

SRI MAGAZINE

SUNNYBROOK RESEARCH INSTITUTE 2018



AGAINST ALL ODDS

**Improving Outcomes for Pregnant Women
and the Sickest and Smallest Babies**

Also in this issue: WOMEN IN SCIENCE

SRI MAGAZINE 2018

Inventing the Future of Health Care

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Messages

Getting Discoveries to People



IN 2018, SUNNYBROOK unveiled its new three-year Strategic Plan. It affirms our commitment to innovation, education and excellent care, and details how we will achieve strategic directions that honour and advance our vital role in the health care system. Ultimately, we seek to provide the best care to the most critically ill and injured patients.

This highly complex care comes to life through the dedication of our teams, as well as inventive research. The strategic direction Personalized and Precise Treatments captures how we are creating and using novel technologies to prevent and diagnose disease, and deliver precise treatments where few or no options exist.

One of the strongest examples comes from a research team who this year used focused ultrasound to open the blood-brain barrier in people with Alzheimer's disease. These landmark results inch us closer to the team's vision of being able to deliver therapies directly to the brain to treat diseases now deemed untreatable. You can read more about this research on page 4.

Also in this issue is a panorama of the tireless work of the Women & Babies Program. In finding new ways to care for women facing challenging pregnancies and creating best practices for babies born too early, all while saving lives along the way, these researchers are driven to rewrite the care manual for high-risk pregnancies and preterm birth or, better yet, prevent them from happening in the first place.

At the heart of it all remains collaboration, not only among teams internally and throughout the province, but also with the community—our patients and their families—supported by indispensable investment from our funding partners and philanthropic champions. Thank you all for helping us to invent tomorrow's health care.

Blake Goldring

Chair, Board of Directors
Sunnybrook Health Sciences Centre

Andy Smith

President and CEO
Sunnybrook Health Sciences Centre



AS A HOSPITAL-BASED research institute, making discoveries and getting them to our patients, and beyond, impels all that we do. Daily, Sunnybrook Research Institute (SRI) scientists and their teams work to close in on clinical impact.

A look back over the last year, captured in part by the stories in this year's magazine, shows they are gaining ground. The translational research of the Women & Babies Program is without parallel, pushing ahead to define and deliver personalized care, and help the most vulnerable babies live and thrive. Earlier this year, led by Dr. Jon Barrett, the program established the Alliance, a massive, province-wide initiative to get knowledge out of its creators' hands and into the real world, where it can prevent preterm birth and save lives on a scale not seen before.

This past year witnessed extraordinary achievement in other urgent-need domains, too. Focused ultrasound, a promising new approach for Alzheimer's disease, passed with flying colours its first clinical test, in a global first. A hand-held device showed that it could be used to print skin to treat burns. A noninvasive imaging technique distinguished benign from malignant tumours in breast cancer, without the need for needle biopsy. Remarkable, all, with many more, besides. Increasingly, our focus will turn to working with the province to streamline adoption of such discoveries into the health care system—an end-to-end solution.

This past year also saw many conversations about gender equity and diversity bubble up. Agencies like the Canadian Institutes of Health Research, the largest for such research, and the Canada Research Chairs Program, are tackling them head-on. Our features on women in science contribute to this conversation, by sharing the thoughts and experiences of successful female scientists at SRI, along with those of the generation coming up behind them.

Enjoy!

Michael Julius

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Digest

A round-up of notable advances at Sunnybrook Research Institute

Focused ultrasound makes major gains in studies of toughest-to-treat brain diseases

RESEARCHERS AT SUNNYBROOK Research Institute (SRI) have shown that it's possible to open the blood-brain barrier in people with Alzheimer's disease safely and repeatedly with MRI-guided focused ultrasound. The noninvasive technology used very low power sonic energy to open the blood-brain barrier and target areas of the brain where amyloid, the "sticky" plaque that signposts the disease, was located.

Results were published July 25, 2018, in *Nature Communications*. Dr. Nir Lipsman, neurosurgeon, scientist and director of the Harquail Centre for Neuromodulation, led the study with Dr. Sandra Black, neurologist, senior scientist and director of the Hurvitz Brain Sciences Research Program.



Sunnybrook scientists have published the first clinical study showing that focused ultrasound can be used to open the blood-brain barrier safely and repeatedly in Alzheimer's disease.

Launched in May 2017, the small trial recruited five patients who had amyloid in their brains and scores on a cognitive test that reflected mild-to-moderate Alzheimer's disease.

During the procedure, patients were fitted with the brain device, which looks like a helmet, and put into an MRI scanner, so that the team could guide and monitor the ultrasound delivery.

Focused ultrasound works by directing sound waves on a target. For the blood-brain barrier, when paired with microbubbles injected intravenously, that sonic energy has the effect of opening the barrier, which otherwise is drum tight to make sure no toxins get into the brain—the flip side of which is that almost no therapies can get in, either.

Within seconds, the blood-barrier was open, and focused ultrasound had reached its target. One month later, patients were treated in the same area but at twice the volume. After each procedure, next-day MRI scans confirmed the blood-brain barrier had closed. There were no serious adverse effects.

This advance is a crucial step toward being able to treat diseases with few, if any, options. Chief among these is Alzheimer's disease; by 2050, 12 million North Americans are likely to be living with this progressive illness.

In other world-first trials, the SRI team is evaluating the safety of focused ultrasound in amyotrophic lateral sclerosis, or Lou Gehrig's disease, which kills two to three people per day in Canada. Brain cancer, too, is under scrutiny, including a trial of focused ultrasound and chemotherapy in glioblastoma, the cancer that took the life of Gord Downie, as it does 96% of people within five years of diagnosis.

On the strength of the Alzheimer's disease trial results, scientists have

turned to a next-phase clinical trial, which will recruit more patients and target a different area of the brain.

Sunnybrook Research Institute has the world's most extensive program of focused ultrasound research. Led by Dr. Kullervo Hynynen, director of Physical Sciences at SRI, who pioneered the technology, physicists, engineers, biologists, neuroscientists and clinicians are working to advance development of the technology; study the mechanisms of how it works, alone and with therapeutics; and lead clinical trials of it.

Depression is also of intense interest. In May 2018, Lipsman launched a trial using focused ultrasound in a different way, as a kind of scalpel-free neurosurgery. When used this way, the beams have slightly higher power, enough that they can, with utmost precision, destroy problem-causing targets in the brain. The trial seeks to help people with a severe form of the disease for whom other treatments have failed. It follows the 2017 launch of a similar trial in obsessive-compulsive disorder.

Elsewhere in the central nervous system, in the spinal cord, SRI scientists have made a key discovery. Dr. Meaghan O'Reilly and Dr. Arjun Sahgal of Physical Sciences showed that using focused ultrasound to sneak a drug into the spinal cord of rats worked to ambush tumours there.

The therapy shrunk by about two-thirds a kind of tumour where cancer spreads from its original site to the cerebrospinal fluid and membranes covering the brain and spinal cord.

The study was published in *Scientific Reports* in June 2018. Apart from being able to treat tumours where palliation is the norm, results have implications for studies into spinal cord injury or neurodegenerative disease. **SR**

The Pitfalls of Split Focus

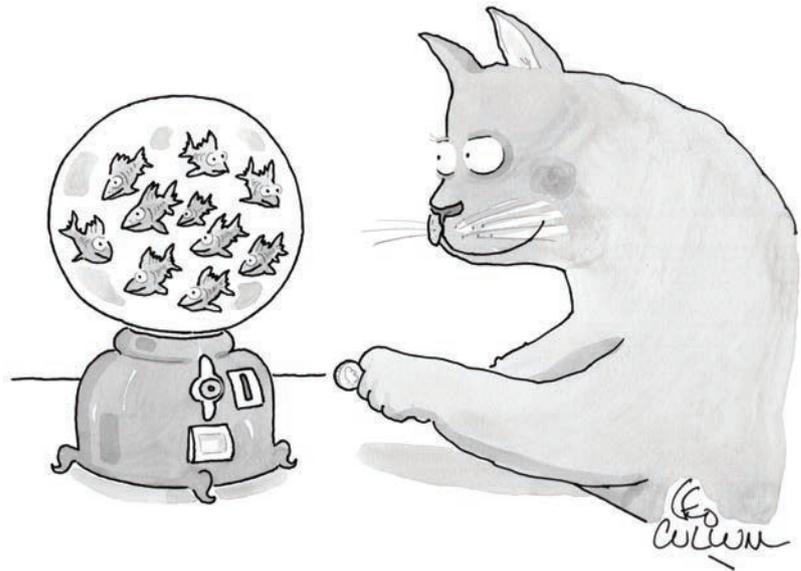
A CONTROVERSIAL PRACTICE is overlapping surgery, or double-booking. It occurs when a single attending surgeon is tasked with simultaneously supervising two or more procedures in separate operating rooms. One might say it's an effective use of resources, but others argue it jeopardizes care.

In the first population-based study to evaluate the implications of overlapping operations at the health system level, a team conducted research into whether these surgeries for hip fractures and hip replacements led to complications up to one year later. Complications examined included infection, dislocation and revision, meaning follow-up surgery performed to correct a misstep from a previous procedure.

Sunnybrook Research Institute scientist Dr. Hans Kreder and associate scientist Dr. Bheeshma Ravi, both in the Holland Bone and Joint Research Program, led the study. The orthopaedic surgeons looked at more than 90,000 operations in Ontario between 2009 and 2014, of which 960 were overlapping hip fracture surgeries and 1,560 were overlapping hip replacement procedures. They defined overlapping as overlap between operations lasting at least 30 minutes.

Although relatively rare, these surgeries were found to be associated with drawbacks. The discoveries, published in *JAMA Internal Medicine*, showed that overlapping procedures were linked to a roughly 90% rise in the risk of complications. These complications were directly tied to the technical aspects of the surgeries themselves. The risk for complications grew as the length of overlap increased, and it was noted that the risk of complications in overlapping hip fracture procedures was greater than that in hip replacement surgeries.

Despite the relative rarity of double-booking for these surgeries in Ontario, the findings underscore the need for surgeons to tell patients during the informed consent process if they will be performing another operation at the same time. **MP**



WORTHWHILE ACTIVITY

THE PROTEIN P53, which normally works to stop tumours from forming, is the most frequently altered gene in human cancers, but there is no clarity on how mutations are related to clinical outcomes. Or, there wasn't.

Dr. Jean Gariépy, a senior scientist in Physical Sciences at Sunnybrook Research Institute, and PhD student Nicholas Fischer are the first to detail a link between p53 mutations and survival in people with cancer. Their research shows that more active mutations of p53 are associated with longer—in some cases by years or decades—survival. The discovery suggests a path by which the gene's mutation status could help determine prognosis and guide treatment. The study was published in the journal *JCI Insight*.

Despite p53 long being linked to cancer, results from past studies looking at the link between the gene and outcomes have varied widely, because the mutations were studied as a whole.

Fischer and Gariépy took a different tack by comparing the activity of p53 mutations of more than 2,000 cancer patients. This activity includes regulating genes that repair DNA, for example. They found that people with a p53

mutation that enabled the gene to have even a small amount of activity lived longer than those who had a mutation that made the gene inactive. Of note, men with brain cancer who had a mutation resulting in up to 5% activity of p53 lived 42 months longer than those who had an idle p53 mutation. In stomach cancer, men with a p53 mutation with up to 5% activity lived 38 months, versus 16 months for men who had a mutation leading to an inoperative gene.

Strikingly, they also found that people who are born with p53 mutations in every cell of the body—a disorder called Li-Fraumeni syndrome, which predisposes people to develop cancer—have drastically different lifespans, depending on their mutation. For example, people with Li-Fraumeni syndrome with a mutation resulting in at least 25% activity lived 20 years longer, on average.

The researchers tabulated all clinically known p53 mutations and categorized them by activity. In the future, the hope is that doctors would be able to sequence patients' tumours and use the table to guide prognosis and treatment, for example, to decide to treat a patient with an idle p53 mutation much more aggressively. **AK**

YOUR HEART

PERIPHERAL ARTERIAL DISEASE (PAD) occurs when arteries carrying blood to the limbs become blocked. For the roughly 800,000 Canadians affected by PAD, endovascular treatment offers a less invasive method to restore blood flow than does traditional bypass surgery. During an endovascular procedure, a guidewire is used to locate the blockage, so that a balloon or a metal scaffold called a stent can be inserted to prop open the vessel.

Not all lesions can be treated this way, however, because some are simply too hard to penetrate. Indeed, 20% of these endovascular procedures fail immediately due to the inability of the guidewire to pass through. Predicting which blockages cannot be opened with a balloon or stent has, until now, been impossible, leading to delays in effective treatment and potentially worse outcomes.

To solve this problem, Sunnybrook vascular surgeon Dr. Trisha Roy developed an MRI technique that can identify which lesions are more difficult to cross. Working in the Schulich Heart Program with vascular surgeon Dr. Andrew Dueck, along with Dr. Graham Wright, director of research for the program at Sunnybrook Research Institute, Roy tested the method on 14 patients with PAD, all of whom had MRI before having the endovascular procedure.

In patients whose lesions were identified as hard by MRI, it took nearly 15 minutes for the guidewire to pass through, and more of these patients required a stent. In contrast, the crossing took just over two minutes in patients who had soft lesions, as shown on the MRI. Findings were published in the *Journal of Vascular Surgery*.

The study highlights the potential utility of MRI for selecting the most appropriate patients for endovascular treatment. **BZ**

Non Sequitur

The largest cherry orchards are in Turkey, which produces about 450,000 tons of this sweet or tart fruit each year, most of which it sends to Russia, which has beget some of the world's most noted writers, including Anton Chekhov, whose last play was *The Cherry Orchard*.



Sobering Study on Perinatal Suicide

IN ONTARIO, ONE in 19 maternal deaths is a suicide. The provincial suicide rate among women in the perinatal stage, the period immediately before and after giving birth, however, has remained unknown—until now.

perinatal suicide rate was 2.58 per 100,000 live births. Further, suicide accounted for more than 5% of deaths in perinatal women in Ontario. It was most common in the third trimester of pregnancy, and nine to 12 months after birth.

It was most common in the third trimester of pregnancy, and nine to 12 months after birth.

A team of researchers co-led by psychiatrist Dr. Sophie Grigoriadis, a scientist in the Hurvitz Brain Sciences Research Program at Sunnybrook Research Institute, investigated perinatal suicide rates in Ontario between 1994 and 2008. They linked coroner death records with health administrative databases to do this. Of the 1,914 women who died by suicide during this 15-year stretch, 51 were perinatal.

Presented in the August 2017 edition of the *Canadian Medical Association Journal*, the findings show that the

Suicide rates were highest in remote and rural regions, and women were more likely to die from violent means. Additionally, only about 40% of women who died by suicide had contact with mental health professionals within 30 days before their deaths.

The results stress the importance of risk assessment. They also emphasize the need for health care providers to focus mental health intervention efforts and suicide surveillance on pregnancy and the entirety of the first postpartum year. **MP**

Putting the Freeze on Pain

THE BEST TREATMENT for liver cancer or other diseases of the liver is to remove all or part of the organ. Researchers have shown that rates of liver surgery in Canada are on the rise—about six per 100,000 adults. The procedure is effective but leaves people in pain, which can cause difficulty breathing, delayed mobility and longer hospital stays. Pain control is therefore critical to a good recovery.

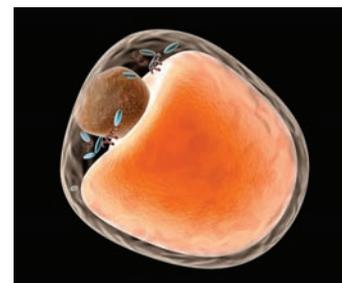
One way of achieving this is through patient-controlled analgesia. Here, patients are given opioids intravenously; at the press of a button, they control how often they get the drug. Opioids like morphine help with pain, but there are drawbacks: nausea, vomiting, constipation, breathing problems and potential addiction. The other option is to give patients a preoperative epidural that works well but also carries risks, like low blood pressure, spinal infection and neurological damage. For these reasons epidurals are not a popular choice among doctors.

Dr. Paul Karanicolas, a Sunnybrook Research Institute surgeon-scientist in the Odette Cancer Research Program, led a clinical trial to determine if delivering a local anesthetic to numb pain nerves—a technique called medial open transversus abdominis plane (MOTAP) catheter analgesia—reduces opioid use. The study,

which was published in the *Annals of Surgery*, included 153 patients who had open liver surgery at Sunnybrook and the University Health Network in Toronto, Canada.

At the end of the operation, doctors inserted catheters at the open surgical site. One-half of the patients were given ropivacaine, a local anesthetic, while the control arm received a saline solution. Patients in the MOTAP analgesia arm continued to receive ropivacaine for three days after the operation. Right after surgery, all of the patients were hooked up to a pump they controlled that dispensed opioid medication intravenously. The researchers studied how much opioids people used in the three days after the procedure.

On average, those who were given ropivacaine used 10 fewer milligrams of opioid 48 hours after surgery than those not given the anesthetic. Moreover, these patients reported feeling much less pain and, on the whole, were discharged one day earlier. Based on these results, Sunnybrook adopted MOTAP analgesia as the standard of care for patients undergoing open liver resection. The team has developed materials to help other surgeons learn the simple technique. **AK**



Revved-Up Fat Loss in Burns

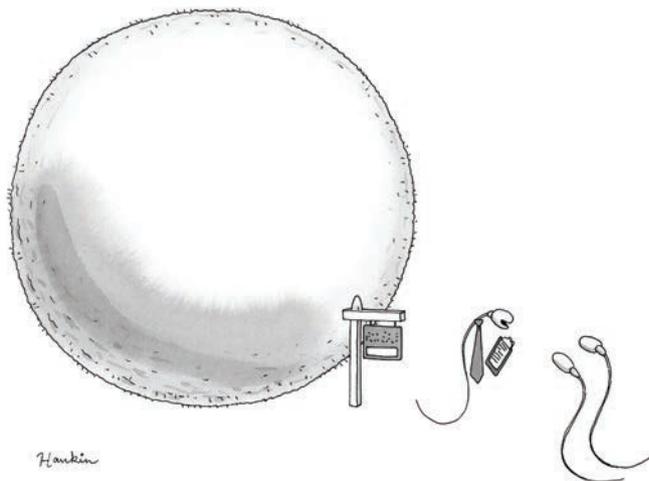
WHEN THE BODY shifts from accumulating fat to burning fat, it begins to burn energy instead of store it. This process is called browning, so named because fat cells change in colour from white to brown. Browning has been hailed as a promising treatment target for obesity and diabetes because it promotes weight loss and improves insulin sensitivity.

Dr. Marc Jeschke, senior scientist in the Tory Trauma Research Program at Sunnybrook Research Institute, and PhD student Abdikarim Abdullahi were among the first to show that browning is harmful in hypermetabolic conditions arising from burns and cancer. In such cases, the body goes into calorie-burning overdrive and begins to waste away.

In a paper published in the *Annals of Surgery*, Abdullahi, the study's first author, and Jeschke zoomed in on the mechanisms of browning that follow burns. They analyzed white fat tissue donated by burn patients and found that compared to samples from non-burn patients, there were more macrophages, a type of immune cell. These cells express a protein called interleukin-6 (IL-6), which activates browning.

They then studied preclinical models of burns and found that macrophages were recruited to white fat tissue, which then browned. Next, they studied mice that had the same injuries but were genetically engineered to produce fewer macrophages. In these models the browning process was impaired.

Results highlight the immune system's role in hypermetabolism caused by burns, and are the first to identify macrophages as central to IL-6-activated browning of fat after these injuries. **AK**



"It's perfect for starting a family."

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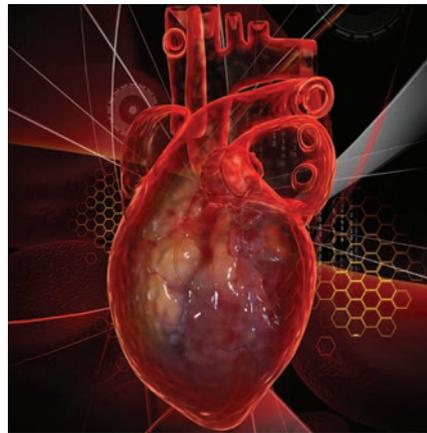
Targeted triage and more funding needed to help patients most likely to benefit from minimally invasive heart valve procedure: study

DEPENDING ON WHOM you ask, the average person spends between two and five years waiting in line. Queuing for the bus or a table at the newly opened restaurant is annoying, but when the payoff at the end is a potentially life-saving medical procedure, a long wait can have grave consequences.

“You have patients who are left waiting with a very serious underlying condition, which is anxiety provoking, but above and beyond that, when they’re waiting, they get worse,” says Dr. Harindra Wijeyesundera, an interventional cardiologist at Sunnybrook and a senior scientist in the Schulich Heart Research Program at Sunnybrook Research Institute. “I can only imagine how difficult it is for families. It is a helplessness situation to be in as a care provider.”

Wijeyesundera specializes in trans-catheter aortic valve implantation (TAVI), a minimally invasive procedure in which a new valve is installed in the heart via a catheter wound through the body’s blood vessels. Since its introduction to Ontario hospitals in 2007, TAVI has become the new standard of care for treating some patients with severe aortic stenosis, a condition in which the aortic valve narrows and restricts blood flow from the heart to the body. It’s a serious disease. Left untreated, the survival rate is 50% at two years and 20% at five years. The valve procedure offers an alternative to the open-heart surgery routinely used to replace damaged valves, but that could not be offered to elderly and frail patients deemed inoperable. Even so, for certain people with aortic stenosis the risk of rehospitalization and mortality remains high, regardless of surgical treatment.

As criteria for TAVI expanded and the province approved funding for the treatment, referrals for TAVI increased from roughly 450 in 2012 to 1,550 in 2015. So, too, did the number of procedures, albeit



DR. HARINDRA WIJEYSUNDERA researches wait times for trans-catheter aortic valve implantation in Ontario.

at a slower pace. “Year on year, the number of TAVI procedures done in this country and in this province has gone up,” says Wijeyesundera. “But has that increase in capacity kept pace with the increase in demand, as reflected by wait times?”

To answer that question, he and his team led by Dr. Gabby Elbaz-Greener, a research fellow in his program, turned to the CorHealth Ontario TAVI registry, which collects data on patient characteristics, referrals and TAVI-related procedures from 10 hospitals across the province and other health information databases. They found that between April 1, 2010 and March 31, 2016, the average wait time from referral to treatment was 105 days. When the researchers compared wait times before and after September 2012—that’s when the Ontario Ministry of Health and Long-Term Care approved funding for the procedure—they observed an initial decline in the pre-funding era, after which wait times remained nearly unchanged at 82 to 84 days.

“The fact that wait times have stayed essentially the same means that we’re in

balance,” says Wijeyesundera. “That’s a good thing, but it’s not necessarily an appropriate thing because that 100 days might be too long.” Indeed, his team found that for patients on the wait list, their odds of being hospitalized with heart failure was 14.7%, while their risk of dying was 4.3%—similar to the post-TAVI mortality rate. “The biggest predictor of dying on the waitlist was being on the wait list,” he says. “We will almost always have some degree of wait time; so, how do we triage patients and decide who should go first?”

One-half of this problem is identifying patients for whom TAVI is not suitable and taking them off the wait list. According to Wijeyesundera’s study, which was published in March 2018 in the journal *Circulation*, cardiologists are getting better at determining which patients would not benefit and would be better served with palliation and comfort care. In these cases, the time from the initial referral to being taken off the wait list dropped from 90 to 32 days.

Armed with these data, Wijeyesundera is working to convince policy-makers that there is a clear need for greater funding for TAVI procedures. He is a member of an advisory group that offers recommendations to the health ministry on how best to allocate funding and improve patient access to life-saving medical treatments. “I’ve been privileged in that I get to do the research, and through my membership in those advisory committees, I’m also able to present that to the policy-makers so that they have this [data] at their fingertips when they make those decisions.”

BETTY ZOU

This research is funded by the Heart and Stroke Foundation of Canada, Institute for Clinical Evaluative Sciences, Ontario Ministry of Health and Long-Term Care, and Ontario Ministry of Research, Innovation and Science.

As Fate Would Have It

Scientist pinpoints factors by which brain cells acquire specific identities

BY THE TIME a person reaches adulthood, they are expected to have figured everything out, including who they are. As for the neurons in their brain, however, their identities are determined long before then.

Understanding how these cells acquire their unique fates is a big part of Dr. Carol Schuurmans' identity as a neuroscientist. She studies how neurons develop in the neocortex, the outermost layer of the brain responsible for sensory perception, movement and language. "This part of the brain is formed of six layers of neurons," says Schuurmans, a senior scientist in Biological Sciences at Sunnybrook Research Institute and a professor at the University of Toronto. She slices her hands through the air to indicate each layer as she counts backwards from the sixth layer at the bottom to the first layer at the top. "Within each of these layers, [the neurons] have separate phenotypes," she explains. Phenotypes are the observable traits like skin colour and height that result from a combination of genetic and environmental influences.

In a study published in the *Proceedings of the National Academy of Sciences*, Schuurmans and her colleagues zeroed in on the fifth and sixth layers of neurons in the neocortex. "These lower layers are the neurons that communicate with the rest of the nervous system. They project out of the neocortex down to the spinal cord and other regions of the brain," she says. The researchers were particularly interested in layer 5 neurons, also known as upper motor neurons, because these are the nerve cells that are damaged in amyotrophic lateral sclerosis (ALS), which gradually paralyzes people as their brains lose the ability to communicate with their spinal cord and muscles. "This paper really sets the groundwork for

understanding how these layer 5 neurons acquire their specific identities, so [that] we can try and make new layer 5 neurons in a disease model," Schuurmans says.

Unlike many cells in the body, neurons stop dividing once they become neurons. The nerve cells then receive further instructions that enable them to gain specialized functions, not unlike doctors who undergo additional training to become specialists in cancer care or emergency medicine. Prior to Schuurmans' study, the genetic circuitry that led a neuron down one path and not another had been mapped out. She wanted to know what factors at the pre-neuron stage influence a nerve cell's final destiny. Extending the analogy, what experiences in a medical student's early education determine whether they became a cardiologist or a pediatrician?



DR. CAROL SCHUURMANS studies how neural precursor cells develop into mature brain cells, with the ultimate goal of replacing neurons lost in neurodegenerative diseases.

The researchers focused on two genes called *Neurog2* and *Ascl1* that are known to play a key role in coaxing neural precursor cells into full-fledged mature neurons. This process, known as neurogenesis, is exquisitely coordinated. Each neuron is born at precisely the right time and place to become part of a functional brain. Using a preclinical model, the researchers found that loss of *Neurog2* and *Ascl1* in neural progenitors causes neuronal specification to go awry in the neocortex. Cells ended up with the wrong layer identities—those destined to have a lower layer fate acquired an upper layer fate, instead, for example—because they were born at the wrong times. They also showed that both *Neurog2* and *Ascl1* are required for the fifth layer neurons to form. The researchers further demonstrated that the two genes control neuronal cell fate by controlling the levels of downstream neural regulators.

"People had known that neural identity is specified at the progenitor level," says Schuurmans. "What people did not know was 'What are the factors in progenitors that are these instructive determinants?'" This study is the first to show that *Neurog2* and *Ascl1* acting in progenitor cells contribute to neuronal identity in the neocortex. Schuurmans and her team are now using this knowledge to devise strategies to make new functional layer 5 neurons, one application of which will be to replace those lost in ALS. "We're targeting ALS, but the possibility is that it can be targeted to other diseases as well."

BETTY ZOU

Schuurmans' research is funded by the Canadian Institutes of Health Research. She holds the Dixon Family Chair in Ophthalmology Research.

Writing the Skin

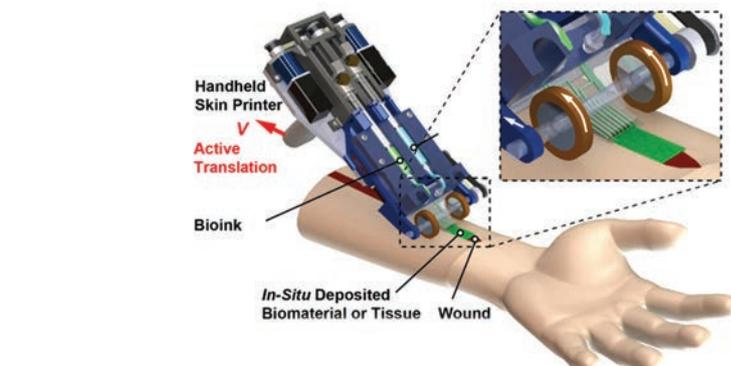
Team develops hand-held device that can deposit wound-healing tissue directly onto severe burns

“NATURE IS VERY clever. It usually outsmarts humans quite significantly,” says Dr. Marc Jeschke, a senior scientist in Biological Sciences at Sunnybrook Research Institute (SRI). He is speaking about the challenges of engineering skin, the body’s largest organ and bulwark against environmental assault.

Also a burn surgeon and director of the Ross Tilley Burn Centre at Sunnybrook, Jeschke isn’t backing down from this challenge. He is working with researchers at the University of Toronto, where he is a professor in the departments of surgery and immunology, to develop a hand-held skin printer. Weighing less than two pounds and resembling a packing-tape dispenser, the skin printer was designed in the lab of Dr. Axel Guenther, an associate professor in the department of mechanical and industrial engineering at U of T, by his PhD student Navid Hakimi. The “bio-ink” is a mixture of cultured cells and proteins. In April 2018, the team published a proof-of-principle study in the journal *Lab on a Chip* showing that the device can produce skin tissue sheets to cover wounds in preclinical models. Jeschke’s role was overseeing the biological studies, all of which were done at SRI.

The collaboration between Jeschke and Guenther began about five years ago. The skin-printing technologies they have worked on have come a long way. The first printer “looked like a fish tank,” says Jeschke, noting the process has been iterative. The early versions were not designed for use at the point of care. “The problem with that is [the skin] is very fragile. How do you carry something that’s printed and looks like a patient’s skin to the operating theatre and put it on a patient? There are many steps in between. Now we [could] print it directly on a patient,” he says.

The clinical need is dire. A third-degree



A rendering of the skin printer that is being developed in the lab of **DR. AXEL GUENTHER** in collaboration with Sunnybrook Research Institute senior scientist **DR. MARC JESCHKE**.

burn, caused by scalding liquid or flames from a fire, for example, destroys skin’s outer layer and hair follicles. Once gone, new skin will not grow. The only treatment for deep burns is to take healthy skin from elsewhere on the body and transplant it to the site of injury. This procedure, called split-thickness skin grafting, results in longer hospital stays, creates more wounds and poses a risk of infection. “Skin is very thin, and it’s being used over and over. It’s not ideal, but it’s currently the best we have,” says Jeschke. Sunnybrook cares for most people in Ontario who have burn injuries—about 300 people annually. Jeschke estimates the burn centre team conducts thousands of split-thickness skin grafts each year.

Other researchers have grown skin substitutes, but the resulting products are not functional, says Jeschke. They blister, and lack pigment and sweat glands. The biggest problem by far, though, is that they take too long to make. A wound from a large burn needs to be covered quickly. “Waiting six to eight weeks is not feasible,” Jeschke says. In addition to depositing skin directly on top of a wound, the hand-held skin printer works fast. As long as

there are sufficient quantities of cells, the printer can produce tissue sheets within minutes.

The next step is to determine the best source and exact composition of the bio-ink. The goal is to use complex and varied cell types like melanocytes, keratinocytes and fibroblasts, as well as sweat glands, to mimic human skin. Whatever the source, for example, from a patient’s biopsy sample, they will need a lot of cells, notes Jeschke. They will then test the formulation clinically to see whether the technology improves wound healing. Jeschke surmises that clinical trials are several years away. “This is just the delivery vehicle,” he says. “Now it’s up to us to study whether, biologically, we can add the components to make this into good, functional skin.”

ALISA KIM

This research was supported by the Canadian Institutes of Health Research, U.S. National Institutes of Health, Natural Sciences and Engineering Research Council of Canada, and Toronto Hydro. The Canada Foundation for Innovation provided infrastructure support through the Centre for Research in Image-Guided Therapeutics.

Sound Goal

Inexpensive imaging technique shows high potential to provide early and precise "acoustic" biopsy in breast cancer

IN CANADA, THE average wait time for a breast cancer diagnosis for women who need a biopsy ranges from five to seven weeks. That's easily more than one month of uncertainty and worry for women and their loved ones.

Imaging scientists in the Odette Cancer Research Program at Sunnybrook Research Institute (SRI) are developing a tool that could give women and their health care providers the answers they need much sooner. Dr. Ali Sadeghi-Naini and Dr. Greg Czarnota, who directs the Odette Cancer Research Program at SRI, led the team that is the first to show that quantitative ultrasound-based imaging can distinguish between benign and cancerous lesions. The paper was published in *Scientific Reports*.

"One of the benefits of this technique is that it's almost real time and it's accessible. Patients usually wait weeks for a biopsy or MRI results, but with this technique we could very quickly triage critical cases," says lead author Sadeghi-Naini.

In the study, 78 women with suspicious breast lesions were recruited from Sunnybrook. The researchers used quantitative ultrasound, a novel, noninvasive technique they developed, to classify benign lesions and malignant tumours. They compared their results with analyses of biopsy samples done by pathologists and studies of MRI scans done by radiologists. Using a hybrid quantitative ultrasound biomarker, the scientists found they could distinguish between benign and cancerous lesions with more than 90% accuracy.

The technique works by using the raw data generated by ultrasound machines and analyzing features of the ultrasound signal. The abnormal makeup of cancerous tissue tends to result in a higher-intensity signal, notes Sadeghi-Naini. "Tumour cells grow much faster and in an irregular manner. Usually, the cells

are dense and very tightly spaced, and the vasculature is very irregular. Potentially, the power of the echo we get from ultrasound is stronger."

Based on measurements of the return of the ultrasound signal throughout the lesion, the researchers are able to "map" its microstructure, which includes cells and blood vessels. Furthermore, by a method called texture analysis, they can show where in the lesion there are differences in signal characteristics that are based, for example, on changes in the size, density and spacing of suspicious cells, which give the images "texture."

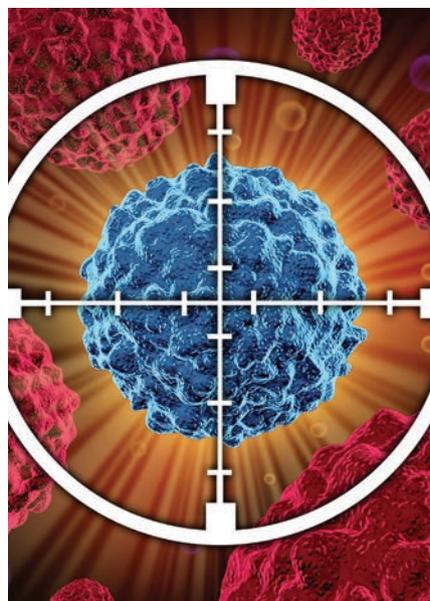
Dr. Belinda Curpen, a radiologist at Sunnybrook and a co-author of the study, notes that women with a breast lump normally undergo mammography, ultrasound and, if necessary, a biopsy. For women who come to Sunnybrook and are not in the Rapid Diagnostic Unit, where those suspected of having breast cancer

get a diagnosis one day after testing, it can take about a month to find out whether a lump is cancerous. Quantitative ultrasound-based imaging could improve efficiency. "We would be able to tell without doing a biopsy if something is malignant or not. We could reduce a lot of the biopsies that we're doing for lesions that are obviously benign on quantitative ultrasound," says Curpen, who says larger trials are needed before the technology can be adopted clinically, trials that Sadeghi-Naini notes are "a few years" away.

The goal, says Dr. William Tran, a scientist at SRI and a co-author of the study, is to be able to characterize different tissue types noninvasively. "That's really what we're chasing with this technique: high accuracy, high sensitivity and high specificity 'acoustic' biopsy in place of traditional pathological [needle] biopsy."

Knowing right away if a tumour is malignant would expedite treatment. Currently, it takes about a week to get a pathology report after a biopsy. If that report confirms someone has breast cancer, then there is another test to determine whether the tumour depends on certain hormones to grow. Chemotherapeutic drugs are prescribed accordingly. If, however, a tumour were to be classified as cancerous using quantitative ultrasound, then hormone receptor testing could immediately follow. "If we could do that right at the patient's appointment and say, 'OK, this is cancer, and this is likely to respond to this type of chemo,' that would be amazing," says Curpen.

ALISA KIM



Scientists at Sunnybrook Research Institute are developing a noninvasive ultrasound-based tool that aims to expedite cancer diagnosis.

This research was funded by the Breast Cancer Society of Canada, Canadian Breast Cancer Foundation, Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and The Terry Fox Foundation. The Canada Foundation for Innovation provided infrastructure support.

AGAINST ALL ODDS

Three peaches weighed more than Ivanna at birth. She was born at fewer than 25 weeks' gestation, 100 days early. A whisper on the scales, she was a scant 390 grams.

Just 48 days later, when this photo was taken, she weighed 1,350 grams.

Ivanna and the too many like her and mom Maria propel the research of the Women & Babies Program at Sunnybrook, which seeks to give pregnant women and the sickest and smallest babies their best chance.

As these stories show, they are in good hands.

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What Happens in Pregnancy Stays in Pregnancy—Not

Complications like diabetes and high blood pressure aren't only dicey while a woman is pregnant; they also can shape her long-term heart health

By ALISA KIM



Photo: Kevin Van Parassen

The physiological changes a pregnant woman experiences are profound, putting her body under tremendous strain. By the end of the second trimester, for example, her heart pumps out 40% more blood to provide more oxygen and nutrients to the fetus, placenta and rest of her organs. Her kidneys work overtime, cleaning her blood, which grows in volume during pregnancy, and filtering out waste from the baby that is released into her bloodstream.

Meanwhile, the placenta, which nourishes the fetus, makes hormones that, although critical to the pregnancy, make the body less sensitive to insulin. To counteract this effect, the pancreas churns out extra insulin. When it can't produce enough, glucose gets trapped in the blood, instead of being shuttled into the cells, causing high blood sugar. Pregnancy, then, can be thought of as a "stress test," where vulnerabilities like diabetes or high blood pressure can be exposed. These complications, say researchers at Sunnybrook Research Institute (SRI), are not simply benign quirks of pregnancy, but rather harbingers of disease that call for action.

"If your metabolism and your pancreas aren't able to handle the stress of pregnancy, and your blood sugars go up as a result, that's a sign that other stressors, like getting older, may also lead to diabetes in the future," says Dr. Baiju Shah, a scientist in the Schulich Heart Research Program at SRI and an endocrinologist at Sunnybrook.

Shah is researching the lasting impact of gestational diabetes, which develops near the end of the second trimester. He says that even though the condition goes away after delivery, it affects women and babies in the short and long term. Babies of women with gestational diabetes are bigger and at greater risk of birth trauma and staying in the neonatal intensive care unit. Moreover, one-half of all women with gestational diabetes develop Type 2 diabetes in their lifetime. These women are also more likely to have high blood pressure, high cholesterol and heart disease, notes Shah.

He is leading a study investigating whether the brief window of high blood sugars during gestational diabetes is associated with related problems like eye disease and kidney disease. "It was always thought that you just have three months of high blood sugars and that



Opposite page and above: **DR. ILANA HALPERIN** at a postpartum education class for women who had gestational diabetes. She is raising awareness that complications like high blood sugar and high blood pressure are risk factors for cardiovascular disease.

shouldn't have any impact on your eyes or kidneys. But increasingly it's been recognized that even people with mild blood sugar abnormalities that aren't diabetes—slightly above normal [sugar levels]—maybe do have an increased risk for these complications. Gestational diabetes is similar to that; they have high blood sugars now, but may have had slightly abnormal blood sugars before that," says Shah.

The researchers are conducting the first study to look at complications of gestational diabetes during pregnancy. They are analyzing images of the retina of women who have gestational diabetes, as well as those of women with a normal pregnancy. They are checking for hemorrhages in the retina, a sign of abnormal blood vessels in women with gestational diabetes. They are also measuring protein in the urine, as too much is a marker of kidney disease.

With patient recruitment complete, Shah is gathering results and will analyze the data for publication this year. He hopes that an upshot of the study is that women who've had gestational diabetes will be motivated to make healthy choices to prevent disease. "When you're 35 it's hard to think about heart disease in your 60s because it seems so far away. That's why we're trying to change that message a little bit, so that women are a little more aware."

Equipping women with resources to help maintain health is a passion of Shah's colleague, Dr. Ilana Halperin. A researcher at SRI in the Veterans Research Program and an endocrinologist at Sunnybrook, Halperin cares for pregnant women with diabetes—those who had it before pregnancy and those who developed it during pregnancy. Even though women with gestational diabetes are at much higher risk of developing diabetes later in life, Halperin notes that about only 30% get tested for high blood sugars after delivery. With reminders the screening rate can increase to 40%, but not all of these women attend postpartum education classes. She says low rates of postpartum diabetes screening and participation in classes are because women are preoccupied with caring for their children. "It's a really busy time of life. Women have a hard time prioritizing their own health. We see a lot of patients who had gestational diabetes and then spent a couple years away from health care. They come back pregnant and actually have Type 2 diabetes, and they didn't know they had it because nobody tested them between pregnancies."

She has partnered with Sunnybrook's diabetes education centre to offer group visits to women with gestational diabetes. The classes are an opportunity to review the results of diabetes screening

blood tests and offer education on lifestyle modification. Halperin notes that participants bring their children and enjoy brainstorming approaches to healthy living with other women. She attends part of the class to answer questions and provide one-on-one advice.

Halperin is the site investigator of a multicentre study called ADAPT-M, which stands for Avoiding Diabetes After Pregnancy Trial in Moms. Led by Dr. Lorraine Lipscombe at Women's College Research Institute, the trial is comparing the effects of health coaching about diet and exercise with that of standard care (providing resources on healthy lifestyle without personalized coaching) in women who've had gestational diabetes. The interventions occur over six months and include education on healthy eating and exercise plans that are individually tailored and delivered through phone-based coaching and follow-up visits.

There were 105 women who completed the pilot study, 32 of whom were from Sunnybrook. The researchers are analyzing the data. "We're looking at [the program's] effectiveness in terms of outcomes—insulin resistance and weight after completing the program, and how feasible it is to train nurses and dietitians to be health coaches for this population and anyone who's at risk for diabetes," says Halperin.

She and Dr. Karen Fleming, a co-investigator of the ADAPT-M study and division lead of family medicine obstetrics at Sunnybrook, are raising awareness that pregnancy complications like gestational diabetes and high blood pressure are risk factors for cardiovascular disease. "It's not really well understood by women or primary care

providers that what happens in pregnancy doesn't just stay in pregnancy," says Fleming.

In 2014, Fleming established the 4P Post Partum Maternal Health Clinic at Sunnybrook for women whose pregnancies were complicated by high blood pressure. The clinic offers counselling and education to improve health by targeting poor diet, lack of exercise and smoking. Fleming says that focusing on these areas significantly reduces the risk of heart disease, and that interventions are particularly important because heart disease is often viewed as a disease of older men. "We're not so good with women and heart disease. We're

“You're having a baby. The last thing you want to do is enter the pushing part of labour having been inactive.”

less likely to investigate; we're less likely to treat with cholesterol-lowering drugs; we're less likely to refer them to cardiac rehab; and they're less likely to stay in cardiac rehab. And heart disease is the number one cause of death in women," says Fleming.

There's also room for improvement in the relaying of pregnancy history to family doctors. There's no standardized process for documenting gestational

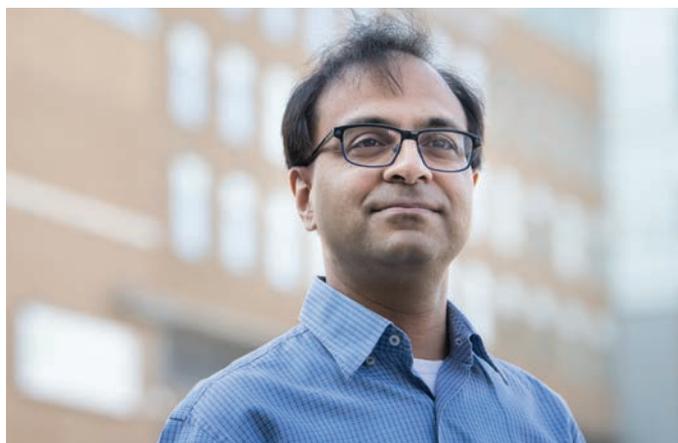
hypertension and diabetes in a patient's electronic medical record, notes Fleming, who says that it's either up to the patient to let her doctor know, or the family doctor needs to know to ask about issues arising during the pregnancy.

Her research bears this out. Her team conducted a survey of female patients of the Sunnybrook Academic Family Health Team to determine if pregnancy history is captured in the electronic medical record and whether primary care practices are identifying and screening women with pregnancy complications like high blood pressure and gestational diabetes. Of the 223 survey responses received, one-quarter of the women reported having a pregnancy complication. Of these, 25% said there was no discussion of future health concerns by their obstetrician or family doctor during a post-delivery visit. The next step is to develop a "prompt" function in patient electronic medical records to remind family doctors to inquire about their patient's pregnancy history.

To raise patients' awareness of this issue, she and her colleagues produced a postcard that is given to discharged patients. It prompts women to notify family doctors of any pregnancy complications and contains a link to online health education resources. Sunnybrook's family medicine obstetrics team now also sends a letter to the family doctors of women who've had complications during pregnancy. The letter lists the complication(s), summarizes the delivery and contains a referral to an education program. It also highlights the patient's risk for future cardiovascular disease and clinical recommendations



DR. BAIJU SHAH holds a drink that is used in a screening test for high blood sugar during pregnancy. He is leading the first study to look at complications of gestational diabetes during pregnancy.



DR. KAREN FLEMING is helping to write the new Canadian guidelines on exercise in pregnancy, which will be published in 2018.

regarding subsequent pregnancies.

One thing women can do to prevent pregnancy complications in the first place is to exercise, says Fleming. “You’re having a baby. The last thing you want to do is enter the pushing part of labour having been inactive. If you’re asking what can you do that’s going to make a difference, the answer is be active and exercise,” she says. She also notes that in addition to reducing rates of gestational diabetes and hypertensive disorders, exercise lowers rates of caesarean sections and depression in pregnancy. One of the challenges of encouraging exercise in pregnancy is countering false notions. “The trick is trying to engage women to be active because people are fearful. For many, pregnancy is a time where you’re encouraged to put your feet up and rest,” says Fleming. She recommends regular low-impact exercise prenatally, unless doing so poses a risk of harm.

Fleming is helping to write the new Canadian guidelines on exercise in pregnancy, which will be published in 2018. The current guidelines, published in 2003, apply only to women with low-risk pregnancies. The updated guidelines will be relevant to more women and are based on extensive research. “We know not everyone is low-risk. Almost one-half of women have a body mass index of over 25 when they come into pregnancy. So what are the recommendations for different populations of people?” says Fleming.

In her practice, she sees elite athletes and professional dancers who are pregnant (she delivered both of the National Ballet of Canada’s Heather Ogden’s babies), and has surveyed Masters swimmers in partnership with Masters Swimming Canada. She found that many were exercising beyond current exercise guidelines and 25% of them competed while pregnant. There were no reported cases of gestational diabetes and low rates of operative deliveries.



Fleming also found that, in many cases, these women were receiving guidance on exercise in pregnancy from coaches, not their doctors. This led to a survey of the coaches, who expressed an interest in online education modules to help them meet the needs of their athletes.

For pregnant women who struggle to access resources on education and exercise, Fleming collaborated with colleagues from Michael Garron Hospital and Thorncliffe Neighbourhood Office to offer yoga classes and group education in Thorncliffe Park, a community that is densely populated with newcomers to Canada. The pilot program, which also provided child care, resulted in increased rates of physical activity among the participants. For women with barriers to attending education

classes, she is looking into the use of technology, including online modules and virtual support groups. These are the kinds of initiatives that Halperin says are needed to prevent chronic disease. “Most people I talk to say, ‘I know I need to exercise more and eat better, but I’m a working mom with two small kids. I can’t find the time.’ It’s about the public health changes we need to do to make [having a] healthy lifestyle more accessible,” she says.

Fleming’s research was supported by Michael Garron Hospital, Sunnybrook and the University of Toronto. The ADAPT-M study, of which Fleming and Halperin are a part, is funded by the Canadian Institutes of Health Research (CIHR). Shah’s research is funded by CIHR.



DR. MICHELLE HLADUNEWICH (left), who formed the Pregnancy and Kidney Clinic at Sunnybrook, evaluates the role of the placenta in pregnant women with kidney disease.

Changing Expectations

The landscape for pregnant women with kidney disease has for years been barren, but advanced technologies and fresh approaches are starting to seed options

By **MATTHEW PARISELLI**

Some scientists are spurred by an insatiable curiosity. A novel idea germinates in their brains, and they're driven to the lab bench to test it. Dr. Michelle Hladunewich, an associate scientist in the Women & Babies Research Program at Sunnybrook Research Institute (SRI), operates differently.

"I do research based on clinical things I see in my practice," says the nephrologist, a type of doctor who specializes in

treating kidney disorders. "There are holes in our ability to care for people properly, and that's what motivates me to study a research question." Hladunewich, who is also an associate professor at the University of Toronto, adds, "I can put a face to pretty much everything I'm doing. I see people who have issues, and I want to help them."

One group she endeavours to help is women with kidney disease who are pregnant or considering pregnancy, a population she says can be tricky to treat because each patient requires an individ-

ualized management strategy. Kidney disease is a term encompassing a variety of diseases and disorders affecting the kidneys, most of which result in the organs' inability to filter waste from blood and remove excess fluid from the body. Ranging from mild to severe, it's estimated that one in 10 Canadians has kidney disease.

Research on pregnant women with kidney disease is sparse. There is no statistic on how many of these women go on to deliver babies—although Hladunewich plans to change this via her work—

and results from a recent survey by the Ontario Renal Network indicate only about 10% of nephrologists are comfortable caring for pregnant women with kidney disease. Hladunewich attributes this to the disease's rarity and those doctors' lack of exposure to kidney-compromised

sions, though."

With the registry and clinic reaching a critical mass, she and her colleagues can apply for grants. One grant they've received is for a study headed by Hladunewich and Dr. Nir Melamed, an associate scientist in the Women & Babies Re-

ing women whose bodies have failed to adapt to pregnancy, and who therefore are at increased risk of complications. At the moment, blood pressure is the only measurement taken in the clinic, which Melamed says may not provide enough information to determine if a woman

"We give our opinion, but it's their choice. I would sure like to be using better data when helping them make such big decisions, though."

pregnant women during training, in addition to lack of evidence-based guidelines.

To assist these women and provide doctors with confidence in treating them, nearly 10 years ago Hladunewich established the Pregnancy and Kidney (PreKid) Clinic—the largest in Canada, which manages pregnant women with kidney disease—and began building a registry that now includes approximately 1,000 women from which meaningful information can be extracted. One of the earliest findings pertains to dialysis.

Canadian women on dialysis, a treatment that partly replaces kidney function, were told to avoid pregnancy five to 10 years ago because the live birth rate for women who did deliver was less than 50%, Hladunewich says. She adds that this remains the case in the U.S. "Our first pregnancy on dialysis was accidental," she says, before explaining that she and her colleagues did not expect fertility to return with dialysis. "With better dialysis, women became pregnant and did well; so, we changed our stance on it and made it an option. Now, we've had over 30 women [between Sunnybrook and Mount Sinai Hospital] deliver on dialysis. It's important to show women that you can have a baby [while] on dialysis."

The aim of the registry, which is the largest in North America, is to arm specialists with the evidence they need to help women make informed choices about pregnancy. "These women are making life or death decisions—whether they should have a child or terminate their pregnancy," Hladunewich says. "We give our opinion, but it's their choice. I would sure like to be using better data when helping them make such big deci-

search Program at SRI and maternal-fetal medicine specialist at Sunnybrook. Together with Dr. Dini Hui, who is also a maternal-fetal medicine specialist at Sunnybrook and who helped launch the PreKid Clinic, they will investigate the role of the placenta in pregnant women with kidney disease.

Their research aims to identify biological substances in the blood, so-called "biomarkers," that can reveal information about the current and predicted future health of a woman and her baby. "We're looking for markers that are released by the placenta into the bloodstream, and we're correlating that with [the woman's] kidney disease and then her baby's outcome," Hladunewich says. Melamed, who is also an associate professor at U of T, adds, "Managing pregnancies in these women with kidney disease can be very challenging, so what we're trying to do is use new technologies and new approaches to help us guide treatment." Launched in January 2018, the study will run for two years.

One such technology is a noninvasive cardiac monitoring system, which takes readings from electrodes placed on a woman's wrists and ankles, and depicts them on a computer screen for practitioners to evaluate. As Melamed gazes toward the machine in his office, his eyes light up, and he says, "This sophisticated device allows us to noninvasively check multiple hemodynamic parameters, such as cardiac output and vascular resistance—things we can't usually measure and record. It gives us insight into what's happening." He equates the device's ease of use to that of an electrocardiogram, and says measuring hemodynamic parameters can be of great value in identify-

with kidney disease is adapting to pregnancy. He adds that other physiological information yielded from the machine would indicate what medication is best suited to a particular patient.

With approval from Sunnybrook's research ethics board to record measurements and track outcomes throughout the pregnancies of consenting women, Hladunewich says the goal is to incorporate the device into everyday practice. She and Melamed will collect data for two years—they need to have data from roughly 200 patients—prior to making a case for the device's routine use to manage blood pressure in the clinic better and identify which women need interventions to help prolong their pregnancies and deliver a baby successfully.

Before Hladunewich returns to one of the 50 patients she sees in a week, she revisits her motivation and the striking figure that only about 10% of nephrologists are comfortable treating pregnant women with kidney disease. "I never, not in a million years, would have thought people were that uncomfortable," she says. "We're filling a big gap here. We have to evolve care for these women. Every woman has her very own reason for [having a child], and we have to be respectful of her choices. Some will feel strongly that they have to have a child, even if it's a peril to their own well-being. It's our job to make it safe, to help them time it, to get them as healthy as possible and then support whatever their decision is."

Hladunewich's research is supported by the Canadian Institutes of Health Research, Cancer Care Ontario, the Kidney Foundation of Canada and Roche Diagnostics.

Sleuthing for the Biological Basis of Pre-Eclampsia

Cells lining blood vessels offer clues to the origin of dangerous disorder

By ALISA KIM

In her 2010 memoir, *Spoken From the Heart*, former U.S. First Lady Laura Bush wrote about a scare during her pregnancy with her twins. During the third trimester, her blood pressure became dangerously high and her kidneys began to fail, causing her doctor to order an emergency caesarean section. Her daughters, Barbara and Jenna, were born five weeks early, putting them at risk for a host of problems, including infections of the lung and brain, poor vision, hearing loss and chronic lung disease.

Her story is one of several high-profile accounts that has raised awareness of pre-eclampsia, a pregnancy complication that is characterized by very high blood pressure and too much protein in the urine, a sign that the kidneys are not working properly. It develops in the second half of pregnancy, usually after the 20th week. Symptoms include sudden weight gain, swelling, headaches and changes to vision. Left untreated, the condition can be devastating, damaging the liver, kidneys or brain in mothers; it is also associated with smaller babies and results in premature birth since the only cure is delivery.

About 10,000 pregnant women in Canada are affected by pre-eclampsia each year. According to the World

Health Organization, pre-eclampsia is a leading cause of illness and death in women and babies. It estimates that between 62,000 and 77,000 maternal deaths are due to pre-eclampsia and other hypertensive disorders each year. The Preeclampsia Foundation notes the condition is responsible for 2.6 million preterm births and 500,000 infant deaths worldwide each year.

“Women with pre-eclampsia might have an underlying cardiovascular disorder, but many of them are considered to be completely healthy before they develop it. These women, for mostly unknown reasons, develop an abnormal placenta, which causes pre-eclampsia later in the pregnancy. In most cases we do not know why they develop an abnormal placenta; sometimes it just happens, or it could be associated with a clotting disorder, unusual immune response, genetic issues or multiple factors,” says Dr. Ori Nevo, a scientist in the Women & Babies Research Program at Sunnybrook Research Institute (SRI), and maternal-fetal medicine specialist at Sunnybrook.

Despite its prevalence and long history—it’s believed that Hippocrates was the first to describe the complication in 400 BC—its exact cause is unclear. It is also called “the disease of many theories,” owing to numerous ideas about its

origins. Nevo is trying to pinpoint its biological genesis. He is the first to analyze maternal endothelial cells, which line the inside of blood vessels, to see if they function differently in women with pre-eclampsia. Why study them? This layer of cells acts as a barrier between the blood and body tissue, while selectively allowing chemicals and white blood cells to move between them. Researchers have shown that endothelial cells play an important role in maintaining the health of the circulatory system; they release substances that control the formation of new blood vessels, relaxation and contraction of vessels, blood clotting and immune function.

After getting consent, Nevo obtained samples from healthy women and women with pre-eclampsia. “We take little samples of fat tissue during a C-section. We have a method of isolating endothelial cells from those samples, and we grow the cells in a dish and see how they behave,” he says. He notes that while there are placental tissue banks for research, the bank of maternal endothelial cells he has created at SRI is unique.

He specifically wanted to know whether the endothelial cells of women with pre-eclampsia express the same genes related to blood vessel function as

“We know these women have long-term cardiovascular issues and their vessels are not responding as well.”

those of healthy pregnant women. “We found differences in several genes that participate in normal vascular function. After several weeks of growing in the dish, those cells are still functioning abnormally. We showed for the first time that the endothelial cells [of women with pre-eclampsia] are abnormal, probably because of the pre-eclampsia,” says Nevo. The study was published in the *American Journal of Physiology-Heart and Circulatory Physiology*.

In particular, he observed that gene expression associated with high blood pressure was exponentially higher in the pre-eclamptic samples. Moreover, there was decreased expression of genes associated with relaxation of vessels. Nevo says the results could provide insight into the risk of cardiovascular disease after pre-eclampsia. Even though blood pressure often returns to normal after delivery, women with pre-eclampsia are not out of the woods. A 2007 study published in the *British Medical Journal* showed these women have almost four times the risk of developing high blood pressure and double the risk of heart disease and stroke. “We know these women have long-term cardiovascular issues and their vessels are not responding as well. What we see might explain those long-term issues,” he says.

Nevo has also looked at the effects of certain drugs on gene expression in maternal endothelial cells. One is magnesium sulfate, which is used to prevent seizures in women with pre-eclampsia. The drug worked differently in the endothelial cells of pre-eclamptic women. Here, magnesium sulfate decreased the expression of substances



DR. ORI NEVO aims to uncover the root cause of pre-eclampsia. He is studying gene expression of maternal endothelial cells, which line the inside of blood vessels.

that cause blood vessels to constrict and that hinder the growth of new blood vessels. That the endothelial cells of women with preeclampsia respond well to magnesium, which dilates blood vessels, suggests there is an intrinsic deficiency in these cells, state Nevo and colleagues in a paper published in the *Journal of Hypertension in Pregnancy*.

Next, he will test the use of drugs to lower cholesterol to see if they reverse abnormal gene expression in endothelial cells of women with pre-eclampsia. He will also investigate how the endothelial cells interact with perivascular cells, the smooth muscle cells that surround blood vessels. The ultimate aim is to find more therapies. Pre-eclampsia is treated with drugs to lower blood pressure or magnesium sulfate to prevent seizures. They are given so that the pregnancy can continue longer. Some blood pressure medications, however, are unsafe in pregnancy, and magnesium, administered intravenously, is only given once a woman is admitted to

hospital.

Bush did everything she could do to prolong her pregnancy, including following the doctor's orders putting her on bed rest at seven months. She was fortunate that she and her daughters had no further health issues following her bout with pre-eclampsia, but as the statistics show, that is not the case for thousands of women and their babies each year. Detecting the condition as soon as possible is critical to managing the illness before it becomes life-threatening, necessitating the emergency surgery that Bush had. So, too, is finding better treatments, which rests in unravelling the biological basis of the disease. As Nevo's research suggests, the cells embedded in the life-sustaining blood vessels that nourish mother and child could hold the answer, a mystery he is tackling one batch of cells at a time.

Nevo's research was supported by the faculty of medicine at the University of Toronto, and the Women & Babies Program at Sunnybrook.



With the help of a Sunnybrook team that cares for pregnant women with physical disabilities, **KALEY ROOSEN** gave birth to her daughter **GWENDOLYN** in 2017.

One Size Does Not Fit All

Designing personalized care for pregnant women with disabilities

By **MATTHEW PARISELLI**

In 2017 Kaley Roosen added a layer to her identity that for years she thought would evade her: mother. On October 18 she and her husband David Preyde welcomed into the world a healthy baby girl at term, whom they named Gwendolyn. It was a joyous day for the newly minted parents.

The birth of Gwendolyn carried deep significance for Roosen, who is a clinical psychologist based in Toronto. As a 12-year-old, Roosen learned she had muscular dystrophy, which comes in many forms and results in the weakening and wasting of the body's muscles. She had known for years that something was wrong because she struggled to keep up with her peers and running was difficult, but she didn't know why. She was hopeful a diagnosis meant that a solution existed.

Her optimism faded, however, when she was told her physical abilities would only worsen.

When she was 16 and became a wheelchair user, Roosen's diagnosis changed from one of the more common dystrophies that also affects the face to limb-girdle muscular dystrophy. The latter is characterized by excessive breakdown of muscles in the shoulders, upper arms, pelvic area and thighs. Determining the incidence is difficult, because features of the condition vary and cross over with those of other muscle disorders, but it's estimated that one in 14,500 to one in 123,000 people have limb-girdle muscular dystrophy.

Instead of fixating on how her condition would alter her life, Roosen vowed to dedicate her energy to pursuing a fulfilling and lucrative career. In 2017 she

successfully obtained her PhD in clinical psychology. Starting a family was not on her to-do list; she didn't think it was even feasible for many years. She reassessed her life plan, though, when she met other mothers with disabilities after moving to Toronto. Later, when she became pregnant, it was a matter of figuring out how best to manage the health of herself and her future baby. Thanks to Sunnybrook's care team, led by Roosen's physician Dr. Anne Berndt, the birth of Gwendolyn was made possible.

It isn't unusual for women with physical disabilities to question their chances of becoming mothers, says Berndt, who is an associate scientist in the Women & Babies Research Program at Sunnybrook Research Institute (SRI) and an assistant professor at the University of Toronto. "If you have people telling you outright or

through suggestion that [being a mother] isn't for you, it's going to make you doubt yourself. Self-doubt comes along if you feel society is not supportive of you, or you're not seen as the image people think of in their minds [when they think of] a mother."

Roosen, a native of Pembroke, Ont., agrees. "I grew up in a small town. I didn't know another disabled person, and I never would have imagined a disabled person married [with] kids. I always felt that wasn't my path." The old insecurities she felt about becoming a disabled parent were later amplified when she found out she was pregnant.

Through her work, Berndl endeavours to dismantle the prejudice she says exists against women with physical disabilities from society and the health care system. She conducts her research via the Accessible Care Pregnancy Clinic at Sunnybrook, which she established in 2017 and has helmed since then. The first of its kind in North America, the clinic manages and cares for women who have disabilities and are pregnant or contemplating pregnancy.

One of Berndl's projects is a breastfeeding study, in which Roosen is participating. Women with physical disabilities who breastfeed their babies are interviewed about how long they breastfeed, when in the day, attitudes they've encountered, support they've received and techniques they use. The objectives are to address challenges women with physical disabilities face when breastfeeding and equip lactation consultants with evidence-based information, to advise better those women.

The study is in the early stages and remains local, but Berndl stresses that the goal is to expand countrywide. "This is part of normalizing and facilitating birth for all women with physical disabilities," she says. Roosen's rationale for participating reflects Berndl's statement. "As a disabled woman, unfortunately, I am used to being overlooked in most research endeavours, particularly around motherhood. I hope [this] study leads to more research in this area, so that other disabled moms don't feel so much like trailblazers for simply having a child, something women have been doing forever," Roosen says.

Berndl is working with Dr. Paige Church, an affiliate scientist at SRI and neonatologist at Sunnybrook, to probe the experiences of women with spina bifida. A birth defect that results in the neural tube's failure to develop properly

or close, spina bifida can cause mobility difficulties, challenges in bladder and bowel control, full or partial paralysis, and hydrocephalus (fluid on the brain). In Canada, about 120 babies are born with spina bifida per year.

Berndl and Church, who has spina bifida herself, sent online surveys to women with the condition in Ontario and plan to conduct one-on-one interviews. Their aim is to understand better the needs of these women during pregnancy, identify areas in which care providers need improved education and encourage more research in a field peppered with gaps.

Two striking findings have emerged out of the 30 surveys returned: most of the women never spoke with their care providers about contraception, and fewer than one-half were told that taking extra folic acid helps to decrease the probability of their offspring developing spina bifida. Dr. Julia Kfoury, a clinical associate at Mount Sinai Hospital, is also involved in the project.

Church isn't Berndl's only research partner at Sunnybrook. Dr. Anne McLeod, a hematologist, is another. They are looking at what should be done from a preventive health perspective for pregnant women with physical disabilities who use wheelchairs. Enter thromboprophylaxis [throm-bo-pro-fi-lak-sis], a treatment given to prevent blood clots.

Berndl says blood clots are a significant risk for pregnant women, who have a higher chance of developing them in their legs or lungs due to hormonal changes. This potentially life-threatening situation is magnified in pregnant

women with physical disabilities. "Having a decrease in mobility increases the chances of getting blood clots," she says. Compounding the problem is lack of knowledge around when and to which patients to give the treatment. "There's nothing concrete to guide us, so we're hoping to develop a set standard by looking at the opinions of hematologists," Berndl says. The goal is to distribute the survey throughout Ontario and beyond, so that a reasonable standard of care can be generated and evidence-based guidelines can be produced.

Berndl is also writing practice guidelines on the management of women with physical disabilities in labour for the Society of Obstetricians and Gynaecologists of Canada. Further, she is researching the pregnancy experiences and outcomes of women with dwarfism, with Little People of Canada, as well as the experiences of women with cerebral palsy and myasthenia gravis—all areas in which research is severely lacking.

As for Roosen, she is healthy, happy and with support from the province's direct funding program, a service that allows her to hire an attendant of her choice to help with child care, loving motherhood. She says she's comforted by the knowledge that if she chose to get pregnant again, Berndl would be there.

Berndl's research is supported by Sunnybrook and the University of Toronto.

Visit sunnybrook.ca/research/magazine to read more about Kaley Roosen's story.



DR. ANNE BERNDL (right) is shedding light on the experiences of women with disabilities before, during and after pregnancy, with one study focused on breastfeeding.

The Grey Zone

There's scant evidence to guide decision-making around babies born at the edge of viability; that needs to change, says specialist, whose research is spawning results

By ALISA KIM

In 2009, Jennifer Lake was just past the midpoint of her pregnancy when she went into labour and gave birth at home. Her 22-week-old son was taken to St. Joseph's Hospital in London, Ont., where he was admitted to the neonatal intensive care unit.

Doctors told her that her son likely would not survive, and if by the slimmest of chances he did, then his quality of life would be dreadful, Lake said in a 2015 article published in the *National Post*. She was counselled by medical staff to take him off life support, but she rejected the recommendations. Six years later, her son, Carter, despite some physical and neurological disabilities, was preparing to enter Grade 1. "He lights up my whole entire life," Lake said in the story.

The case highlights how thorny the issues are around counselling and management of babies born extremely early. At the time of Carter's birth, the Canadian Paediatric Society's guidelines for managing extreme preterm birth strongly recommended that babies born at 22 weeks of gestation not receive life-saving measures, only comfort care. In 2017, the organization revised its guidelines, stating: "When an extremely preterm infant is born but no decision has been reached regarding the management plan ... the infant should usually receive early intensive care until shared decision-making or further discussion with the parents can occur."

According to Statistics Canada, about 8% of all births in the country are preterm, or before 37 weeks—the point at which fetal development is thought to be complete. Premature birth can result in difficulty breathing, bleeding in the brain and major intestinal disease; the more premature a baby is, the greater the problems are likely to be. A fetus is

considered viable if it is capable of surviving outside the womb. For those born at the brink of viability—between 22 weeks and 24 weeks plus six days of gestation—survival is lower, and the odds of severe disability are high. These include intellectual disability, cerebral palsy, blindness and deafness.

The occurrence of extreme preterm birth is about 2% of early deliveries, notes Dr. Noor Ladhani, an associate scientist in the Women & Babies Research Program at Sunnybrook Research Institute and a maternal-fetal medicine specialist at Sunnybrook who treats women with high-risk pregnancies. Her practice includes women who've had a stroke or a history of preterm birth or stillbirth, and women with either blood clots or the human immunodeficiency virus. I meet with Ladhani to discuss her research on medical interventions performed on babies born at the borderline of viability. They are, according to her, "the most vulnerable." A baby born at 23 weeks' gestation, for example, typically weighs about 500 grams.

The more premature a baby is, the greater the problems are likely to be.

Her research aims to provide evidence that will help with decision-making in situations that are unexpected and distressing for parents, and difficult to manage medically and ethically for practitioners. The challenges are significant, Ladhani says. "Research is hard in this area because the rates [of extreme preterm birth] are low, and because every case is different. And because it's such a stressful time for families, doing a ran-

domized controlled trial is not feasible."

She notes that there are studies showing the benefits of obstetric interventions used on babies who are between 28 and 30 weeks' gestation. These include administering steroids, delivery via C-section and giving magnesium sulfate. The outcomes of these babies are also better if they are delivered at a centre with a neonatal intensive care unit. There is very little published, however, on babies born at the lower limit of viability. "Until a few years ago we weren't even resuscitating these babies, so the data are really sparse," says Ladhani. "In women who were at 23 weeks, we were using a 'wait and see' approach. It didn't make sense because we know those interventions can improve outcomes. My interest came from seeing if those interventions would be of benefit to those babies."

Ladhani has studied whether extremely preterm babies in the breech, or feet-first, position have improved survival if they are born via C-section. She examined records of breech births of babies who were between 23 and 25 weeks' gestation and delivered at Sunnybrook between 2003 and 2013. She found the rate of death was about 20% lower in the babies who were delivered surgically. "There's lots of controversy because we know that a C-section at that early stage can have dramatic effects for a woman. Women bleed more, and it affects their future pregnancies. But if we think it confers survival benefit to the baby, then we have to give a woman the choice," says Ladhani.

She is also conducting a study on the use of steroids on babies born between 23 and 25 weeks' gestation. Steroids generally improve outcomes for infants born prematurely by reducing the risk of respiratory distress syndrome, bleeding in the brain and damage to the intestinal



DR. NOOR LADHANI researches the use of obstetrical interventions on babies who are born at fewer than 26 weeks of gestation—the borderline of viability. She is studying whether use of steroids on babies born between 23 and 25 weeks' gestation improves outcomes.

tract. They have also been shown to shorten stays in the neonatal intensive care unit and improve survival. The results of the study are not yet available, but she cites a systematic review and meta-analysis by researchers at McMaster University showing that giving steroids to babies born before 24 weeks of gestation reduced the risk of death to discharge by about 50%.

As the use of life-saving measures on babies born extremely prematurely evolves and the lower limit of viability shifts, both families and care providers need guidance. To this end, Ladhani and colleagues published clinical guidelines for the management of infants born before 26 weeks' gestation. Published in the *Journal of Obstetrics and Gynaecology Canada*, the guidelines summarize findings from published research in this area, like giving steroids to babies after birth and using continuous fetal monitoring. For her next project, she will interview women with a history of extreme preterm birth to understand how to improve counselling in these difficult situations. Ladhani says she is eager to learn what information they want to help them decide what to do. "Because decision-making is so important for family outcomes, and because survival—and survival without disease—is not guaranteed, we need to help families make a decision that they can live with."

Ladhani's research was supported by the Women & Babies Program at Sunnybrook.

Evidence-Based Care for Extremely Early Birth

The right interventions give babies born at the edge of viability (defined as less than 26 weeks of gestation) the best chance of survival. Led by Dr. Noor Ladhani, researchers in maternal-fetal medicine at Sunnybrook Research Institute combed through the literature to create guidelines to help clinicians manage these complex cases. Published in 2017 in the *Journal of Obstetrics and Gynaecology Canada*, here are the recommendations for extreme premature birth:

Provide women with counselling from an expert multidisciplinary team, as well as data on national and local survival rates.

Offer women transfer to a hospital with a neonatal intensive care unit. Gestational age, estimated fetal weight and parental preferences should factor into the decision.

Allow for first-trimester ultrasound in all pregnancies, especially when women are at risk for early delivery.

Give women a single course of antenatal corticosteroids if delivery is expected within seven days and resuscitation is planned. When an initial course of corticosteroids is given before 25 weeks of gestation, do not give a rescue dose of corticosteroids, as there is no evidence for doing so.

Give magnesium sulfate to babies if delivery is imminent and resuscitation is planned.

Avoid delivery by C-section, unless required to protect the mother. If the fetus is in an abnormal position or there are other obstetric indications, then a multidisciplinary approach should be used to come to a decision that considers the outcome of both mother and baby when active care is planned.

Use fetal monitoring during labour and delivery when planning to use life-saving measures.

Delay cord clamping.



Twins **REY** and **RON WALTERS**, born at 26 weeks' gestation, are among the preemies delivered at Sunnybrook, one of the largest multiple-babies birthing centres on the continent.

When More Isn't Better

Multiple pregnancies are laden with perils, preterm birth included. Researchers are pushing to deliver techniques to mitigate risks and avert poor outcomes

By **MATTHEW PARISELLI**

Photographed kneeling among an elaborate presentation of blossoming flowers, Beyoncé stuns. Surrounded by captivating colours, she is dressed in lingerie and draped in a pastel green veil; however, the focus of the highly stylized image, which the multi-Grammy winner shared on Instagram in February 2017, isn't the amount of skin she's showing—it's the baby bump she's cradling in her hands. Via the accompanying caption, she reveals she is expecting twins. In June 2017, Rumi and Sir Carter joined a growing number of twins in North America.

On Canadian soil, more than 6,000 sets of twins are born each year, contributing to the current rate of multiple births, which is roughly one in 31. A multiple birth is defined as a birth in which two or more babies are delivered from a single pregnancy on the same

occasion. As per 2013 numbers from Statistics Canada, 3.3% of live births in the country were multiples, a 1.2% increase from 1993.

Twin pregnancies are associated with serious adverse outcomes, one of which is preterm birth. The World Health Organization defines preterm birth as one in which a live baby is born before 37 weeks of pregnancy is completed. A normal gestation period is 37 to 41 weeks. Roughly 15 million babies are born prematurely every year worldwide, and the number is growing. Complications arising from it, including respiratory distress syndrome, chronic lung disease and cardiovascular disease, are among the leading causes of death for children aged under five years. It's estimated nearly one million deaths globally were a result of preterm birth in 2015. In this country, there were 29,716 preterm births in 2013, or 7.8% of total births.

The rise of preterm birth can be attributed to a few issues, Dr. Nir

Melamed says. "There are many changes that happen at the level of population. Women are more likely to postpone childbearing, and we know that a more advanced maternal age can predispose to complications leading to preterm babies. There's also an increase in the prevalence of obesity, which can predispose to complications that result in prematurity," the associate scientist in the Women & Babies Research Program at Sunnybrook Research Institute (SRI) says.

The last issue he underscores circles back to multiples. "More people are now using fertility treatments, which often result in twin pregnancies. Twin pregnancies are a major risk factor of prematurity. Even though only 1% to 3% of pregnancies are twins, twins are responsible for 25% to 35% of all cases of prematurity. Some people are happy about having two babies at the same time—it's an efficient way to increase your family—but it's pretty risky."

There are three categories of

premature babies, grouped by how early they're born. Infants born between 32 and 37 weeks' gestation are moderate to late preterm; those born between 28 and 32 weeks are very preterm; and those born before 28 weeks of pregnancy—the smallest and sickest babies—are extremely preterm. Sunnybrook cares for infants in all three sets.

To understand the biology of multiples and predict women at risk of preterm birth, scientists in the Women & Babies Research Program at SRI are pursuing several research ventures under the guidance of Dr. Jon Barrett. A senior scientist and director of the program, Barrett spearheaded the landmark twin birth study, which proved that vaginal birth is as safe as caesarean section for women pregnant with twins. Before this, and based on weak evidence, Barrett notes, the prevailing belief was that C-sections were safer. The pioneering study profoundly informed obstetrical care worldwide when it was published in *The New England Journal of Medicine* in 2013. The decade-long massive undertaking involved 2,804 women with twin pregnancies across 106 centres in 25 countries. "There will never be another trial like this," Barrett, who is also a professor at the University of Toronto, says.

As central as Barrett is to multiples and preterm birth research at SRI, he is nonetheless preparing the next generation of scientists to take the reins. "I'm not going to be around forever—I have to think about the future. I needed to find someone like I was 20 years ago; I found someone better," he says. The person he's referring to is Melamed, whom he recruited. "He's got the same energy and enthusiasm, but he's much smarter than I ever was. Nir has the same love for twins as I do, so he's taking over [this area of research]."

Melamed explains the significance of Sunnybrook for multiples research: "Dr. Jon Barrett established the Twins Clinic here many years ago, which puts us in a unique position to answer questions. We have large populations of twins coming to Sunnybrook—it's one of the largest twin centres in North America. What we want to do is study various aspects of twin pregnancies." The maternal-fetal medicine specialist at Sunnybrook and associate professor at U of T elaborates: "We study preterm birth in twins, investigate the growth of twins compared with singletons, conduct studies on diabetes and pre-

eclampsia in twins, and so forth."

Because multiples and preterm birth are so tightly intertwined, the research of Melamed, Barrett and colleagues can be categorized broadly as projects aiming to identify early which women might be at risk of premature delivery, and those seeking to reduce negative outcomes associated with it.



Melamed says identifying women at risk of premature birth is easy when they have contractions or are in pain; contrarily, detecting such women when they don't present with symptoms is tricky. Enter repeated cervical length measurements. Cervical length is measured in women pregnant with twins via transvaginal ultrasound once at 20 weeks' gestation. Then, a decision is made if she's at risk of early delivery based on whether the cervix has shortened. Melamed and Barrett, however, believe a single measurement isn't enough. "It's not sufficient to assess the cervix only once. In some cases, the measurement might change later on in pregnancy; not necessarily at 20 weeks, but instead at 24 or 26 weeks," Melamed says.

To see whether early birth could be forecasted by measuring the length of the cervix more than once, they took serial measurements of asymptomatic

women pregnant with twins at mid-gestation and every two to three weeks thereafter until 28 to 32 weeks' gestation. The main discovery by the investigators, which included Dr. Roberto Romero, chief of the perinatology research branch at the National Institute of Child Health and Human Development in the U.S., was that serial measurements predict preterm birth in women pregnant with twins better than does a single measurement. "With the use of serial measurements we can identify many more women who are at risk of preterm birth who may benefit from preventive interventions; many of these women would have been missed if we were to use only one measurement," Melamed says. Published in the *American Journal of Obstetrics & Gynecology*, the findings were well-accepted and highly cited, he adds. The goal now is to find other tools or biomarkers that can be used alongside serial measurements of the cervix to improve prediction.

Identifying women at risk of preterm birth as early as possible is also a goal of Dr. Phyllis Glanc's, an associate scientist in the Women & Babies Research Program at SRI and a radiologist at Sunnybrook, one of five radiologists partnering with maternal-fetal medicine specialists at the hospital. Working in conjunction with Barrett and Melamed, Glanc, who is also an associate professor at U of T, is studying



DR. JON BARRETT, with twins **ONYX** and **NASIR ANDERSON-JOHN**, and their parents **DEBORAH ANDERSON** and **KHADEL JOHN**. The twins, who were kept in the neonatal intensive care unit for two months, weighed 2 pounds each when they were born at 29 weeks and six days of gestation.

whether utero-cervical angle (UCA) measurements, captured via ultrasound, can be used to predict early labour. Typically, before a mother delivers, her cervix is at a 90-degree angle at the base of her uterus, forming a reverse “L” shape. “As [a woman goes] into labour, the cervix not only shortens and opens, but the angle goes from 90 to 180 [degrees] to give the baby an exit route,” says Glanc, who is the specialty chair of the women’s imaging section on the American College of Radiology Appropriateness Committee, a rare position for a Canadian to hold. Her team is looking into whether UCA measurements close to 180 degrees at 24 to 29 weeks’ gestation indicate a woman is at risk of early delivery.

Thus far, results suggest a trend in the 76 women studied, whereby larger UCA measurements do point to higher rates of premature birth. She notes that more cases need to be assessed, however, before she can come to a firm conclusion.



The placenta is also a focal point for SRI researchers. One of the most vital organs in pregnancy, the placenta is rich in biological information and serves as the lifeline between mother and baby—or babies. “Think of it as a black box,” Melamed says. “After the baby is delivered, the placenta is delivered as well. By examining the placenta, we can understand what processes happened—whether there was an infection, insufficient blood flow to the placenta or bleeding from the placenta.”

A debate that rages among those in the maternal-fetal medicine community is whether smallness in twins is caused by placenta-mediated factors, as it is in singletons who are born small. In this case, small describes a baby whose birth weight is less than the 10th percentile. To address this, Melamed and Barrett enlisted Dr. Christopher Sherman, a pathologist at Sunnybrook, to help investigate the placentas of small twins and small singletons. “Based on our study, as well as other studies, we believe that the slower growth of twins compared with singletons that is observed starting at about 28 weeks is in many cases not due to failure of the placenta, but instead due to adaptation of the twins to the more crowded intra-uterine environment,” Melamed says.

He adds, “This adaptation may buy the twin fetus more time in utero at the expense of slower growth.”

The trio also worked together to determine whether there is an association between placental blood flow abnormalities and low birth weights of the nonpresenting fetus—the twin farthest from the cervix—in dichorionic [di-kor-ee-on-ik] twin pregnancies, or twins with separate placentas. Looking at over 1,300 women who delivered these types of twins between 2002 and 2015, they noted a correlation between low-birth-weight nonpresenting babies and less blood flow to those babies. The work was outlined in *Obstetrics & Gynecology*. Barrett says the goal is to use advanced technology such as ultrasound texture analysis to determine when nonpresenting babies may be at risk of low birth weight before they’re born and then intervene. “If we can tell that these babies have [placental] abnormalities, maybe we can do something about it; maybe we can give a drug to increase blood flow. That’s why this is really important.”

Glanc sees potential in studying the placenta, too. In her work with Barrett on women pregnant with twins in separate placentas, they, along with colleagues, added a test to their routine exams between 11 and 14 weeks’ gestation to gather 2D and 3D measurements of the organ. They were interested in learning whether the insertion point of

the umbilical cord in the placenta might contribute to fetal growth restriction, which in turn could cause premature birth. Babies deemed to be at risk of fetal growth restriction might be delivered early because they have a higher chance of stillbirth. “When life is good, the umbilical cord inserts right in the centre [of the placenta], so nutrition spreads out evenly. In singletons, there is some evidence to suggest that when the umbilical cord inserts at the edge, it’s bad,” Glanc says.

If umbilical cords insert in placentas at the edges, meaning there is a short distance between the insertion points, then Glanc asked whether that could lead to weak nutrition flow throughout the placenta and consequently adverse outcomes. Her second question, which looked to 3D measurements for answers, was whether a smaller placenta similarly led to an adverse outcome. The team, which includes Barrett, is awaiting the birth of some babies in the study and will need to recruit more participants before they can draw a definitive conclusion, but Glanc says a trend in the data has emerged that confirms her suspicion. It seems when the distance between two cord insertion sites is shorter—when the cords don’t insert in the middle of two placentas, but instead on the periphery—there’s an increase in fetal growth restriction, which could result in stillbirth, preterm delivery and other health issues.



The placenta is among Dr. Phyllis Glanc’s research areas in her pursuit to predict and prevent early birth.

Glanc has joined forces with Melamed and Barrett to look at aspects of the cervix other than length. They have teamed up with Dr. Anne Martel, a senior scientist and physicist in the Odette Cancer Research Program at SRI, who is an expert in image analysis and machine learning. “We know that the shorter the cervix is, the higher the risk is of preterm birth, but looking just at the length is quite limited,” Melamed says.



Changes occur to the cervix at a structural level during pregnancy and include softening and tissue breakdown, Melamed says. “The software looks at many tiny features of the image—things we cannot see with the bare eye—and identifies patterns within the ultrasound image of the cervix. Then, we use machine-learning algorithms to analyze these patterns and identify women who might be at risk,” he says.

The proof-of-concept unpublished study, done last year, used images of 98 women’s cervixes taken at 22 and 26 weeks of gestation. With these data in hand, Melamed says the next step is to validate the results prospectively by running the algorithm on more images and determining if it’s an accurate tool to predict adverse outcomes. “This is important because ultrasound images are great; they’re cheap, and everyone does them. It would be helpful if you could predict that someone was going into preterm delivery, so you could appropriately manage that patient and make sure they’re taken care of,” says Martel, who is also a professor at U of T.

Another promising area of research involves medication. To prevent complications associated with preterm birth, Melamed and Barrett turned to antenatal corticosteroids. Given to pregnant women to decrease neonatal morbidity and death by making the baby’s lungs



DR. NIR MELAMED, who says twin pregnancies are responsible for at least 25% of all cases of prematurity, a rate his research seeks to slash, helped care for REY and RON’s mom, CAMIELE WALTERS.

more “mature,” as Melamed says, antenatal corticosteroids are highly effective in neonates of a size appropriate for their gestational age; however, their usefulness is unclear in preterm babies that are small for their age, or of a birth weight that’s less than the 10th percentile. To test if the drug has similar benefits in fetuses of all sizes, they collected data on more than 6,500 newborns in Canada between 2010 and 2014.

They found that when antenatal corticosteroids were given to pregnant women who delivered preterm babies that were small for their gestational age, rates of neonatal death were lower than among babies whose mothers didn’t receive the intervention. Further, the study showed that benefits of the drug are maximized when given to the mother no earlier than seven days before delivery. “If the baby is born more than seven days after administration, [the drug’s] beneficial effect decreases by 50%,” Melamed says. Should corticosteroids be delivered,

timing needs to be optimized, he adds. The results were published in *Obstetrics & Gynecology*.

Navigating the waters encompassing multiple and preterm births can be disheartening at times, Melamed says. “In many cases we feel a bit frustrated in our ability to help women who we know are at high risk of preterm birth. We have a very limited set of interventions. That’s why this [work] is very important.” Emphasizing his interest in multiples, he adds, “Twins are very high-risk pregnancies, and they’re prone to many complications—not only preterm birth, but also high blood pressure and diabetes. Most of the studies done so far on the mechanisms of pregnancy complications focused on singletons, so that we don’t have a good understanding of how we should approach these conditions in twins.”

Barrett holds the Fred Waks Chair in Maternal-Fetal Medicine Research at Sunnybrook.

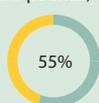
Multiples by the Numbers

Canadian live births that are multiples*



*Statistics Canada (2013)

Canadian multiples that are low birth weight (born weighing less than 5.5 pounds)**



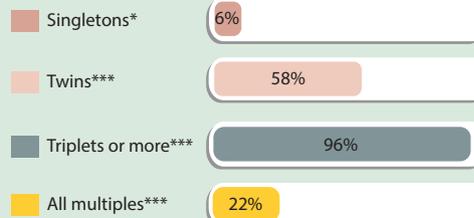
**Multiple Births Canada, *Preterm, Low Birth Weight and Multiple Births: An Information Guide for Parents* (2005)

***Multiple Births Canada, *Multiple Births Facts & Figures* (2011)

Canadian low birth weight babies that are multiples: 28%***



Canadian babies that are preterm





Tiny Answer

Chasing solutions to help the sickest and smallest babies and their families survive and flourish

By ALISA KIM

Just one generation ago it would have been unfathomable to try and resuscitate a baby born at only 23 weeks of gestation. Through medical advances, however, the limit of viability—the age at which a fetus can survive outside the womb—has shifted to include these fragile infants, many of whom now receive life-saving measures.

“I think the days of us telling parents we will or will not resuscitate are gone. When we’re at the edge of viability, I think it’s best for parents to be involved in whether or not they want their child

to be resuscitated,” says Dr. Paige Church, an affiliate scientist in the Women & Babies Research Program at Sunnybrook Research Institute (SRI) and a neonatologist at Sunnybrook. She notes that of the 600 babies cared for in Sunnybrook’s neonatal intensive care unit (NICU) annually, about 220 children are born at fewer than 30 weeks of gestation. The Canadian Neonatal Network stated in its 2015 annual report that 75% of babies born at 23 weeks’ gestation received intensive care.

Being born too early is the leading cause of infant death in Canada. About 29,000 babies are born preterm (less

than 37 weeks’ gestation) in the country each year. Micro preemies, the most premature babies, are born at fewer than 28 weeks of gestation and account for 2% of preterm births. In the NICU, babies born very early are hooked up to a plethora of equipment—machines to help them breathe; intravenous and other feeding tubes; and devices to monitor their heart and breathing rates, blood pressure and blood oxygen content.

Survival rates of preterm babies have improved significantly over the past few decades. American researchers have studied outcomes of extremely preterm infants over a 20-year period. They

found that in 1993 the survival rate of babies born at 24 weeks of gestation was 52%. In 2012, the survival rate of these babies rose to 65%. This is a positive trend, but preterm infants—who can weigh as little as 500 grams or about three apples—are still susceptible to major illness, like bleeding in the brain and difficulty breathing. Lifelong health issues caused by prematurity may include hearing loss, neurological conditions like cerebral palsy and lung disease.

Church and her colleague, Dr. Elizabeth Asztalos, an associate scientist in the Women & Babies Research Program at SRI and a neonatologist at Sunnybrook, are studying whether certain interventions help preterm babies in the short and long term. Asztalos is a co-investigator of a follow-up study that evaluated the lasting benefits of caffeine citrate, a treatment that helps premature babies breathe. “Caffeine is medication that we use almost routinely in preterm babies for prevention of apnea of prematurity,” she says, noting the therapy is started on day 1 and lasts up to 10 weeks, depending on how early the baby is born. “You don’t even think twice about breathing, because there’s a whole mechanism in place. But when babies are born preterm, that’s not fully in place yet, so babies will have a tendency to kind of forget to breathe. Caffeine, the drug, will stimulate the control centre in the brain to breathe.”

Asztalos co-authored the original study, which was published in 2006 in *The New England Journal of Medicine*. It showed that caffeine therapy decreased the rate of chronic lung disease by 10% in babies with a very low birth weight. The follow-up study then looked at 920 children from the original trial to see whether the therapy had longer-term benefits. The researchers assessed the participants, who were 11 years old, and found that while caffeine therapy did not significantly reduce the combined rate of academic, motor and behavioural impairments, it was tied to a smaller risk of motor problems. “We wanted to see whether that benefit sustained itself over time. We still see the benefit [of the therapy] from a motor perspective, but not from a cognitive one—we find that the kids all catch up with each other, whether they were in the active treatment or placebo treatment,” says Asztalos.

Preterm infants not only have trouble breathing, but they also are prone to

Lifelong health issues caused by prematurity may include hearing loss, neurological conditions like cerebral palsy and lung disease.

infections due to their immature immune systems. One in particular, necrotizing enterocolitis (NEC), a bacterial infection that damages the bowel, can be fatal. “The smaller the baby, the chances of these babies surviving [it] is almost nil,” says Asztalos.

A major victory in the battle against this scourge was discovering that feeding premature babies human milk is paramount. “When we made the move to human milk with donor milk, our NEC rate plummeted substantially. At the same time, we recognized that giving [babies] their mother’s milk is equally, if not more, important, because there are properties within a mother’s milk that are important and specific to the baby, especially as it relates to developing protective mechanisms and transferring antibodies,” Asztalos says.

Some mothers of preterm infants, however, are unable to produce enough milk. Asztalos led a study to find out whether a drug called domperidone increases milk supply. Intended to

stimulate the digestive system and treat stomach-related ailments, domperidone has a side effect of increasing prolactin, a hormone that triggers breast milk production. Ninety mothers whose babies were born at fewer than 30 weeks of gestation were randomized to receive either the drug or a placebo. After two weeks, the proportion of women who increased their milk supply by one-half was 20% higher in the group that received the drug. “It was validation that this is a medication that can be used in mothers, but like [with] any medication, there are many people providing caveats. It is a drug that has been unfortunately associated with sudden death or a cardiac arrhythmia called prolonged Q-Tc syndrome. The drug comes with a warning, and it’s something we have to share with mothers, so that they understand what the potential drawbacks of the medication might be,” she says. Given this concern, Asztalos says that mothers need to weigh the risks and benefits of the drug and decide



Opposite page: DR. PAIGE CHURCH, director of the Neonatal Follow-Up Clinic at Sunnybrook, and Judah Flynn, who was born two-and-a-half months early and visits the clinic periodically. Above: DR. ELIZABETH ASZTALOS is leading a clinical trial to determine if a protein in cow’s milk reduces rates of severe eye disease, breathing problems and infection in premature babies.

BORN TOO SOON

Preterm birth

A birth that occurs before 37 weeks of gestation.

Micro preemie

A baby that is born at fewer than 28 weeks of gestation.

Borderline viability

Birth that occurs at fewer than 26 weeks of gestation.

15 million

Babies born prematurely worldwide annually.*

1 million

Deaths of kids under age five caused by prematurity each year globally.*

75%

Preterm babies who die that could survive if inexpensive treatments like steroid injections were available worldwide.*

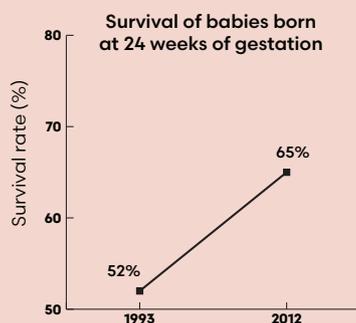
29,000

Babies who are born early in Canada each year. Preterm births have increased by 20% over the past two decades.†

One-third

Proportion of infant deaths in Canada caused by preterm birth.†

Preterm birth is higher among Aboriginal Canadians. For example, this risk is 1.5 times higher among Inuit Canadians than the rest of Canada.†



Source: Stoll et al. JAMA. 2015;314(10):1039-51.

*Born Too Soon: The Global Action Report on Preterm Birth. 2012.

†Canadian Premature Babies Foundation.

whether they want to use it.

Asztalos is also helming a clinical trial that was funded by the Canadian Institutes of Health Research to study whether bovine lactoferrin, a protein in cow's milk, reduces rates of severe eye disease, breathing problems and infection in premature babies. The study will recruit 500 infants from across Canada with a birth weight of less than three pounds. One-half of the babies will be randomly assigned to receive the supplement. After two years, the children will undergo neurodevelopmental assessments. "Our hypothesis is, if you give more of this specific lactoferrin to the babies every day, then the protective components of this compound will have a benefit in reducing a lot of the long-term morbidities in the preterm population that are often related to infection and inflammation," says Asztalos.

The results of the study, which will take about five years to complete, could

change practices in NICUs, just as the caffeine trial did more than a decade ago. "If we see a benefit, then it will mean that units can decide to start adding lactoferrin to the daily care of babies," she says.

Home, but not home free

A child's development after premature birth takes time and continues after discharge from the hospital. Important issues that require ongoing surveillance include possible vision or hearing loss and potential neurodevelopmental delays. "The extreme preterm child can have difficulties in school with attention, behavioural regulation and learning," says Church, who directs the Neonatal Follow-Up Clinic at Sunnybrook. It is the only clinic of its kind in Canada that sees children up to the age of 10 years. "Historically, many clinics were cut off after [the age of]

three or four," says Church, adding that schools are expected to pick up where clinics leave off.

She is leading research on teachers' knowledge about the development of children who are born prematurely. She surveyed teachers in Ontario and asked them what they knew about preemies' learning and behavioural needs. The respondents admitted to knowing little. "[Teachers] want to know more, but they don't necessarily have avenues to do that. We also found that the parents felt that the teachers' knowledge wasn't that great. The teachers admitted it, and the parents said, 'Yeah, we see it.' But if we're relying on people who don't know anything about prematurity and the unique aspects of it, we sort of drop the ball," says Church, who has submitted the study's manuscript for publication. Armed with evidence of this gap in knowledge, school boards can now make the case for increased funding for training and targeted interventions, she says.

Church also hopes to improve the lives of preterm infants by supporting the health of their greatest advocates: their parents. She says that parents of children who stay in the NICU for a prolonged period are under "tremendous stress." Experts say that these parents experience multiple traumas, beginning with early delivery, followed by a steady stream of frightening news, and are at risk of post-traumatic stress disorder. Addressing parental well-being, says Church, is important to the health of children born preterm. "If a mother is really struggling with her own feelings of grief around a delivery, then it's harder for her to fully attach to her child, and that's the platform from which all of our development happens. We need that to be a healthy first step. It's very important to hear from parents if they are struggling," she says.

Church is the site investigator of a multicentre trial that is comparing the current way in which parents of kids in the NICU interact with their children's care providers with a model that provides more help and resources while a child is in the NICU and during the transition home. It is called the Coached, Coordinated, Enhanced Neonatal Transition study.

Typically, the support parents in the NICU receive consists of involving them in their children's care (for more on family-integrated care, see sidebar). Research on family-integrated care shows that it decreases parents' stress

and improves infant growth. Here, parents are not considered visitors to the NICU but rather an active part of the care team. Under the new model, which complements family-integrated care, a support worker coaches parents using a mindfulness technique called accep-

Addressing parental well-being is important to the health of children born preterm.

tance and commitment therapy. The intervention teaches people to accept what is out of their control, and to commit to action that enhances their lives. The researchers will assess if this approach helps parents to manage stress better than simply allowing them to do some of their baby's care. "The problem is, if you ask a parent in the NICU if they're anxious, they'll say, 'Yes.' If you tell them they shouldn't be, they'll say, 'You're crazy, because my baby is sick,'" Church says. "That's not a great therapy in the NICU because their worry and anxiety are appropriate.



DR. PAIGE CHURCH is studying whether coaching parents of babies in the neonatal intensive care unit using a mindfulness technique helps them to manage stress better.

Instead of telling them that it's wrong to be anxious, we're telling them, 'How do you let your anxiety live with you, without it taking over your life and changing who you are?'"

She urges parents in the NICU to prioritize their mental health. "I think that's huge. You are the ones advocating

for your child and pushing for the schools to learn about prematurity. Parents often are the ones that move mountains."

Asztalos' and Church's research studies are funded by the Canadian Institutes of Health Research.

Fine-Tuning Care for Delicate Newborns

Little changes can add up to big improvements for Sunnybrook's smallest and sickest patients, says Dr. Eugene Ng, an associate scientist in the Women & Babies Research Program at Sunnybrook Research Institute. Ng is also the head of neonatology and medical director of the neonatal intensive care unit (NICU) at Sunnybrook. For these babies, who in some cases are born as early as 23 weeks of gestation, making sure that their head position is neutral and not off to one side, or clamping the umbilical cord just a little after birth—around 60 seconds later—can reduce the chances of bleeding in the brain, a devastating brain injury to which micropremature infants are particularly susceptible. Micro preemies are babies who are born younger than 28 weeks or weigh less than 800 grams. Sunnybrook cares for 70 to 80 of these incredibly tiny babies annually. "We have created a niche in

focusing on this group," he says.

Researchers in Sunnybrook's NICU are studying whether measures like these are better for very vulnerable babies. "If we can protect the brain even from when the mom presents with preterm labour, to how we transition from birth and how we care for them in that critical time in the first week or two, then we might produce better outcomes," says Ng, who refers to these changes as practice "bundles." "For example, in the brain care 'bundle,' we included a few things that we think will optimize brain protection and put them all in place at once, and look for improvement in rates of brain hemorrhage," he says.

Ng has also studied whether parents being more involved in caring for their children in the NICU is beneficial. He was the site investigator of a large, multicentre clinical trial that was the first to evaluate the effectiveness of family-integrated care in this setting. More than 200 families were recruited

at Sunnybrook. Parents in the intervention arm spent at least six hours a day, seven days a week at their baby's bedside, and provided care by feeding, dressing and bathing their child. They were also encouraged to participate in ward rounds and document their child's growth and progress. Babies who received family-integrated care gained more weight than did those in the standard care group. Parents in the family-integrated care group had lower average stress scores than parents in the control group. Ng says that he considers parental well-being the most important metric in the study, and that family-integrated care, which is now standard practice at Sunnybrook, is gaining traction in NICUs worldwide. "Ultimately, what we want is a less-stressed parent because they feel like they're in control in the unit, but also to get them ready to be the best advocate for their babies. That, in essence, is what family-integrated care is all about."

Live From the Neonatal Intensive Care Unit

The neonatal intensive care unit (NICU) at Sunnybrook, which admits about 600 babies annually, is one of eight level III units in Ontario. This is the highest level of care, reserved for the province's sickest and smallest babies. As these glimpses into it show, the NICU supports family-integrated care, where parents are a vital part of their baby's care team.

Photography by KEVIN VAN PAASSEN and NATION WONG

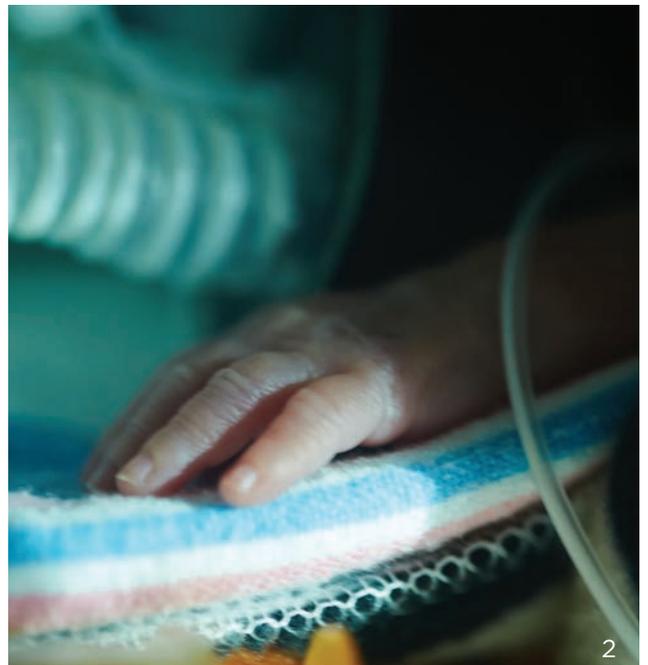
Text by ALISA KIM



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Photos: Nation Wong

Facing page: 1. Ezra Hewlett was born on Feb. 12, 2018, at 23 weeks and three days to mom Émilie Rioux and dad Robert Hewlett. Ezra was delivered via emergency C-section at a hospital in Sudbury after Émilie's placenta ruptured. The family, who lives in Espanola—about 45 minutes away from Sudbury—made it to the hospital in time, but Émilie had life-threatening blood loss. The hospital in Sudbury did not have an NICU, but was able to stabilize Ezra until his transfer to Sunnybrook the next day. 2. Light therapy is routinely used to help get rid of the bilirubin that causes jaundice. 3. Mom, dad and big sister Demera visit Ezra in Sunnybrook's NICU.

This page: 1. Noah Crouch, born on June 9, 2018, at 22 weeks of gestation, is held by his mom Arlene. 2. Matt Genorio provides kangaroo care to his son Oliver. Oliver was born February 20, 2018, at 26 weeks. He weighed 850 grams at birth.



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This page: 1. Ivanna Marie was born on March 20, 2018, at 24 weeks and six days. She weighed 390 grams at birth. 2. The NICU team monitors babies 24/7. 3. Ivanna’s mom, Maria, gives a tender touch. Her pregnancy was high risk, because Ivanna was not growing in utero.

Facing page: 1. Ivanna and Maria with an NICU nurse, who provides specialized care. 2. Dr. Liz Asztalos (right) cared for Maria during the last two weeks of her pregnancy. Asztalos has described Ivanna as an “against-all-odds” baby. Ivanna is enrolled in a clinical trial led by Asztalos that looks at whether a protein in cow’s milk reduces rates of complications in premature babies.

Photos: Kevin Van Passen and Nation Wong



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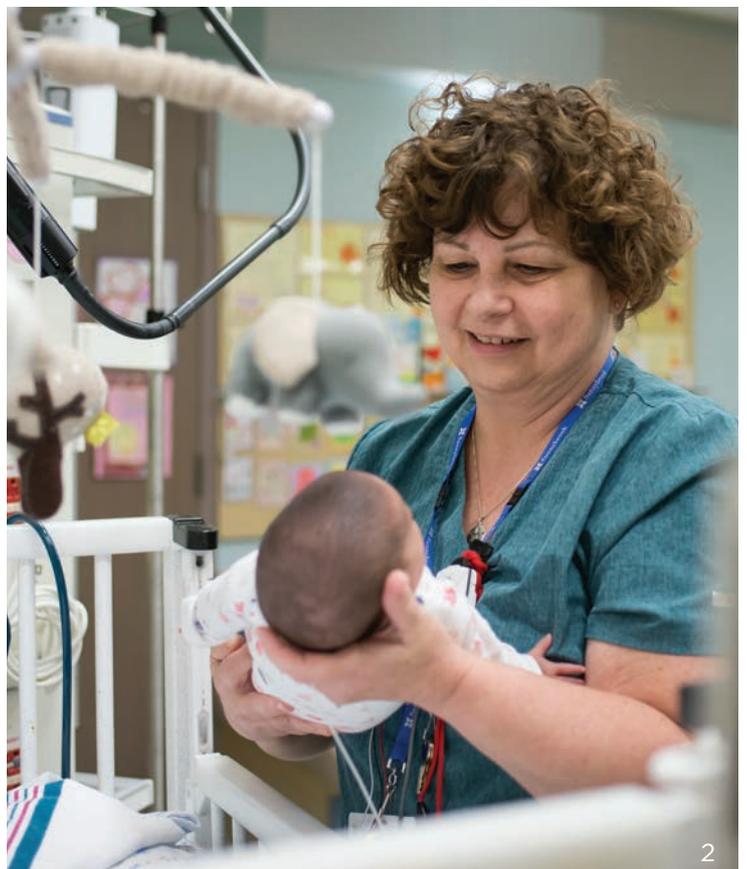
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Photos: Kevin Van Passen

Facing page: 1. Viviane and John Nguyen welcomed their daughters, Maddie and Ellie, on March 13, 2018. 2. Marie Bagg, a nurse in the NICU, is part of a multidisciplinary team. Of everyone on the care team, the staff nurse is the person with whom parents have the most contact. 3. The beginning of a lifelong bond between sisters Maddie and Ellie Nguyen.

This page: 1. Dr. Eugene Ng (third from left), director of the NICU, leads clinical rounds. 2. Violet gives a big yawn during kangaroo care with mom Daphne Schibler. In the NICU, parents provide skin-to-skin contact with their babies for several hours each day. Research shows that kangaroo care helps babies to regulate their body temperature, and it stabilizes their heart and breathing rates.



Pre-empt, Where Possible; Be Primed, Where Unavoidable

Is this the best Rx for postpartum hemorrhage?

By MATTHEW PARISELLI

The interpretation section of an eagerly awaited landmark paper summarizing a trial that investigated treatment for excessive after-birth blood loss noted that tranexamic acid should be given immediately after bleeding onset. Any finding addressing this high-priority area of research is paramount—it's estimated that 18% of maternal deaths in 2015 were a result of hemorrhage; yet, upon reading the section, Dr. Asim Alam asked, 'But if all women have some degree of bleeding

during delivery, shouldn't the drug be administered before hemorrhage starts?' Having already toyed with the idea of using the drug pre-delivery, the obstetric anesthesiologist's impulse to act was stoked.

Tranexamic acid, otherwise known as TXA, helps to stop bleeding by preventing the breakdown of blood clots. Drs. Shosuke and Utako Okamoto, a Japanese husband-and-wife research duo, invented it in the 1960s, and it has been proven to be highly effective, especially when used in trauma scenarios. The World Maternal Antifibrinolytic (WOMAN) trial

mentioned earlier stressed it could, and should, be used to treat extraordinary blood loss after giving birth, but Alam seeks to home in on the period prior to bleeding onset to prevent it from beginning in the first place.

While discussing this research question, Alam, an affiliate scientist in the Tory Trauma Research Program at Sunnybrook Research Institute (SRI), draws attention to an area of the world where postpartum hemorrhage (PPH) is alarmingly prevalent: sub-Saharan Africa. The paper detailing the WOMAN trial, published in *The Lancet*, says PPH is responsible for 100,000 deaths every year, and that 99% of fatalities occur in low- and middle-income countries. In 2010, it was estimated that 800 women worldwide died every day due to birth complications; of those 800 deaths, about 440 occurred in sub-Saharan Africa, with bleeding out after birth being the central cause. The high number of hemorrhage cases results from lack of training, expertise and adequate facilities, Alam says. "We have a lot of resources at our disposal, but people in these areas do not have the readily available systems that have taken us years, much science and a lot of people to develop."

On the Canadian front, Alam, who is also an assistant professor in the University of Toronto's department of anesthesia, says the incidence of hemorrhage after giving birth is roughly 6%. Prince Edward Island's rate of less than 4% and Nunavut's rate of more than 17% contribute to this number. At Sunnybrook the incidence is about the same as the national average, attributable to the hospital's tendency to take on the riskiest deliveries. Other hospitals that care for this population report similar rates. Clinically defined as blood loss greater than 500 millilitres, or half a litre, within 24 hours of spontaneous vaginal birth, or one litre within 24 hours of caesarean section, PPH is the leading cause of maternal morbidity and mortality worldwide. Re-



DR. ASIM ALAM is exploring whether tranexamic acid can be used to prevent after-birth hemorrhage.

ports indicate the incidence is rising. There are several risk factors, including weak uterine contractions, being pregnant with two or more babies, prolonged labour, infection, obesity and the placenta's early detachment from the uterus.

To diminish cases of significant post-birth blood loss, Alam is leading a Health Canada feasibility trial on the use of TXA at Sunnybrook. Feasibility trials are carried out to help design larger trials by answering basic questions related to if the trial can be done. Partnering with a multidisciplinary team of experienced SRI investigators and Dr. Shelly Au, the research manager in the department of anesthesia whom Alam calls “the scaffolding behind the project,” the team will recruit 58 patients into a randomized control trial to see whether it's possible to carry out a larger trial involving about 3,000 patients. To be considered feasible, most of the patients in the trial will need to receive the intervention. “If we can't give 85% of those people [who are] randomized the intervention, then there is no way we can feasibly do a larger trial. There are also secondary calculations, like the time it takes to achieve that number and the costs involved. Let's say it takes two years to randomize 85% of people—from a time and cost perspective, then it may not be feasible to do a larger study,” Alam explains. This will be the first trial done to explore the effectiveness of TXA to prevent PPH.

The protocol for the trial has attracted the interest of many experts. Two years in the making, it began March 1, 2018. When it ends, Alam hopes the team will be equipped with all the information required to approach a funding agency for support in executing a full-scale trial.

“If there are 100,000 women dying from PPH around the world every year, and we can reduce that by 15%, then I've helped save a great deal more people than I could have by working in the hospital,” says Alam. “I want to make a big impact, and if there are no adverse events [associated with the drug], then I believe we should be using TXA routinely.” Given intravenously, TXA is around an affordable \$6, he notes.

As this is the first trial in which TXA is being administered to prevent extreme after-birth blood loss, Alam and his team



DR. JORDAN TARSHIS leads medical simulation activities to help prepare teams for real-life events. He carried out Sunnybrook's first labour unit exercise in spring 2018.

have sought out colleagues to help them ensure the project satisfies Health Canada standards. One of those experts is Dr. Jordan Tarshis, an anesthesiologist at Sunnybrook and a member of the hospital's research ethics board. In addition to reviewing the study, Tarshis, an associate professor at U of T, will be one of the anesthesiologists delivering TXA to the pregnant women.

While his practice is not limited to obstetrics, Tarshis says he's seen enough to know that rates of hemorrhage after giving birth need to be improved. One way to do this is through education, and as director of the Sunnybrook Canadian Simulation Centre, he leads medical simulation activities. He explains: “Medical simulation is analogous to airline flight simulation. We have a full-size body manikin—with a pulse, heart sounds, breathing sounds—that can be hooked up to our anesthesia machines and our monitors. You can get readings, and then [the medical team] can behave and practise rare or dangerous events in a safe environment.”

In spring 2018, Tarshis led a simulation activity that he had been trying to launch for five years on the fifth floor of Sunnybrook's main wing. “We did a massive bleeding scenario on the labour and delivery floor involving multiple health care practitioners to practise our protocol,” he says. “We stressed the system, saw what happened and learned from it, so when it happens in real life we're more

prepared.”

Based on his experience, Tarshis says teams perform better in real-life scenarios if they've practised their communication and medical management strategies, for example. His faith in the exercises runs deep, evident by his initiation of outreach simulation activities to be taken to hospitals in the Greater Toronto Area. This work entails transporting Sunnybrook's manikin, assembling a team of people similar in structure to the one that formed during Sunnybrook's labour ward exercise and putting team performance to the test. “What you find is that sometimes there are communication challenges or local resource challenges, like trying to find equipment and realizing it's locked away in a cupboard,” he says. “We stress their systems, and they're tasked with following up to fix those systems.”

Returning to the TXA trial, Tarshis is enthusiastic. “This could really advance the science and have implications for changed practice—not just locally, but nationally and internationally,” he says. Alam is equally optimistic: “We're talking about making a major change to the way we practise obstetrics, something with a potentially life-saving impact.”

The TXA (TAPPH-1) trial is funded by a Sunnybrook AFP Innovation Fund. The simulation outreach program is funded by Ferring Pharmaceuticals and the Sunnybrook Canadian Simulation Centre.

Mighty Alliance

Network aims to ensure more women carry their babies to full term

By **MATTHEW PARISELLI**

Dr. Jon Barrett's discovery that delivering twins by planned caesarean section is no safer than planned vaginal delivery has significantly informed obstetrical care worldwide. The landmark study on twin births that led to the finding involved 2,804 women in 106 centres across 25 countries, and was published in 2013. Its home is *The New England Journal of Medicine*, the world's leading general medical journal with a history extending over 200 years. Having his paper presented in what Barrett calls

"the holy grail" for researchers was a momentous accomplishment; and, to commemorate the occasion, he framed the publication and hung it on his office wall. Barrett, however, found himself gazing at it, unmoved. 'So what? Big deal,' he said to himself. "I informed practice, but the trouble with informing practice is that it doesn't change practice," he says from his office at Sunnybrook, framed paper hanging feet away. As he contemplated the embodiment of 10 years' work, his focus shifted to implementing knowledge, and not just in twin births, but also in preterm birth.

The World Health Organization defines preterm birth as delivery before 37

weeks of gestation. More than one in 10 babies, or 15 million, are born prematurely every year, with one million of these dying. Further, the incidence is rising. Complications from early birth are one of the leading causes of death among children under five years of age. In Canada each year about 8% of pregnancies are preterm, which translates to more than 25,000 premature babies. Because most survive with disabilities, and there's a lifelong impact on the child as well as families and society, the estimated yearly cost on the country's health care system exceeds \$8 billion.

Contrary to the state of affairs when Barrett began in the field—a period when nothing could be done to predict, prevent or treat premature delivery, he notes—research has advanced, and the growing problem of early birth can be addressed. The task now is to ensure knowledge gleaned through research is woven into practice widely to prevent preterm birth and save lives. Barrett says that to do this, researchers must collaborate instead of working "in pillars of academic isolation," as many have done. The director of the Women & Babies Research Program and a senior scientist at Sunnybrook Research Institute (SRI) says, "One thing I've learned over the years is that you can't do this in one network. You have to get multiple partners because it's a complex problem." His solution: the Ontario Alliance for the Prevention of Preterm Birth and Stillbirth, or simply, the Alliance.

The Alliance, which is a collaboration among families, hospitals, maternal-child networks in the health system and maternal-newborn care providers, has several goals. Barrett, the medical director of the Alliance, says the first priority is to drum up funding from the government and philanthropists to implement existing knowledge on predicting, preventing and treating preterm birth. "It's a tragedy that babies are dying, yet we know we can prevent it," says Barrett, who knew by the age of five that he wanted to follow in his



DR. JON BARRETT is the medical director of the Alliance, which hopes to reduce the number of preterm deliveries in Ontario by 15%.

late father's footsteps by becoming an obstetrician. He says he could have applied for grants to assist in this endeavour, but typically, organizations like the Canadian Institutes of Health Research provide funding for research, not health care implementation. "It became very frustrating for me to know that there's this body of evidence that can prevent babies from dying, but I'd have to wait on a 15% chance [of funding] rate in order to implement it. I'm not the kind of person who likes those odds."

The second part of the project will entail getting blood samples from pregnant women in the first trimester, evaluating their DNA and protein levels, and correlating the findings with later outcomes, including those of their babies. Another objective is developing clinical trials to generate new knowledge. The Alliance will also instruct health care providers and parents-to-be on how to prevent stillbirth and preterm birth simply, safely and inexpensively; identify at-risk women by linking data with screening programs; and improve care coordination so that unavoidable cases of early labour happen in hospitals equipped to deal with them. Additionally, it will implement a "bundle" of standard treatments through its networks. If successful in achieving these goals, then the Alliance could usher in an era of support and understanding for families affected by preterm birth and stillbirth, which Barrett notes is lacking.

Dr. Nir Melamed, who is a member of the Alliance, says it strives to standardize care: "It doesn't make sense that different physicians who are practising only a few kilometres from each other will do things so differently when it comes to the care of low- and high-risk pregnancies." The associate scientist in the Women & Babies Research Program at SRI and maternal-fetal medicine specialist at Sunnybrook also says it will enable researchers to do joint projects. "There are some questions you simply don't have enough patients in a single centre to address, so by doing multicentre studies we have [this] power."

The expected outcomes of the Alliance are ambitious, but measurable. There could be a reduction in premature deliveries—a 15% drop is the aspiration—and stillbirths; a decline in the number of babies in neonatal intensive care units; a decrease in disability rates; and millions saved in health care costs.

Before the Alliance, Barrett, who is also a professor at the University of Toronto, founded the Greater Toronto

The Alliance will implement a "bundle of care"—treatments to prevent stillbirth and preterm birth, which include:

Administering low-dose aspirin (75 mg) once per day to women with risk factors for pre-eclampsia, a precursor to early labour. Risk factors include previous pre-eclampsia, diabetes, renal disease and being pregnant with more than one baby.



Giving a daily dose of progesterone (200 mg) until 36 weeks' gestation to women with a history of early birth or with short cervixes.

Measuring the length of the cervix routinely between 16 and 24 weeks' gestation.



Screening women at prenatal care intake for risk of preterm birth and stillbirth using health history and prior pregnancy registry data.

Tying fetal awareness teaching into routine pregnancy care, and using prompt electronic fetal monitoring when fetal movement is much reduced.

Aims for select regions and groups in Ontario:

Doing more ultrasound screenings for prenatal patients at higher risk in northern Ontario.

Gaining approval of the Non-Insured Health Benefits Program for First Nations and Inuit to cover early labour prevention drugs.

Collaborating with Aboriginal Health Access Centres to improve outcomes.

Offering online pregnancy resources in Indigenous languages.

Tailoring traditional, electronic and social media knowledge translation campaigns to populations with higher rates of stillbirth and preterm birth, including Aboriginal, black, and other racialized people and their families.



Area-Obstetrical Network, which was fuelled by a similar desire to encourage collaboration. Since its inception in 2013 it has attracted the attention of specialists outside the GTA; to accommodate other centres, the name was modified to Southern Ontario Obstetrical Network. Better known as SOON, it will apply the Alliance's strategies (see sidebar).

The Alliance isn't the first network of its kind built on the premise of collaboration. Similar networks in Ireland, the Netherlands and the U.S. have been developed with great success, says Melamed, who is also an associate professor at U of T. "They've managed to conduct beautiful, amazing research through multicentre cooperation. That's what we're trying to replicate here."

Launched at the end of 2017, the Alliance has high hopes, Melamed says. "We have a real opportunity. When you make

a small change in your own hospital, you can affect a small number of patients. When you make a similar change across a much broader population, such as across the GTA or eventually throughout the whole province, what you do can have a much greater impact on the health of women and their babies." As Barrett considers the road ahead, he says, "It's time for the government, philanthropists and research funders to work together by putting patients first, and together with them, implement what we know, find out what we don't, save lives and improve the health of all Canadians."

Donor seed funding and the Canadian Institutes of Health Research are supporting the research of the Alliance, the latter through a grant to study outcomes in preterm birth.

A LAB OF THEIR OWN



From left to right: Dr. Michele Anderson, Sonam Dubey, Miho Tanaka, Dr. Isabelle Aubert and Dr. Joyce Chen.



Successful female scientists reflect on their journeys and offer counsel to the next generation looking to them and wondering: Is it possible to have it all?

By ALISA KIM
Photography by NATION WONG

“I WAS TAUGHT THAT THE WAY OF PROGRESS IS NEITHER SWIFT NOR EASY.

—Marie Curie, Nobel laureate in physics

DR. MICHELE ANDERSON has fond childhood memories of being in a lab, watching as her father, a physiologist at Johns Hopkins University, did experiments to understand the causes of high blood pressure. As a student, she excelled in science; the more she did, the more her passion for it grew.

Her love of research notwithstanding, Anderson didn't think that she would one day run her own lab. During her PhD, Anderson, who is now a senior scientist in Biological Sciences at Sunnybrook Research Institute (SRI), thought she would become “someone who worked in the lab over a longer term, but not the person who wrote the grants and travelled,” she says. “I was brought up to think that that's not what women do. I was told if I wanted a family, I couldn't do both.”

Anderson, who is a mother to two sons, persevered. Also an associate professor in the department of immunology at the University of Toronto, she creates and studies mouse models to understand how T cells develop. She is working on a way to manufacture T cells from stem cells derived from human skin cells. She recently was awarded a grant from the Canadian Institutes of Health Research (CIHR) at a time when average funding rates hover at about 16%, and she has published two papers within the last year in the highly regarded journals *Nature Communications* and *Stem Cell Reports*. She's staying put.

Other women with PhDs in science, however, are dropping out of the field—a phenomenon known as “the leaky pipeline.” Census data on university academic staff published in 2018 by Statistics Canada show that although the numbers of men and women who obtain PhDs in the health sciences are comparable, the representation of women drops off with each step up the faculty ladder. Among health researchers at the assistant professor level, there are 1.24 times more males than females; at the level of full professor, men outnumber women by 3.55. These numbers are reflected at U of T, where the proportion of full-time, tenure or tenure-track women holding the rank of assistant or associate professor is close to parity, at 43% and 42%, respectively; however, women account for 27% of all full professors.

Why are women leaving science? One still-resonant reason, and one not exclusive to science, is the challenge that comes with juggling work and children. A 2018 survey on work-life balance by *Times Higher Education* reveals that 43% of female academics with children say that parental responsibilities hold back their careers “significantly” or “a great deal.” Moreover, among respondents who do not intend to have children, 63% of female academics attribute this decision in part to the fear that having kids would be irreconcilable with their career. Tellingly, nearly one-half of the respondents, who work in Europe, the U.S., Canada and Australia, were younger than 40 years of age, suggesting that concerns about balancing work and

family are very much a contemporary issue.

This is not to say that men don't feel pressure or experience issues balancing life in the lab with that at home, but research shows women in science disproportionately bear the burden of family responsibilities, making it harder for them to engage in career-building activities like attending conferences and networking events outside regular work hours. In 2017, the Equity Challenge Unit published a report on gender equality in science, technology, engineering and mathematics (STEM). The report, which surveyed close to 5,000 academics from the U.K., revealed that more female than male respondents had taken parental leave, or were caregivers for another adult. Statistics Canada data from 2015 show that women spend 50% more time than men doing unpaid household work, including chores and caring for children or adult family members. Reflecting on the early part of her career, Anderson says she can relate. “There weren't a lot of faculty leaving to pick up their kids at 5 p.m. They would schedule a meeting for 5 or 6 p.m. and say that time was necessary for the clinicians to be there. I think the majority of men older than me had other people taking care of their kids, [whereas] the majority of women didn't. That was very difficult because the people making the rules didn't have the same constraints.”

Dr. Joyce Chen, a scientist in the Hurvitz Brain Sciences Research Program at SRI, says the demands of her job influenced the decision to have one child. “I'd be lying if I said that [work]

didn't factor in," says Chen, who took a shorter maternity leave to return to work early. Her research is on rehabilitation after stroke. She is studying how to recover movements using noninvasive brain stimulation. The Heart and Stroke Foundation recently awarded her a grant to develop a personalized approach to motor recovery using transcranial direct current stimulation.

Chen's decision is not an uncommon one. In a 2011 study published in *PLOS One*, Drs. Elaine Ecklund and Anne Lincoln showed that female scientists at universities in the U.S. have fewer children than do their male colleagues, and are more likely to say that they have fewer children than they want owing to their careers. "I would have liked to have had two [children], but it was the stress of being a woman in science and needing to get all these grants. There was never a good time, and time ticked away," says Chen. "Now the [age] gap is too big. Being able to keep up at work and wanting to have a family is just not compatible, in a sense."

She is careful to note that all scientists face the same pressure to get funding, and have to sacrifice some of their personal lives—whatever that looks like—to do their jobs. She says that it's a

trade-off she is happy to make. "For most academics, I am assuming based on my experiences, we enjoy work, and so, the line gets blurry between work and play. It is easy to get caught up in work. When I was a grad student, that wasn't a problem because I was single. Now that I have a family, I need to achieve a balance," she says. Chen, who is also an assistant professor in the faculty of kinesiology and physical education at U of T, credits having a supportive spouse with being able to juggle work and family, but even so, she says that trainees should have no illusions about what a future in academia is like. "This is the lifestyle that you will experience, and somehow you're going to have to figure out how your life fits in. I've gone to panels about work-life balance in academia—by the way, which were dominated by females—but no one has the answer. It's specific to each individual. You have to make peace with whatever balance you achieve," she says.

Anderson also doesn't pull any punches when describing the life of a scientist. She says that she encourages trainees to pursue this path, but warns that it will be hard. "There can't be anything else you'd want to do, or even consider doing. Science has to be the love of

your life." She also says that she doesn't regret her choices. "I'm very grateful to have this chance to do what I love for a living."

Universities have tried to address the issue of work-life balance with policies like "stopping the tenure clock," which enables faculty to delay their tenure review due to family responsibilities. One limitation, however, is that those on evaluation committees don't always understand how parental leaves affect productivity, a finding that is noted in a 2012 report published by the Council of Canadian Academies. To this point Chen says, "[Maternity leave] is taken into account, but not quantified, and I think it should be—for example, 'if you've taken a mat leave, we expect two fewer papers from you.' There's no practical, objective measure of the effect of mat leave."

DR. ISABELLE AUBERT, a senior scientist in Biological Sciences at SRI and a professor in the department of laboratory medicine and pathobiology at U of T, also took shorter maternity leaves after the birth of each of her two daughters so as not to fall behind. "During my mat leave, I occasionally brought the kids to my office and worked from home, developing innovative ways to hold a baby and type. It was challenging, but I was happy to be able to work and be with my kids at the same time. The flexibility of an academic career definitely helped," she says.

Like Chen, Aubert credits a highly involved partner. "When the kids are sick, my husband and I take turns to stay home with them," says Aubert. "Being a scientist as well, he is able to adjust his schedule. The lifestyle of a scientist has many positive aspects. We can be with our kids when needed, and can even travel the world with them." Anderson is equally positive about the benefits that come with the challenges. "It comes with wonderful activities like travel and meeting amazing people around the world. And having a family is also amazing, and something I wouldn't want to have missed out on," she says.

Also funded by CIHR, Aubert is developing therapies to stop neurodegeneration and promote regeneration in Alzheimer's disease. She is evaluating the capacity of drugs, immunotherapy, and gene and cell therapies to maintain the health of neurons and induce brain



DR. MICHELE ANDERSON (left) and **DR. JOHANNA SELVARATNAM**, a postdoctoral fellow in the lab. The Anderson lab is studying preclinical models to understand how T cells develop.



Dr. JOYCE CHEN is researching the use of noninvasive brain stimulation to help people recover movement after a stroke.

repair. Her research using focused ultrasound to deliver therapies directly to the brain in preclinical models of Alzheimer's disease has led to several world-first publications in this hot area. In addition to being a mother, Aubert is an avid skier and teaches martial arts. In the past, colleagues have told her that her life outside the lab would compromise the quality of her science. Initially, such comments undermined her confidence. "At the start of my career I didn't talk about my karate, my skiing and my family because the feedback I was getting suggested that I was not a committed scientist when I was," she says. She has since learned to shrug off dismissive remarks.

WOMEN IN SCIENCE contend with subtle forms of discrimination arising from stereotypes about gender roles, as well as systemic inequities in hiring, promotion and compensation. According to 2016 Statistics Canada data, female academics on average make 90% of male scholars' salaries when pay is broken down by hourly rate. A 2016 study by Dr. Catherine Buffington and colleagues published in the *American Economic Review* looked at the salaries of about 1,200 U.S. PhD graduates in STEM. Even within the same field, women made 11% less than men in

first-year earnings, a gap based on the finding that married women with kids earned less than men. Neither married men with children nor unmarried women without kids were disadvantaged in pay.

In the realm of publishing, Dr. Luke Holman and colleagues published a study in 2018 in *PLOS Biology* that reported a gender gap across journals in science and medicine. They determined the numbers of men and women authors listed on more than 10 million academic papers and found that women are less often the last author or sole author—positions denoting seniority. For example, in 2016, the proportion of female last authors published in *Nature* and *Science* were 18.3% and 21.9%, respectively. The researchers made a worrisome prediction that in certain fields like physics, surgery and computer science, equal representation won't be reached this century, given how slowly the rates of women authors are climbing.

Gender disparities also exist around colloquium talks, which not only enhance a researcher's reputation, but can also lead to collaborations and job offers. A 2018 study by Dr. Christine Nittrouer and colleagues published in the *Proceedings of the National Academy*

of Sciences analyzed thousands of talks across six disciplines. The researchers found that men gave more than twice as many talks than women overall. This gap could not be attributed to women declining invitations to give talks more frequently or valuing such opportunities less. On the flip side, 2014 research by Drs. Arturo Casadevall and Jo Handelsman published in *mBio* showed that women's participation on organizing committees for scientific symposia is correlated with a much higher proportion of invited female speakers.

Women are also under-represented in the upper echelons of academia. In 2008, the federal government created the Canada Excellence Research Chairs Program to attract the world's best researchers. Each university successful in securing a chair is awarded up to \$10 million over seven years. In the inaugural competition, 19 chairs were awarded—all to men. The outcome prompted the minister of industry to form a committee to examine the selection process. It found that no universities had nominated a female candidate in the second phase of the competition. To this day, 25 of the 26 program chairholders are men; Dr. Luda Diatchenko, of McGill University, became the first female chairholder in September 2013. (Another was awarded to Dr. Jennifer Hoffman, then at the University of British Columbia, but she returned to the U.S. soon thereafter.) A new competition is in play.

Gender bias can also be overt and egregious, as in sexist comments made in 2015 by Tim Hunt, a Nobel-winning biochemist from England, who caused a furor by saying that male and female scientists should work in segregated labs to prevent romantic entanglements and because "when you criticize [females], they cry." More often, though, gender discrimination is unconscious. A heavily cited 2012 paper led by Dr. Corinne Moss-Racusin that was published in *Proceedings of the National Academy of Sciences* showed that when it comes to hiring, both male and female science faculty members exhibit a bias that favours males. In the study, 127 science professors were randomly assigned to evaluate an application for a lab manager position that had either a stereotypically male or female name. The participants, male and female alike, rated

the male candidate as significantly more competent and deserving of a higher starting salary even though the applications—save the name—were identical.

Is gender bias at work in decisions made by Canada's largest health research investment agency? An analysis of CIHR funding from 2000 to 2015 shows that, on the whole, grants awarded to males were longer in duration and higher in value, with the average grant size for males being \$505,000 versus \$336,000 for females. A 2018 analysis of cancer research funding in the U.K. led by Dr. Charlie Zhou and colleagues in *BMJ Open* yielded similar results: male principal investigators (PIs) were awarded 1.3 times the median award value of grants allocated to female PIs.

The evidence for gender bias in science is considerable, but there are signs that progress is afoot. The Canada 150 Research Chairs Program, announced in Budget 2017 by Justin Trudeau's government, is a one-time investment of nearly \$118 million to court the world's best researchers, including Canadian expatriates. The program notes "equity and diversity will be given strong consideration." As part of this, it further noted that career interruptions due to family or health reasons, for example, would not disadvantage candidates under consideration. In March 2018, the federal government announced 24 chairs, more than 58% of them women.

The Trudeau government has also announced an action plan to address under-representation of women, Indigenous peoples, people with disabilities and members of visible minorities in the Canada Research Chairs (CRC) Program. It arose partly in response to a 2006 settlement with eight women who went to the Canadian Human Rights Commission charging the CRC Program with discrimination, but its rollout has taken time. At the behest of Minister of Science and Sport Kirsty Duncan, the CRC secretariat instructed universities to develop equity and inclusion plans to address lack of diversity among their chairholders or lose funding. Furthermore, institutions are required to report annually on their equity target results and post this information on their websites.

In response to the mandate, U of T and its affiliated teaching hospitals,

including SRI, developed equity and diversity plans. Likewise, the Canada Excellence Research Chairs Program is working to ensure recruitment practices are transparent and fair. Given this, the Canadian government expects greater diversity in upcoming competitions. Aubert is doing similar work for her university department, where she will collaborate with search, promotion and award committees to support diversity.

THAT ALL OF this is happening matters because, as Anderson notes, it's particularly important for female trainees in science to observe women in positions of leadership. She points to the department of immunology at U of T where women make up 42% of its full professors, and the past interim chair and the head of graduate studies are women. "Both are at the top of their field," says Anderson of her colleagues Drs. Dana Philpott and Jennifer Gommerman (whom she notes are also parents). "There are a lot of other women in the department who are very visible. It's a good thing for young women to see." The strong presence of senior female faculty at U of T's department of immunology contrasts starkly

with the "leaky pipeline" detected in immunology departments at American institutions. A 2016 study by Dr. Virginia Smith Shapiro and colleagues published in the *Journal of Immunology* shows that although women make up 50% of all U.S. graduate students and postdoctoral fellows in immunology, they are under-represented among immunology faculty members, accounting for 39.6% of assistant professors, 31.8% of associate professors and 22.3% of professors. It also showed that only three of the 25 responding departments or programs currently had a female chair.

Yet, helped by studies like these, awareness around diversity and equality is increasing; Anderson cites the list of female speakers compiled by the American Association of Immunologists that is promoted on its website as an example. "We want to show female trainees that they, too, can become PIs. If women sit in the audience [at conferences] and don't see anyone like themselves up there at the podium, why should they think they are equipped to do that job if they don't see anyone like them succeeding?" she says.

Women like Anderson, Chen and



DR. ISABELLE AUBERT (right) and PhD student SONAM DUBEY. They are studying the use of focused ultrasound to deliver therapies directly to the brain to treat Alzheimer's disease.

Aubert are role models for the next generation of female scientists. Sonam Dubey is a PhD student supervised by Aubert. Her research is on the use of focused ultrasound to open the blood-brain barrier and deliver antibodies to the brain to treat Alzheimer's disease. She will defend her thesis next year and plans to continue a career in research, potentially pursuing a postdoctoral fellowship. She says that throughout her studies she overcame difficulties and occasional self-doubt, but feels optimistic. "I feel like that imposter syndrome is going away slowly. I think I would make a good research scientist. I am hopeful in terms of getting somewhere, even with all of the funding issues and competition in academia. I'm lucky because I picked an area that is really growing in recognition and impact on health care," she says.

SEEING AUBERT FLOURISH professionally while raising children and doing the things she loves is another source of optimism for Dubey. "Having that strong, supportive social circle is important, and having a family down the road is important to me. Doing something you love that helps you keep learning and growing would be, for me, having it all," she says.

Like Dubey, Miho Tanaka, a PhD student in the lab of SRI senior scientist Dr. Jim Carlyle, also overcame a crisis of confidence during her doctoral research. Her thesis is on a type of immune cell called natural killer cells, which fight cancer and infection. She is studying how cancer alters the activation of natural killer cells and their ability to destroy cancer cells. She says that Carlyle's support has helped her manage difficult moments during her studies. "He gives me space to deal with my issues when I have them. He is very understanding," she says. Carlyle has also offered to connect her with a female scientist he knows, so that Tanaka can have a mentor with a different perspective.

The importance of mentoring was underscored by Dr. Mona Nemer, Canada's Chief Science Advisor, in an address at the 2017 Gender Summit. Nemer recounted meeting an accomplished female biologist when she was a postdoctoral fellow. This scientist became a role model who showed that it was possible to have a thriving career while raising children. Nemer also said

that 30 years after raising concerns about juggling work and family with this scientist, she encounters young female researchers contending with doubts about whether it is possible to have children and a successful scientific career. "Science and family are not mutually

THE EVIDENCE FOR GENDER BIAS IN SCIENCE IS CONSIDERABLE, BUT THERE ARE SIGNS THAT PROGRESS IS AFOOT.

exclusive for men, why should they be for women?" said Nemer.

Dr. Claudine Hermann, who in 1992 became the first female professor appointed to École Polytechnique, a prestigious engineering school in France, said in a 2018 article in *Science* that her "greatest" challenge was juggling three sons and her career as a scientist. "Fortunately, my children were in good health, I had excellent help at home with a nanny, and my husband has always been very supportive." Now vice-president of the European Platform of Women Scientists and president of honour of the Paris-based Femmes and Sciences Association, she noted, too, that she thinks it's harder for this generation: "I believe that life as a woman scientist is more difficult nowadays than during my time. The many years of job instability that early-career researchers now typically go through and the increasing need for mobility can make private life difficult. My advice to women scientists is to be confident in your abilities, choose your partner well, and find good support in your network."

Against this backdrop, when asked how she sees her prospects as a woman in science, Tanaka sighs. "That's a difficult one. As a female PI, it's really hard to take maternity leave, for example.

You have to be there or else the lab will not move forward. That makes it hard to plan anything, even in the short term," she says. Nonetheless, after defending her thesis in 2018, she plans to apply for postdoctoral fellowships and then look for a faculty position.

It is this drive that Chen and others underscore is essential to persevering. Her advice to any student, male or female? "I won't take on a PhD student now unless you're absolutely passionate or you have the potential and you want to continue in academia. There are too many people and no jobs. These students are talented, and there are other things they can do. Steve Jobs said that if you follow your passion, it'll all work out. It might, but it might not; I think it's harder now to do research than [it was for] the generation above me."

For those who do persevere, there are insights to be had from those who have gone before them. What is Aubert's secret to balancing her career and personal life? She says that while she generally integrates into her life the things she loves—family, science and athletics—she also has to prioritize duties. "Now it's grant season, so I really need to buckle down and work on getting those grants written. There are times where having it all at the same time is not going to happen. So I'll have all of my science for the next two months, and I'll do more of the other things [later]."

System issues are being addressed, with positive change on the horizon and in some cases already happening, but these are largely outside any one person's control and will take time. Not so solutions that focus on the day-to-day. Anderson's advice when it comes to "having it all" is multifold, with a healthy dose of the pragmatic that echoes the counsel of other academics, male and female, who recommend getting help with caregiving and housework, which requires moving past stereotypes about gender roles. "You really should know what you're up against and plan for it—have family around, have financial resources to hire people. That stuff should be in place and it will be much easier. Don't expect to have to do it all yourself. Having it all doesn't mean doing it all."

For the list of works cited in this story, visit sunnybrook.ca/research/magazine.

The Gendered Path to Science



Boys and girls are equally likely to associate intelligence with their own gender.

Girls are significantly less likely to associate brilliance with their own gender.

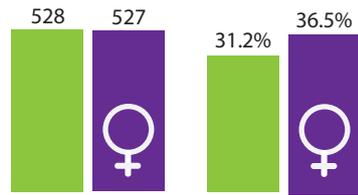


Six-year-olds show equal interest in a game described as being for "children who try really, really hard."

Compared to boys, girls are significantly less interested in a game for "children who are really, really smart."

Source: Bian L et al. Gender stereotypes about intellectual ability emerge early and influence children's interests. *Science*. 2017;355(6323). doi: 10.1126/science.1256254.

Female and male students in Canada show similar aptitude and interest in science in high school.

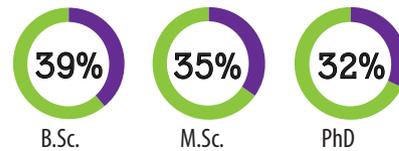


Average science score in 15-year-olds

Students with science-related career goals

Source: Organization for Economic Co-operation and Development. 2015 Programme for international student assessment; 2018.

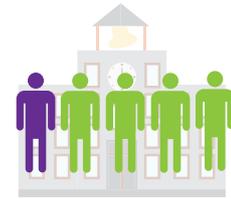
In 2014, women in Canada received



degrees in natural sciences & engineering (NSE).

Source: Natural Sciences and Engineering Research Council of Canada. Women in science and engineering in Canada. October 2017. www.nserc-crsng.gc.ca/_doc/Reports-Rapports/WISE2017_e.pdf.

But women make up only 18% of full-time NSE faculty at Canadian universities.

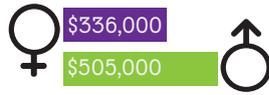


And, once there ...

Differences in funding emerge



Women holding Canada Research Chairs in 2017.



Average grant from the Canadian Institutes of Health Research over the last 15 years

Disparities in journal publishing emerge

1.7 to 2X

Males invited to submit papers to journals at double the rate of women



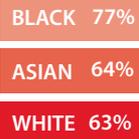
Women hold only 18% of last author positions, denoting seniority.

In physics, it is 13%.

The higher the journal impact, the less likely a woman is to be last author.

Sources: Canada Research Chairs Program. www.chairs-chaires.gc.ca/home-accueil-eng.aspx. Canadian Institutes of Health Research. Gender equity data analysis. 2017. www.cihr-irsc.gc.ca/e/50463.html. Holman L, et al. The gender gap in science: How long until women are equally represented? *PLoS Biology*. 2018;16(4):e2004956. doi:10.1371/journal.pbio.2004956. Bendels M, et al. Gender disparities in high-quality research revealed by Nature Index journals. *PLoS ONE*. 2018;13(1):e0189136. doi:10.1371/journal.pone.0189136.

The path of women of colour in STEM is hindered by biases based on gender and race, a so-called double jeopardy.



Female scientists in the U.S. who report having to prove themselves over and over again.

Source: Williams, J et al. Double jeopardy? Gender bias against women of color in science. 2014. doi:10.13140/2.1.1763.8723.

Visible minorities comprise 21% of Canadian university teachers. 13% of Canada Research Chairs.

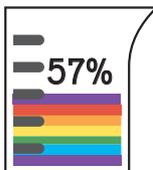
Aboriginal peoples comprise 1.4% of Canadian university teachers. 1% of Canada Research Chairs.

2% of Canada Research Chairs are held by persons with a disability.



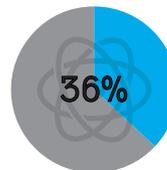
Sources: Canada Research Chairs Program. www.chairs-chaires.gc.ca/home-accueil-eng.aspx. Canadian Association of University Teachers. Underrepresented & underpaid; April 2018. www.caut.ca/sites/default/files/caut_equality_report_2018-04final.pdf.

It's not just about gender



Lesbian, gay, bisexual, trans, queer or asexual (LGBTQA) people in STEM, including faculty, staff and trainees, who are out to all or most of their colleagues.

Source: Yoder JB and Mattheis A. Queer in STEM: workplace experiences reported in a national survey of LGBTQA individuals in science, technology, engineering, and mathematics careers. *J Homosex*. 2016 63(1). doi:10.1080/00918369.2015.1078632.



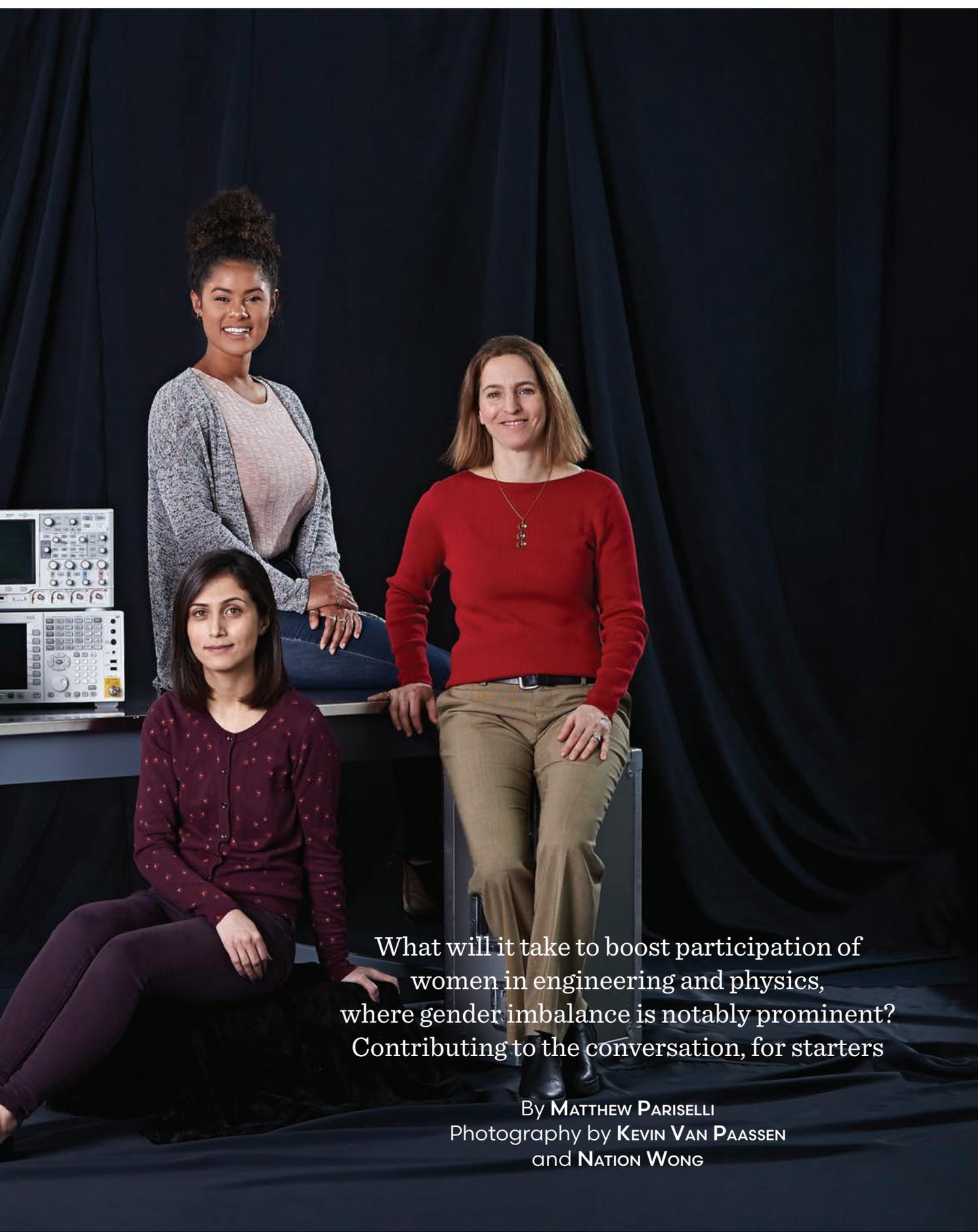
LGBT physicists who have considered leaving their institutions because of an unwelcoming climate.

Source: Atherton, TJ et al. LGBT climate in physics: building an inclusive community. *American Physical Society*. 2016.

LET'S TALK (WOMEN IN SCIENCE)



From left to right: Dr. TRISHA ROY,
STECIA-MARIE FLETCHER, HANIEH ARJMAND,
PAIGE SMITH and Dr. CARL WHYNE.



What will it take to boost participation of women in engineering and physics, where gender imbalance is notably prominent? Contributing to the conversation, for starters

By **MATTHEW PARISELLI**
Photography by **KEVIN VAN PAASSEN**
and **NATION WONG**

“LIFE NEED NOT BE EASY, PROVIDED ONLY THAT IT IS NOT EMPTY.

—Lise Meitner, physicist who discovered nuclear fission

IN A PHOTO Dr. Trisha Roy posted to Twitter, she stands above bloody gauze and surgical scissors. She has donned a face mask, cap, gown and gloves, and it's clear from her caption that she's training to become a vascular surgeon. Her caption also indicates she's adding to a discussion around women in science. Shared Aug. 10, 2015, Roy's post includes the hashtags #ILookLikeAnEngineer and #ILookLikeASurgeon.

Days before Roy's tweet, female engineer Isis Wenger launched a social media campaign using the hashtag #ILookLikeAnEngineer after an ad she was featured in ignited a fiery reaction. Several people were outraged, claiming Wenger was “too attractive” to be a “real” engineer. In response, Wenger encouraged engineers to share photos of themselves with the hashtag #ILookLikeAnEngineer to debunk myths about how engineers are “supposed” to look. A debate had begun to blaze on the role of gender stereotypes in engineering, and Roy was lending her voice to the dialogue. In her view, awareness is the first step to deconstruct this complex issue.

Gender equality and diversity remain issues in contemporary workplaces, affirmed by a substantial body of research, said keynote speaker Dr. Curt Rice at the 2017 International Conference on Medical Image Computing and Computer Assisted Intervention (MICCAI). “What's clear at this point is that there is a considerable literature making the strong case

that women and men are treated differently in the workplace,” he said to the crowd of engineers, physicists and others involved in biomedical imaging. Rice, who is the president of the Oslo and Akershus University College of Applied Sciences, and who leads Norway's Committee for Gender Balance and Diversity in Research, noted that addressing imbalances benefits everyone, but to do this, “We have to reconceive the whole system.”

Reforming the system includes tackling low numbers of women in science. According to a 2017 Engineers Canada report, data from 2016 show that 12.8% of practising professional engineers and 17% of newly licensed engineers are women. The gender imbalance doesn't exist only in the workforce. Canadian census numbers from 2017 show that about 25% of women with doctorate degrees went into architecture, engineering and related technologies. Of people with bachelor degrees or higher, five times as many men as women elected to go into science, technology, engineering and math (STEM). Engineers Canada reports that women made up 20% of those enrolled in Canadian undergraduate engineering programs, which aligns with U.S. numbers. A 2016 news article in *Nature* states that although 49% to 58% of U.S. undergraduates and graduates in the social and life sciences are women, that number plummets to about 20% in physics, a gap that has stubbornly persisted.

Other research has emerged. A 2018 *PLOS Biology* study by Dr. Luke Holman

and colleagues looked at how long it would take women to catch up to their male counterparts in science publishing. The team examined the number of male and female authors on more than 10 million academic papers published over the last 15 years, and found that, overall, it would take 16 years before parity is reached. In physics, it would take roughly 258 years for the gap to close if nothing is done. The study also shows that the rate of published female authors in physics—slightly more than 15%—is among the lowest of all fields. Women in biomedical engineering and diagnostic imaging fare better, but still hover around the bottom, at roughly 25% and 30%, respectively.

Although the ratio of men to women in engineering and physics is better today than it was years ago, it remains uneven. Stecia-Marie Fletcher, a PhD student at Sunnybrook Research Institute (SRI), says she was one of two women out of 100 students in a master's level class while pursuing her undergraduate degree in the U.K. Fletcher, who is helping to investigate the use of focused ultrasound to open the blood-spinal cord barrier to deliver treatments, was born in Trinidad and Tobago. Being a visible minority and a woman is what she laughingly calls “a double whammy.” She says, “Usually, if I'm not the only woman in the room, I am the only black person in the room.” Indeed, there's evidence to show that women of colour in science face unique barriers. Of the 60 female scientists of colour interviewed for a 2016 study led by Joan Williams published in the

Journal of Research in Gender Studies, 100% reported encountering gender bias.

Fletcher's supervisor is Dr. Meaghan O'Reilly, a scientist in Physical Sciences at SRI and an assistant professor in the department of medical biophysics at the University of Toronto. O'Reilly says she notices how few women there are when she attends conferences. "At a conference, you might see a two to one ratio [of men to women], or it's even more skewed," she says. O'Reilly is pioneering new research into focused ultrasound. She recently helmed a study published in *Scientific Reports* that is the first to show that using focused ultrasound to deliver a drug to treat tumours in the spinal cord has a therapeutic effect.

Hanieh Arjmand also identifies conferences as sites of unequal gender representation. A PhD student at SRI who models the craniofacial skeleton to optimize fracture fixation techniques following traumatic injuries, Arjmand completed her undergraduate degree in Iran. She immigrated to Canada five years ago to continue her studies. "You go to conferences, and the first thing that strikes me at the registration table is that it's mostly females, and then the people introducing speakers and doing

the planning, they're mostly males."

O'Reilly's and Arjmand's observations about gender imbalance at conferences has support. A 2018 *Nature Communications* article by Dr. Heather Ford and colleagues shows that fewer women are invited to submit abstracts than men. Looking at career stage, mid-career and experienced women are least likely to receive invitations. The same paper also demonstrates that women choose poster-only presentations more than men, which the authors attribute to lack of confidence and women's tendency to underestimate their ability and performance in science.

Although low numbers of women in physics and engineering continue to plague the fields, clearly some women do choose—and thrive in—these areas. This could be a result of not having experienced severe forms of sexism, or having support to manage family matters that disproportionately affect women. It could also mean early exposure to math and science.

"I was really good at math growing up, really good at physics," Fletcher says. She adds that she was teased for this, as the subjects weren't "traditionally" what girls gravitated toward. Dr. Anne Martel, a senior scientist in Physical

Sciences at SRI and a professor in the department of medical biophysics at U of T, as well as a MICCAI board member, also warmed to science at an early age. "I liked the fact that it wasn't subjective," she says. She has since become a significant contributor to the field of medical imaging, recently publishing a paper in *Radiology* showing how extracting features from images and feeding them into computer algorithms can help radiologists identify benign versus cancerous lesions.

O'REILLY MUSES THAT having four brothers encouraged her access to non-gender-stereotypical activities and pastimes. "I ended up doing a lot of things that my brothers did. I think in that sense I was always comfortable in some of the 'non-traditional' fields for girls," she says. "My sister and I were both hockey players at a time when it was not really that common for girls to play hockey. I was on the chess team—I never understood why there weren't more girls on the chess team in elementary school; it doesn't seem like it should be a gender-specific thing, but for some reason it was. I was on the robotics team, and again, my sister and I were the only two girls in our high school on the robotics team." She says stereotypes were not imposed on her as a child, and that this granted her freedom to explore her interests in math and science.

Arjmand's enthusiasm for math was cultivated by her father, a civil engineer. She says he would ask her to answer math equations when she was a child. Eventually, even after she had finished classes for the day, she'd ask her father to teach her material she hadn't learned in school. "I really loved that. It was fun," she recalls. There's a clear parallel between Arjmand's upbringing and Roy's introduction to engineering. Roy, a vascular surgery resident who successfully defended her PhD in November 2017 and splits her time between research at SRI and surgery at Sunnybrook, says, "My dad is a mechanical engineer, so he really inspired me to become an engineer, too." She adds that the same bug bit her older brother—he's a nuclear engineer.

Co-supervised for her doctorate by surgeon-scientist Dr. Andrew Dueck and senior scientist Dr. Graham Wright at SRI, Roy developed a new MRI method for use in surgery to restore



DR. TRISHA ROY, who followed in her father's footsteps by becoming an engineer, divides her time between research at Sunnybrook Research Institute and surgery at Sunnybrook.



HANIEH ARJMAND, a PhD student at Sunnybrook Research Institute, cites conferences as areas with glaring gender imbalances.

blood flow to the legs of people with peripheral arterial disease. The tool can identify what lesions are made, which helps doctors determine treatment routes. The guiding aim is to prevent limb amputation in this population.

FOR WOMEN WHO do enter into engineering and physics, deep-seated stereotypes can manifest in bias. A 2016 paper by Dr. Sarah Banchevsky and colleagues in *Sex Roles* outlined a study that presented photos of male and female STEM faculty to people who were unaware of the subjects' occupations. The participants were asked to rate the photos on femininity and likelihood of being a scientist or teacher. Results indicate that the more stereotypically feminine a woman appeared, the less likely she was to be deemed a scientist and the more likely she was deemed to be a teacher. Perceived femininity had no bearing on the judgment of male scientists.

"The ways in which we currently treat men and women differently are not about maliciousness. They're for the most part not about explicit sexism. They are about implicit bias, and that concept deserves your attention," Rice said. He stressed the importance of acknowledging the effect this bias has

on the careers of women.

Indeed, for the most part, it's not about egregious sexism; rather, it's about subtle, even unintentional, bias, which itself is problematic. When Roy considers her career path, she relives an experience in which she confronted a sexist response from a male peer. During her studies at U of T, she was ranked first in her class. Disappointed his name wasn't at the top of the list, the classmate who ranked second incredulously remarked, "You? Smart?!" It was a condescending reaction she met with astonishment and laughter.

A chuckle is also Roy's response when she thinks back to receiving an email in December 2017. Designed to notify recipients of a symposium, it was addressed to "Mr. Roy." "I get that often! [laughs] Every time I'm shocked, and I don't know why I'm still shocked," Roy says. "It's just ridiculous. It makes my heart sink a little." She tweeted a screenshot of the email, noting: "Most of the engineering-related e-mails I receive are addressed to 'Mr. Roy'. This is what happens when < 13% of engineers in Canada are women. We can do better!" Citing Isis Wenger's social media campaign, Roy included the hashtag #ILookLikeAnEngineer and

#ILookLikeASurgeon.

Martel recalls an example of subtle bias that she encountered concerning a reference letter written for her. Although positive traits were highlighted, nothing was mentioned of her scientific capabilities, totally unintentionally, she underscores. This, it turns out, is fairly common. Published in *Nature Geoscience* in 2016, a study led by Dr. Kuheli Dutt that looked at more than 1,200 recommendation letters showed that female applicants were only one-half as likely as males to receive excellent letters. Further, there was no difference between men and women writers—both crafted stronger letters for males.

Like Martel, Dr. Cari Whyne, a senior scientist in Physical Sciences and director of the Holland Bone and Joint Research Program at SRI, and Arjmand's supervisor, hasn't had to deal with overtly inappropriate behaviour. She revisits what she calls a "small" brush with sexism that occurred several years ago when she received a forwarded email from someone outside the institute. Since she hadn't read the previous messages, she scrolled to the bottom and found statements about her made by a male employee of the company. "We were supposed to be working professionally, and he was commenting on my appearance. It was a physical description of me, and it was very inappropriate for the workplace," she says.

The professor in the department of surgery at U of T, whose research is in the area of orthopaedic bioengineering, notes that she didn't let the incident affect her. Whyne recently published a paper in the *Journal of Biomechanics* that investigates load transmission through different pelvic shapes and the implications this might bear on fixation in trauma patients, but the biggest focus of her work is on spinal metastases, or cancer that has spread to the spine. Her research explores how practitioners can better assess the likelihood of fracture in patients with tumours of the spine and develop minimally invasive devices to improve treatment.

Having her appearance be the subject of a remark is an experience to which Arjmand can relate. She says after delivering a talk at a conference, a male peer approached her. Instead of talking about the content of her presentation, he

commented on her lipstick. “It was very inappropriate. I know he didn’t mean it as an insult, but it embarrassed me,” she says. Arjmand adds that unconscious or unnoticed sexist comments are still problematic, stressing that both men and women can be guilty of making them, and that it’s everyone’s responsibility to be aware of and speak up about sexist behaviour. This point resonates with Fletcher. “I think we need to start talking about it more. It’s good that we talk about it in the global sense, but I think in science we should start our own conversations about it, especially in a field where women are such a minority and probably feel that they can’t speak up for themselves,” she says.

Speaking up is the topic of a 2016 *Nature* column written by Dr. Tricia Serio, dean of the College of Natural Sciences at the University of Massachusetts in Amherst. “To improve the climate for women in science, it’s time to share our stories of microaggression,” she urges, using a term meant to speak to the everyday slights against any marginalized group, though originally it was specific to such behaviour directed against African-American people. Serio discusses her own experiences, and compels those who have received comments they perceived as sexist, as well as those who realize they have made comments that could be perceived as sexist, to submit their stories to her website, www.speakyourstory.net. Participants can write anonymously what was said to them and how they interpreted the comment. The purpose is not to identify anyone, but rather to make the unconscious, conscious—and eventually to eradicate such behaviour.

Subtle sexism aside, a big challenge faced by women in engineering and physics, and some men, is impostor syndrome, Whyne says. The term refers to the belief of a person—often a woman—that she is an impostor among those in her ranks, that her success is a product of luck rather than intelligence and hard work. Despite her achievements, she feels like a fraud at risk of having her cover blown.

Martel substantiates Whyne’s assertion on this, linking impostor syndrome in women to lack of confidence. Having recognized impostor syndrome in herself, she says, “Women are much more circumspect about what they’ll claim,

and tend to underestimate or undersell themselves.”

Martel’s argument rings true when considering Fletcher’s comments about impostor syndrome. “I always think, ‘I can’t possibly do this.’ I doubt all of my results. I always feel as if I’m not good enough to do this or to be here,” Fletcher says. Roy’s sentiments differ little. “I always thought even when I did well in engineering, I was very clear that I’m just a book engineer. I know how to do tests. I’m not a real engineer,” she says. “Impostor syndrome is a huge issue for me to this day. It’s very pervasive,” says the woman who received a three-year \$150,000 Vanier Canada Graduate Scholarship in 2016.

WHEN ARJMAND CONSIDERS the role impostor syndrome plays in her life, magnified, she says, by coming from a male-dominated mechanical engineering background, she mentions an article she read noting women generally apply for jobs only when they’ve satisfied all requirements, whereas men might apply even if they’ve only met one or two requirements. Rice talked about this at the MICCAI conference, pointing to relevant studies, and adding that higher qualified women choose not to apply for positions because they don’t expect to

get them.

Taking impostor syndrome one step further is Paige Smith, who is a master’s student in O’Reilly’s lab. She is contributing to the blood-spinal cord barrier research by developing a controller to ensure the delivery of ultrasound is safe and can be tailored for various treatments. Smith says due to restrictions, some of which are self-imposed, women tend to feel unworthy in their roles and thus fail to negotiate or advocate for themselves. “We’re not supposed to fight for what we think we deserve, just take what we get and sit down because we should be happy that we got the position at all,” she says. Martel builds on this: “If you’re already [asking yourself], ‘How did I get to where I am?’, you’re not going to be stirring the pot by going and asking for more money.”

Rice also asserted that institutions are underperforming if they’re not working to fix the system. He was referring specifically to a system that unfairly evaluates women with children, and discussed as evidence a 2007 foundational study by Shelley Correll and colleagues in the *American Journal of Sociology*. The authors found that based only on a paper file, mothers—or women thought to be mothers—were



DR. MEAGHAN O'REILLY (right) and her PhD student STECIA-MARIE FLETCHER explore how focused ultrasound can be used to open the blood-spinal cord barrier to deliver therapeutics.

judged as significantly less competent and committed than women without children; they were held to harsher performance and punctuality standards; when they were hired, their salaries were lower than non-mothers; and they were considered less well-suited for promotions. “Biology matters. Motherhood matters. In fact, even the perception of motherhood matters,” Rice said. More recent studies have shed further light, showing that women in STEM with children are paid less and have less opportunity to engage with mentoring or to benefit from formal or informal networks within the institution and at conferences.

ADDRESSING ALL OF this won’t happen overnight, but helping mothers receive equal treatment at work could entail something as simple as instilling a rule that prevents meetings from interfering with child care responsibilities, Martel suggests. “If you’re having to do daycare drop-off and pickup, it’s discriminatory to have a meeting that you can’t attend,” she says. “Avoiding meetings after 5 p.m. also benefits fathers who have young children. Many policies that are initially aimed at reducing bias often have the effect of benefiting both men and women,” adds Martel.

Seeing first-hand women who’ve managed careers as scientists while juggling motherhood is an experience the younger generation values. Speaking about O’Reilly, who delivered a baby girl in the summer of 2017, Smith champions her “inspirational” ability to handle her duties as mother and supervisor, an acclamation Fletcher reiterates: “It’s something I admire her a lot for, and something I think about because one day I want to have a family.” Similar praise is sung for Whyne. Arjmand, who shares that she really wants kids but doesn’t want to “sacrifice” her career, says, “She’s my role model. She’s one of the very few people I know who has the perfect balance between life, having kids, managing a lab and managing students. I’m very happy to be working with her.”

Having mentors is a concept that was emphasized by Dr. Cristina Amon, dean of U of T engineering, at the 2017 Women in Science and Engineering Conference: “As scientists and engineers, we are global citizens and collaborators. But let’s not forget that we are also role models, and it is up to each one

of us to set an example and to enable young women and girls to imagine themselves as scientists and engineers with the potential to change the world.” It’s interesting, although perhaps unsurprising, that a study by Drs. Tara Dennehy and Nilanjana Dasgupta published in 2017 in *Proceedings of the National Academy of Sciences* noted that the existence of female peer mentors in college had a positive impact on women’s academic experiences and led to greater retention in engineering.

Nonetheless, the lack of female representation, and therefore role models, in senior academic positions is startling. In Canada 5.6% of full professors in physics, and 11.1% of full professors in engineering physics, are female. As per numbers shared at the 2017 Gender in the Global Research Landscape Summit, 22% of engineering and physics researchers in Canada are women. That’s 20% below the overall proportion of female researchers in the country.

When Arjmand reflects on her 11-year post-secondary career, she remembers being taught by two female professors. Smith’s experience was similar, and she says that although she only had three women teach her engineering courses in university, it was significant. “Having them there teaching you, showing you what they’ve done through their careers, is really motivating. Representation makes such a difference because if you don’t see yourself in that position, it’ll be way harder for you to get there.” Fletcher agrees: “You want to know people who are like you have succeeded in similar fields. It’s hard if you look to senior scientists and see no one.” The void of black women in leadership roles doesn’t inspire confidence. “It makes it seem like an impossible goal. [Engineering] doesn’t seem like a thing people like me do, but it makes me want to work harder to get there.”

Dr. Bilge Demirköz, a professor in high-energy physics at Middle East Technical University in Ankara, Turkey, was one of more than a dozen women included in a 2018 *Science Magazine* article on the experiences of women in science. “In class, I love telling my students, ‘If I have done it, you can do it too’ and seeing their eyes light up. They go from questioning whether they can be successful to asking questions about how they can be successful,” her

reflection reads. “Especially for women, who even at a young age can internalize impostor syndrome, this is a big step forward.”

Reserving spots on staff for females is one way to increase representation, and what the renowned Max Planck Society in Germany, called that country’s most successful research institution for having had 18 Nobel laureates emerge from it, did when it launched a women-only hiring initiative in November 2017. Action like this is supported by studies that suggest that efforts to recruit women elevate the overall quality of the organization.

A 2012 study by Drs. Loukas Balafoutas and Matthias Sutter in *Science* explored affirmative action policies for women in a simulated lab setting. Explaining the results, Rice said, “The strongest women opted out of competition by default. And the effects of manipulating the instructions to say, ‘we encourage women to participate; we’ll give half the earnings to women; all other things equal, we’ll go for the woman, or if a woman is close to a man we’ll go for the woman’—the effects of those types of manipulations drew the stronger women into the competition.” Further, he added, “One of the most interesting results is that the balance was achieved without having to use the quota.” That is, the mere announcement of the interventions was enough to reach gender balance. Moreover, increasing women’s participation in competitions didn’t affect the chances highly skilled men had at success, and post-competition cooperation between men and women was unaffected.

Another study, published in the *Journal of Economic Behavior & Organization* in 2014 by Drs. Oded Stark and Walter Hyll, looked at real-world situations and the impact of gender quotas on promotion. It found that quotas discouraged less qualified men from applying for promotions while more qualified women were encouraged to do so, which raised the overall quality of applicants. Similar findings emerged from a study led by Timothy Besley in *American Economic Review*. The effects of quotas on the lists of political parties were analyzed, specifically the impact of a “zipper” quota, whereby local parties alternated between men and women on a ballot. In his unpacking of the results,

Rice said that the competency of the group increased when the zipper quota was introduced, as did the individual competency of men. This means strong women replaced weaker men. “This is an example of where a super-rigid quota has the effect of lifting the overall competency of the group,” he said.

It’s important to keep studies like these in mind, given, as Arjmand says, the assumption is sometimes made that if a woman gets a faculty position, it’s a reflection of her sex—she didn’t get the job because of her qualifications, but because an organization had to fill a quota. “It always bothers me,” she says. This line of thinking can create doubt for women who do get hired, and deepen the roots of impostor syndrome, Martel says—when, as research shows, the competency of those hired should not be in question.

Organizations appear to be receiving the message that it’s advantageous to include women. For example, Martel says MICCAI has taken measures to strive for equal representation, citing Rice’s invitation to speak at its 2017 conference, and an effort to facilitate roundtable discussions for young women to share concerns. Engineers Canada is another organization making headway. It launched an initiative called 30 by 30, which seeks to raise the rate of newly licensed engineers who are female from 17% to 30% by 2030.

Whyne says other ways to boost the number of women in physics and engineering include ramping up the presence of outreach programs, and making math and science as engaging as possible in school to attract girls at a young—very young—age. This idea connects to a 2017 study led by Dr. Lin Bian in *Science* on children’s perception of brilliance. It was found that at age five years, girls and boys each associated brilliance with their own gender. By age six to seven, girls were less likely than boys to attribute brilliance to their own gender. Further, the older girls were less interested in games meant for “really, really smart” children.

Findings such as these have repercussions. A 2015 study by Dr. Sarah-Jane Leslie and colleagues in *Science* showed that in many academic fields, including math and physics, success was deemed to depend on “raw, innate talent”—and that emphasis on this “brilliance

required” notion led to fewer female PhD students. As Dr. Sarah Eddy, assistant professor in biology at Florida International University, put it in 2017 while commenting on the study in *The Atlantic*, “Unfortunately, this reveals another hurdle for efforts to recruit more women and girls into STEM. Not only do we need to break down the ‘science is male’ stereotype, but now we need to break down a ‘brilliance is male’ stereotype, too ... We have to be more deliberate about presenting examples of brilliant women to girls and boys as young as five to help them avoid developing this association.”

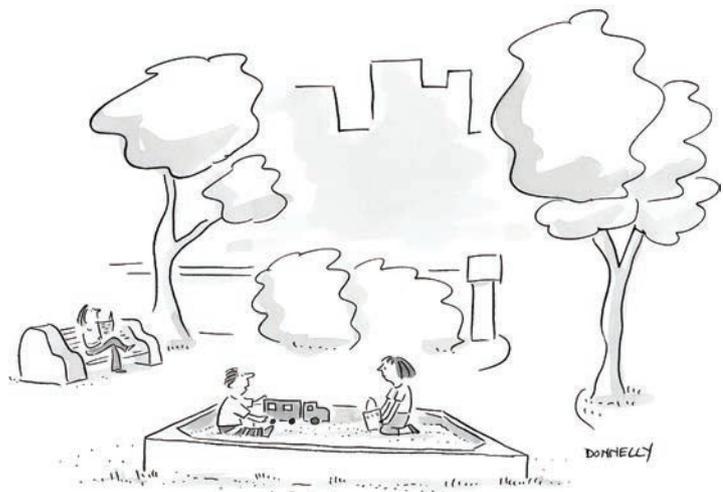
FOR ROY, THE significance of speaking up about issues in physics and engineering cannot be stressed enough. The #ILookLikeAnEngineer movement continues to gain momentum, and has now spawned a community of LGBTQ+ engineers, who have adopted the hashtag #ILookLikeAnLGBTEngineer. The mother of the modified hashtag is Elena Rodriguez-Falcon, the inaugural provost and chief academic officer of the New Model in Technology and Engineering, a university scheduled to open in the U.K. in 2020.

Evidence suggests women are making inroads. Although enrolment of females in undergraduate engineering programs at Canadian post-secondary institutions peaked in 2001 at 21%, Engineers Canada says it has been climbing by roughly 1% every year since 2008. It also says that in 2016 40.1% of first-year

students in U of T’s engineering programs were female, a record for the faculty. While discussing her school’s improvement at the 2017 Women in Science and Engineering Conference, Amon added, “I am pleased to say that the proportion of women professors in our faculty has more than doubled over the past decade to 21%, expanding our research strengths and the range of exceptional opportunities that are available to all of our students.”

Despite women only accounting for 12.8% of practising professional engineers in the country, Engineers Canada says the number of them employed has increased from 12,740 in 2006 to 26,113 a decade later. “It’s getting better as more [women] start populating [the field]. There are far more younger women, but if you start looking for women my age there are virtually none. That’s when it becomes striking. My hope is that it’ll gradually even out,” Martel says. Smith agrees: “I hope more girls do get into science because it’s a really rewarding field. If I can eventually motivate anyone to do that, that would be really cool. I hope I can see that change over my lifetime.” With such a change, Roy underlines, everyone benefits. “To get the best talent, you need women. I want to emphasize that piece. Diversity is crucial to advance science and engineering.”

For the list of works cited in this story, visit sunnybrook.ca/research/magazine.



“I don’t see liking trucks as a boy thing.
I see it as a liking-trucks thing.”

Their Way

With PhDs in hand, two SRI alumni chart custom-fitted courses

Dr. Patrycja Thompson is used to asking why. As a child in Poland, she accompanied her mother to her job as director of a hospital lab. Once there, she'd plead with scientists to show her the magic to be found in a microscope's lens and explain why the slide was being evaluated. Her inextinguishable curiosity was instinctive, so it's unsurprising she gravitated toward an undergraduate degree in biology, followed by a PhD and postdoctoral fellowship in immunology.

Today, however, the question of why is directed at her. Seated in a lounge within Toronto's bright—figuratively and literally—MaRS Centre, which is so abuzz with creative ideation one can almost hear the hum, the question is posed: why did you quit academia?

Now the manager of technology sourcing and evaluation at the Centre for Commercialization of Regenerative Medicine (CCRM), located in Toronto's MaRS Centre, Thompson draws on three reasons in her response. The first pertains to family. As a woman in the field, she was aware of the compromise she was expected to make. She says, "I was told this by female scientists: 'You have to choose between being a scientist and having a family.'" Now the mother of a five-year-old son, she adds, "I thought it was completely ridiculous. Why should that be a choice I have to make?" Her goal was to have a successful career as a scientist and a family.

It became apparent to Thompson that supporting a family on a "ridiculously low wage," which she says she would have had for at least five years before possibly securing an academic position, was a heavy burden. Under the supervision of Dr. Juan Carlos Zúñiga-Pflücker, a senior scientist at Sunnybrook Research Institute (SRI) and the chair of immunology

at the University of Toronto, Thompson explored the development of T cells en route to earning her PhD in 2015. Essential for immunity, T cells are white blood cells. They recognize and target invaders in the human body, including viruses and bacteria, and have become central to modern cancer treatments. After her PhD, Thompson relocated to Philadelphia, where she was a postdoctoral fellow. This was when she felt another push to leave academia, as she began thinking about the money she was making—or rather, not making. "At one point I said to myself, 'It's time I start valuing myself and my own abilities,'" she says. "Getting a PhD is a big deal; it's almost as high in education as you can go. I said, 'This is it? This is how much my education and knowledge are appreciated?'"

The final nudge was lack of research funding. "When I heard of academics I knew having to close their labs, that didn't inspire me to keep trying and push

against all odds," she says. One can hardly blame her for harbouring hesitancy. The national average success rates of the Canadian Institutes of Health Research's 2016 and 2017 Fall Project Grant competitions were 16.5% and 15%, respectively. Such grants are fundamental for independent investigators; without them, running a lab is nearly impossible.

The bleak research funding climate was also a variable Dr. Jasty Singh contemplated when planning her future post-PhD. Like Thompson, Singh completed her doctorate in Zúñiga-Pflücker's lab at SRI, where she worked with progenitor T cells, investigating their function in cancer transplantation and anti-HIV models. She says, "[The work] was really exciting because progenitor T cells have a lot of potential for clinical translation—they're more likely to be accepted by the patient and less prone to causing side effects compared to current approaches." She successfully defended her



DR. PATRYCJA THOMPSON, who did her PhD training at Sunnybrook Research Institute, has found satisfaction outside of the lab at the Centre for Commercialization of Regenerative Medicine, where she evaluates new cell- and gene-based technologies.

PhD in September 2017. Since October she has been a postdoctoral fellow in Dr. Peter Zandstra's lab at U of T, a position she's confident will help thrust her toward her goal of teaching at the university level. Her desire to teach science rather than sit at the bench is largely a product of funding, or lack thereof, Singh notes. In a growing pool of scientists competing for few grants, receiving the means to carry out one's research has never been tougher.

In Zandstra's lab of engineers and one chemist, Singh is the only biologist. She brings a unique perspective to their projects, one of which involves engineering a system to scale up the production of progenitor T cells. She heads the lab's immunology projects and manages the researchers in "the blood group," a team that works on therapeutics for blood diseases. "In addition to working on my own project, I advise anyone doing immune-cell-related work on their projects and help them plan out different experiments," she says. Singh sees a direct association between her position in Zandstra's lab and her dream job, which she says would be composed of 80% teaching and 20% research. "This contributes well to my end goal in that I'm working with and mentoring a group of individuals who aren't necessarily biologists, which is what I'm used to. It really challenges me in a way that I haven't been challenged before."

Tackling a new challenge is a task to which Thompson can relate. In her role at CCRM, which she has held since November 2017, she sources and evaluates new gene- and cell-based technologies. She obtains disclosures from technology transfer offices about inventions, and if they fall within CCRM's realm of interest, then she evaluates the scientific merit and patentability of the technology, and whether it has a place in the market landscape.

The duties Singh and Thompson complete in their positions are partly made possible by the abilities they gained at SRI. For Singh, explaining her work to various people is a skill she fashioned while doing her PhD, practised while teaching a statistics course in 2018, and is sharpening further in Zandstra's lab. Collaborating with engineers, a group with a much different background than biologists, one of her jobs is to describe concepts that may be new or foreign. "It's very much about figuring out how to

communicate things in a way that makes sense," she says. She adds that she could build on this by relocating to the U.S. "There, they have postdoc positions that are geared toward the teaching stream, which allows you to focus solely on teaching during your postdoc. I think this is an exceptional opportunity. It is definitely something I would consider in the future."

For Thompson, it's the capacity to digest scientifically dense material that she values. "Doing a PhD and postdoc gave me the scientific exposure I need for this job," she says. "I get bombarded by news about science and regenerative medicine. I have to scan for things, and if something catches my eye and I go to the primary article, I have the ability to read it and scientifically analyze it to extract pertinent information in a short amount of time." Zúñiga-Pflücker and her lab mates at SRI were instrumental to learning this skill, she says.

Thompson also delves into a role at SRI she held outside the lab that equipped

her with tools to perform her current work. Under Kevin Hamilton, director of strategic research programs, she navigated new territory as a projects officer. "Kevin taught me how granting works so I could understand the system. I gained a totally different perspective," she says. Assisting in the writing of grants, including the commercialization sections, enabled her to be a prime candidate for her CCRM job, she notes.

Singh may be on an unconventional path toward academia and less time in the lab, and Thompson may not don a white coat, safety goggles or gloves anymore, but they've each channelled their passion for science into fulfilling roles. "Being an academic was a dream I had to give up pursuing, and it was very painful. I wrestled with the decision for a year, but now I like this idea that if I can't do science, maybe I can help someone else with their process," Thompson says. "This new position fits perfectly."

MATTHEW PARISELLI



Former Sunnybrook Research Institute PhD student **Dr. Jasty Singh**, a biologist, now works in a lab mostly made up of engineers, which she says connects to her goal of teaching at a university.

“What is your guilty pleasure?”

EDITED BY **STEPHANIE ROBERTS**



CLARE ATZEMA

I'M ADDICTED TO puzzles. Old fashioned, 1,000+ piece puzzles. It's a controlled addiction—I don't do them often, because I know that once I start I won't be able to tear myself away, and everything else will be put on hold for a few days, until I finish it. I get to bed well past 2 a.m. on those nights. I'm methodical about how I approach one (border first, always!). I load the dishwasher in the same way, I'm embarrassed to admit.

I also love coming up with new cocktails. I like to have a new one for every dinner party. I've bought old-fashioned 1950s coupe cocktail glasses, which I'm certain make my cocktails taste better. I make mocktails for my kids, and they think I'm the female equivalent of Tom Cruise in *Cocktail*. I love that it gives me street credibility in their eyes!

Lately, I've been binge-watching *The Handmaid's Tale*. It's riveting, in a terrible way. I'm almost done: I've encountered that bittersweet place where you know it's going to be over soon, so you kind of don't want to keep watching, to save some for later. . . .

Atzema is a scientist in Evaluative Clinical Sciences and the Tory Trauma Research Program at SRI. This spring, she secured a Project Grant from the Canadian Institutes of Health Research of almost \$530,000 over three years. She will use the fund to create an online appointment scheduling tool for emergency departments to improve the transition between emergency and primary care.



CHINTHAKA HEYN

MY GUILTY PLEASURE is a lazy Sunday (when I am not on call!). It generally starts off with coffee and *The New York Times* at home. My wife (a Sunnybrook internist and the brains in the family) reads the paper, and I usually stick to the magazine. One of my favourite sections is “Diagnosis,” where a real-life medical mystery is told. We sometimes work through the case together in a bit of a competition to see who can make the right diagnosis: neuroradiologist versus internist. You can guess who usually wins that one.

After, we like to head out to the Brickworks, grab another coffee and lunch at the café or food vendors, and peruse the artisan market. On the way home, we might hit up our favourite fishmonger, butcher and bakery on Bayview Avenue and pick up a few things for dinner. Cocktails and a nice glass of Pinot on our patio to end the day.

I should add that since we had a baby girl this past May, much of the above has been significantly curtailed.

Heyn is an associate scientist in Physical Sciences and the Odette Cancer Research Program at SRI. His research focuses on bio-heat exchange, the study of heat transfer within living things. Last year, he led a Toronto group that was the first to measure the temperature of flowing blood noninvasively in mice with a novel MRI contrast agent. The team's findings were presented in *NMR in Biomedicine*.



JUAN CARLOS ZÚÑIGA-PFLÜCKER

I DERIVE ENORMOUS pleasure from seeing those working in my laboratory succeed in their research endeavours, so much so that I almost feel guilty about this vicariously earned enjoyment.

When the time comes to do things outside research, I find myself enjoying a round of golf, which is a bit of a guilty pleasure, as it does take many hours to play. However, the game provides a total change of scene and pace, while offering a new set of challenges and rewards.

Having a great drive or nailing an approach shot next to the flag gives you a great feeling, which unfortunately does not happen all the time, but like a “Skinner box,” partial reinforcement does make golfing a very addictive game.

When winter comes around, my other guilty pleasure is watching old movies and, whenever possible, indulging in a streaming binge of *Homeland* or *Stranger Things*.

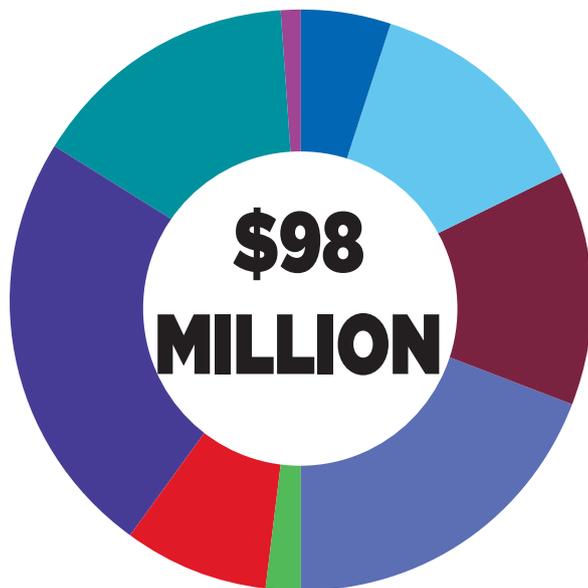
Of course, that's only if I'm not listening to the masterful tunes of Abba.

Zúñiga-Pflücker is a senior scientist in Biological Sciences at SRI and chair of the department of immunology at the University of Toronto. He holds the Canada Research Chair in Developmental Immunology. This year, he received a Disease Team Grant of \$250,000 from the Ontario Institute for Regenerative Medicine, to further his work to establish a more efficient way to generate new T cells in people who have lost them owing to a bone marrow stem cell transplant.

Quick Statistics

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

MAJOR SOURCES OF FUNDING 2016-2017



Sources	\$(M)	%
Canada Foundation for Innovation	4.5	4.6
Contracts With Other Private/Public Organizations	12.9	13.1
Industry	13.1	13.4
Internal Funding	18.2	18.6
Ontario Ministry of Research, Innovation and Science	1.8	1.8
Other Government Sources Within Canada	8.2	8.4
Private Sector Funding From Philanthropic Organizations	23.1	23.6
Tricouncil Funding: CIHR, NSERC and SSHRC; also includes Canada Research Chairs Program	14.9	15.2
U.S. Government	1.3	1.3
Total	98	100



118 senior scientists and scientists



74 postdoctoral fellows



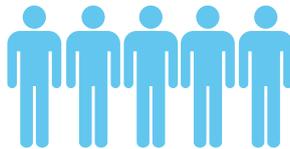
78 associate scientists



480 research assistants and coordinators, lab and project managers, programmers and data analysts, and technicians



127 affiliate scientists



383 graduate, undergraduate and high-school students



93 research associates, engineers, physicists and technologists

Total research staff: 1,353

Q&A



DR. JULIE LOVSHIN joined Sunnybrook Research Institute as a clinician-scientist in September 2017. She is also an assistant professor of medicine in the division of endocrinology and metabolism at the University of Toronto. She spoke with Betty Zou about her research.

What is the focus of your research?

I am interested in reducing the complications of Type 2 diabetes. My research focuses on diabetic heart and kidney disease, which are the leading causes of premature death among people with Type 2 diabetes. Over the last three years, there have been big changes in the way we treat Type 2 diabetes. In 2015 the first large-scale trial in patients with Type 2 diabetes with heart disease was done for a newer class of diabetes drugs known as SGLT-2 inhibitors, showing these drugs were not only safe, but were also protective in the kidney and heart. Surprisingly, these effects were happening within three to six months. No diabetes drug had shown such positive effects before. A few years later, another diabetes drug that is a GLP-1R agonist showed similar protective effects. At the time, I was studying how these drugs lower blood pressure and affect kidney function. These results launched a whole new area of investigation for me.

Why were you interested in studying the effects of diabetes drugs on sodium metabolism?

In a prior study, we were investigating mechanisms of blood pressure reduction for GLP-1R agonists, which led us to study urinary sodium excretion. We wanted to ask whether another class of diabetes drugs known as DPP-4 inhibitors also increases urinary salt loss. In this study, we found that in patients with Type 2 diabetes DPP-4 inhibitors increase urinary sodium excretion. Curiously enough, it didn't immediately impact kidney hemodynamic function. What are these sodium pathways important for, then? One reason might be for reducing inflammation in the kidney. Sodium

DIABETES AND ITS COMPLICATIONS

2,100,000

Canadians aged 12 years and older were diagnosed with diabetes in 2016

People with diabetes are



three times more likely to be hospitalized with heart disease



12 times more likely to be treated for end-stage kidney disease



20 times more likely to undergo non-traumatic lower limb amputation

excretion seems to be common to all three of these newer diabetes drugs, so it's important to understand how each of these drugs impacts sodium metabolism, because many of these drugs are used in combination to treat patients with Type 2 diabetes.

What are the most pressing questions in Type 2 diabetes complications research?

A new area in diabetes research is focusing on the effects of diabetes on the brain. It's an evolving area where researchers are asking if there are any links between diabetes and cognition and executive function, and even brain diseases such as Alzheimer's disease. If so, is it because of diabetes and blood sugar control, or other factors associated with diabetes, like increased inflammation? These are critical questions, as we know that as we reduce heart and kidney disease in people with diabetes, these patients will live longer and be at risk for dementia.

Why did you become a clinician-scientist?

I did my PhD in basic science on the gut hormones known as GLP-1 and GLP-2. I started as a master's student. I was never intending to do a PhD; I just got drawn into it. To me, the questions we were asking were so interesting and relevant to the treatment of diabetes. Once I finished my PhD, I entered medical school and completed my residency in internal medicine and endocrinology. Now, as a clinician-scientist, it's very impactful for me to ask my research questions in humans to see if basic science findings are translatable to human disease.

Lovshin's research is funded by the department of medicine at the University of Toronto, Merck and Sanofi. For more, visit sunnybrook.ca/research.

Through the Wormhole

Journey into a different time in medical science



VIRGINIA APGAR created a test that is still used to determine the health of babies.

ASKED BY A medical student what to look for when assessing a newborn's health, American anesthesiologist Virginia Apgar (1909–1974) swiftly scrawls a few notes on a piece of paper. Unbeknownst to her, she's just drafted a list of signs that will become her claim to fame—one she will develop further and publish in 1953, and that will be practised around the globe as a test to evaluate quickly the state of newborns.

Still used today, the appropriately titled Apgar score is a simple test that involves reviewing a baby's appearance, pulse, grimace, activity and respiration upon delivery, and assigning a grade to each factor. Zero, one or two are the options—in other words, poor, fair or normal—and a total of seven out of 10 means the baby is healthy. If the total is less than seven, then the test is repeated at five-minute intervals until a score of seven or higher is achieved.

The result immediately indicates

whether a baby requires extra attention and helps care teams decide on treatments from heart monitoring to resuscitation. The test is widely praised for increasing neonatal survival rates at a time when the focus of medical professionals was on mothers, an approach that led to many newborn deaths.

In addition to shaping the course of neonatology, Apgar helped blaze the trail for women in medicine by becoming the first female at Columbia University to hold full professorship in 1949. **MP**

CHANGING MEDICINE FOREVER FOCUSED ULTRASOUND

The Gairdner Foundation and Sunnybrook Research Institute present an international symposium on focused ultrasound, a new frontier for brain therapy.

The event kicks off with a public lecture: Guest speakers Alan Alda and Brian Greene will talk about the journey from scientific discovery to impact, and the art of communicating about such discovery.



Alan Alda

TV icon and science communicator



Brian Greene

Physicist, string theorist and author

The symposium will bring together the world's leading scientists, including keynote speaker and renowned neuroscientist Dr. Cori Bargmann.



Cori Bargmann

Neuroscientist and president of science for the Chan Zuckerberg Initiative

November 20–21, 2018

Koerner Hall, The Royal Conservatory of Music, Toronto, Ontario

**Open to all
Free to attend**

Register at focusedultrasound.ca