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

UNLOCKING THE SECRETS OF THE HEART WITH GENETIC REPROGRAMMING

BY JUDY GERSTEL
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, curing 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 through heart cell proliferation, which, until recently, was regarded as almost impossible, and the Director of Research at PMCC.

Working in the cardiac clinic, Dr. Billia is acutely aware of the toll of heart failure. It's the leading cause of mortality and morbidity 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 about 750,000 Canadians have heart failure. It's just as common in women as in men we treat 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 working 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, she was focused on repairing damaged heart cells to divide. She 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 tried the theory on mice, knocking out p53 and one of its master regulators from their hearts. "The 'reels,'" she says, "were astounding." What she found was that, when the gene was knocked out in the mice's hearts, the mice died within 10 days. "Looking into the microscope, I could see that the cardiomyocyte - 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 breaking the genome, getting rid of the roadblock, the p53 gene pathway."

There are a lot of downstream targets in its eight- or nine-protein network that interact with the p53, other tumour suppressors, injury mediators 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, whose lab is one of the few with women and young scientists on the staff, that's their only job. Phyllis is always a doctor. "They know I'm working 24/7. They know I'm running back and forth between the lab and the clinic."

And there could be no greater mentorship to achievement 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. "I just never be 100 per cent positive about research, but what we're seeing is striking."

The next step is testing in larger animals and developing what is known as "preclinical proof of concept."" Pressed for a timeframe, Dr. Billia predicts that in five to 10 years, genomic research will result in the heart repair everyone is expecting.

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

If the title "heart whisperer" existed, it would belong to Dr. Phyllis Billia.
They’re not making whole new heart cells, but the collaboration of the Peter Munk Cardiac Centre (PMCC) and the McEwen Centre for Regenerative Medicine with the Technion Institute of Technology is making advances in heart research faster and heart care that we hope one could have imagined even five years ago.

“Last year, when I came here to Gord’s lab,” says Dr. Gepstein, “we didn’t have any idea of how to deliver them, where and when and how to deliver them. The doctors have done such a wonderful job in improving my quality of life,” says Mr. Wilkinson. “The doctors have done such a wonderful job in improving my quality of life,” says Mr. Wilkinson.

Mr. Allan says the team’s expertise and stayed for a year’s collaboration really move the field forward.”

It’s the perfect example of translational medicine. We take cells from a patient’s blood, make them into heart 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 ideal models for assessing the disease and trying different drugs to see which work best without hurting or even harming the patient — a blood test or a simple sampling.

Dr. Rubin explains: “We could recapitulate the patient’s heart disease in a dish before treating the patient. Now, when we give patients drugs as a condition,” says Dr. Rubin, “we have the ideal model for assessing the disease and trying different drugs.”

Mr. Allan says, “That’s very exciting. We have a lot on the go. You can do this work somehow.”

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 lifestyles 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 and avoid high-fat diets. 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 can do this work somehow.”

Who could possibly doubt it?