Nova Scotia Health Authority

Research focus

transplantation

Halifax is a major centre for organ transplantation – and one of North America's top centres for organ transplantation research – performing more than 120 solid organ transplant surgeries a year on patients from all across Atlantic Canada. Over the past 20 years, researchers at the QEII Health Sciences Centre, IWK Health Centre and Dalhousie University have played key roles in international efforts to introduce new-generation immune-suppressing drugs that have radically improved the results of transplant surgeries.

Now that fewer patients' immune systems are rejecting donor organs, researchers in the Multi-Organ Transplant Program (MOTP) have turned their attention to the next most pressing problems in transplant research. Foremost among these is the growing shortage of healthy donor organs, which has researchers searching for ways to improve the function and long-term viability of lower-quality organs.

At the same time, transplant researchers in Halifax are leading the way to more efficient tissue-matching protocols, tackling life-threatening infections that can arise with immune suppression, and studying the long-term outcomes of organ transplant procedures. Their goal is to ensure long, healthy, complication-free lives for transplant recipients in Atlantic Canada.

A new lease on life for Jason Barnaby

In early 2012, Jason Barnaby of Burnt Church, N.B., started feeling unusually tired. He had no appetite and noticed a persistent bad taste in his mouth. Bloodwork revealed kidney disease so advanced, he would need to be evaluated for transplant. In the meantime, he required three four-hour dialysis treatments a week.

"It took a year to complete all the tests," recalls Mr. Barnaby. "Quite a few people volunteered to be live donors, but no one qualified, so I was put on the waiting list in December 2013." One year later, he got the call and hurried to Halifax for transplant surgery.

Prior to surgery, Mr. Barnaby agreed to take part in a clinical trial of a drug typically used to protect the kidneys from damage caused by a rare immune disorder. "The study is testing the drug's ability to kickstart kidney function after transplant, to avoid what's known as 'delayed graft function,'" notes Laura Sills, clinical trials coordinator at the QEII. "This would reduce the risk of the organ failing and extend its functional life."

Mr. Barnaby's new kidney began working right away. This could be thanks to the drug – although neither he nor the researchers will know until the study is over, since the study is double-blinded and he could be taking the placebo. Either way, he recovered well and appreciates the extra care he receives through the clinical trial. "It could be helping me, and it could help others in the future," he says.

Kidney transplant recipient Jason Barnaby is taking part in a clinical trial of a drug that may improve the organ's function after transplant. He travels to Halifax from Burnt Church for a detailed check-up with clinical trials coordinator, Laura Sills, RN, every month.

Clinical trials improve transplant success

Atlantic Canadians receiving organ transplants in Halifax often have the opportunity to take part in clinical trials. The Multi-Organ Transplant Program (MOTP) runs as many as 15 clinical trials at a time, in its ongoing efforts to improve outcomes for patients.

"The majority of clinical trials are conducted in kidney patients, as this is by far the most common transplant," notes Dr. Christopher Daley, a pharmacist and MOTP's director of clinical research. "If the drugs are proven to be safe and effective for kidney patients, they are made available to liver, pancreas and other transplant recipients as well."

The shortage of healthy organs available for transplant presents a constant challenge. "We need to make the best use of the organs we can get," says Dr. Bryce Kiberd, nephrologist and medical lead of the MOTP. "This means we need to do everything we can to ensure the organs function as well as possible at the outset."

Kickstarting organ function

Sometimes there's a delay of several hours between when a transplanted organ goes in and when it starts to work properly, which can compromise the organ's viability. This delayed graft function is more likely when the organ comes from an older or not very healthy donor, or spends a prolonged period of time on ice before it's implanted.

"We want to know if medications can avert some of the problems that prevent organs from working shortly after transplant," says Dr. Kiberd. "We're one of a small handful of Canadian centres involved in international drug trials in this area."

In 2014, researchers led by urologist Dr. Joseph Lawen concluded the QEII's involvement in a phase two study of a new class of drugs that blocks cell death. The study tested the drug's ability to allow a deceased donor's kidney to start working quickly, unhindered by injury that typically occurs when the recipient's blood flows into their newly implanted organ. Results were promising enough that the drug will soon be tested in a phase three trial.

The researchers launched a new trial near the end of 2014 – led by Dr. Kenneth West, head of the Division of Nephrology – to see if a drug that blocks part of the immune system (known as "complement") can also help the kidneys function better after transplant. Jason Barnaby signed up for this trial (see page one), which will follow him and the other patients very closely for three years after their operation.

Pharmacist and MOTP clinical research director Dr. Christopher Daley works with QEII pharmacy research technician Patrice Gallant to fine tune the logistics of clinical trials conducted through the Multi-Organ Transplant Program. Their careful oversight ensures patient safety and high-quality data.

Dr. Bryce Kiberd

Blocking the threat of infection

Infection is a serious risk to transplant patients – even common infections that don't provoke symptoms in people with fully functioning immune systems can lead to serious illness in people on immune-suppressing drugs. They can also cause the transplanted organ to fail. Cytomegalovirus (CMV) is a prime example.

"Almost everyone is exposed to CMV at some point... it doesn't normally cause disease, but remains dormant in the body," notes Dr. Kiberd. "Dormant CMV can act up in transplant patients, because their immune systems are down, or the virus can come in with the donor organ... either way, it can cause major problems." These range from potentially fatal pneumonia and diarrhea, to long hospital stays and a much-increased risk of transplant failure.

Patients currently receive antivirals to keep CMV at bay for the first few months after transplant, when immune suppression is most intense. But, as clinical trials coordinator Laura Sills explains, these costly medications produce side effects. Patients stop taking them once their immune suppression therapy is tapered back – but this puts them at risk. She's excited to be enrolling patients in a clinical trial for a vaccine that could prevent CMV from flaring up in transplant patients. "This would be such a huge advance," she says. "We are so pleased to offer a CMV vaccine to our patients through this trial."

Understanding viral threats

Human polyomavirus (also known as BK virus) is another pathogen almost everyone picks up in childhood. It sits quietly in the kidney, but comes to life when that kidney is transplanted. No longer constrained by the donor's immune response, the virus replicates, damaging the transplanted kidney in its recipient and escalating risk of graft failure.

Dr. Kiberd collaborates with Dr. Philip Acott, a pediatric nephrologist at the IWK Health Centre, to understand and address polyomavirus. They and their colleagues have developed a protocol for screening for the virus in kidney transplant patients that has since been adopted by many other centres.

Dr. Acott is one of the few researchers in the world who studies the basic biology of polyomavirus. He and his team have perfected a system for growing polyomavirus in cells, which allows them to test various drugs to see how the virus can be controlled. "This is very important," says Dr. Acott, "because polyomavirus is the leading viral cause of kidney injury leading to loss in kidney transplant patients."

In terms of other viruses that affect transplant patients, Dr. Acott and his colleagues were the first to show that Human Herpes Virus type 6 (HHV-6) accelerates organ rejection in children with kidney transplants. Other types of human herpes viruses are also problematic in transplant – infectious mononucleosis (Epstein Barr Virus), for example, can trigger post-transplant lymphoma.

Dalhousie medical student Melissa Wallace is working with Dr. Ian Alwayn, QEII Foundation Endowed Chair in Transplantation Research, to improve the quality of fatty livers prior to transplant.

Improving organ quality: Research chair seeks solution to fatty liver challenge

The tragic fact that hundreds of people die each year waiting for a transplant is compounded by another tragic fact: as many as 20 per cent of potential graft organs must be discarded, instead of transplanted, because they are not healthy enough to withstand the procedure or function well enough after.

"We have a particular problem with liver transplants, due to ever-increasing rates of fatty liver disease," says the MOTP's surgical lead, Dr. Ian Alwayn, a QEII surgeon and Dalhousie professor who holds the QEII Foundation Endowed Chair in Transplantation Research. "Fatty livers do not do well after transplant... we often can't use these organs."

An organ has to be in good condition to tolerate the rigours of transplant – being removed from the donor's body, drained of blood, perfused with protective solutions and stored on ice takes a toll. Exposure to the recipient's blood upon transplant triggers inflammatory responses that can further damage the organ. Known as ischemia reperfusion injury, if this damage is severe enough, the organ will fail.

Dr. Alwayn and his team have developed a new technology to protect donor livers from ischemic reperfusion injury. "Our invention uses small protein chains, or peptides, that penetrate the cell walls of the organ to deliver a cargo of injury-protecting agents," he explains. "If we can protect fatty livers from this injury, we will be able to use a lot of organs that would otherwise not be suitable for transplant." A patent application is in the works for the new technology.

Meanwhile, Dr. Alwayn is co-supervising Dalhousie medical student, Melissa Wallace, on a project to see if fatty livers can be de-fatted prior to transplant, to improve their viability. They're working with Dalhousie lipid scientist, Dr. Neale Ridgway, to see if their experimental system for metabolizing the fat before transplant enables the liver to function well in its new owner.

Even healthy organs are subject to damage upon transplant. Dr. Alwayn and his team are looking into molecules known as DAMPS, released by an organ's cells in response to stress. "We think the level of DAMPS in an organ could be used as a marker of how much it is likely to be damaged upon transplant. This would help us determine an organ's suitability." Better yet, Dr. Alwayn would like to find a way to block the DAMPs from being released altogether.

The power of a research chair

Transplant research at the QEII Health Sciences Centre will be funded forever, thanks to the QEII Foundation and generous donors who together raised $2.5 million to create the QEII Foundation Endowed Chair in Transplantation Research. The chair's endowment will generate funds every year, to be channelled directly to transplant research. Dr. Ian Alwayn is the first holder of the chair. The funds are supporting exploration in his lab (see page four), as well as a number of clinical research projects. Dr. Alwayn is a key member of the Canadian National Transplant Research Program, which is focused on repairing organs prior to transplant.

Preventing organ rejection: There's an app for that

It's vitally important that transplant patients take their immune-suppressing, anti-rejection drugs as prescribed. If they start to miss doses, they run the risk of their immune systems inflicting damage on the transplanted organ. This could lead to organ failure. Dr. Alwayn is collaborating with computer scientists at Dalhousie University to develop an app to help transplant patients stay on track with their meds and cut their risk of organ rejection.

Tackling tough questions in liver transplant

Transplant surgeon and professor Dr. Michele Molinari is not afraid to ask tough questions. Are patients living in rural areas more likely to die while waiting for a liver transplant than those living in urban areas? Is the bias against transplanting livers into obese patients justified? Are liver transplant recipients able to return to their previous lives? Are people willing to risk their lives by donating half their liver to save the life of someone they love?

"My aim is to inform clinical decision making, shed light on understudied or controversial topics, and gain a better sense of how patients are doing after surgery," notes Dr. Molinari.

Dr. Molinari hopes his finding that people are very willing to donate half their liver to save a loved one's life may someday lead to a live liver donor program in Halifax. "We have a shortage of healthy organs, and the risk to a healthy person of donating part of their liver is extremely low," he explains, adding that the liver regenerates up to 90 per cent after the procedure. "This might be a possible strategy for expanding our pool of organs for transplant."

Thankfully for people in Atlantic Canada, Dr. Molinari found that people in rural areas have the same access to organs as people in urban centres.

Dr. Michele Molinari

Better, faster, stronger: HaliFAST protocol confirms organ matches in fraction of time

Halifax researchers led by pathologist and professor Dr. Robert Liwski have cut the time it takes to confirm an organ match by an astonishing 70 per cent. While dramatically increasing the speed of the HLA cross-match testing process, they've also made it more accurate, ensuring patients receive good matches in record time. Other centres around the world are adopting the new HLA crossmatch protocol, dubbed HaliFAST by Dr. Liwski's colleagues in Brazil.

"I get requests all the time," says Dr. Liwski of world-wide interest in his lab's protocol for HLA-crossmatch testing. "All centres in Canada and more than 30 in the U.S. are now using this method, along with centres in Australia, the U.K., Brazil, Poland, Germany, and the United Arab Emirates, so far."

HaliFAST is just one of three new protocols Dr. Liwski and his team in the QEII's HLA Typing Laboratory have developed to streamline the HLA testing process. In all, the lab members have cut a four to five-hour process down to about 90 minutes.

"This time savings is crucial," says Dr. Liwski, "because while we're doing the tests, the donor organ is sitting on ice and the surgical team and potential recipient are waiting to hear if the organ's a match."

As Dr. Liwski explains, there's more to organ-recipient matching than blood type. The recipient must not be sensitized to human leukocyte antigens, or HLA, in the donor organ. "Some people are sensitized to just a few of these antigens, others are sensitized to a lot," he says. "If a person receives an organ with antigens they react to, their immune system will attack the organ. We need to avoid this by matching organs to recipients with similar HLA profiles."

Preliminary matching is done by computer, but final confirmation requires real-world mixing of donor cells with serum from candidate recipients. It's a multi-step process that used to involve long incubation times and painstaking pipetting (filling with a special instrument called a pipette, see photo below) of individual test tubes.

"We examined every step and asked, 'does it really need to be done this way?'" Dr. Liwski says. He and his team began running careful experiments to see where they could safely shave away minutes – resulting in massive time reductions coupled with improvements in accuracy. "Better, faster matches cut the chances of an organ being rejected and allow centres across Canada to share organs with confidence."

Dr. Rob Liwski (back) observes how quickly Geoff Peladeau (front) transfers samples into a micro-titre plate using a multi-channel pipette – as called for in the HaliFAST protocol – compared to the old method of single-channel pipette and individual test tubes Geoff Adams (centre) is using. This is just one step of many the lab team has streamlined to get faster HLA crossmatch results.

Taking heart: Mechanical hearts and other advances

Cardiac surgeon and professor Dr. Jean-François Légaré now implants as many mechanical hearts into patients as he does hearts from deceased human donors. "They can last for years and there's no chance of rejection," says Dr. Légaré of the metal devices, which are used to keep people going while they wait for a donor heart. It's possible they could provide a longer-term solution, in the face of limited donor hearts. "We've been using mechanical hearts with great success for the past five years, but we need to study patient outcomes over many more years to know if they could ever really replace a human heart."

Roughly the size of a cell phone, mechanical hearts are implanted in patients' left ventricles to assist the pumping action. Patients wear a small battery pack strapped to their waists.

Dr. Légaré and his colleagues are taking part in global studies investigating the use of mechanical hearts. "We need to know which patients will benefit most, which type of devices work best for which kind of patient, what is the safest implant procedure," he says.

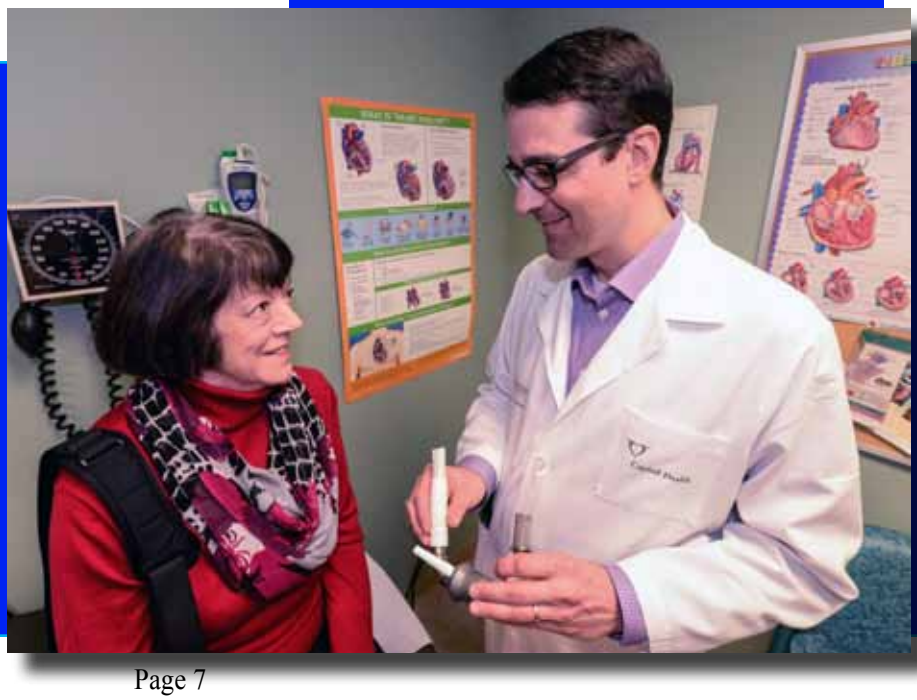
Someday, Dr. Légaré hopes it will be possible to avoid heart transplants, by preventing heart failure. He and his team are exploring how inflammation and resulting scar-tissue formation lead to heart failure. "We're pursuing potential strategies for delivering agents directly into the heart, to heal scar tissue and keep the heart pumping strongly."

The science of chronic rejection

Over the past decade, immunologist Dr. Tim Lee and cardiac surgeon Dr. Greg Hirsch have steadily uncovered the mechanisms behind chronic rejection in heart transplant. Unlike acute rejection – the immediate post-surgical immune reaction to a donor organ – chronic rejection creeps up slowly over 10 to 20 years. It continues to be the most important limiting factor in the long-term success of heart transplants.

"Virtually all heart transplant recipients develop allograft vasculopathy," notes Dr. Lee, explaining that this is a thickening of the cardiac arteries. "It blocks the arteries that move blood into the heart and can cause heart attack."

Dr. Lee and his collaborators, including a team in the Netherlands, are developing experimental models to study how this thickening of the inside arterial wall develops over time. They hope to identify a pathway they could block to stop the process: "We'd like to extend the average lifespan of a heart transplant, so recipients can live out the rest of their lives without facing chronic rejection."



Jaqueline Bowker is going strong with help from her mechanical heart, which Dr. Légaré implanted in 2013. Due to the condition of her circulatory system, Ms. Bowker was not eligible for a human heart transplant, so the device was her only hope in the face of advanced heart failure. In this follow-up visit, Dr. Légaré explains how the device is positioned in her chest.

Speeding the time to transplant

The Multi-Organ Transplant Program (MOTP) quality committee has set an ambitious target – a 25 per cent reduction in the "work-up" time for potential liver transplant patients.

"This is the interval between when a person is referred for a liver transplant, and when they are fully assessed and added to the waitlist for a suitable matching organ," explains Katherine Connell, RN, health services manager for the MOTP. "We're mapping all the steps in the process, to identify roadblocks and inefficiencies so we can create a more streamlined process."

The work-up process includes consultations, blood work, and diagnostic tests and procedures to determine a person's suitability for transplant. It can take several months to complete. Unfortunately, some patients die during this time.

"While mapping our own processes, we are exploring best practices in other centres," says Ms. Connell. "We are determined to examine every facet of our process and develop a new and more efficient process, from the ground up."

The multidisciplinary quality committee began this project by participating in learning sessions with the Institute for Healthcare Improvement's Rapid-Cycle Evaluation for Health Care Improvement Program.

The MOTP quality committee (l to r): Amal Abel Magid, quality leader; Erin Galliott, clinical nurse educator; Mary Jane MacNeil, recipient transplant coordinator; Katherine Connell, health services manager; Wendy Roberts, social worker

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Research Services produced *Research Focus on Transplant* in April 2015 .
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