

# Ontario Institute Offers New Model of Cancer Research

By Ken Garber

Then next-generation DNA sequencers fill two rooms in the gleaming MaRS Centre, a modern laboratory and office building in downtown Toronto. These machines symbolize today's genetics. They belong to the Ontario Institute of Cancer Research (OICR), a 3-year-old nonprofit corporation that will soon use the machines to sequence the genomes of hundreds of human pancreatic cancers to identify cancer-associated gene alterations.

Five floors below, near the MaRS Centre reception area, sits a plain wooden desk. For Canadians, the symbolism here is equally potent: It's the desk of Frederick Banting, M.D., the University of Toronto surgeon who, with student Charles Best, discovered insulin in 1921. Within 2 years, insulin was fully available commercially and was transforming the lives of diabetic children and adults. The province of Ontario plans to fund OICR with about \$80 million a year in hopes of having the same kind of effect on cancer with their new sequencers and other technologies.

Despite its short history, OICR is already supporting efforts to decipher the cancer genome. It's coordinating the newly announced International Cancer Genome Consortium, a 10-country effort to comprehensively analyze the genomes of 50 human cancer types over the next decade. OICR is also embarking on ambitious programs to expand on key Canadian discoveries in cancer stem cells and cancer imaging and to bring them to human testing and eventual clinical use.

"This is a new model," said Nobel laureate Phillip Sharp, Ph.D., of the

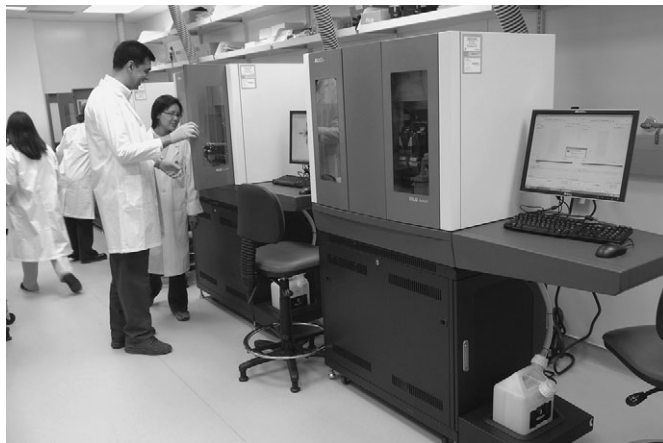


Photo credit: CPImages/S. Sacco.

Next-generation DNA sequencers in Toronto. OICR will soon employ these machines to sequence hundreds of pancreatic cancers to identify cancer-causing gene alterations.

Massachusetts Institute of Technology in Cambridge, citing OICR's breadth of activities, provincewide reach, and international leadership. "I don't think there's another institution in North America that has been given the agenda that this one has."

## Spreading the Wealth

OICR may be new, but it is building on more than a half-century of important cancer discoveries in Ontario. In the mid-1950s, the provincial government established the Ontario Cancer Institute (OCI) at Princess Margaret Hospital in Toronto mainly as a radiation therapy center but also with three floors for research. Important discoveries followed. In the early 1960s, OCI researchers Ernest McCulloch, M.D., and James Till, Ph.D., were the first to prove the existence of hematopoietic stem cells. In 1971, Victor Ling, Ph.D., discovered P-glycoprotein, the molecule involved in cancer cell multidrug resistance. Immunologist Tak Mak, Ph.D., isolated the T-cell receptor in 1983.

OCI researchers "weren't trying to be the best in Toronto, they were trying to

be the best internationally," said Robert Phillips, Ph.D., one of Till's former postdoctoral students.

Basic research at OCI continues to be productive. But by the late 1990s, government officials were impatient for new discoveries to be translated to the clinic, and they wanted to help diversify Ontario's manufacturing-based economy. To that end, Phillips and prominent organ transplant specialist Cal Stiller, M.D., helped establish OICR's precursor, the Ontario Cancer Research Network (OCRN), in 1999. The

OCRN expanded cancer clinical trial participation across the province and established a provincial tumor bank.

The OCRN broadened its mission when it became the OICR in May 2005. "The big vision was to create a cancer institute that would focus on translation," Phillips explained. "Ontario, while it's been very good at discovering things, has not been very good at capturing the commercialization benefit of that. So [the] government said they thought the only way to change that would be to put a new body right in the middle of everybody [and] charge them with the responsibility of making sure that stuff didn't get stuck in notebooks."

OICR's current president and scientific director, Thomas Hudson, M.D., came on board in July 2006 and drafted an ambitious strategic plan. The institute is organized along two general themes. The innovation programs are designed to lead to major discoveries in cancer prevention, early detection, and therapeutics by building on the existing expertise of OICR investigators, mainly in stem cells and imaging.

The second theme is translation, the institute's ultimate *raison d'être* and a more ambitious goal. "The main goal of the institute—it's not discovery, it's bringing things to the population," Hudson said. "Not only what we discovered here in Toronto but what's discovered anywhere in the world."

The institute is recruiting investigators internationally and will employ researchers across Ontario. About 40% of OICR's 50 principal investigators will work at the downtown Toronto site, with the other 60% scattered at universities and research institutes across the province. This internal-external integration model, Sharp said, is comparable to that of the U.S. National Cancer Institute, though much smaller in scale.

Although OICR has a competitive grants program, most programs are non-competitive. Instead, the best groups in Ontario are identified and charged with coming up with 5-year research plans that undergo peer review before funding—similar to the Howard Hughes Medical Institute model. And, unlike government grant programs in Canada,

investigators are not required to obtain matched funding from other sources, although they will be expected to do so eventually. Cofunding is controversial because it favors well-connected investigators and large projects, and partnering with industry too early can compromise research goals. "Not making [cofunding] mandatory gives you more ability to really develop technologies and get them to the stage where they really will be attractive to industry," said John Bell, Ph.D., a cancer researcher in Ottawa and OICR's program leader for immuno- and biotherapies.

### Targeting Stem Cells

One major program already under way is the cancer stem cell project, led by

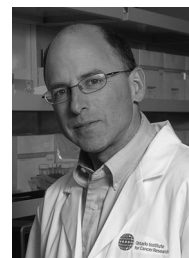
John Dick, Ph.D. Toronto researchers have been leaders in the cancer stem cell field since 1963, when the OCI's Robert Bruce, M.D., Ph.D., using tools developed by Till and McCulloch, first proved the existence of leukemia stem cells. In 1994, Dick's lab isolated such cells for the first time, boosting the cancer stem cell hypothesis, which holds that only a limited tumor cell population can initiate a tumor. Cancer stem cells have since been found in a variety of solid tumors, and the stem cell hypothesis has become broadly, although not universally, accepted. The goal of OICR's project is to answer the "So what?" question: How can knowledge of cancer stem cells translate into earlier detection and more effective treatment of cancer?

*"The main goal of the institute—it's not discovery, it's bringing things to the population. Not only what we discovered here in Toronto but what's discovered anywhere in the world."*

posing is if cancer stem cells drive tumors, perhaps ... these signatures in the cancer stem cells might have more prognostic power than the bulk tumor," Dick said. OICR researchers will look for such signatures in six cancer types: blood, brain, breast, lung, colon, and musculoskeletal. Teams of surgeons, pathologists, and biologists will collect hundreds of patient samples, put the live cells into mice to create xenograft tumors, isolate the stem cells, and use arrays and other methods to generate stem cell RNA and protein expression signatures. The signatures will then be compared with clinical outcomes for patients to see if they can predict the course of the disease.

Parallel projects are under way to develop new ways to image cancer

stem cells in patients and to screen for drugs that specifically kill these cells, which conventional chemotherapy often misses because they're generally quiescent at the time of treatment. "The home run is to say, 'Well, let's find a way to target cancer stem cells, put them into humans in clinical trials, and show that you have improved outcomes compared with conventional therapy,'" Dick said. "That will tell you then that cancer stem cells are relevant, beyond an experimental mouse model." For example, a Toronto-based biotechnology company, Arius Pharmaceuticals, has created antibodies against surface receptors expressed by leukemia stem cells and has begun human trials. OICR hopes to develop stem cell therapies against many tumor types and is building a medicinal chemistry group to aid this effort.



Thomas Hudson, M.D.

### Freeing the Imaging Imagination

Another project already under way is the One-Millimeter Cancer Challenge, the use of sensitive biomarkers and imaging to detect millimeter-size tumors for early detection of cancer. (Most tumors now are at least 1 cm when first found.) The project is more about applying molecular and functional imaging to cancer than meeting a particular physical target for detection because tumors much larger than 1 mm, of course, may be indolent. This project, like the stem cells program, builds on Ontario's strengths. Harold Johns, Ph.D., the Canadian medical physicist who pioneered cobalt-60 radiation therapy for cancer in 1951, began medical imaging research in the early 1970s at OCI. His students and trainees are now investigators and group leaders in labs throughout Canada, and Ontario researchers are world leaders in cancer imaging.

Martin Yaffe, Ph.D., a physicist who played a central role in studies that led

to the recent wide adoption of digital mammography, is OICR's imaging program leader. His basic approach is to take existing systems—x-ray, ultrasound, magnetic resonance imaging, positron emission tomography, and optical techniques—and add probes that make them much more sensitive and specific for early-stage cancers. One project involves the use of microbubbles to enhance ultrasound imaging (microbubbles vibrate particularly strongly at ultrasound's high frequencies), using attached tumor-specific ligands. Many other projects are under way, including some that could be in use by doctors within a few years, such as digital tomosynthesis (three-dimensional x-ray imaging of the breast) using contrast agents. Others, such as cancer stem cell imaging, are at an early stage.

Yaffe stressed the integrated and multidisciplinary nature of OICR's approach, encompassing physicists, molecular pathologists, and biologists to select the best biomarkers and design probes, chemists to make them, manufacturing specialists who will ready the probes for clinical trials, and oncologists and radiologists who will test them in patients. "If you ask me to point to another program that's this comprehensive, I'm not sure I could," Yaffe said.

The molecular imaging field suffers at times from both hype and hopelessness, as intriguing new ideas crash against the realities of biological complexity and regulatory barriers. Yaffe knows the obstacles but also sees opportunities. "There's a sense that some of these really good ideas are just kind of sitting there," he said. "It's our job to develop the new ideas and to take them as far as we can."

### Deconstructing Pancreatic Cancer

Unlike stem cells and imaging, there is no strong history of genomics work in Ontario. But the arrival of Hudson and John McPherson, Ph.D., who came to OICR in July 2007, is changing that. While working at MIT's Whitehead

Institute, Hudson was the project leader for the physical map and, later, the sequence map of the human genome. Before moving to OICR, he directed the Montreal Genome Centre at McGill University. McPherson, a longtime collaborator, was codirector of the key genome sequencing center at Washington University in St. Louis, where he made major contributions to the human and mouse genome projects. "Tom called me up and described what was going on up here, and I came up for a visit," McPherson said. "I just was really excited by the whole concept. The OICR is a real comprehensive program, from one end to the other."

McPherson's pancreatic cancer DNA sequencing project faces challenges. To begin with, about 500 tumor samples and matched control samples must be col-

*"There's a sense that some of these really good ideas are just kind of sitting there. It's our job to develop the new ideas and to take them as far as we can."*

lected to enable the identification of mutations present in at least 3% of samples—a generally accepted minimum standard because of the wide genetic variation present in human cancer. To generate enough tumor cells from these samples, which are thick with connective tissue and other nontumor material, the team will transfer them to mice for expansion as xenograft tumors. And with the expense of whole-genome sequencing (currently about \$200,000 per genome), McPherson's team will sequence only the coding regions, or exons, initially. Besides resequencing for mutation detection, early analyses will also identify chromosomal rearrangements and translocations and copy number gain and loss.

With the demands of this and other projects, the 10 sequencing machines now at the MaRS Centre may not be enough. "We do plan to expand, at least a doubling in our [sequencing] capacity," McPherson said. Because of the many data to be generated, bioinformatics is set to become OICR's single biggest program, under the leadership of Lincoln Stein, M.D., Ph.D., who ran the data coordination center for the International HapMap project while at the Cold Spring Harbor Laboratory in New York.

### Ontario and the World

The International Cancer Genome Consortium owes its existence, in part, to Hudson's initiative. Planning to do large-scale genomics work on cancer, Hudson last year approached cancer genomics groups in other countries to collaborate and avoid duplication of effort. These conversations led to a strategy meeting last October in Toronto—22 countries participated—and the birth of the International Cancer Genome Consortium.

Toronto is a logical site for the secretariat. "Canada is specifically a country that understands that it can amplify its impact by engaging with international cooperation," said Sharp, who pointed out that Hudson's genomics work has always involved working across borders. "I think it comes naturally to Tom."

OICR itself is a work in progress. As of late May, Hudson had recruited 12 of 14 group leaders, although only 18 of 50 principal investigators. "OICR is not a done institute; we're still ramping up," he said. But its young and ambitious leadership, its international prominence, and its generous funding are creating excitement and optimism. OICR's existence "allows us to begin to push our work from the lab into the clinic, where we can really see if it's going to work," Bell said. "For Ontario it's a tremendous leap forward."