Dr. Phyllis Billia's unique research into heart regeneration holds great promise

UNLOCKING THE SECRETS OF THE HEART WITH GENETIC REPROGRAMMING

BY JUDY GERSTEL

IF THE TITLE "HEART WHISPERER" EXISTED, IT WOULD BELONG TO DR. PHYLLIS BILLIA.

While most physicians only listen to the heart, Dr. Billia is unlocking its secrets, modifying its behaviour and persuading the heart to regenerate.

It's not that the physician needs yet another title.

She's a clinical cardiologist, caring for patients at the Peter Munk Cardiac Centre (PMCC).

She's Co-Director of the Peter Munk Cardiovascular Biobank, which provides living tissue and blood for research.

She's the mother of a 13-year old daughter and the wife of a physician with a private practice.

She's a medical volunteer, travelling with her husband and daughter every year to British Guyana, where she works at a heart function clinic, tending to patients with heart failure.

And she is a scientist, a PhD in biochemistry, researching the genetic pathway to heart regeneration though heart cell proliferation, which, until recently, was regarded as almost impossible, and the Director of Research at the PMCC.

Working in the cardiac clinic, Dr. Billia is acutely aware of the toll of heart failure. It's the leading cause of morbidity and mortality in North America. Heart failure patients have poor quality of life and a poor prognosis.

"Heart failure is an epidemic and it's on the rise," says the cardiologist. "There are about 50,000 new cases a year in Canada, and a million Canadians have it. It's just as common in women as in men as women get older."

In her lab, on the third floor of the Max Bell Research Centre, affiliated with the PMCC, Dr. Billia and her team are intent on reversing heart failure. They are seeking to turn the almost impossible into the possible, coaxing the heart to heal itself with genetic reprogramming.

Having worked on a postdoctoral fellowship with cancer researcher Dr. Tak Mak at the Princess Margaret Cancer Centre after completing medical school and specializing in cardiology, Dr. Billia recognized "a lot of genomic similarities between cancer and heart failure."

Untangling the spider's web of genes implicated in both diseases led to Dr. Billia's elegant and potentially game-changing hypothesis.

"I started thinking about tumour suppressor genes," explains Dr. Billia, "especially the master regulator: p53. When it mutates, it's one of those permissive signals that allows cancer cells to divide. I wondered what would happen if you knocked it out, just in the heart."

Would permitting heart muscle cells to divide create new healthy cells that could compensate for damaged ones?

She tested the theory on mice, knocking out p53 and one of its master regulators from their hearts. "The result," she says, "was astounding."

What she found was that, when the genes were knocked out in the mice's hearts, the mice died within 10 days.

"Looking into the microscope, I could see that the cardiomyocytes" – the heart muscle cells – "were tiny. 'Could this be happening because they were dividing?'" she wondered.

The mice were dying because "when you let the whole heart proliferate, it fails," she explains.

"So the next step was, 'How do we target this at a site of injury?' You may still have damage, but you get surrounding cells to regenerate and compensate."

Dr. Billia acknowledges that her approach to healing hearts through regeneration is different than the path being followed by most heart research colleagues.

They're trying to grow stem cells into heart cells to replace those that have been damaged.

"There's a lot of work being done on that around the world," explains Dr. Billia, "but there are a lot of questions about what cell to use, how to deliver it, what's the best timing and for what condition."

What Dr. Billia is attempting, she says, "is more complex. We're tweaking the genome, getting rid of the roadblock, the p53 gene pathway."

There are a lot of downstream targets in her sights: other proteins that interact with the p53, other tumour suppressors, injury models and then, the Holy Grail, localized regeneration in the heart and other organs, including the lungs and kidneys, that were long thought to be resistant to regeneration.

But when asked about the biggest challenge she faces in her work, Dr. Billia doesn't hesitate.

"Money," she replies.

The funding she's received so far, mainly from the Canadian Institutes of Health Research and the Canadian Cardiovascular Society, has allowed her to establish her own lab bearing her name.

"I've had great mentorship," she says, giving credit to both Dr. Tak Mak and to PMCC cardiologist Dr. Heather Ross. "I have a grant. And we're getting past some of the conventional thinking to get to the next great leap. It's not that the ideas aren't there and the know-how – it's the money to get the work done."

Having her own lab – her name is prominently displayed – is a significant achievement, physical evidence of the Canadian research establishment's confidence in the woman, the scientist, the potential and the commitment.

She's especially proud of her team, six women, including a summer student, and the feeling is mutual.

Technician Daniela Grothe has worked with Dr. Billia since they were together in Dr. Tak Mak's lab at Princess Margaret.

"If she wants something, she works hard for it," says Ms. Grothe, about Dr. Billia. "She works her ass off. We worked six years to set this up. This lab was a dream. Now a lot of our ideas are coming to fruition," says Ms. Grothe, who adds: "Most people who have labs, that's their only job. Phyllis is always a doctor at the same time. She's 100 per cent research scientist and 100 per cent doctor. There's never anything lacking on either end."

"My patients are used to seeing me in jeans," says Dr. Billia. "They know I'm running back and forth between the lab and the clinic."

And there could be no greater motivation for commitment and success in the lab than seeing her clinic patients suffer from heart failure.

"My gut says it will work," she says about the genomic approach to healing hearts. "You can never be 100 per cent positive about research, but what we're finding is quite striking."

The next step is testing in larger animals and developing what is known as "preclinical proof of concept."

Pressed for a timeline, Dr. Billia predicts that in five to 10 years, genomic research will result in the heart repairing itself.

Genes, she believes, are the key to heart failure.

Dr. Phyllis Billia and her research team at the Peter Munk Cardiac Centre are focused on reversing heart failure by coaxing the heart to heal itself with genetic reprogramming.

"We're trying to understand, at the molecular level, the cascade of events that lead to the heart muscle failing. But we're just at the tip of understanding every pathway and exactly why the heart fails and why some people recover and some don't. There are so many unanswered questions."

The heart, she suggests, for all that it is part of us, is as mysterious to us as the solar system.

One of the unknowns, Dr. Billia explains, is that, while there may be a genetic predisposition to developing heart disease, it's not clear whether improved lifestyle at an early age can prevent onset of the disease.

But no matter what our genes dictate, she says, "we can improve longevity and quality of life. There are things that you can do."

If you do only one thing, it's to stop smoking, she advises.

Dr. Billia is her own example for lowering risks of disease that can lead to heart failure.

"I decided not to get diabetes," she says.

Because "diabetes is thought to be polygenic" – that is, caused by more than one gene, and it runs in her family – she made up her mind to lose 50 pounds when she turned 50 this year.

She walked at a fast pace on the treadmill at home for 55 minutes most days at maximum incline while watching episodes of *Game of Thrones*, limited her calories to 1,000 per day on days when she didn't exercise and lost the 50 pounds in six months.

"I feel better, sleep better and stopped snoring," she says.

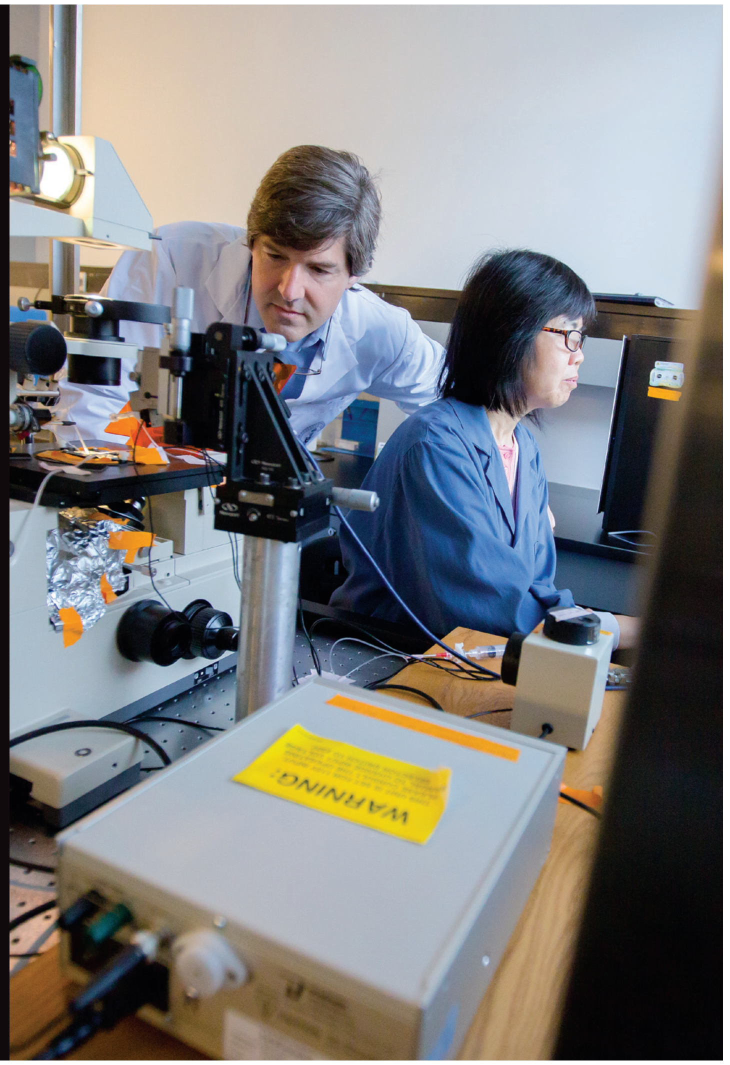
She reads a lot to relax – Robert Sanderson is a new favourite author. "I read every night before I go to bed," she says. "It helps me shut down at night. It's a necessary part of my routine."

She has a small, close group of friends – "a ladies' club. We meet once a month and catch up. I'm the only physician."

But she also admits to waking up in the middle of the night and thinking about work – "because the work is so exciting. We have a lot on the go. You worry about keeping it all going."

Asked whether she worries that her research will bring the results she's looking for, she replies, "We'll make it work somehow."

Who could possibly doubt it?



Internationally-renowned cardiologist and scientist, Dr. Michael Gollob, and his research assistant Qiuju Li, conduct experiments to better understand how gene mutations change how heart cells function and make them prone to arrythmias (irregular heartbeats).

Unique international collaboration poised for breakthroughs in cardiovascular therapy

They're not making whole new hearts yet, but the collaboration of the Peter Munk Cardiac Centre (PMCC) and the McEwen Centre for Regenerative Medicine with the Technion Israel Institute of Technology is making advances in heart research and heart care that no one could have imagined even five years ago.

"I never dreamed that someday I'd be sitting with clinicians and cardiologists, and looking at taking cells from a petri dish and putting them in a patient's heart," says biochemist Dr. Gordon Keller, Director of the McEwen Centre.

What has made that possible is the synergy of having world-renowned researchers and clinicians working together here in Toronto, where some of the sickest heart patients are treated, says Dr. Barry Rubin, Medical Director of the PMCC. "We're used to trying new things."

The scientists and cardiologists are taking the breakthrough of growing heart cells from a patient's own blood or tissue to the next level and beyond.

"The first application is to try to treat patients with heart failure," says Dr. Rubin. "There are more hospitalizations for heart failure than for all forms of cancer, and the average life span from diagnosis of heart failure to death is only 2.1 years. That is worse than most cancers"

But the challenge is growing the right cells for the right part of the heart and determining when and how to deliver them.

That's where Dr. Lior Gepstein comes in, literally, all the way from Israel. Working with biochemist Dr. Keller at the McEwen Centre, Dr. Gepstein and the Keller team discovered how to make different types of heart cells.

"Last year, when I came here to Gord's lab," says Dr. Gepstein, "we didn't have any idea of how to make different cells."

Dr. Keller explains the importance of that differentiation: "There's no point making ventricular cells if the problem is atrial," he says. "What was absolutely crucial was that Lior came with his clinical and heart cell expertise and stayed for a year's sabbatical. It's an example of how synergy and international collaboration really move the field forward."

There's also the challenge of developing medical devices to deliver the cells to a patient's heart. Technion is a world-leader in biomedical engineering and commercialization of devices, and Dr. Rubin would like Canada to become more competitive in that area.

But there's another reason why this research is so valuable that has nothing to do with putting new cells in patients' hearts.

It's the perfect example of personalized medicine.

We can take cells from a patient's blood, make them into stem cells and transform those cells into beating heart cells growing in a petri dish. These cells have the exact same genetic makeup as the patient's own heart cells, and they are the ideal model for assessing the disease and trying different drugs to see what works best without harming or even involving the patient beyond a blood test or a simple tissue sample.

Dr. Rubin explains: "We could recapitulate the patient's heart disease in a dish before treating the patient. Now, when we give patients drugs for a condition, say, arrhythmia, often the first choice of drug doesn't work, and may have side effects.

"Rather than trying the drug for the first time in the patient, we take a sample of blood, make stem cells, make them into heart cells, put the cells in 10 different dishes, squirt in 10 different drugs and see which works best," he explains.

Touching lives from coast to coast

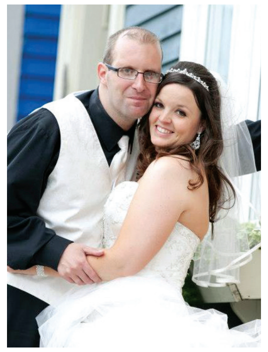
The circle of care at the Peter Munk Cardiac Centre (PMCC) extends far beyond the boundaries of Toronto. Each year, thousands of patients from communities across the country come to Canada's leading cardiac care centre.

Jamie Wilkinson, a music teacher from Flatrock near St. John's, Nfld., was flown by air ambulance to the PMCC in July 2012, just two weeks before he and his fiancée were set to tie the knot. Born with a defective heart, Mr. Wilkinson was struggling to breathe because his heart wasn't pumping properly, resulting in a buildup of fluid around the organ.

"The doctors at [the] PMCC got rid of 25 pounds of fluid, and during the two weeks I was in the hospital, the congenital cardiac team was in constant touch, explaining what they were doing and why," recalls Mr. Wilkinson, who is 37 years old. "I was discharged July 25, and two days later I got married."

Mr. Wilkinson and his wife have relocated to Toronto to be near the PMCC, where Mr. Wilkinson was recently implanted with a pacemaker, a defibrillator and a ventricular assist device, which helps his heart pump blood to all parts of the body.

"The doctors have done such a wonderful job in improving my quality of life," says Mr. Wilkinson. "They're the best group of doctors I've encountered, that's for sure. They're so knowledgeable and intelligent, and they treat us like we're part of the team."



Newfoundland resident Jamie Wilkson (left) and Jeff Allan from Calgary (right) are among PMCC patients from across Canada.

It's been 24 years since Jeff Allan travelled to the PMCC for valve-sparing surgery, a technique developed at the hospital to save the defective valve, instead of replacing it with an artificial or porcine valve. The 53-year-old software developer and resident of Cochrane, Alta., still remembers the world-class care he received in 1991.

Mr. Allan has Marfan syndrome, a genetic disorder that causes problems with connective tissue throughout the body. In Mr. Allan's case, the disorder had led to a dilated aorta, which was stretching to the point where it might rupture. To address this problem, Dr. Tirone David removed the enlarged valve, inserted it into artificial tubing and attached the entire assembly back to Mr. Allan's heart.

"I have not had any problems related to the surgery and have not needed to go back," says Mr. Allan. "When I hit the 20-year anniversary of my surgery, I compiled a little video for Dr. David basically saying, 'Here I am. Life is good.'"

Life is definitely better for Katjana Biljan, an Ottawa psychotherapist with congenital heart disease. By 2013, after four decades of heart problems, she was a palliative care patient whose day-to-day survival depended on an oxygen machine, which kept her homebound. She was referred to the PMCC that year, where doctors performed tissue implant surgery to fix a hole in her heart.

"They gave me my life back," says Ms. Biljan, who is 42 years old. "I'm a really complex patient, and this is one of the top centres in the world that specializes in complex cardiac cases like mine."

Ms. Biljan says she no longer needs daily doses of oxygen from a machine. She's looking forward to resuming her career after more than two years of not working.

– MARJO JOHNE