

PRESERVING FERTILITY

BY JENNIFER LANTHIER

Surviving childhood cancer comes at a cost; along with temporary but gruelling side effects, the life-saving treatments children receive may render them infertile as adults.

Enter Dr. **Kirk Lo**, assistant professor of urology.

"In adolescents and young adults, chemotherapy and radiation can wipe out sperm production permanently in about half of patients — it depends on what kind of cancer and what kind of therapy they receive," said Lo. "So we advise them to bank sperm if they can and we're trying to make that option accessible."

With survival rates for many pediatric cancers approaching 70 to 80 per cent, post-therapy infertility is a problem that could affect many thousands of young men in years to come. So Lo is working with the Pediatric Oncology Group of Ontario to develop guidelines around fertility counselling and sperm banking for young cancer patients. But for boys whose cancer strikes before puberty there are no sperm to store.

"We've had quite a few requests to preserve stem cells from the testes of these patients before the chemotherapy in the hopes that if they survive, we can use this to establish sperm production in the future."

Across the globe, researchers are trying to grow sperm from stem cells. Scientists are so confident the puzzle will be solved that hospitals in some countries have established clinical and research protocols to harvest cells from young cancer patients for later use.

"We would go in and take out tiny pieces of testicular tissue when the patient is having another procedure done under general anesthesia — but it is an invasive procedure nonetheless so people have concerns," Lo said. "They say: If you do not have a reliable way to grow sperm today, is it ethically justifiable to perform an invasive procedure on these boys, who already have cancer?"

"But we ask, Is it ethical not to preserve their fertility?"

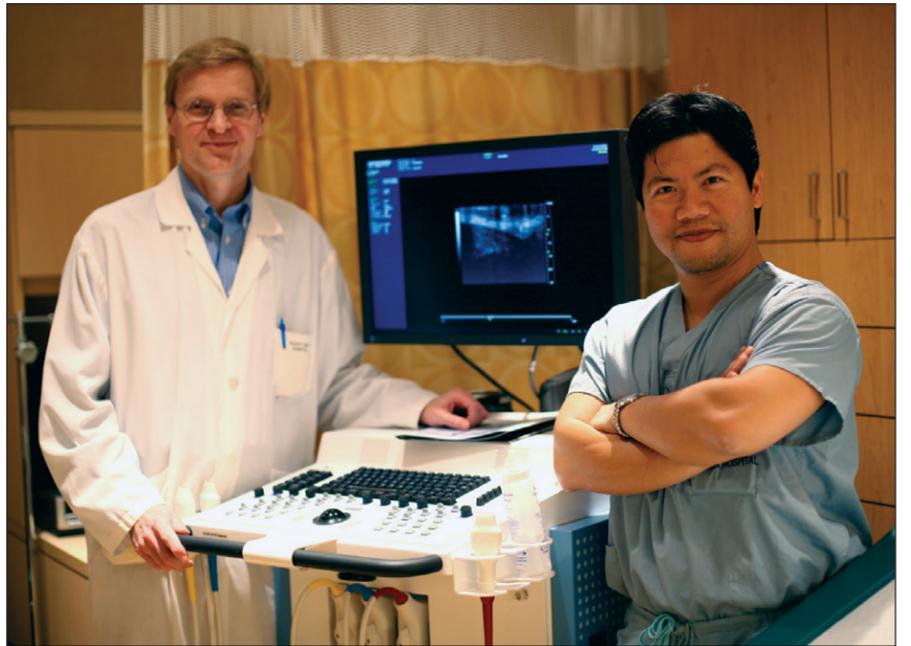
In a research project supported by the National Institutes of Health, Lo is grafting human testes cells onto immune-deficient mice and experimenting with ways of encouraging the tissue to grow and mature to the point where it could produce sperm.

"The cells are starting to divide and we're basically at the stage where we're trying to determine what kind of factors we need to simulate puberty, what kind of change in environment," Lo said. "So we're challenging it with different agents including gonadotropins."

"We can see the germ cells go from gonocytes to becoming spermatogonia and a paper from Japan came out this year saying they've seen them start to differentiate into spermatozoa. So we're competing to see who gets there first."

These experiments won't necessarily produce "a final technique," Lo said, but they may help establish the viability of the concept.

"If we can prove that it is possible to grow sperm outside of humans, then more people will find it acceptable to start banking testicular stem cells from these patients," he said.



DIANA MCNALLY

Professors Keith Jarvi (left) and Kirk Lo in the ultrasound lab at Mount Sinai Hospital's urology unit.

The concept still requires fine tuning, Lo said, but given the sophistication of in vitro fertilization programs, "all we need is a single sperm" to allow a boy who survives cancer today to become a father in a decade or two.

Lo's work is "groundbreaking and incredibly important," said Professor **Keith Jarvi**, head of the men's fertility program at U of T.

"He is one of the first investigators in the world to mature these testes," Jarvi said. "He's gone from a couple millimeters to almost one centimetre in size, so it's increased multiple-fold."

The potential applications for Lo's research extend beyond preserving fertility.

"It's also a model for chemotherapy, for looking at how to reduce or prevent the toxicity of the chemotherapy,"

Jarvi said. "He's building a human testes model in an animal that would be able to tell him if there were chemotherapeutic agents for this age group that were less toxic or if there were ways of avoiding the toxicity — for example, by giving them some protective agents at the same time."

Although his focus now is on preserving fertility, Lo hopes his model might eventually provide a way to test more than drugs.

"We can introduce toxins at any stage and see if it affects stem cells, does it affect cell division or cell death," Lo said. "The applications for this are huge because we can use this to find out what can go wrong, we can restore fertility and in the future it could be a way to test the effects of new drugs."

MALE INFERTILITY ADDRESSED AT U OF T

BY JENNIFER LANTHIER

When the U.S. Centers for Disease Control convened its first-ever conference on men's reproductive health in September, one Canadian researcher attended: Professor **Keith Jarvi**.

Jarvi, a micro-surgeon who directs the male infertility program at U of T, is head of urology at Mount Sinai Hospital and director of the Murray Koffler Urologic Wellness Centre.

"We have the biggest infertility clinic in Canada right here," said Jarvi. "And we've trained fertility fellows from across Canada, we've trained people who now work in South America, the United States, Europe, the Middle East — we have a really big academic program here in male fertility."

Yet 20 years after the birth of the first test-tube baby, reproduction is still largely viewed as a women's health issue.

"Men don't tend to be as protective of their health; the drivers are the women," Jarvi said. "But they have similar rates of depression with infertility and diminished quality of life."

Jarvi welcomed the CDC conference, which declared "the ability to have a responsible, satisfying and safe sex life and the capability to reproduce as well as the freedom to decide if, when and how often to do so" as its working definition of men's reproductive health.

"They're looking at men throughout their lifetimes, so for younger males it's sexually transmitted diseases and how to prevent unwanted pregnancy," Jarvi said. "But as they become young adults, fertility becomes an issue."

Today, an estimated 19 per cent of couples in Canada

have infertility issues and a male factor contributes about half the time, Jarvi said.

"The numbers are approximate, but between eight and 10 per cent of men have fertility issues," said Jarvi. "So it's a huge issue."

Developing less invasive ways to identify and treat fertility problems is a priority for researchers and U of T has groundbreaking work in that area, Jarvi said.

"About 20 per cent of men with infertility have no sperm in the semen and that's the worst kind, the most severe kind of infertility," he said. "They may not be producing sperm at all or they may be producing it but it's blocked, it's obstructed and can't get out."

Differentiating between the two types of patients is key because "it opens up a whole host of different therapies and options," Jarvi said. But traditionally that requires a testicular biopsy.

"You have to take a piece of testicular tissue and examine it to see if it's working or not," he said. "Because that's an invasive procedure, there is risk, it's painful, there's a recovery time."

In a bid to avoid biopsies, Jarvi is collaborating with Professor **Eleftherios Diamandis**, head of clinical biochemistry in the Department of Laboratory Medicine and Pathobiology, on a project to identify biomarkers in semen.

"We have found markers that, so far, have been extremely sensitive in predicting sperm or no sperm in men who have no sperm in ejaculation," Jarvi said. "MaRS innovation has picked it up and it's being patented now."

"It's hard to say how widespread the use will be but it potentially could be used by millions of people across North America. It could have a very large impact on the

way we treat men with infertility."

And it's the kind of multidisciplinary collaboration the Murray Koffler Urologic Wellness Centre was designed to encourage.

"There's a tight interaction between clinicians and researchers — we're right beside each other," Jarvi said. "It may sound strange in an era when you can have direct connection with someone in Australia, but it does make a difference having someone next door."

In fact, a suggestion from a colleague in gynecology opened up another new approach for Jarvi's team in determining whether testicles are functioning.

"Some men with infertility may be producing sperm in only a little bit of the testicle," he said. "Now, what we have to do for those patients is open the testicle wide in a three-hour operation."

Surgeons piece through the entire testicle "to try to find these little areas" that look encouraging, Jarvi said.

"Under a high-powered microscope we can say these look like they have sperm, we take them out, dissect them and find sperm," Jarvi said. "This operation has been used for close to 10 years now and it's successful in finding sperm, although by successful I mean 50 per cent of the time we find sperm."

Harvested sperm is then used with in vitro fertilization and the success rate of the procedure draws patients from all over the world. But a colleague in gynecology suggested Jarvi might find an alternative to "cutting these guys open" by using high-resolution ultrasound.

"It took us four years to get approval from Health Canada but we started on Sept. 17," he said. "Now we can literally look at something that's smaller than the size of a hair, a centimetre deep inside the testicle."

"We can now say, OK, you have larger tubules so you're more likely to have sperm — but if you don't have the larger tubules, you may be able to avoid the surgery."

