an effect on the cells, because you can't afford to test 150 genes one at a time in the mouse model to look for metastasis.

"Then you can ask, of those 150 changes, which are crucial for getting that metastatic phenotype? Those are your drug targets. Once you know which ones are required, then you can say, what's known about these? Which ones are the best targets? Then you can try and identify a small molecule that will inhibit that protein and then demonstrate to pharma whether you've actually identified a druggable target."

Andrews will use the "knockdown technology" to advance his work on interrupting protein-protein interactions as a way to reinstate cells' natural—but in cancer, faulty—impulse to commit suicide via apoptosis. He's identified a small molecule that he thinks has great cell-killing potential, but the class of proteins to which it belongs has a tendency to overexpress another protein that could make the cancer cells resistant to the small molecule. "It's what comes up with most targeted therapies: there's lots of ways around apoptosis, and tumours use most of them," he says. He will use the technology to see what's going on, and then find a compound to suppress that protein.

"It's very impressive," says Seth, who will use the system to watch how IGFBP7 does its thing in real time. He'll then combine these data with those from his next-generation sequencing of patient samples to distinguish which tumours will and will not shrink in response to the treatment, and from there figure out with which other compounds to pair the therapy, to be able to target tumour types defined by their molecular profile, in what he insists is the only way forward: "a multi-pronged approach."

On this, everyone seems to agree. First, targeted therapies will work best as part of a cocktail. With few exceptions, they will not be super drugs, able to take out disease with one perfect hit. Even before then, though, the processes of diagnosing, treating and tracking the outcome of disease need to be integrated, to use the knowledge streaming out of genomics and related fields. Globally, more than 70 research organizations (including Sunnybrook) in 40 countries have partnered to share genomic and clinical data. This is certain to accelerate the pace.

The goal is to achieve a standard of care when patients seeking treatment for any disease will have their genome sequenced toward delivery of much more precise treatment. Results would guide which targeted drugs to give, to ensure the best therapeutic response with the least toxicity. Recovery would be monitored biologically, allowing for therapy changes as needed, for example, if resistance emerges. Patients' lives would be drastically prolonged, and in some cases saved; quality of life, enriched.

An ambitious journey, to be sure. Are we on course? "I'm always optimistic," says Andrews.

Andrews' research is funded by the Canadian Cancer Society Research Institute (CCSRI), Canadian Institutes of Health Research (CIHR) and Ontario Institute for Cancer Research (OICR). Infrastructure support comes from the Canada Foundation for Innovation (CFI) and Ontario Ministry of Research and Innovation (MRI).

Kerbel's research is funded by the Canadian Breast Cancer Foundation (Ontario), CCSRI, CIHR, National Institutes of Health (NIH) and OICR. He holds the Canada Research Chair in Tumour Biology, Angiogenesis and Antiangiogenic Therapy.

Seth's research on targets in breast cancer is funded by the Canadian Breast Cancer Research Alliance, CIHR, National Cancer Institute of Canada and NIH. Infrastructure support comes from the CFI and MRI.

WHY PAY LE$S?

Quality health care doesn't come cheap, says research that links hospital spending with outcomes—but there's more to it than dollars in, care out

PHOTO: DOUG NICHOLSON

Everyone loves a bargain, but sometimes you get what you pay for; it's an old adage, and usually true, except if the "product" in question is hospital-delivered care.

When it comes to health care, "it's not how much you spend, it's how you spend it," says Dr. Thérèse Stukel, a scientist in health services and policy at Sunnybrook Research Institute.

In a provincial study on hospital spending, Stukel and colleagues investigated whether seriously ill hospitalized patients who were admitted to higher-spending hospitals in Ontario received better quality of care and had better outcomes compared with patients admitted to hospitals that spend less.

They did.

The study assessed patients admitted to hospital for the first time with a heart attack, congestive heart failure, a hip fracture or colon cancer between 1998 and 2008. Results showed patients in higher-spending hospitals had lower rates of death and readmission, fewer repeat cardiac events and higher quality of care. The paper was published in the *Journal of the American Medical Association* in 2012.

Stukel examined Ontario's health care system, which, unlike that of the U.S., has global hospital budgets, selective access to medical technology, and fewer specialists and specialized services. Hospital spending was categorized into low, medium or high. Total costs related to study patients were measured for all hospital, emergency department and physician services over one year following patients' date of admission, averaged to the hospital level and attributed to the index hospital of admission. This measures the intensity of a hospital's medical spending—how resources are spent on similarly ill patients—during the year, based on the average adjusted spending for hospital, emergency department and physician services.

"We basically saw that hospital spending varied by twofold across hospitals for similarly ill patients," says Stukel, who is also a scientist at the Institute for Clinical Evaluative Sciences. "Highest-spending hospitals spent twice as much in one year than the lowest-spending hospitals."

Spending intensity for the acute care index ranged from $19,300 to $32,580 per study patient over the year.

Stukel found that higher-spending hospitals in Ontario were typically large teaching or community hospitals located in urban areas, and were associated with regional cancer centres. They offered specialized services, such as onsite cardiac catheterization (an advanced procedure where a catheter is inserted into the heart to diagnose or treat heart conditions), cardiac surgery and diagnostic imaging, including computed tomography and magnetic resonance imaging. These hospitals also had more nursing staff, who provided, on average, 30% more inpatient nursing hours. Attending physicians were more likely to be specialists or general internists who treated high volumes of these conditions.

Moreover, patients admitted to higher-spending hospitals had longer stays and were less likely to be admitted to an intensive care unit. They also had more visits from medical specialists while in hospital, and cardiac patients were more likely to receive cardiac interventions and medications.

"What's driving some of the spending is that everyone wants access to more high-tech services [such as] diagnostic testing, and equipment is getting more expensive and complicated," Stukel says. "These are things that are not exported easily to a low-spending, small, rural hospital."

Yet, it's not just about access to higher-cost or more resources. In a similar study Stukel and colleagues conducted a decade ago examining the U.S. health care system, they found that greater hospital spending in the U.S. did not lead to better patient outcomes.

"The U.S. is the highest spender on health care," Stukel says. "They spend 50% to 60% more per capita than anybody in the world."

She says that despite "scarce resources" in this country, Canada is spending more efficiently and effectively on its health care system than is the U.S. Accordingly, she cautions that the results of this study do not imply that spending more will lead to better patient outcomes.

"The public needs to understand that it's not just about infusing more money into the health care system. We need to spend resources wisely and where it provides benefit to patients," she says. "There's a limit to how much health you can buy with more spending, and it can have a marginally small effect on outcome improvement."

- ELENI KANAVAS

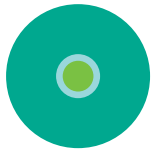
Stukel's research was funded by the Canadian Institutes of Health Research, National Institute on Aging, and Ontario Ministry of Health and Long-Term Care.

How Canada stacks up against the U.S. and the average across the 34 Organisation for Economic Co-operation and Development (OECD) countries when it comes to health care

Overall health spending per capita ($USD)

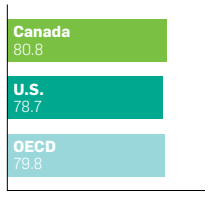
Canada	U.S.	OECD
$4,445	$8,233	$3,268*

Number of magnetic resonance imaging scanners in hospitals

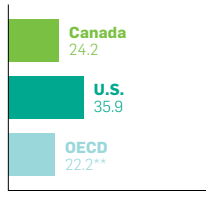


Canada	U.S.	OECD
218	5715	470^

Average life expectancy (years)



Obesity rate among adults (%)



Rates of obesity are rising among OECD countries, and this condition is set to put serious strain on future health care spending, owing to its association with health conditions like diabetes and heart disease.

* Based on the 29 OECD countries with data
^ Based on the 22 OECD countries with data
** Based on the 15 OECD countries with data
Source: OECD Health Data 2012: www.oecd.org/health/healthdata

Dr. Victor Yang operates on David Spencer on Apr. 11, 2013. Spencer, who has since made a full recovery, had a rare condition that can lead to bleeding in the brain and brain damage.

The Medical Innovators

Scientist by day, clinician by, well, day, too—and to that mix, add entrepreneur. How two original thinkers are devising solutions to complex health conditions

BY **ALISA KIM** PHOTOGRAPHY BY **CURTIS LANTINGA**

Thomas Edison, a pioneer of the motion picture camera, electric light bulb and phonograph, famously said, "Discontent is the first necessity of progress. Show me a thoroughly satisfied man and I will show you a failure." Edison, who held 1,093 U.S. patents, was uncommonly prolific, but his dissatisfaction with the status quo is characteristic of all inventors.

When Dr. Victor Yang was in the final year of his undergraduate engineering science studies, he was developing an imaging system for surgery to remove brain tumours. Although his system met the design specifications, it was cumbersome and unsuitable for the operating room (OR). When he asked how he might improve the design, Yang's mentor, a neurosurgeon, told him if he wanted to build something neurosurgeons would use, then he'd have to become one.

So he did.

"Engineers and clinicians speak different languages," says Yang, newly recruited as a senior scientist to the Brain Sciences Research Program at Sunnybrook Research Institute (SRI). "I'm happy to be the bridge, to help translate for each group, and articulate things that wouldn't have been [said] otherwise."

Yang is an engineer, physicist and neurosurgeon. He dedicates most of his time to research. One day a week, he treats patients with neurovascular conditions

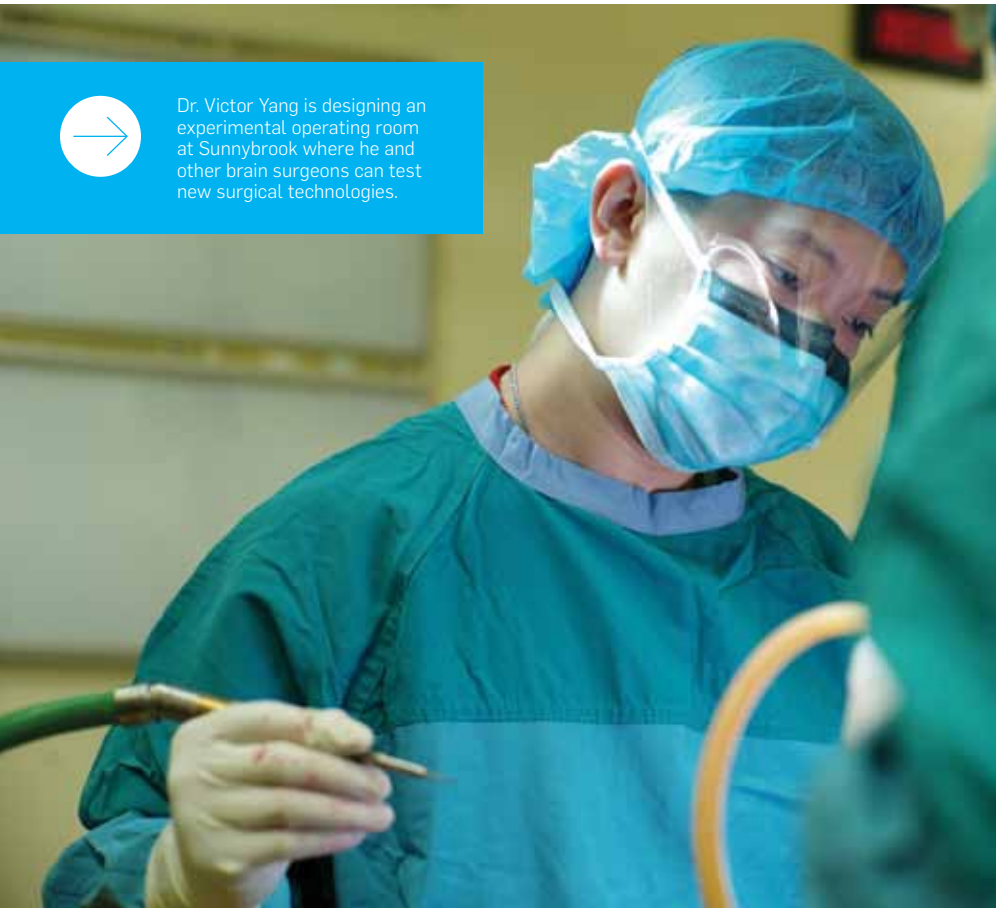
due to stroke at Sunnybrook Health Sciences Centre. On these days, he can be found dislodging a blood clot in the brain or neck artery, the cause of ischemic stroke. Or, you might find him in the OR, removing a tangle of abnormally formed blood vessels leading to hemorrhagic stroke, or bleeding in the brain.

He joined SRI for the opportunity to tether his research and clinical activity. Yang is designing an experimental OR at Sunnybrook in which surgeons can test new technologies, including ones he developed. He wants to maximize the OR's research potential while maintaining clinical functionality. "Even if you have motivated surgeons who want to be involved in engineering research, the moment you interrupt their workflow, this whole concept falls apart," he says. Thus, the experimental OR will be indistinguishable—at least superficially—from a typical OR.

Yang's area of expertise is biophotonics, the use of optical methods—light, basically—to study biological systems like people. He is developing technologies that harness the power of light to detect and diagnose disease, and monitor response to therapy.

His inventions are based on optical coherence tomography (OCT), which works in a similar fashion to ultrasound, but instead of sound waves bouncing back from tissue, light waves are reflected from tissue. These "echo" time delays of light are collected and analyzed. "We measure where they are coming from, how bright they are, and then we make a picture," says Yang, who is also an associate professor of surgery at the University of Toronto.

Optical coherence tomography, which images at the micron scale (one-thousandth of a millimetre), was developed for ophthalmology to allow doctors to see a patient's retina in detail, noninvasively. Scientists are now studying its potential for other uses. Yang adapted the Doppler technique used in ultrasound to study blood flow in large vessels, to OCT, to visualize the microvasculature, exquisitely small vessels of the circulatory system that are impossible to see noninvasively. These vessels—microns in diameter, 200 times smaller than the head of a pin—and their blood flow patterns can provide important clues in the progression of disease, Yang says.



Dr. Victor Yang is designing an experimental operating room at Sunnybrook where he and other brain surgeons can test new surgical technologies.

He is developing technologies that harness the power of light.

In OCT, the Doppler effect is the ever-so-slight change in colour—one fraction in one trillion—that is observable when light is reflected from moving red blood cells. When red blood cells move toward the optical fibre, the light frequency is a little higher; when they move away from it, a little lower. Where Doppler OCT prevails over ultrasound is in its ability to detect the small frequency shifts generated by slow-moving red blood cells.

"With Doppler OCT, red blood cell movement produces a larger frequency shift than that resulting from ultrasound, so it's easier to detect. The red blood cell is basically crawling, and you can see flow rate and measure it. We can actually see red blood cells moving to their neighbour positions; it's very sensitive," he says.

The resolution of Yang's Doppler OCT technology is seven microns, the size of a red blood cell. His team was the first to use Doppler OCT preclinically to study blood flow in the carotid artery, which delivers blood to the brain and head. At SRI, Yang will study plaque buildup in the carotid arteries of patients using a fibre optic catheter. He'll be looking for stroke-causing plaque lesions and their associated capillaries, which also supply blood to the carotid artery wall. He'll also use Doppler OCT to look for relationships between abnormalities in the retina and cerebrovascular disease in patients with dementia.

As Yang has also shown, the technology can detect cancers of the lung and gastrointestinal tract. He has used it to study small vessel characteristics associated with Barrett's esophagus, a precancerous lesion that leads to gastrointestinal cancer,

and is working with the B.C. Cancer Agency to use Doppler OCT to assess microvasculature blood flow patterns in the lung for early detection of lung cancer.

In addition to seeing how cancer is progressing, Doppler OCT can be used to track if antiangiogenic therapy, which aims to stop new blood vessel formation in tumours, is working. "You want to monitor how tumour cells are growing, how they're getting their nutrients," says Yang. "Imaging these will allow you to assess whether you have the right treatment and the right response."

Another way in which Yang has been inspired by ultrasound is by applying the "multifoci" technique to create the world's first multibeam OCT system. Phased-array ultrasound uses a probe made of many small elements that send and receive high-frequency sound waves. A computer steers these sound waves and maps returning echoes to produce a cross-sectional image with multiple focal points. Similarly, Yang's multibeam OCT technology uses multiple emitters and receivers of light; compared to single-beam OCT, it enables greater depth of focus over a large field of view without sacrificing image resolution.

In 2007, Yang licensed this invention to Michelson Diagnostics, a British company. Dermatologists now use it to detect skin cancer and other abnormalities. He says he hopes it will be used to monitor response to treatments like radiation therapy, especially on delicate areas of the face where biopsy is undesirable.

Yang holds 15 patents, and says getting inventions to patients would be impossible without commercialization. "You have to commercialize [a technology], so that some company can manufacture, deliver and service it. Research groups are not designed to do that, and we shouldn't do that. We're best suited to discovery." He is working on a way to use the multibeam technique clinically in a neurosurgical endoscope, a device made of a long tube with a light and video camera at one end that allows doctors to see inside the body.

He says he's looking forward to marrying his two vocations at SRI. "We're hoping this will be a prescription for success for surgeon-scientists. Once the experimental OR is up and running, operating days will combine clinical [work] and research. In that case, I might be able to push the research component to 80% of my time," he says happily.

Dr. Bradley Strauss, in his lab at Sunnybrook Research Institute, talks about a biological therapy he has developed to unclog blocked blood vessels of the heart.

Clearing the Way

On the day of our meeting, Dr. Bradley Strauss is one-half hour late. I arrive at his office to find he's been called into the catheterization lab for an urgent case. Strauss, a senior scientist in the Schulich Heart Research Program at SRI, still has his lab coat on as he apologizes for being late. As head of the division of cardiology and chief of the hospital's Schulich Heart Program, research and administration take much of his time, but he says his clinical work is critical. "I have many patients that I feel very close to, and who I like looking after."

Seeing patients is not only rewarding; it also informs his research. For more than a decade, Strauss has been developing a treatment for chronic total occlusions (CTOs) of the heart, where blood vessels have been completely blocked for three months or longer.

Cardiovascular disease is the number one killer in Canada. Coronary artery disease, narrowing of the arteries that supply blood to the heart, is its most common form. This narrowing is caused by atherosclerosis, a buildup of fatty materials and plaque on the inner walls of blood vessels. About 20% of patients with coronary artery disease have a CTO identified at coronary angiography, a type of X-ray to see inside blood vessels.

One treatment for this condition is angioplasty. Under X-ray guidance, doctors use a catheter to insert a guide

wire into the blockage and inflate a balloon at its tip to crush the plaque and restore blood flow. Sometimes they insert a stent, a metallic mesh tube, to keep the vessel open. Most patients with a CTO are treated with drugs to manage chest pain, or if symptoms are severe, referred for bypass surgery. Medication is often ineffective and restricts patients' lifestyles. Although percutaneous, or through-the-skin, interventions are less invasive than surgery, and pose fewer risks of complications, they are attempted only in about 10% of all CTO cases. Doctors are reluctant to try interventions like inserting a stent for a few reasons. In addition to concern over prolonged radiation exposure, success rates of angioplasty for CTOs vary from 55% to 80%. Procedures usually fail because cardiologists cannot get the guide wire through the blockages, which are made mostly of collagen and are generally old and hard.

It was against this backdrop that Strauss' invention was born. "It was always a great challenge to get the wire across when [the vessel] is totally blocked. There were so many times it failed. I had so many frustrations that I could not do it," says Strauss, who is also a professor at U of T.

Unwilling to accept defeat, he thought about how the materials that constitute these blockages could be used therapeutically. "I had done a lot of work with collagen and these collagenase enzymes, so I had a good understanding of the biology of it all. It just made sense to me: why don't you inject something to break down the collagen so you can get through the occlusion easier?"

An enzyme-based therapy to soften artery-clogging plaque seemed like a promising idea, but before he could test it Strauss had to develop experimental models. He then used an off-the-shelf enzyme mixture made from the bacterium C. histolyticum that degrades collagen, and injected it into the models—and waited.

Three days later, he had his answer.

"I couldn't believe what happened," says Strauss. "I was never as excited as the first time I saw the collagenase work. I thought I'd truly seen something unique."

He published preclinical results in 2003, by which time he learned the enzyme needed only 24 hours to work. He began to commercialize his invention, a process he found unfamiliar and at times overwhelming. "Doctors have no training in this. When I started, there were no mentors. I couldn't call up someone and ask, 'How do you do this?'"

It took several years for Strauss to test collagenase in patients. One hurdle was finding a manufacturer who could make a formulation pure enough to use in humans. He also had to obtain research ethics and regulatory approval, not to mention find money to do the work.

Through a grant, Strauss led a Phase 1 clinical trial, the first in humans. He recruited 20 patients; each had undergone one previous failed angioplasty. Strauss was eager to test the therapy in patients, but says the fear of causing harm weighed heavily upon him. "You have no idea what's going to happen. You're frightened because you don't want to make someone worse. Every time we changed the dose, I'd worry [about doing] something dangerous to someone."

Given he was testing the drug in patients with blockages that had already stymied doctors, Strauss set the crossing success rate at a modest 35%. To his delight, doctors got through blockages in 75% of patients. Moreover, they could

Interventional cardiologists Dr. Bradley Strauss and Dr. Harindra Wijeysundera stand in the catheterization lab moments after a failed angioplasty attempt. Strauss says such challenges underpin his motivation for developing a treatment to get through blocked blood vessels.

trade stiff-tip guide wires—used routinely for CTOs for their increased probing force—for soft-tip guide wires in most procedures. At three months, there were no complications and patients reported less chest pain.

"I don't know if I can describe how wonderful it feels to think something you worked on did something profoundly important in someone's life. There are no words for it," Strauss says.

Immediately after the trial, he started Matrizyme Pharma to help bring the drug to market. It is difficult to license a new therapy, especially early on, because of financial risk. To this point, Strauss has taped to the back of his office door an email from a drug company executive, who, clinical trial results notwithstanding, says he remains skeptical of the enzyme's promise. "There are huge obstacles. This just reminds me of that," says Strauss, referring to the email. "You either give up, or try and draw some strength to say, 'They're wrong.' It gives me strength to know that I have to overcome huge challenges."

Strauss also notes that in his field, a play-it-safe mentality won't yield advances. "Interventional cardiology is by nature and historically a very innovative place. We're constantly doing new things to try and treat difficult coronary arteries easily. To put a stent into a patient for the first time, you have to be able to take risks. If you take a conservative approach, you won't improve things because you'll accept what's there," he says.

"I was never as excited as the first time I saw the collagenase work."

Matrizyme has raised the millions needed to do a Phase 3 randomized controlled trial, the gold standard of clinical testing. It will enrol 400 patients at 30 sites in North America. "We're going right for the big game," he says, smiling.

He hopes to complete recruitment within 18 months. The litmus test will be how patients feel immediately after the procedure and their quality of life two months later.

If results mirror the earlier ones, then it is likely that a large drug company will license collagenase, says Strauss. "It would be difficult for us to take it past this stage, because you really need to have a big sales force to show [the drug] to people all over the world. I expect that it will make its way across the globe, which is kind of neat. I can see that happening now; maybe I couldn't a few years ago. I feel pretty confident that we can do this."

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. Yang is also supported by the Canada Research Chairs program; he holds the Canada Research Chair in Bioengineering and Biophotonics.

Strauss' research on collagenase was funded by the Canadian Institutes of Health Research, Heart and Stroke Foundation of Ontario, Reichmann Research Chair at Sunnybrook and St. Michael's Hospital Research Foundation. The Canada Foundation for Innovation and Ontario Ministry of Research and Innovation provided infrastructure support.

Where Are They Now?

We track yesterday's trainees into their present-day careers

"So, **what are you going** to do next?"

It's a question that dogs graduate students and postdoctoral fellows, because on top of the scarcity of university faculty positions, trainees must weigh their job options in light of considerations such as family ties and lifestyle.

The following stories reveal the interplay of these factors in shaping the careers of three former Sunnybrook Research Institute (SRI) trainees. They also show that the time spent at SRI has had a lasting impact. Here are the journeys of these trainees—where they are now, what they're doing and why they wouldn't have it any other way.

AN INDUSTRIOUS MANOEUVRE

In the spring of 2000, Dr. Ross La Motte-Mohs moved from the U.S. to Toronto to work as a postdoctoral fellow in the lab of Dr. Juan Carlos Zúñiga-Pflücker, a senior scientist in Biological Sciences at SRI. Zúñiga-Pflücker invented a way of generating T cells—those building blocks of the immune system—in a Petri dish, a method now used by labs worldwide. La Motte-Mohs helped develop this technology. It has potential therapeutic applications for people with autoimmune disorders, or whose immune systems have been damaged by toxic cancer treatments or depleted by human immunodeficiency virus infection.

Seeking a change in his career, La Motte-Mohs moved back to the U.S. in December 2009 to work as a scientist at Wellstat Therapeutics, a biopharmaceutical company in Gaithersburg, Maryland. He was also offered a policy position in San Francisco and an academic position in Spain. In weighing his options, La Motte-Mohs says that on

AFTER COMPLETING A POSTDOC IN OTTAWA, DR. ALISON BURGESS accepted a research associate position at Sunnybrook Research Institute, where she began as a summer student and got her PhD.

PHOTO: DOUG NICHOLSON

top of the competitive salary, the industry position offered other advantages.

"I wanted to be closer to my family, and this job allowed me to do that while developing my career," he says, noting his family lives in the neighbouring state of Virginia. "The nice thing about industry in D.C. is that there are a lot of biotech firms and supportive structures such as the Food and Drug Administration and the National Institutes of Health. There's a huge science critical mass that's based in Washington. You have flexibility to move from job to job and develop your career as you see fit."

La Motte-Mohs was quickly promoted to senior scientist. While he still does some lab bench work, 90% of his focus is on business development—taking a discovery and developing it into a product that can be sold to clients. His responsibilities include getting patents, creating business plans and analyzing his company's market niche for a product. "You can train people to execute experiments and be competent so that your efforts can be focused on seeing the larger picture. That's kind of exciting," says La Motte-Mohs from Maryland through crackly cell phone reception.

His job also affords him the opportunity to network with people within the legal, regulatory, banking and financial sectors. "Our reach is local, national and international. We're trying to tap into emerging markets like Brazil and Turkey. It's a much different network than you'd be exposed to in academia," he says.

La Motte-Mohs finds his work life regular and structured. For confidentiality reasons, he's not permitted to take data out of the lab to analyze at home. Aside from reading journals, he leaves work at the office, which wasn't possible during his postdoc. Another difference is in the approach to the science. "It's not the type of science you'd find in academia where you ask a question, get an unexpected result and you try to explore that further. In industry, you need a really solid business rationale for why you'd pursue a certain line of investigation," says La Motte-Mohs.

He keeps in touch with his former boss. They usually share a meal when they are in the same city, which is a few times a year. He also says that his time at SRI, particularly conversations with vice-president of research Dr. Michael Julius provided valuable exposure to commercialization.

He describes working in industry as a "nice change," but says he feels free to take his career in various directions. "Something I've realized is that once you make the transition from academia to industry, you can keep making transitions. I could move into government or policy, or even go back into academia. It's really what you want at that time in your life."

SUNNYBROOK RESEARCH INSTITUTE launched Dr. Ross La Motte-Mohs from a postdoc position to that of senior scientist at Wellstat Therapeutics in Maryland.

ACADEMIA OR BUST

Dr. John Ebos started at SRI in 2000 after completing his undergraduate studies at McGill University. "I came as a summer student and didn't leave. It was a situation where I got hooked," says Ebos.

He came to work with Dr. Bob Kerbel, a senior scientist in Biological Sciences at SRI. Kerbel is a trailblazer in the field of antiangiogenic therapy, treatments that aim to halt a tumour's growth by cutting off its blood supply. Ebos took his PhD from the department of medical biophysics at the University of Toronto in 2008, and continued training in the Kerbel lab for another two-and-a-half years as a postdoc.

In the fall of 2011, Ebos accepted a position as an assistant professor in oncology at Roswell Park Cancer Institute in Buffalo, New York. He is studying mechanisms of antiangiogenic drug resistance; specifically, how tumours adapt to treatments and how the body responds to these drugs. Ebos says the position is an ideal match in terms of interests and geography, and that he wants to foster collaborations between researchers in southern Ontario and upper-state New York. Being close to Toronto was also advantageous because it would enable him to stay in contact with family, an important network for this first-time dad.

"It's been a big adjustment and a really fun and interesting year on many different levels," says Ebos, who welcomed son Maxim last spring.

Ebos has been learning how to run his lab, at times through trial and error. "To be a PI [principal investigator] you need to not only be self-motivated and have a thick skin for scientific criticism and failure, but you also need to be a highly effective manager of personnel, budgets and, critically, of ideas," he says.

Unsurprisingly, Ebos works long hours and says that one of his biggest challenges is maintaining balance. "It's 24/7 whether you're in the lab doing it or just thinking about it. That's the nature of being a scientist doing something you love. It doesn't necessarily fit in the nine-to-five framework."

While things have worked out well, getting to this point was not without its struggles. He says it was his hope to land an academic position, but not an expectation. "There's no handbook on the method or route to take. That's something everybody has to learn on their own. Every postdoc has to decide if it's not going to be this year, how many years do you put into training? I think it's a tough, tough decision. I was motivated to stay in academics for the long run."

He remembers his time at SRI fondly, not only because of the weekly soccer games played behind McLean House, but for what he learned and the close relationships he formed. He also appreciates how things have come full circle, and relates easily to students in his lab because he was once in their shoes.

"It feels surreal, and I don't necessarily want that to change because it gives me a better perspective on how a student is approaching a meeting with me. I think it's critical to be positive, because that was what was most helpful in getting me to do better. There was a lot of mentoring at SRI that made a big difference, and I want to do that here," he says.

PHOTO: JUAN CARLOS ZÚÑIGA-PFLÜCKER

When asked what he most enjoys about being a scientist, Ebos is quick to answer. "It's an innovative, creative experience. We get to think of new things every day. There are no limitations on what you can do in terms of putting things together. If you're really motivated, you can put together some really big things, and that's exciting and unique in terms of jobs. We're pretty lucky."

"It's 24/7 whether you're in the lab doing it or just thinking about it."

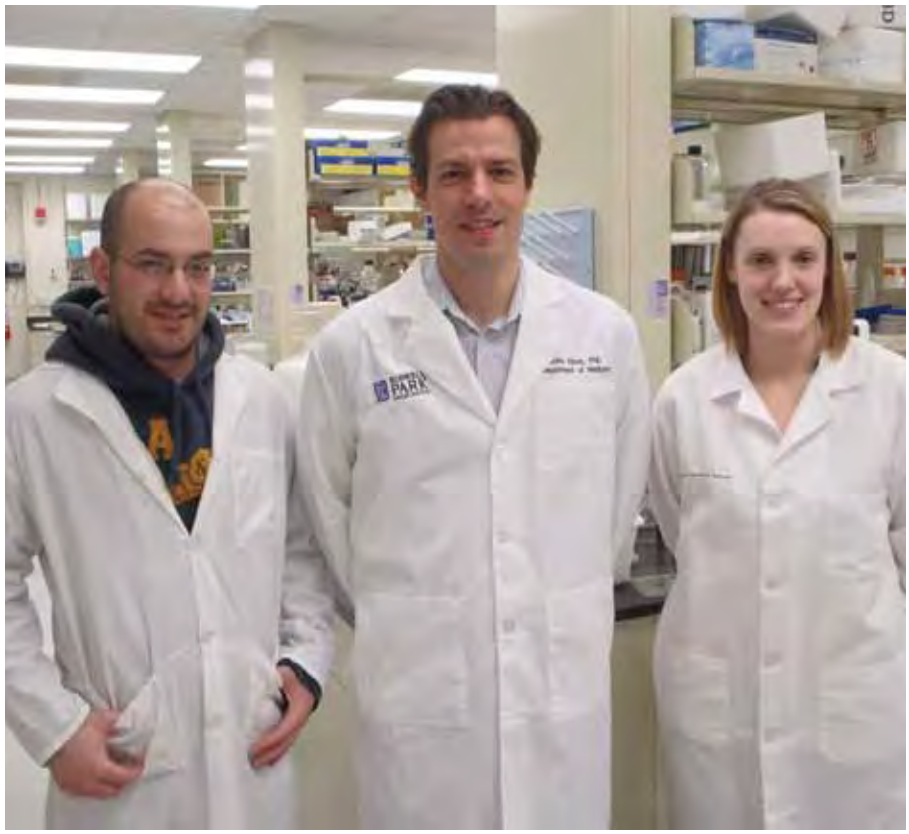
BIOLOGIST FINDS FOCUS

A summer studentship also led Dr. Alison Burgess to SRI. She remained here another five years, getting her PhD in neuroscience supervised by Dr. Isabelle Aubert, a senior scientist in Biological Sciences at SRI. Her thesis was on the role of polysialic acid, a molecule found in normal brain development that is also expressed by stem cells in the brain.

Just before finishing her doctoral studies, Burgess got married. While doing her postdoc at the National Research Council in Ottawa, she had two daughters, Lily, who is now four years old, and Hannah, who is three.

In September 2010, Burgess accepted a position as a research associate in the lab of Dr. Kullervo Hynynen, SRI's director of Physical Sciences. She took the job because she found Hynynen's work intriguing, and with two young children, wanted to be close to family.

She brings her biology expertise to bear on Hynynen's research on therapeutic ultrasound. Hynynen is working on a way of treating brain tumours and other brain diseases through a technique that uses focused ultrasound and microbubbles to penetrate the blood-brain barrier. Tiny gas bubbles are injected into the blood-stream and activated by ultrasound. The process is guided by magnetic resonance imaging (MRI). It opens temporarily this barrier, which consists of a clump of tightly packed cells that blocks substances —bad and good—from the brain.



DR. JOHN EBOS (CENTRE) JOINED THE FACULTY OF ROSWELL PARK CANCER INSTITUTE in New York after spending 11 years at Sunnybrook Research Institute. He stands with his Roswell Park lab members Dr. Michalis Mastri and Amanda Tracz.

Burgess is evaluating the use of this technique to deliver therapies such as stem cells and antibodies to treat neurodegenerative diseases. She prepares the stem cells in culture, performs the experiments and examines changes in brain tissue after the therapy is delivered. "My role as the biologist in the lab is to study some of the mecha-nisms underlying how this technology is affecting the brain," she says. "I provide a different side of the story in terms of what the other types of cells are in the brain, what they could be doing and how they are responding to this treatment."

There was a steep learning curve in understanding the physics of MRI and ultrasound, which Burgess overcame by doing lots of reading after putting her kids to bed. "My first MRI experiment day was nerve-wracking. I don't think I slept the week beforehand," says Burgess. She also relies on her physicist and engineer colleagues for any knowledge gaps and they, in turn, consult her on the biology aspects.

Most days, she leaves the lab on time to pick up her kids from day care, catching up on work, if needed, in the evening. Burgess says she manages her family life and career thanks to a supportive work environment and the ability to tag-team with her husband. "If I ever have to do some more work when the kids go to bed, my husband is there to help with whatever needs to be done to keep functioning. We have a good system," she says, smiling. Burgess says she enjoys working in translational medicine. She is eager for the technology to be used clinically, but knows it will take time. "If we can do these studies and show that it is safe and effective, we can maybe treat patients in the near future, which is really exciting, and I'm happy to be a part of it. I can see that focused ultrasound is going to be used. I completely believe in it."

– ALISA KIM

PHOTO: LEIGH ELLIS

What Are You Reading?

Three brain scientists at Sunnybrook Research Institute reveal the books they pick up when they put their journal articles down

EDITED BY STEPHANIE ROBERTS

DR. BEN GOLDSTEIN

I just started *American Pastoral* by Philip Roth, having previously enjoyed several of his books. I have a short attention span for non-work reading, but Roth gets his books up to speed within a few pages, and it's easy to stay interested throughout. I enjoy his punchy sentences that say a lot using few words. Maybe I admire his ability to share ideas so efficiently because this is such a valued attribute in scientific writing. Roth has an amazing ability to convey the perspectives of his characters, portraying their flaws and turmoil without judgment. As a psychiatrist, I appreciate his multifaceted portrayal of characters, blemishes and all, and the recurrent theme in his work that we are all human, fallible, imperfect and deserving of acceptance.

Dr. Goldstein is studying bipolar disorder in teenagers. He wants to identify biomarkers to help inform clinical treatment. In one study, he leads a team of researchers who are investigating if specific markers in the blood can provide a better understanding of mood symptoms and the greater risk of heart disease in teens with bipolar disorder.

DR. PEGGY RICHTER

What Disturbs Our Blood by James FitzGerald is a fascinating journey into 20th-century medicine in Toronto. It chronicles the story of three generations of FitzGeralds, as told by James, son of physician Jack and grandson of medical pioneer Gerald, whose story is grand: founder of Connaught Labs and pioneer in public health and hygiene; creator of mass immunization programs for diphtheria, typhoid and other diseases; and partner in manufacturing his friends' Banting and Best's newly discovered insulin. Son Jack makes contributions in the emerging fields of allergy and immunology. James also tells a compelling story of the family's multigenerational struggle with depression and suicide, and the emotional fallout he struggles with. I picked up the book expecting to find a medical history of Toronto, but was also drawn in by the sad psychopathology. Mental illness was hushed up then, and this story of the fathers of psychiatry in this city, and their struggles with limited or damaging biological treatments, strongly resonated with me.

Dr. Richter is studying the genetic and biological basis of obsessive-compulsive disorder, and working to improve treatment outcomes for this and related disorders. She leads the Frederick W. Thompson Anxiety Disorders Clinic, founded in 2012 by a $10-million donation.

DR. BOJANA STEFANOVIC

I recently read Daniel Kahneman's *Thinking Fast and Slow* on the failings of the human mind from the psychological perspective. I am ambivalent about psychology, but I enjoy stealing books from my husband, which is how I picked this one up. It's a fascinating work, starting from the incredibly understated tone of this great thinker. He ascribes much of the theoretical work that led to his Nobel Prize to his long-term collaboration with Amos Tversky and their daily, conversation-based approach to research. It's hard to read this book and not feel more (slow) thinking would propel us all. He coins an abbreviation so awkward that it stuck with me: WYSIATI, "What you see is all there is." While it's clear that this visionary, like many others, would not have survived in sales, WYSIATI is a great mnemonic to remind yourself of the importance of deliberation and perspective shifting.

Dr. Stefanovic is developing new methods for imaging brain function. In one project, she is looking at changes that occur in the brain's neurons and blood vessels after a stroke. Her aim is to understand how such changes support rehabilitation, toward guiding the creation of new treatments for stroke.

PHOTOS: DOUG NICHOLSON

Allies in Academia

Sunnybrook researchers are steering the course of some of the most dynamic departments at the country's largest university

The University of Toronto has three campuses, boasting enrolment of over 80,000 students. It offers more than 900 undergraduate and graduate programs and courses to suit every intellectual fancy. As the research enterprise of Sunnybrook Health Sciences Centre, a teaching hospital fully affiliated with the university, Sunnybrook Research Institute (SRI) is one of U of T's partners in education.

"It's a big, complex organizational unit," says Dr. Juan Carlos Zúñiga-Pflücker, a senior scientist in Biological Sciences at SRI. In July 2012, he began a five-year term as chair of the university's department of immunology. Two other SRI senior scientists, both in Physical Sciences, also chair U of T departments: Dr. Alan Moody leads medical imaging, Dr. Peter Burns, medical biophysics. Herein, a peek at the paths they are setting.

AS CHAIR OF MEDICAL IMAGING, DR. ALAN MOODY says translating research into better patient outcomes is a priority.

PHOTO: DOUG NICHOLSON

A NEW CHAPTER

At the end of 2012, Moody ended 10 years of service as radiologist-in-chief at Sunnybrook. He also began his five-year term as chair in July, and is in the thick of strategic planning, something all new chairs must do.

Through extensive consultation with faculty (which sits at 173 members), students and alumni, Moody is writing a strategic plan to articulate a vision for the department: how it will look and where it will be in five years.

"It is a good thing to do your soul-searching at the beginning of your term instead of looking back and saying, 'I wish we'd done this.' It's much better to look ahead and say, 'How can we get this done?'"

Research will be a high priority, says Moody. "Our job is to take cutting-edge imaging research into clinical practice. Our aim is to be at the forefront of translational research."

Imaging research involving technologies like magnetic resonance imaging (MRI), computed tomography (CT) and ultrasound will aim to invent new ways of diagnosing, treating and preventing disease safely and cost-effectively. "We are fortunate to have access to these powerful technologies in clinical practice, but we're now at a stage where we must step back and examine the best way of using them to improve patient outcomes," says Moody.

Despite the large commitment of time and energy the position entails, Moody says he was pleased to accept responsibility for leading this highly regarded department.

"I was fortunate to be involved with some of the pioneers of CT and MRI who inspired me to follow this specialty. I feel there is now a great opportunity to continue the work they started, as well as to position medical imaging as an integral element of patient management within the health care system," he says.

CONNECTING THE DOTS

It didn't require a lot of arm-twisting for Zúñiga-Pflücker to accept the chair

position. "I really love the department," he says. "I have a great appreciation for what it does and what it can do.

"It's a challenging, exciting job. I get to interact with people at the University and [the affiliated hospitals]. This is a more global view of the immunology community in Toronto, which is really quite strong. You see it from a different viewpoint," he says.

Born in Peru, Zúñiga-Pflücker did his scientific training in the U.S. He was recruited to U of T in 1994 by Dr. Michael Julius, vice-president of research at Sunnybrook and SRI, who was then chair of immunology.

He, too, is writing a five-year strategic plan. One of his goals is to strengthen linkages among the 60-plus immunology faculty doing research at the affiliated hospitals, comprising SickKids, University Health Network, St. Michael's, Mount Sinai and Sunnybrook.

"All of our students do work in hospital-based research institutes like SRI."

Another aim is to boost specific areas within the field. These include fundamental research into the workings of the immune system, and mucosal immunology, specifically, how micro-bacteria interact with host pathogens in mucosal areas.

While being chair takes him away from the lab somewhat, he notes that his administrative duties do not supplant his science. He says having more senior staff allows his lab to run smoothly by requiring less hands-on oversight on his part.

Zúñiga-Pflücker also says having department chairs at SRI has a beneficial impact on his research and that of his colleagues. "Having these leadership positions here are important; they play a different role in that they unify units that are very broad. Immunology is a broad unit that's city-wide. [Being chair] allows me to connect in a different fashion with the rest of the hospital-based researchers. It adds connectivity and resources to the work we do here."

DR. JUAN CARLOS ZÚÑIGA-PFLÜCKER, chair of immunology, wants to strengthen ties among faculty working at the affiliated hospitals.

DR. PETER BURNS, CHAIR OF MEDICAL biophysics, aims to uphold the department's culture of multidisciplinary research.

SECOND TIME'S A CHARM

When Dr. Peter Burns joined the department of medical biophysics more than 20 years ago what impressed him most was the quality of its graduate program. "The graduate students I've met during my time [here] have been the best I've met in my life," he says.

Now in his second term as chair of the department, Burns says what sets its graduate program apart is the unique way in which students are educated. "All of our students do work in hospital-based research institutes like SRI. We have no students on campus. We don't teach undergraduate courses. We are a university department wholly dedicated to collaborative, translational research," says Burns, who notes there are 80 medical biophysics graduate students training at SRI.

This research, says Burns, takes place in a clinical setting, but is undergirded by the university's promotion of knowledge and learning. "The university provides a wider cultural and academic environment in which SRI scientists participate. That benefits SRI because no single institution is capable of providing all of the resources of fundamental learning and discourse that really drive creative science."

One of his priorities is to uphold the department's culture of multidisciplinary research even as biomedical research becomes more specialized. He says that within the department, scientists in biology and physics don't just co-exist; they collaborate. He points to the groundbreaking discovery of the stem cell by Toronto researchers Dr. Jim Till, a physicist, and Dr. Ernest McCulloch, a clinician and biologist, as an emblem of the potential of this synergistic approach.

Many SRI scientists are graduates of the department—"something we're quite proud of," says Burns. Stepping out of his office on the sixth floor of the research institute's S wing, Burns notes many of his floor mates are medical biophysics alumni.

He says nurturing the next generation of scientists is what he most enjoys in his role. "We have such great young people in our training programs, some of whom are going to do wonderful things in medical science. I look forward very much to seeing what they'll achieve."

– ALISA KIM

PHOTOS: DOUG NICHOLSON

Where in the World Is SRI?

We unzip the globe to show you where the Sunnybrook Research Institute scientists featured in this year's magazine are collaborating with others—research knows no boundaries!

Dr. Victor Yang and researchers at the B.C. Cancer Agency are using imaging technology he developed for early detection of lung cancer. For more on Yang's innovations, see page 28.

Dr. Marc Jeschke and researchers at Shriners Hospitals for Children in Galveston, Texas, measured the threshold for burn size to determine at what point children should get immediate, specialized care: page 9.

Dr. Jon Barrett led a twin birth study spanning 106 hospitals in 25 countries. A hospital in São Paulo, Brazil, was one of 13 participants in this country: page 12.

Researchers at the Reta Lila Weston Institute of Neurological Studies in London, U.K., partnered with **Dr. Sandra Black** on an 11-centre study looking at enzyme mutations in dementia with Lewy bodies. Black leads many dementia studies: page 8.

Researchers in Malawi and **Dr. Michael Schull** are working to improve care in that country's rural centres. Schull's work here is featured on page 14.

Scientists at the Netherlands' Utrecht University are using preclinical models provided by biologist **Dr. Bob Kerbel** to study how cancer spreads. For more on his research, see page 18.

The All India Institute of Medical Sciences in New Delhi, India, is one of 12 sites in the PREDICT study, led by **Drs. David Gladstone** and **Richard Aviv**, stroke experts: page 4.

Dr. Arun Seth is collaborating with a group at King Fahd University Hospital, in Al-Khobar, Saudi Arabia, on the molecular genetics of breast cancer, as part of his work to find new therapy targets: page 18.

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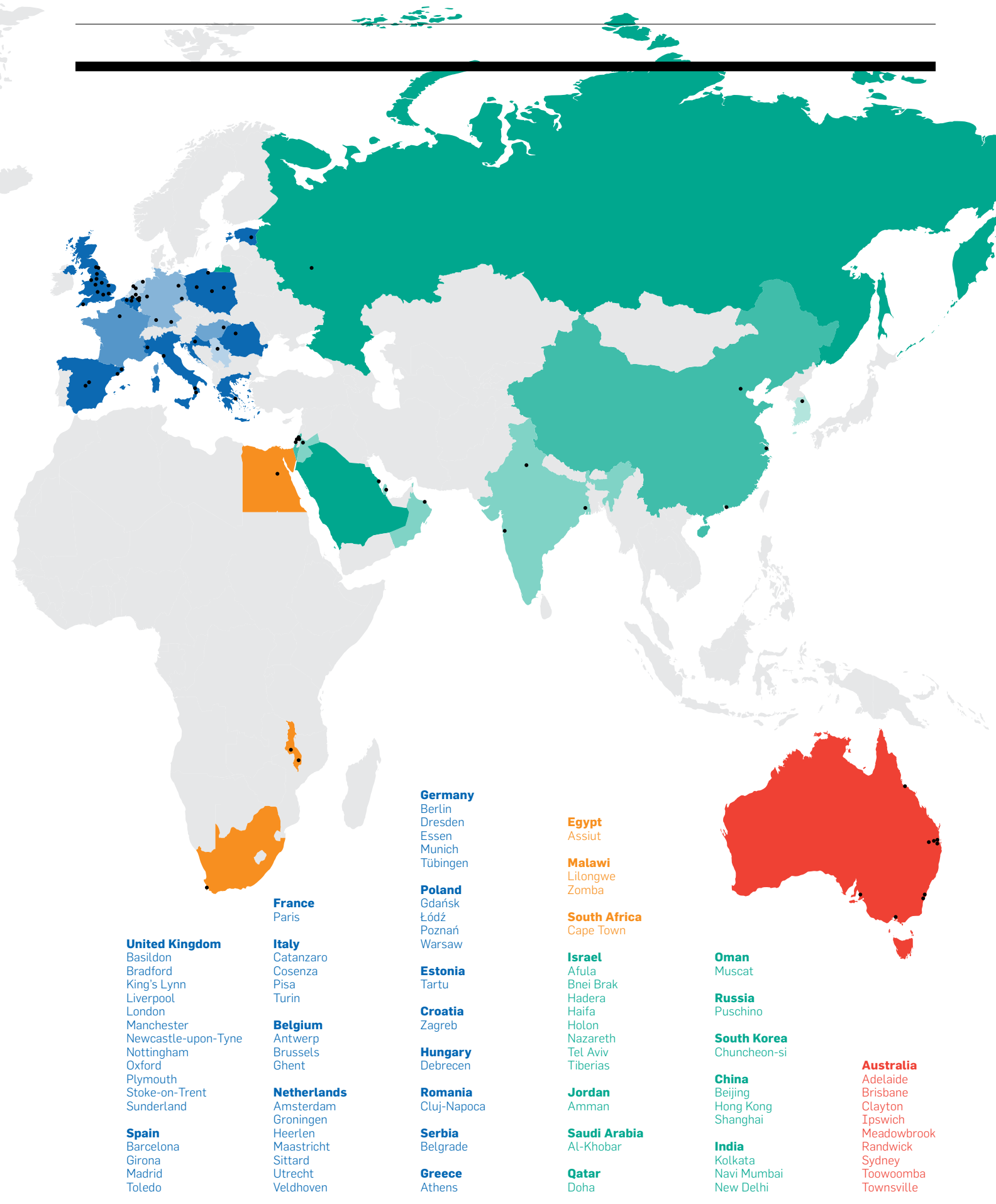

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Outstanding Corporate Philanthropy

Introducing the D+H Summer Student Research Program at Sunnybrook Research Institute

Gerrard Schmid, CEO and director of D+H, speaks with Alisa Kim about his company's five-year, $250,000 investment into hands-on learning at SRI.

Why is D+H investing in the summer student research program at Sunnybrook Research Institute specifically? You had your pick of institutes, I'm sure.
There are a couple of reasons why this particular program is of interest to D+H. First, we really believe in the program mandate itself. The opportunity to help students who are going to be the researchers and innovators of the future is really compelling for a company like ours. D+H has been in business for over a century, and innovation in order to stay relevant to our customers today and tomorrow is the cornerstone of our success. The tie-in to the SRI summer student program is a natural fit for us. Second, the geographic proximity of the program is attractive to us. Sunnybrook is very close to the D+H corporate office, and we have a strong history and firm commitment to give back to the communities in which we live and work.

What do you hope the donation will do?
Every brilliant invention starts with an idea. As a society, we need innovation more than ever to identify viable new technologies and solutions that will reinvent health care to create more capacity, develop less invasive procedures, and create more rapid and accurate diagnostics. Our hope is that our support of the summer student research program will help spawn some of those ideas and innovations and give them an early start.

D+H IS THE FIRST CORPORATE SPONSOR OF THE SRI Summer Student Research Program. Gerrard Schmid, CEO of D+H, says the donation was fuelled by the opportunity to help students become the innovators of tomorrow.

There's a culture of innovation at D+H. How does this gift fit with your corporate mandate?
There's a real recognition in our company that innovation plays, and will continue to play, a key role in our success. We have to be constantly innovating to meet our customers' evolving needs, much in the same way as advances in medical research continue to make a difference for its "customers," the patients. The medical advances resulting from research at Sunnybrook are a shining example of the difference true innovation can have in people's lives. There is a pretty clear parallel for us, and because the program aligns so well with our corporate mandate, it was an easy decision for us to support it.

Community involvement is a core value of D+H. Why is philanthropy so important to the company?
We believe that corporate community involvement and philanthropy deliver value to society and to our business. We see an inextricable link between behaving well internally and externally—whether it is by respecting our employees, delivering value to our customers or engaging with the community in which we operate. Therefore, it is very important to us to be a "good corporate citizen."

Why do you think it's important for corporations to give back to the community?
None of us operates in a vacuum, whether as individuals or as corporations. We are part of a bigger community, and it is important to respect and appreciate that fact. It's imperative to recognize that delivering value to the community delivers value to a corporation also.

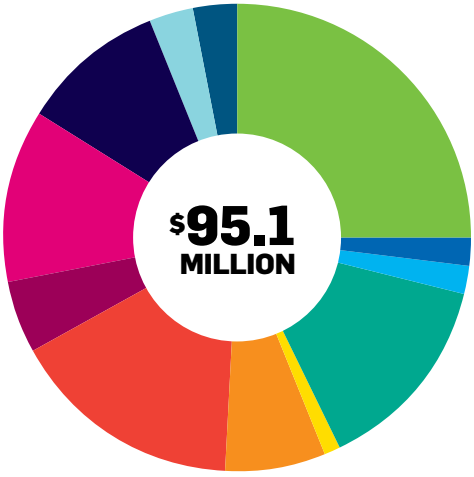
D+H is a leading provider of secure and reliable technology solutions to North American financial institutions. With a long history as a trusted partner to banks, credit unions and other financial services providers, D+H's solutions help customers grow, compete and optimize operations. D+H is ranked #24 on the Branham 300 listing of Top Canadian Information and Technology Companies and #35 on American Banker, Bank Technology News, and IDC Financial Insights FinTech 100. For more information, visit www.dhltd.com.

PHOTO: MATTHEW SHERWOOD

Quick Statistics

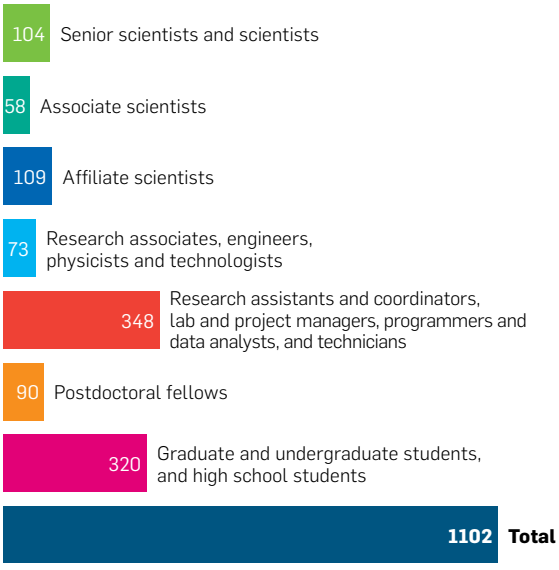
Sunnybrook Research Institute is grateful to the many sponsors who, with each dollar they give, help support research here.

MAJOR SOURCES OF EXTERNAL FUNDING 2011–2012

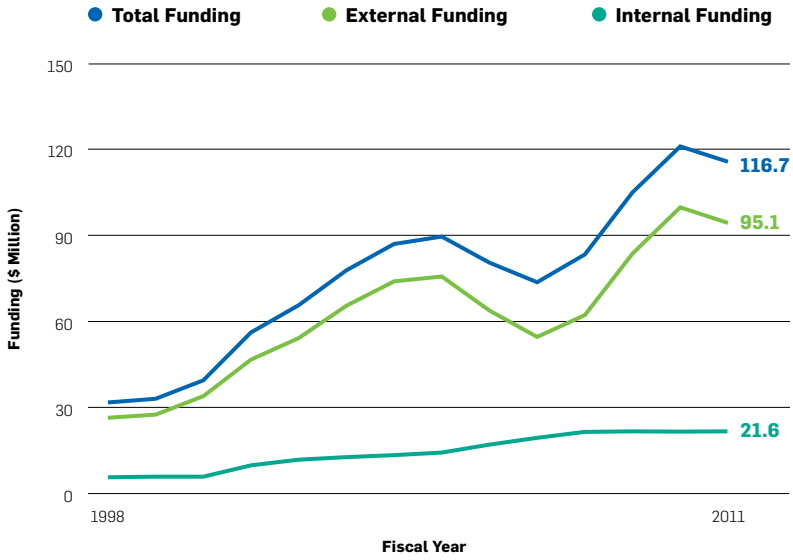


Source	$ (M)	%
Canada Foundation for Innovation	24.2	25
Canada Research Chairs Program	1.7	2
Canadian Cancer Society Research Institute	2.2	2
Tricouncil Funding: Canadian Institutes of Health Research, and Natural Sciences and Engineering Research Council	13.4	14
Donations and Trust Income	1.3	1
Foundations	6.4	7
Industry	15.4	16
Ministry of Health and Long-Term Care	4.7	5
Ministry of Research and Innovation	11.3	12
Other Funding Sources	9.1	10
Other Government Sources	2.7	3
U.S. and International Sources	2.7	3
Total	**95.1**	**100**

RESEARCH STAFF



HISTORY OF RESEARCH EXPENDITURES AT SUNNYBROOK RESEARCH INSTITUTE



Q&A

DR. JEFF KWONG *is an associate scientist in the Veterans & Community Research Program at Sunnybrook Research Institute. He is also a scientist at the Institute for Clinical Evaluative Sciences, an assistant professor at the University of Toronto and a family doctor at Toronto Western Hospital. He spoke with Alisa Kim about his research.*

How did you become interested in infectious diseases?
It was a bit of serendipity. When I was doing my master's thesis, I was supposed to be looking at diabetes in immigrants. We got caught in a lot of red tape, and my thesis supervisor, Doug Manuel, said, "I've got this project looking at Ontario's universal flu shot program." I switched projects, then became an influenza guy.

Why is a personal decision—whether to get the flu shot—a public health issue?
Influenza, as with a lot of infectious diseases, is not just about protecting yourself. By getting vaccinated, you also protect others. What's interesting about the flu shot is that the people who need it most are the people who get the least protection from it: the elderly, young children and people with chronic diseases. They're most likely to get sickest from influenza, but because their immune systems don't work as well, the flu shot doesn't work as well in them. So, it probably makes sense for everyone around these individuals to get the flu shot to prevent infecting them.

The data suggest that about only one in three Canadians get the flu shot. Why is that?
I think there are a few issues. People don't think influenza is a big deal, and that's true for most people. But some people get really sick and die from it. A lot of people don't realize that. Second, because you have to get it every year, it's not as convenient as other vaccines where you get it once, or [get] a series of shots, and you're done for the rest of your life. That you have to get a vaccine every single year [seems like] a lot to ask of people.

FACTS ABOUT FLU IN CANADA

- Between 2,000 and 8,000 Canadians die of flu and its complications annually.
- In the 2011–2012 flu season, British Columbia had the highest rate of vaccination in Canada, at 52%; Ontario's rate was 32%.
- It takes about two weeks after immunization before the flu shot gives you full protection.
- This year, the flu vaccine in Canada reduced the risk of infection by about 50%.

What has been your most interesting finding?
We showed that people who are severely obese are more likely to be hospitalized during flu season. Before the 2009 H1N1 pandemic, we didn't appreciate obesity as being a risk factor for influenza, like lung diseases, heart disease and diabetes. We did a study using data from health surveys where we had information about body mass index (BMI) and linked that to administrative data. [In] people with a BMI above 35 (30 is considered obese; over 35 is considered severely obese), [there was] a big risk in being hospitalized during non-pandemic flu seasons.

So, if you had to prioritize who to vaccinate, if you have somebody who's morbidly obese, you want to consider him just as you would somebody who's got asthma.

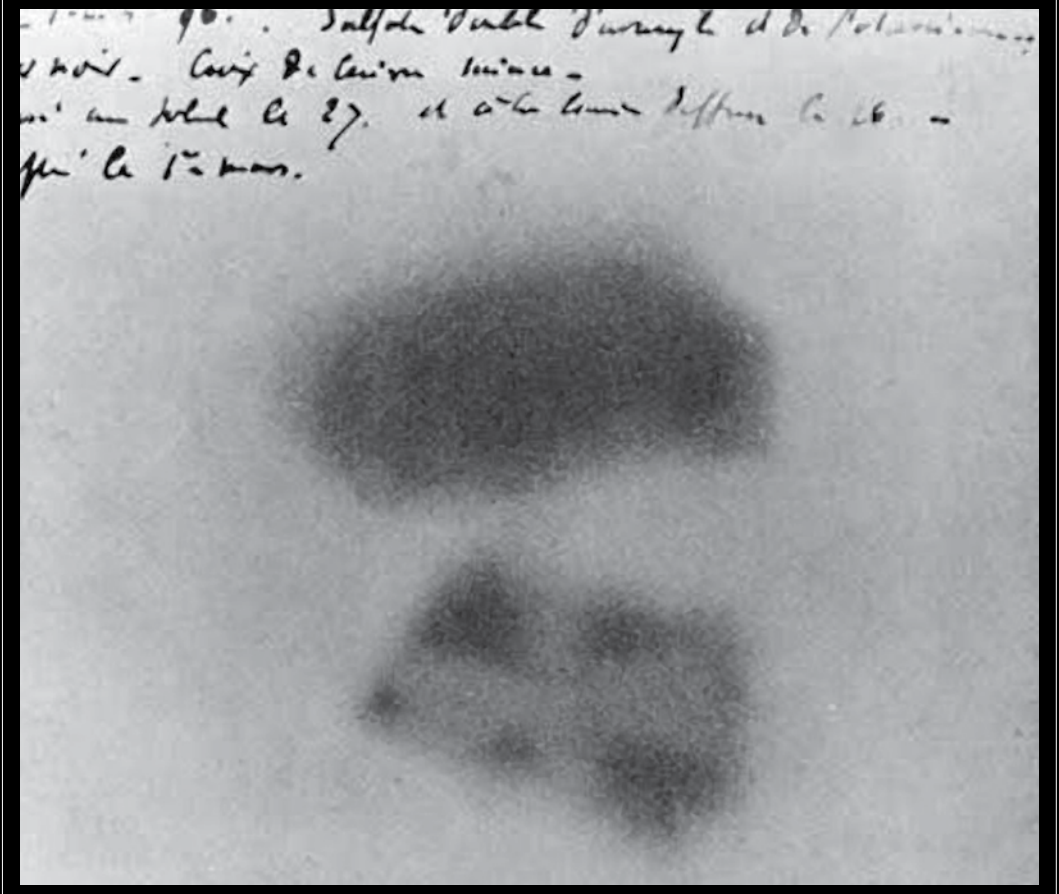
What should people know about the burden of infectious diseases?
We haven't conquered infectious diseases—far from it. People think of the big diseases like cancer or heart disease, and a person may have died because of lung cancer, but oftentimes the pneumonia is actually what killed them. It affects potentially everyone, from babies to the elderly. We're all susceptible. [With the] H1N1 pandemic, we were lucky it was a very mild virus; if there's a bad one, then it could be very bad.

Kwong's research is funded by the Canadian Institutes of Health Research. For more on his research, visit **sunnybrook.ca/research**

ILLUSTRATION: **ANTHONY HARE**

Through the Wormhole

Journey into a different time in medical science



The discovery of radioactivity is owing to a stretch of cloudy days in February 1896, in Paris, France.

On the heels of Wilhelm Röntgen's discovery of X-rays, a form of radiation that penetrates solid matter, Antoine Henri Becquerel hypothesized the phosphorescent uranium salts he was studying absorbed the sun's energy and gave off X-rays. He tested the idea by placing uranium crystals on photographic plates wrapped in black paper and leaving them in sunlight. Upon developing the plates, he saw an outline of the crystals. He planned to continue these experiments, but the skies were grey those last few February days. Becquerel shoved his materials in a drawer, postponing his work until the next sunny day. On March 1, he opened the drawer and developed the plates. To his astonishment, the image (above) was strong. The uranium had emitted radiation on its own!

For this discovery, Becquerel, along with his former doctoral student, Marie Curie (who coined the term radioactivity) and her husband Pierre Curie, shared the Nobel Prize in Physics in 1903.

The legacy of this discovery is profound. Radioactive substances, the foundation of nuclear medicine, are used to image the body and treat disease. It and related discoveries paved the way for the testing and validation of procedures like radiotherapy and brachytherapy.

COVER SLIP

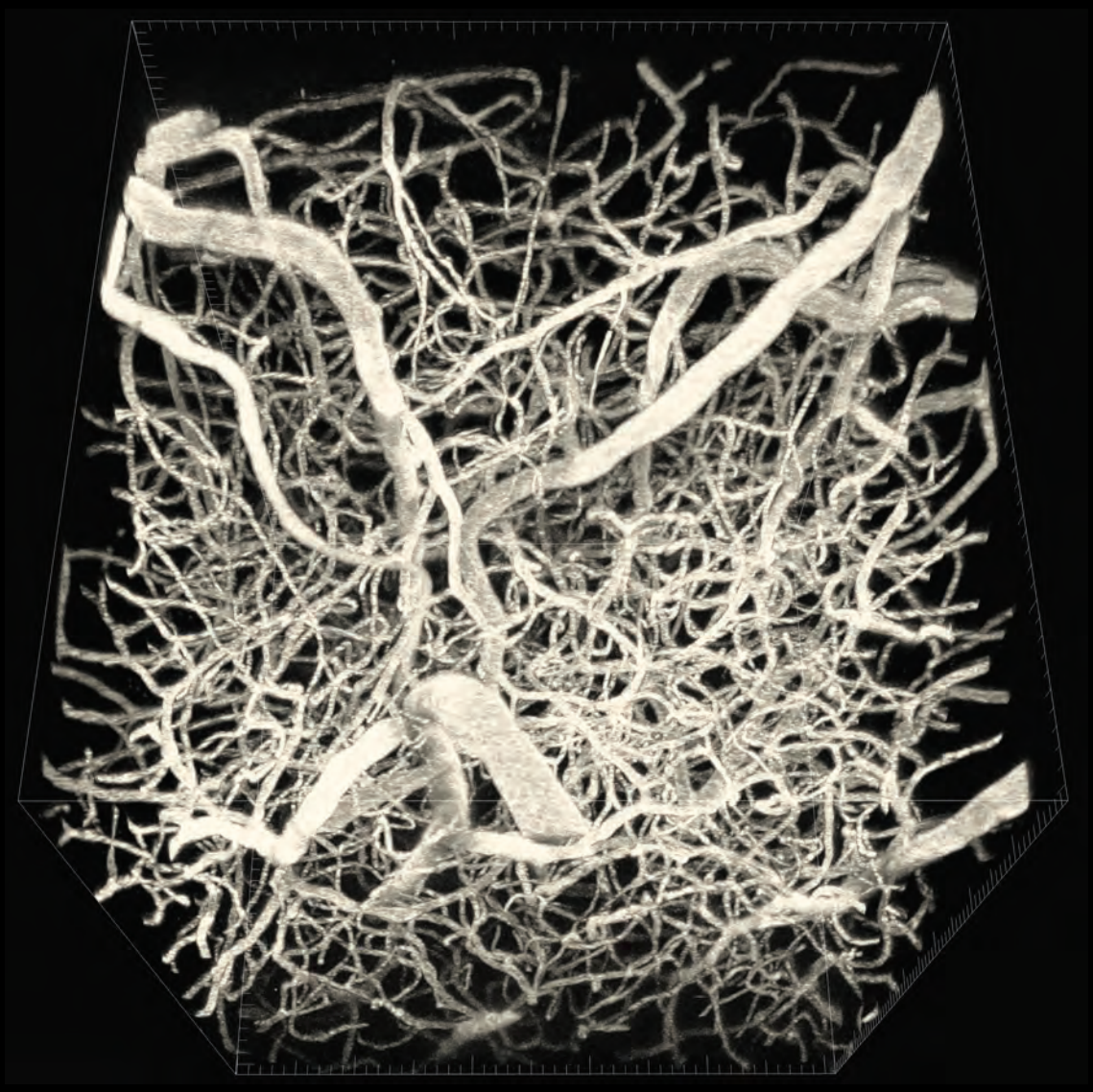
In addition to affecting neurons, or brain cells, most brain diseases, such as stroke and dementia, also cause injury to brain vessels.

Physicists and biologists at Sunnybrook Research Institute (SRI) are studying the mechanisms underlying changes in the structure and function of blood vessels in the brain following stroke or over the course of dementia, toward being able to understand these changes better, and, ultimately, translate that understanding into better care.

As part of this, they're using two-photon fluorescence microscopy. This noninvasive imaging technique allows an extremely detailed view of living brain tissue. With it, scientists can see into the working brain as much as one millimetre below the surface—very deep for brain imaging.

In this image, fluorescent dye is injected into the blood vessels of an adult mouse brain, allowing visualization of all vessels in a region of the neocortex that is one-half millimetre cubed—about the size of a needle's tip.

Image: taken with an Olympus FV1000MPE microscope. Adrienne Dorr, a research assistant in the lab of Dr. Bojana Stefanovic, acquired the image. The Canada Foundation for Innovation and Ontario Ministry of Research and Innovation provided funding for the microscope.



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