A MATTER OF DEVOTION

AS MANY AS 26 RESEARCHERS ARE COMING TOGETHER UNDER A NEW INITIATIVE THAT WILL MAKE MANITOBA A LEADER IN THE STUDY OF CHRONIC CHILDHOOD DISEASES SUCH AS ASTHMA AND TYPE 2 DIABETES By Joel Schlesinger

The walls of the pediatric clinic at the Children's Hospital Research Institute of Manitoba are covered with photos of smiling children.

There's also considerable paraphernalia from popular animated films such as *Minions* and *Frozen* – perfect for easing the anxiety of children at a doctor's appointment.

In this respect, no detail is overlooked. There is even a cut-out of Olaf – the snowman from *Frozen* – attached to the gauge that is used to measure the blood pressure of children.

All of this helps make things a little easier for five-year-old Hailey Pinkerton as she rolls up her sleeve and gets ready to have her blood pressure checked by research technician Ingrid Loewen.

The test is one of several Hailey will undergo today, and she seems particularly interested in how Olaf will respond once it is underway.

"He is awake," says Loewen in reference to Olaf. "I thought he was going to sleep all morning, but all you have to do is sit still and be very quiet and wait for him to sing when he's done."

And Olaf does sing: "Beep, beep, beep," indicating that the blood pressure reading has been taken.

"There, we did it," Loewen says once the test is complete.

Over the course of the morning, Hailey will undergo several other tests, including one for allergies involving skin testing, a breathing test and a blood draw. Once those tests are completed, she will be examined by a pediatrician.

Hailey Pinkerton takes a breathing test for nurse Doug Houlbrook as her mom, Sherri Pinkerton, looks on.

The data gathered on this morning will provide the medical team at the clinic, located at the Children's Hospital Research Institute of Manitoba (CHRIM), with a snapshot of Hailey's well-being. But there is more going on here than a simple checkup to confirm that Hailey is in perfect health.

In fact, Hailey is one of 3,500 children across Canada participating in the Canadian Healthy Infant Longitudinal Development study (CHILD), which tracks the health of kids who were born between 2010 and 2012. Over the years, information provided by Hailey and other children through this study has helped inform numerous research projects in child health issues.

As one of Canada's pre-eminent child health research centres, CHRIM has played an important role in supporting the CHILD project (the CHILD Manitoba site is led by Dr. Allan Becker, another DEVOTION scientist), the DEVOTION project, and other related research. That role is expected to grow with the creation of a new initiative that promises to further establish Manitoba as a leader in the field.

Led by researchers Jon McGavock and Andrew Halayko, the new initiative is called the Developmental Origins of Chronic Disease Network, or DEVOTION for short.

As the name implies, DEVOTION's mandate is to facilitate local research into the early development of chronic childhood diseases, specifically asthma and Type 2 diabetes. This is a relatively new field of inquiry, which essentially asks whether environmental factors may affect the onset of disease.

As McGavock explains, "We want to focus on the early life origins of chronic diseases – things that mothers may be exposed to or children early in life may be exposed to – and then develop early interventions to overcome those factors."

Currently, there are as many as 26 CHRIM-based scientists conducting work in these areas. DEVOTION's goal is to create an opportunity for these scientists to share the expertise they've gained over the years and help fund new research projects.

"The research will lead to identification of new outcome predictors and methods for determining treatment effectiveness," says a backgrounder on the initiative. "It will also create new possibilities for targeted therapies that can enhance the quality of life, improve disease prevention strategies, and reduce health-care costs in Manitoba."

> The rates of of diabetes and asthma among children are on the rise and the health-care system is grappling for solutions.

To help make that happen, Research Manitoba has provided DEVOTION with funding amounting to $500,000 annually for the next five years. That ranks as the largest investment Research Manitoba has ever made in a single research team – testimony to the importance it places on child health research and the ability of CHRIM scientists to deliver on the promise of improved care for children.

The timing of the initiative could not be better.

As McGavock and Halayko explain, diabetes and asthma rates among children in Manitoba are a serious issue and the health-care system is grappling for solutions.

"There are one or two new cases of Type 2 diabetes in a child every week in Manitoba," says McGavock, adding that early onset of the disease increases risk of heart disease and chronic kidney failure.

"Based on a study published a couple of years ago, 50 per cent of youth diagnosed with the disease as a teenager could be on dialysis before they're 35," he says.

While DEVOTION is relatively new, McGavock and Halayko have been involved in child health research for many years.

McGavock is an associate professor in the Department of Pediatrics in the Faculty of Health Sciences at the University of Manitoba. Halayko, meanwhile, is a professor in the Departments of Physiology and Pathophysiology, Internal Medicine, and Pediatrics and Child Health.

In addition, each researcher heads up an area of study at CHRIM. Halayko leads the Biology of Breathing research arm, also known as BoB, while McGavock is the lead investigator for Diabetes Research Envisioned and Accomplished in Manitoba, which is known as DREAM.

Although their work seemingly involves disparate areas of research, both have recognized the potential for synergy between their respective groups over the years, says Halayko.

"Jon and I had begun a series of meetings as leaders of these two groups, trying to sort out

how we can get better levers between the two groups: BoB and DREAM," he says. "We were always asking: 'How do we sort out the work better – together – so we're not reinventing wheels and instead taking advantage of the strength of each group so that one-plus-one can equal three?'"

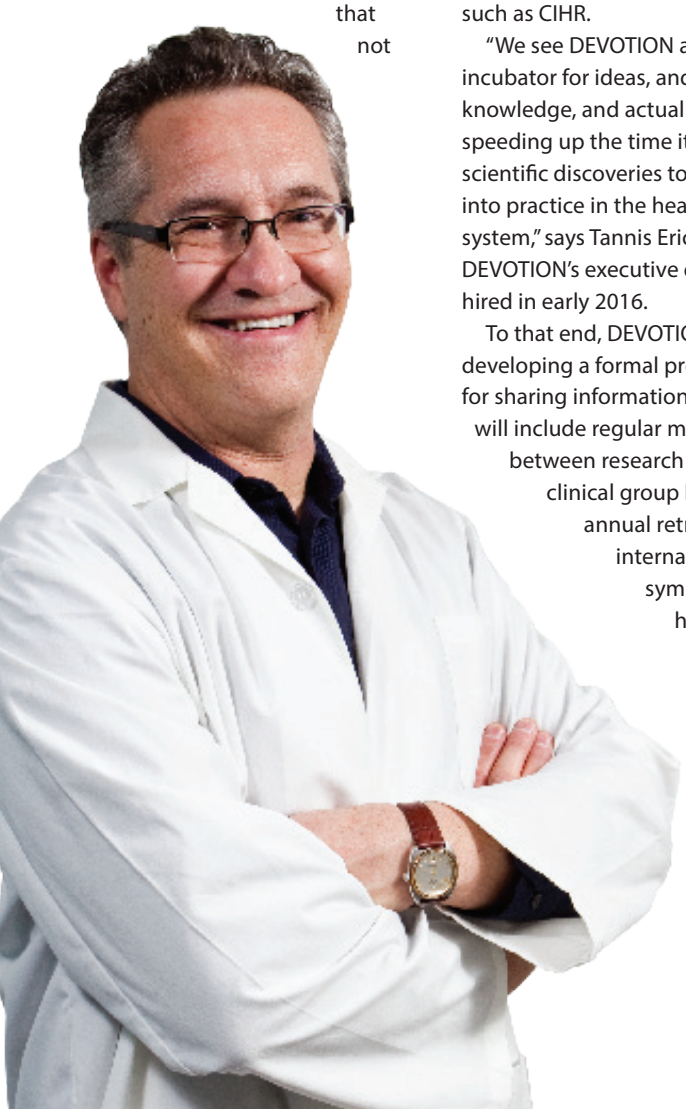
The collaborative model envisioned by McGavock and Halayko is in keeping with the way research is increasingly being conducted in Canada.

For most of the last decade, major funding organizations, like Research Manitoba and the Canadian Institutes of Health Research (CIHR), have been moving toward supporting research that not only addresses specific areas of interest, such as cancer, heart disease or diabetes, but also cuts across boundaries. Referred to as clustering, this approach brings continuity to endeavours in the lab, in the community, around policymaking tables, and, most importantly, at the bedside.

In keeping with this notion, DEVOTION will create opportunities for BoB and DREAM researchers – along with health-care providers on the front lines – to work together and share knowledge that has been gained from previous studies. But it will also initiate new research and help local scientists get additional funding from other groups or agencies, such as CIHR.

"We see DEVOTION as an incubator for ideas, and sharing knowledge, and actually speeding up the time it takes for scientific discoveries to be put into practice in the health-care system," says Tannis Erickson, DEVOTION's executive director, hired in early 2016.

To that end, DEVOTION is developing a formal process for sharing information that will include regular meetings between research and clinical group leaders, annual retreats and international symposiums hosted by CHRIM.



Andrew Halayko says the collaborative model being used for DEVOTION is in keeping with the way research is increasingly being conducted in Canada.

> "We're not just engaging patients and policymakers: we're actually partnering with them."

There will also be the regular DEVOTION rounds, McGavock says. "Once a month, members will present on their work related to developmental origins."

The creation of DEVOTION has also prompted the BoB and DREAM research groups to make other changes.

"One of the novel aspects of this – and a brave move by Research Manitoba – is we are aligning our vision," says McGavock, who is also a CIHR Applied Public Health Chair in Resilience and Childhood Obesity. "We want to be where we think the research priority for child health is in Canada."

DEVOTION will draw from scientists working in four pillars of research:

* Basic science: This involves lab-based research to test maternal exposure to different conditions, how that affects infants and children, and pre-clinical assessment of emerging therapeutics.

* Clinical populations: Gathering information from children like Hailey Pinkerton who are participating in group studies to determine how and why kids develop chronic disease.

* Population-based data sets: Drawing on information collected by the Manitoba Centre for Health Policy and others to test against data gathered from clinical populations.

* Policy implementation: Working with provincial health officials to develop evidence-based interventions that can be implemented province-wide.

In addition to drawing from the four pillars, DEVOTION is also working to ensure Indigenous communities are also actively involved in the project.

This is of particular importance to researchers like McGavock whose work on Type 2 diabetes, obesity and kidney disease has direct implications for Indigenous youth, who are often disproportionately affected by these illnesses compared with similar cohorts.

"Having Indigenous stakeholders at the table is another very Manitoba-centric concept that we wanted to highlight and prioritize," he says.

Yet it's more than just talking to stakeholders, Halayko says.

"We're not just engaging patients and policymakers, like Rob Santos of Healthy Child Manitoba, we're actually partnering with them," he says.

"That's a significant thing because we're not just asking, 'What do you want us to do?' and then going off and doing it. "We're actually asking, 'What do you think we should do? What's important?' and then working with the partners and

stakeholders along the way to understand where we should go next."

To start, much of the work underway through DEVOTION involves consolidating the knowledge gained through previous studies or expanding the scope of work that is currently underway.

One example of the kind of research DEVOTION will support involves the work of Dr. Brandy Wicklow and Vern Dolinsky, who are looking into the effects of maternal diabetes on obesity, diabetes and cardiovascular risk in children.

Operating under the DREAM umbrella at CHRIM, Wicklow and Dolinsky are following 110 women with maternal diabetes and their children. The hypothesis is that moms who have maternal diabetes while carrying their children in the womb will have offspring at higher risk of obesity, diabetes and more long-term cardiovascular disease.

Wicklow, an endocrinologist, works with patients to gather clinical data. And Dolinsky, CHRIM's basic science lab chief, works with diabetes models in pregnant mice to see if their offspring develop problems similar to what is being observed by Wicklow among her patients.

Then there's more lab work involved at the cellular and molecular levels, including assessing genetic information like DNA to understand the mechanisms of how disease develops.

Meghan Azad is another local researcher who is benefitting from DEVOTION.

She is currently conducting research using data gathered through CHILD, the study that Hailey Pinkerton is involved in. The goal is to investigate possible connections between a child's microbiome – the bacteria found in intestines – and their health, particularly as it relates to the development of asthma and Type 2 diabetes.

As Halayko, a Canada Research Chair in Airway Cell and Molecular Biology, explains, the actual CHILD database Azad is tapping into was created through funding from other agencies. But all that information

Jon McGavock says having Indigenous stakeholders at the table is critical to DEVOTION's success.

INDIGENOUS MATTERS

ENSURING FIRST NATION, MÉTIS AND INUIT COMMUNITIES ARE MAJOR STAKEHOLDERS IS ESSENTIAL TO HEALTH RESEARCH

There really is no way to sugar-coat it. Children in Indigenous communities in Manitoba suffer from poorer health than children elsewhere in the province.

As a result, it is absolutely critical to ensure that any research into diseases such as Type 2 diabetes and asthma include children living in Indigenous communities, says Tannis Erickson, Executive Director of the Developmental Origins of Chronic Diseases in Children Network (DEVOTION).

DEVOTION recently secured funding to help make that happen.

The Lawson Foundation, a national organization supporting wellness initiatives for children, has agreed to provide $250,000 annually for five years to help make Indigenous-centric investigation a major piece of DEVOTION's broader efforts to research childhood diseases.

This is largely in recognition that some of the most prevalent and pernicious childhood illnesses – such as Type 2 diabetes – affect Indigenous children more than other populations, says Erickson.

"What we know, for example, is that especially with respect to children with Type 2 diabetes, the majority of cases are in Indigenous communities," she says. "You're 12 times more likely to develop it as a youth if you live in an Indigenous community."

For researchers like Jon McGavock, a DEVOTION team leader, bringing Indigenous Manitobans on board as research, clinical, community and policy-making partners isn't just an afterthought. It's essential because his research directly involves these communities.

"For me, for example, the biggest thing I'm interested in is reducing inequities that exist in our Indigenous population: inequities in diabetes, obesity and high blood pressure," says McGavock.

The problems affecting youth in these communities often start early in life – maybe even while still in the womb, he says. "More and more studies are coming out stating the reason these inequities exist is because of factors that have happened early in a child's life."

Research can make a difference, says McGavock. For example, studies have found that breastfeeding or better daycare can have huge impacts on reducing health inequities.

While these are straightforward solutions, more work needs to be done to ensure this knowledge can be used effectively in programs at the community level.

"The more I work with youth with diabetes from Indigenous communities and childhood obesity, the more I see that there is possibly a big impact we can have by designing early life interventions that would try to bridge the gap so Indigenous youth are not affected by these chronic diseases," McGavock says.

But putting knowledge into practice can be a challenge, particularly in remote areas of the province.

Lawson's funding will be invaluable in this respect because the money is earmarked specifically to support researchers and initiatives in Indigenous communities. While the exact details still have yet to be determined, Erickson

DEVOTION team members, from left: Vern Dolinsky, Tannis Erickson and Dr. Brandy Wicklow.

says the funds "are going to help develop programs based on the findings from research under the DEVOTION umbrella" for the benefit of Indigenous communities.

For the time being, DEVOTION's main areas of interest will be Type 2 diabetes as well as asthma and other allergies. But over the next five years its focus will grow, thanks to ongoing funding from Lawson, Erickson adds.

"It is the extra link from the research down to the community hopefully in the form of developing effective programs that make a difference in the lives of our province's Indigenous people."

can't help anybody if no one is using it. "DEVOTION funding enables her to use that resource," he says.

Azad, an assistant professor in the Department of Pediatrics & Child Health and Community Health Sciences at the University of Manitoba, says she is interested in two specific questions. "First, the microbiome is formed in early life, so what factors are influencing that? Then when the kids grow up, how does that microbiome influence health?"

To that end, Azad, along with other researchers, believes the environmental clues that have been gathered through CHILD will ultimately help explain why asthma and other pediatric immunological disorders – especially nut allergies – have been on the rise over the last two decades. Similarly, her work is suggesting that there may be environmental factors that contribute to higher rates of obesity.

"It can't be due to genetics because our genetics don't change that quickly, so it's something in the environment that is causing this rise in allergies, for example, but we don't know what," she says.

Some of Azad's new research that is being enabled by DEVOTION involves teaming up with fellow scientists to examine mechanisms that determine whether children whose mothers use artificial sweeteners while pregnant are at increased risk for becoming obese or for developing asthma.

Here she is teaming up with Dolinsky and Halayko, who will test the theories emerging from Azad's work in humans, by feeding artificial sweetener to pregnant mice or rats and observing whether their offspring have higher rates of asthma or obesity in animal models that are unique to the DEVOTION team.

Leveraging the power of the bench in the lab involves more than firming up a potential association. It also allows researchers to explain at the molecular level why artificial sweetener may increase the risk.

Adds McGavock: "It's a really nice example of how taking evidence from population health and clinical data creates a question: 'Is this real, and if it is, why? What's the mechanism?'" With support from DEVOTION, "She can tap into the expertise of the basic scientist using animal models – a clinically equivalent paradigm – and then asking questions that may lead to an intervention."

McGavock says that DEVOTION has the potential to serve as a model for how research can and should be done, not just in Manitoba, but in Canada. Manitoba, he says, is one of the few jurisdictions where this idea could take off because the province has long been working toward greater collaboration across the health-care system – from the bedside to the lab to the levels of policymaking.

"That link between stakeholders, basic science, clinical science and policy – we don't think it could be done as well in any other province," he says.

Halayko adds that the main advantage is being able to take good research further and faster by addressing the questions that often arise from it.

"We can now do fundamental research that goes beyond answering questions that guess at a cause-effect association; instead we can direct studies based on evidence from the real world to more directly get at the true, underlying causes," he says.

"That's a big plus of DEVOTION: It opens the door to have research home in on real challenges and problems sooner than later."

"When you put all that together, we hope five years from now, we'll be leaders in Canada in understanding and shifting policy for chronic diseases in children."

Joel Schlesinger is a Winnipeg writer.

Researcher Meghan Azad is looking into possible causes of childhood asthma.