Ontario Institute for Cancer Research 2013–2014 Annual Report

Fighting cancer with a virus
Immunotherapy targets cancer cells. **P.11**

CHALLENGE

SOLUTION

IMPACT

Tobacco control – the world's first health treaty
Warning labels, advertising restrictions, smoke-free laws. Are they working? **P.21**

Using better data to improve care for patients
The Ontario Cancer Data Linkage Project gives academic researchers across Ontario direct access to provincial data. **P.32**

Message from the Minister of Research and Innovation

On behalf of the Government of Ontario, I would like to thank the Ontario Institute for Cancer Research (OICR) for another outstanding year. With its partners in academia and the private sector, OICR has attracted many globally-recognized scientists who are conducting leading-edge cancer research across Ontario.

They are improving methods of cancer diagnosis and developing more targeted therapies that have fewer side effects. Their research is generating knowledge that OICR's networks are moving out of the lab and turning into diagnostic tools and treatments that can be used for patient care in the clinic.

Cancer is now the leading cause of death in Canada. This year more than 73,000 people in Ontario will be diagnosed with the disease. There is an urgent need to find solutions that provide better outcomes and to give hope to cancer patients, their families and friends. OICR's collaborations with academia, industry and the international cancer research community are accelerating the pace of discovery and transforming care.

Under the leadership of Dr. Tom Hudson, OICR's President and Scientific Director, the Institute helped create the Global Alliance for Genomics and Health (GA4GH). It brings together more than 200 leading institutions to create a common approach to sharing genomic and clinical data to enable rapid progress in biomedicine. Investments in the GA4GH and the International Cancer Genome Consortium (ICGC) have established OICR as an international "Big Data" powerhouse in genomics and health. OICR's data portal for the ICGC currently provides cancer genome datasets generated by 49 cancer genome projects involving 11,633 donors. The data can be used by cancer researchers around the world to better understand the genomic basis of cancer, accelerate cancer research and help the development of more targeted treatments.

OICR is helping drive Ontario's innovation economy. The Institute provides expert guidance in commercialization to university researchers developing prototypes for devices and equipment that have the potential to revolutionize cancer treatment. OICR's work to help discoveries graduate from the lab into clinics is resulting in the creation of new companies that are attracting private sector investment and driving the creation of high-quality jobs in Ontario.

Congratulations to OICR for their achievements over the past year and best wishes for continued success in the years ahead.

Sincerely,
Reza Moridi
Minister of Research and Innovation

Improving the treatment of early breast cancer P.14

Finding the source of cancer P. 24

The Next Generation: Jeremy Cepek P. 37

About the Ontario Institute for Cancer Research

OICR is an innovative cancer research and development institute dedicated to prevention, early detection, diagnosis and treatment of cancer. The Institute is an independent, not-for-profit corporation, funded by the Government of Ontario. OICR's research supports more than 1,700 investigators, clinician scientists, research staff and trainees located at its headquarters and in research institutes and academia across the Province of Ontario. OICR has key research efforts underway in small molecules, biologics, stem cells, imaging, genomics, informatics and bio-computing.

OICR's Translational Research Mission

OICR's unique translational research model leverages Ontario's province-wide strengths in discovery research, translational medicine and commercialization to maximize impact on prevention, screening and treatment for cancer patients.

OICR's Translational Research Priorities

- **Therapeutic discovery:** find new ways to treat difficult cancers;
- **Clinical development:** use personalized medicine to optimize patient treatment decisions;
- **Population health:** improve cancer care through innovation in prevention, diagnostics, screening and treatment delivery.

Institute for Clinical Evaluative Sciences

University of Ottawa

Queen's University

University of Toronto

Ontario Institute for Cancer Research

McMaster University

Cancer Care Ontario

University of Waterloo

Western University

By the numbers

- 5 partnerships with national organizations that support cancer research and commercialization in Canada;
- 19 startup companies with a total of 172 employees developed out of OICR's investments and research, 7 with prototypes manufactured, 4 with products sold, 4 commenced first-in-man studies;
- 108 patent applications filed between April 2010 and March 2014 arising from OICR-funded research;
- 565 papers published in scientific journals between April 2013 and March 2014 arising from OICR-funded research.

For more information, please visit www.oicr.on.ca

From the Chair of the Board of Directors and the President and Scientific Director

We are pleased to present the annual report for the Ontario Institute for Cancer Research for the year 2013–2014.

OICR was created to tackle the big questions in cancer with a focus on translational research. During the past year we have made excellent progress on the research priorities we set in our strategic plan. The Institute's 33 outstanding investigator award recipients and all the researchers involved in OICR's programs are engaged in projects which collectively will make a contribution to the prevention and treatment of cancer.

Year after year, the Institute's growth is reflected by a number of indicators, including funds leveraged by OICR's programs and spin-off companies, the number of scientists, clinicians, staff and trainees working in multidisciplinary programs, companies enabled by the Institute, and publications (see pages 5–8). The stories behind these numbers are compelling, as they demonstrate that important challenges affecting cancer patients, clinicians and the Ontario health care system are being tackled in the province. Internationally recognized scientists are leading ambitious programs that are translating research into applications.

The creation of predictive and prognostic genetic tests, and identification of biomarkers as well as diagnostic and monitoring tools will guide the use of cancer therapies tailored to the patient. An example is prostate cancer, which is often over-treated with devastating consequences to the patient's quality of life. In this report you will read about approaches to the treatment of prostate cancer that are tailored to the patient and cause fewer side effects (see pages 26, 28). Another challenging issue in the clinic is the use of chemotherapies that have serious side effects in all patients, even though they appear to only benefit a subset of patients. A breast cancer research team is in the process of identifying biomarkers that indicate which patients might benefit from the use of a particular class of drug (called anthracyclines), in order to ultimately spare other women from undergoing a treatment not likely to be effective (see page 14).

Dr. Steven Gallinger is Director of OICR's Pancreatic Cancer Translational Research Initiative and leads OICR's pancreatic research project in partnership with the Canadian Friends of the Hebrew University.

Treasa McPherson, Jacob Diskin and Iris Selander, researchers on the pancreatic project in Toronto, are collaborating with colleagues in Israel to identify the molecular drivers that cause metastatic pancreatic cancer to develop.

Among our priorities is finding solutions to the high fatality rate of pancreatic cancer. OICR supports linked projects that integrate genomics, bio-informatics, drug discovery, biology, imaging and innovative pre-clinical models to develop new treatment approaches for pancreatic ductal adenocarcinoma. A partnership with the Canadian Friends of the Hebrew University, formed with a significant, multi-year commitment by Sylvia M. G. Soyka, director, and the Board of Trustees of the SMGS Family Foundation, launched an international research project in pancreatic cancer, one of the most deadly common solid tumours in developed countries. Ms. Soyka was motivated to support this research by watching her father Alex U. Soyka's unsuccessful battle with the disease. Researchers at the Institute for Medical Research Israel-Canada at the Hebrew University of Jerusalem and Sheba Medical Center in Israel and at OICR will work together to uncover the molecular landscape of pancreatic cancer and the underlying pathways that are driving metastatic forms of the disease.

As we increase our appreciation of the biological complexity of cancer, the digitization and interpretation of genomic cancer data and the development of a comprehensive environment to store, exchange and analyze datasets obtained from human subjects are critical tools. To help address the daunting issues of managing large and complex datasets OICR has been instrumental in the launching of international collaborative initiatives such as the Global Alliance for Genomics and Health and the International Cancer Genome Consortium (ICGC), which involve Big Data (see pages 16, 18, 31, 32).

OICR has taken a leadership role, developing the tools required to catalog, store and retrieve data and establishing Ontario as a hub for international cancer data collection, storage, analysis and redistribution to the worldwide research community.

Left to right:
Dr. Calvin Stiller, Chair, Board of Directors
Dr. Tom Hudson, President and Scientific Director

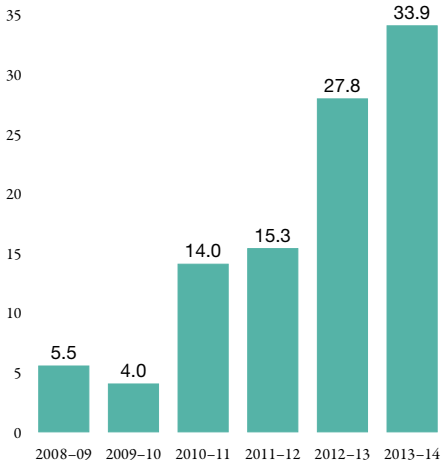
To develop computing tools to manage and use the huge flow of data arising from genomics research, which are needed to find better treatments for cancer, OICR conducts research in its Informatics and Bio-computing Program. The Institute has received funding from the Natural Sciences and Engineering Research Council of Canada's Discovery Frontiers for the Cancer Genome Collaboratory, a cloud computing facility. It will be able to process genetic profiles collected by the ICGC, which is sequencing more than 25,000 tumour genomes worldwide. The University of Chicago is providing key computing resources and the tools developed should be ready for beta testing by 2015.

The report highlights a number of other outstanding teams evaluating tobacco policies (see page 21), developing new therapies (see page 11), networking clinical trials sites across Canada (see page 30), making breakthroughs in understanding the biology of cancer cells (see page 24) and the next generation of cancer researchers (see page 33).

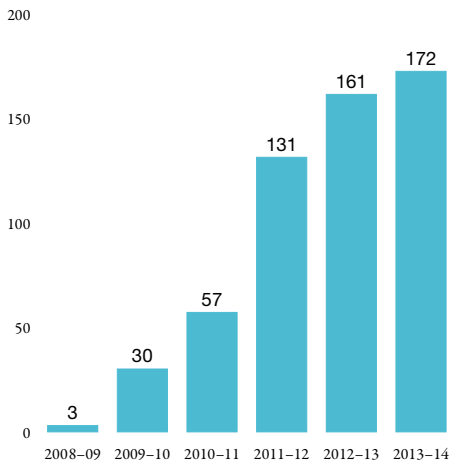
To benefit patients, therapeutic and diagnostic discoveries must be moved quickly from the lab into the clinic. To foster commercial development of Ontario discoveries, the Institute established the Fight Against Cancer Innovation Trust (FACIT) as a vehicle with the capacity to play a wide-ranging role in direct investment in cancer innovation. Under the direction of Jeff Courtney, FACIT goes beyond technology transfer models and is creating new sustainable companies and jobs in Ontario. The Trust looks at multiple ways to help transform cancer discoveries and innovations into viable commercial opportunities and reach the marketplace. Since 2008, OICR funding for the development and commercialization of new discoveries has leveraged $105 million in private sector funding and there are now 172 employees at new OICR-funded startup firms in Ontario.

Jeff Courtney, Chief Commercial Officer, FACIT

Private sector leveraged funds invested in startup companies 2008–2014 (in millions of dollars)



Number of employees at startup companies 2008–2014



We congratulate DVS Sciences, which was acquired by Fluidigm for $207.5 million. DVS was the recipient of funding and business development expertise from OICR to develop the prototype and for the commercialization of the CYTOF® high-throughput mass cytometer for individual cell analysis based on a novel elemental mass spectrometry detection technology. DVS built a manufacturing plant in Ontario which currently employs 59 people.

This past year we welcomed the appointment of Cindy Ward as the Chief Financial Officer. Ms. Ward has extensive experience in finance and administration gained in academia and healthcare. She oversees OICR's finance and human resources portfolio which includes procurement, grants and awards, and the risk management program.

We welcome Robert Klein and John Riesenberger, who joined the Board of Directors this year. We thank Janet Davidson, John Morrison, David Parkinson and Graham Scott, whose terms have ended, for their valuable contribution. We welcome Patricia Ganz, Michael Morin, and Dennis Sgroi, to the Scientific Advisory Board and thank Lewis Cantley, Arul Chinnaiyan and Jane Weeks, whose terms have ended, for their advice and support which has enhanced our programs.

We acknowledge with gratitude, the financial and moral support we receive from the Government of Ontario through the Ministry of Research and Innovation. That support ensures that Ontario remains a world leader in cancer research and that the people of Ontario receive both health and economic benefits.

The high skill level and strong teamwork of our staff make our remarkable progress possible. Through their efforts we are unravelling the mystery of cancer and we thank them for their continued commitment to excellence.

Dr. Calvin Stiller
Chair, Board of Directors

Dr. Tom Hudson
President and Scientific Director

Congratulations to the following OICR Program Leaders

Dr. Janet Dancey
Director, High Impact Clinical Trials Program, OICR;
Professor, Department of Oncology, Queen's University

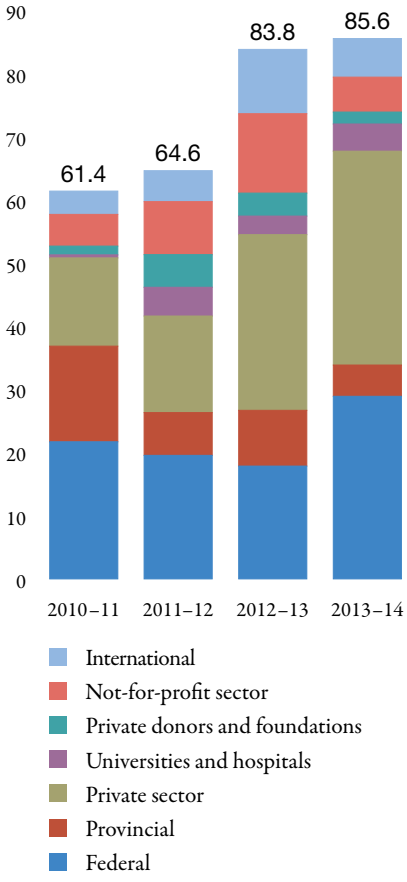
Appointed Director of the NCIC Clinical Trials Group.

Dr. John Dick
Director, Cancer Stem Cell Program, OICR;
Professor, Department of Molecular Genetics, University of Toronto;
Senior Scientist, Division of Cellular and Molecular Biology, Toronto General Research Institute, Princess Margaret Cancer Centre, University Health Network

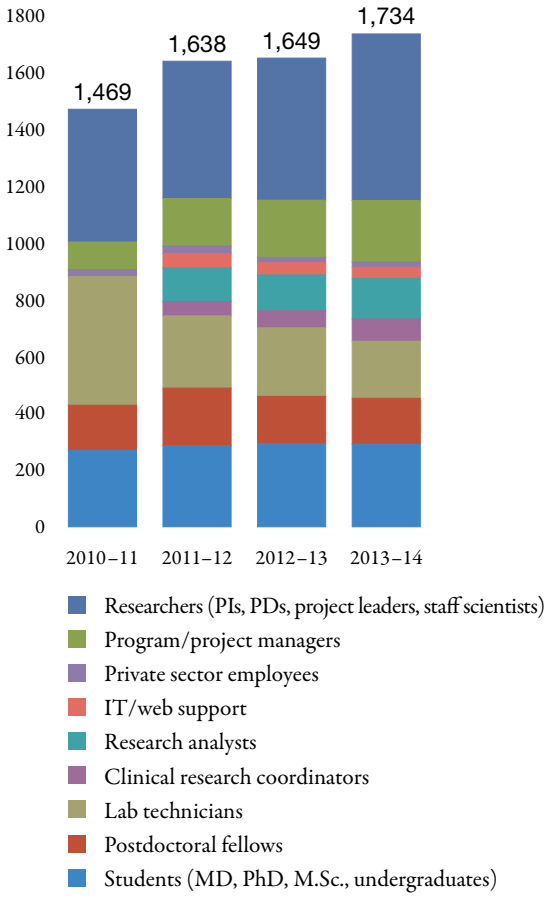
Elected a Fellow of the Royal Society.

MONITORING RESULTS

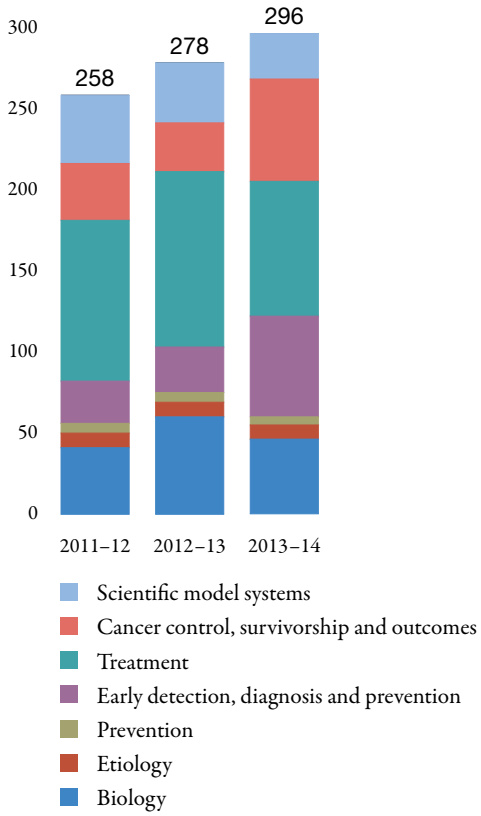
Leveraged funds for projects and awards expended by OICR 2010–2014 (in millions of dollars)



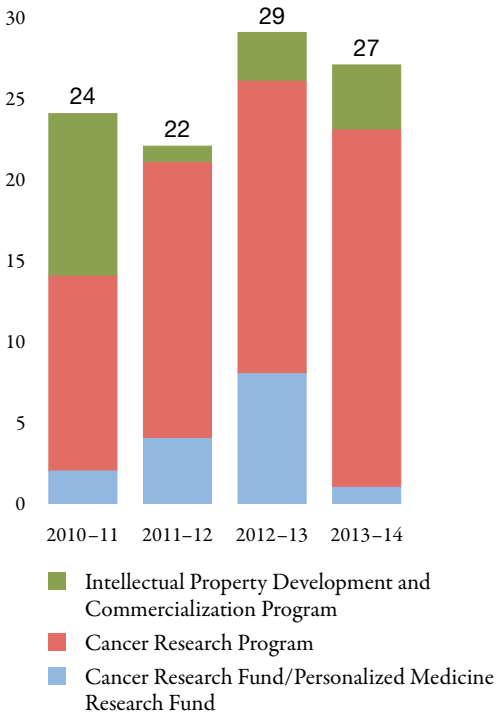
Highly qualified personnel working on funded projects 2010–2014



Intended impact of research 2011–2014 (more than one category may apply to a project)



Patent applications 2010–2014



OICR's investments and research have resulted in:

19
Startup companies

7
With prototypes manufactured

4
With products sold

4
Commenced first-in-man studies

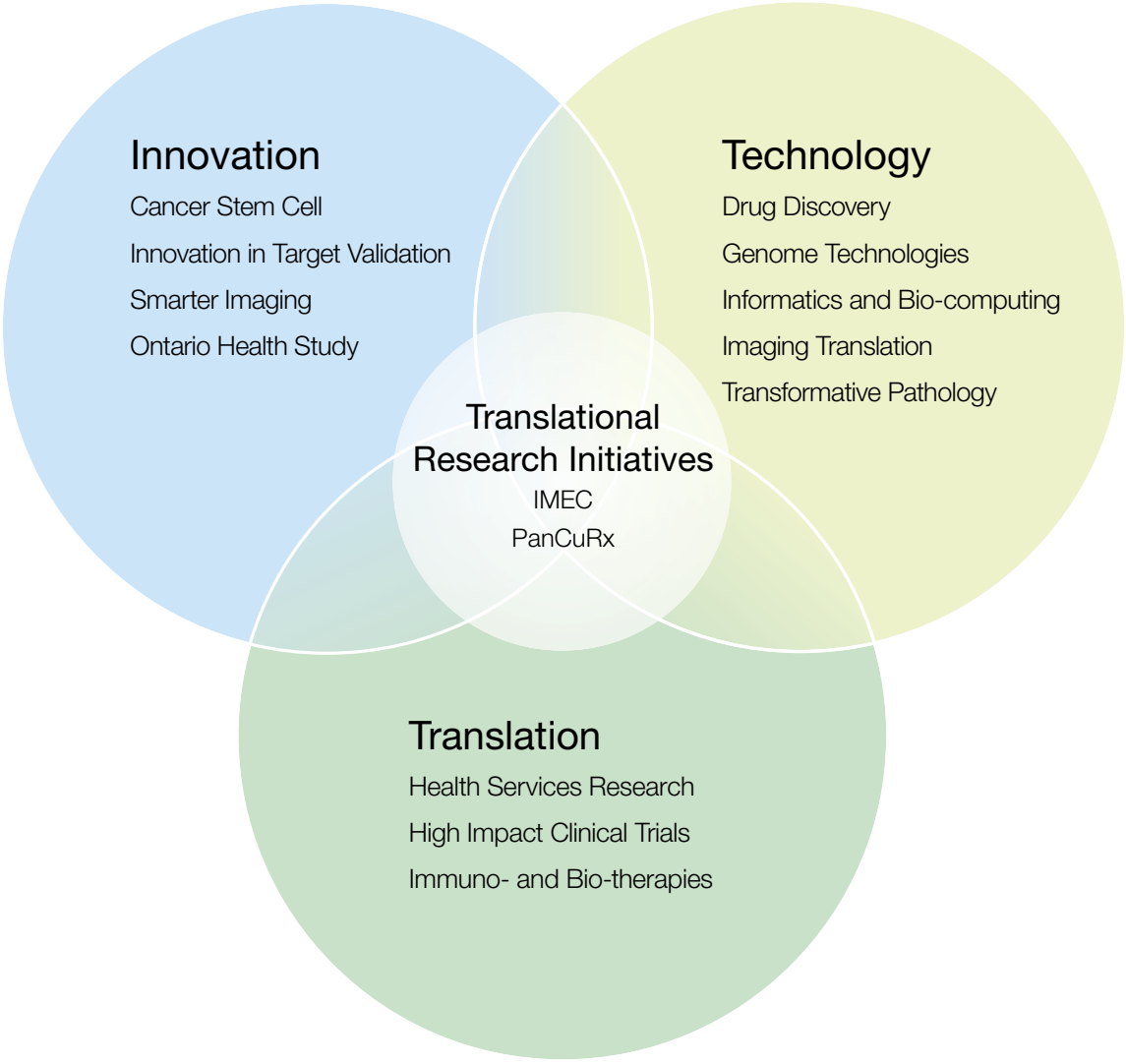
$105M
Private sector investment

INNOVATIVE APPROACHES TO TACKLING THE BIG QUESTIONS IN CANCER

The Ontario Institute for Cancer Research's focus on multi-disciplinary research teams, a collaborative approach and on moving discoveries into the clinic more quickly, has advanced both discovery and translation. On the pages that follow you can read about the Institute's scientists and how they are responding to the cancer *challenge* and creating *solutions* which have an *impact.*

OICR's research framework

Since its launch in 2005, the Ontario Institute for Cancer Research has recruited top scientists from around the world to serve as leaders for its research programs and developed a robust research infrastructure to improve the translation of the latest research discoveries in Ontario into new methods to prevent, diagnose and treat cancer patients.



Collaboration among programs, e.g., Translational Research Initiatives, accelerates the flow of research discoveries for testing in the clinic. The Improved Management of Early Cancer (IMEC) is developing new approaches to distinguish aggressive versus non-invasive disease for patients with early breast or prostate cancer. PanCuRx integrates genomics, bio-informatics, drug discovery, biology, imaging and innovative pre-clinical models to develop new treatment approaches for pancreatic ductal adenocarcinoma.

Fighting cancer with a virus

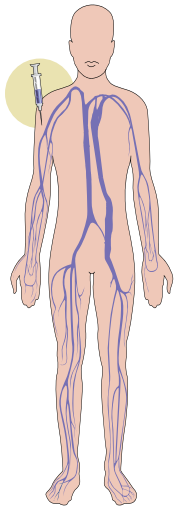
The sand fly is known to be a source of protozoan parasites, which carry Leishmaniasis, a disease that can lead to skin ulcers and other conditions. However this tiny insect may soon be associated with something more positive – a new cancer therapy.

This is because the Maraba virus, which was first isolated in Brazilian sand flies in 1984, is at the centre of a virus-based therapy being developed by a group of Ontario researchers.

Using a virus to fight cancer may seem counterintuitive, but viruses have many advantages as therapies. Oncolytic viruses are a specific type of virus that take advantage of the mutations within cancerous cells, causing them to lose the natural protection that normal cells have and making them more susceptible to infection. The ability of oncolytic viruses to replicate selectively and destroy cancerous cells means that patients treated with these viruses should experience far fewer side effects because fewer normal cells are harmed.

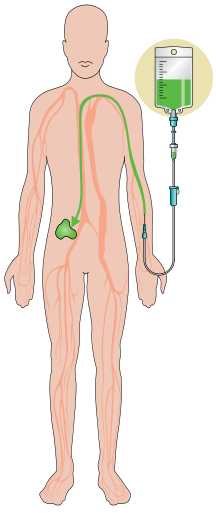
Dr. John Bell is a world leader in the field of oncolytic viruses. Recently, he has been involved with a therapy called JX-594, which is currently being tested in clinical trials. Working to build on this success, Bell and his collaborators began looking for a new virus on which to base an innovative oncolytic vaccine strategy. This search took place in the lab of Dr. David Stojdl, a member of Bell's team based at the Children's Hospital of Eastern Ontario. Stojdl took a library of RNA viruses and applied them against 60 different cancer cell lines to test their anti-cancer potential. This experiment identified the Maraba virus as being the best choice for further development.

A NOVEL ONCOLYTIC VACCINE IN THE FIGHT AGAINST CANCER



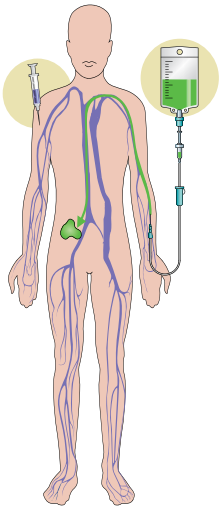
Tumour vaccines

Traditional cancer vaccines "prime" the immune system, helping it to identify and destroy tumour tissue.



Oncolytic viruses

Oncolytic viruses selectively replicate in and destroy cancerous cells.



Oncolytic vaccines

Dr. Bell's approach combines the advantages of a traditional cancer vaccine with an oncolytic virus. Patients' immune systems are stimulated to a much greater degree to attack and control the tumour.

Although Maraba was already a potent oncolytic virus the researchers saw room for improvement. "Through genetic engineering Dave created a new version called MG1, which has increased anti-cancer properties and a better safety profile," explains Bell.

Once the researchers had selected and improved the Maraba virus they turned to another group of their collaborators at McMaster University to enhance its activity even further. Drs. Jonathon Bramson, Byram Bridle, Brian Lichty and Yonghong Wan began working to pair it with an anti-cancer vaccine against Mage A3, a commonly expressed tumour antigen, to increase its effectiveness.

Oncolytic viruses destroy cancer cells through the traditional method of infection and replication, but they also work by generating an immune response from the body against cancer. The adenovirus vaccine that the McMaster team paired with Maraba virus gives it a unique advantage over other immunotherapies. In animal models this combination showed promising results, so Bell and his team began to prepare for testing in humans.

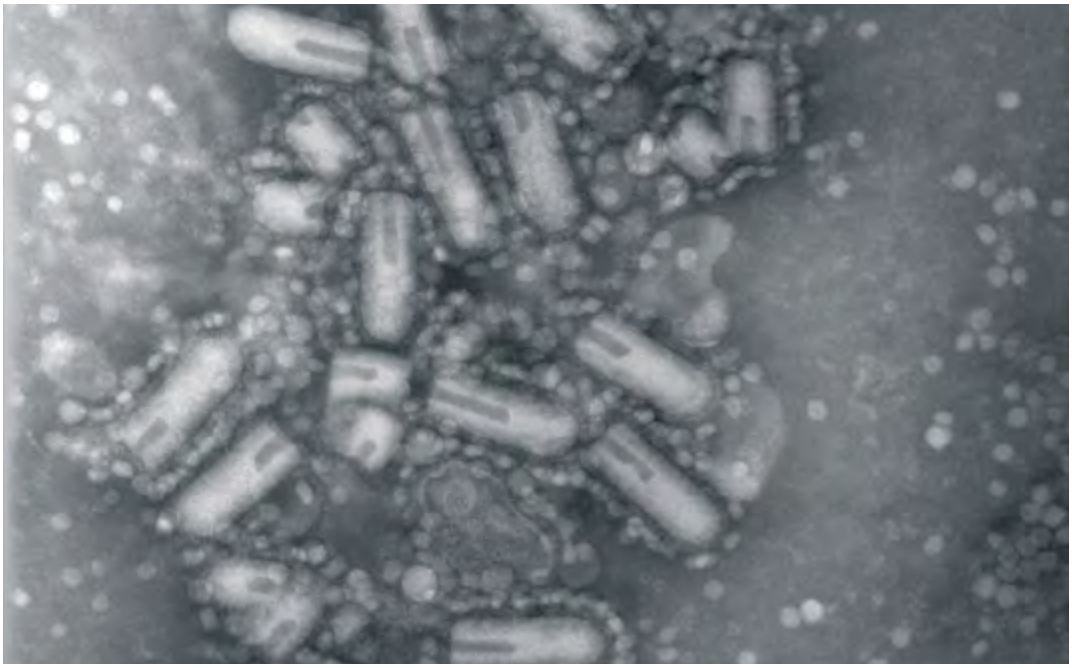
To be tested in a clinical trial the oncolytic vaccine comprising the combination of the adenovirus and the Maraba MG1 both engineered to express the tumour antigen Mage A3 had to be prepared in pharmaceutical-grade GMP manufacturing facilities. The team established a GMP facility for the Maraba virus at the Ottawa Hospital Research Institute and one for the adenovirus vaccine at McMaster University. "Getting these facilities up and running was a major challenge for our group. I am happy to say now that both the virus and vaccine have almost completely passed toxicology testing and have been deemed safe to test in humans," says Bell.

/// "The vaccine serves to prime the immune system, meaning that the patient will generate a stronger anti-cancer response than if they were treated with the single virus alone," explains Bell. ///

Dr. Bell's team, along with the NCIC-CTG recently received approval from Health Canada to test the Maraba virus in select cancer patients. The clinical trial is scheduled to start in the fall of 2014 in Hamilton, Ottawa and Toronto. Accrual of patients for the trial will take place at four cancer centres in Canada and is expected to take about two and a half years. Seventy patients with solid tumours that express the Mage A3 antigen are expected to enroll during the course of the trial. The principal investigator for trial is Dr. Derek Jonker at the Ottawa Hospital Cancer Centre.

DEFINITION

- **GMP**
  Good manufacturing practice (GMP) facilities adhere to strict practices in order to comply with specific guidelines to control the authorization and licensing of food, drug and active pharmaceutical products.



A preparation of the Maraba virus for use in a clinical trial.

Oncolytic virus-based therapies, like the one being developed by Bell and his collaborators, have the ability to replicate selectively and destroy cancerous cells. Patients treated with these viruses should experience far fewer side effects because fewer normal cells are harmed.

Dr. John Bell is Director of OICR's Immuno- and Bio-therapies Program (ORBiT), Senior Scientist, Cancer Therapeutics at the Ottawa Hospital Research Institute and a Professor in the Departments of Medicine and Biochemistry, Microbiology and Immunology at the University of Ottawa.

"When this trial opens we will have hit our biggest milestone to date in the development of the Maraba-based therapy. We will finally be able to assess the safety of the therapy and get some preliminary information on the clinical benefit," says Bell. One of the primary advantages of the Maraba-based therapy is that it has shown only a few minor side effects in animal models so far. "Given our initial testing we are expecting side effects such as nausea and fever in patients, but luckily these can be easily treated with over-the-counter medications," says Bell.

"If things go well in this initial clinical trial we could then test the therapy in a larger trial, start others to test different versions of the Maraba virus we have developed and test the virus in combination with other therapies," Bell suggests.

Dr. Neil Berinstein, Director of Translational Research for OICR's ORBiT Program, thinks that clinical trials, with innovative and promising targeted therapies such as the Maraba-based therapy, are a crucial step in advancing immunotherapies toward routine clinical use.

"Over the last 20 years there has been a steady increase in the understanding of how the immune system functions in cancer and now we have tools that have been proven to be clinically valuable. I think we are going to see an explosion of interest in the field because there is more confidence now that the immune system can be a potent form of cancer therapy," says Berinstein.

Berinstein doesn't see immunotherapies replacing other forms of cancer therapy but rather as another tool to be used in concert with them. Bell agrees, saying that while the Maraba-based therapy could be used as a frontline therapy it will probably be most useful when it is in combination with some other form of treatment such as chemotherapy, radiation or a targeted therapy. "I think that this is necessary given the complexity of cancer and to provide the maximum benefit for patients."

Immunotherapies have been receiving increased attention from clinicians and the pharmaceutical industry, but Bell and Berinstein note that more work still needs to be done in educating people about the science. "I've had both patients and clinicians raise an eyebrow when you suggest treatment with a virus," Bell says. "But once they learn more about it they are on board and really want to understand what's behind it." Berinstein thinks that we may see a similar trend amongst regulators, "Once the first generation of immunotherapies gain the approval of regulators and prove to be effective and important therapeutic tools in cancer, it should become easier for future therapies of this kind to reach the clinic more quickly. Further evidence that these drugs are safe and effective in clinical use will be a big step forward for the field."

Research in immunotherapies is growing and Berinstein sees an opportunity for Ontario and Canada to use their existing expertise to establish themselves as a front-runner in the field. "In a field as diverse as immunotherapies you cannot be a leader in all areas. However in Ontario we have a foothold in cancer virology because of Bell, who is internationally recognized as a leader, and his network of collaborators. Through ORBiT at OICR we are attempting to bring all these pieces together and accelerate the science. The recent support and optimism for the field present us with a great opportunity that we must seize." •

Improving the treatment of early breast cancer

A new diagnostic test being developed by Dr. John Bartlett and his collaborators aims to bring a more personalized approach to the treatment of early breast cancer.

In the late 1990s and early 2000s a number of clinical trials showed that the addition of anthracyclines to conventional CMF-based chemotherapy improved outcomes for patients by preventing relapse of the disease. Anthracyclines were shown to reduce by 20 per cent the number of women who would relapse and die following treatment. Stated differently – six to seven per cent of women avoided relapse due to the inclusion of anthracyclines.

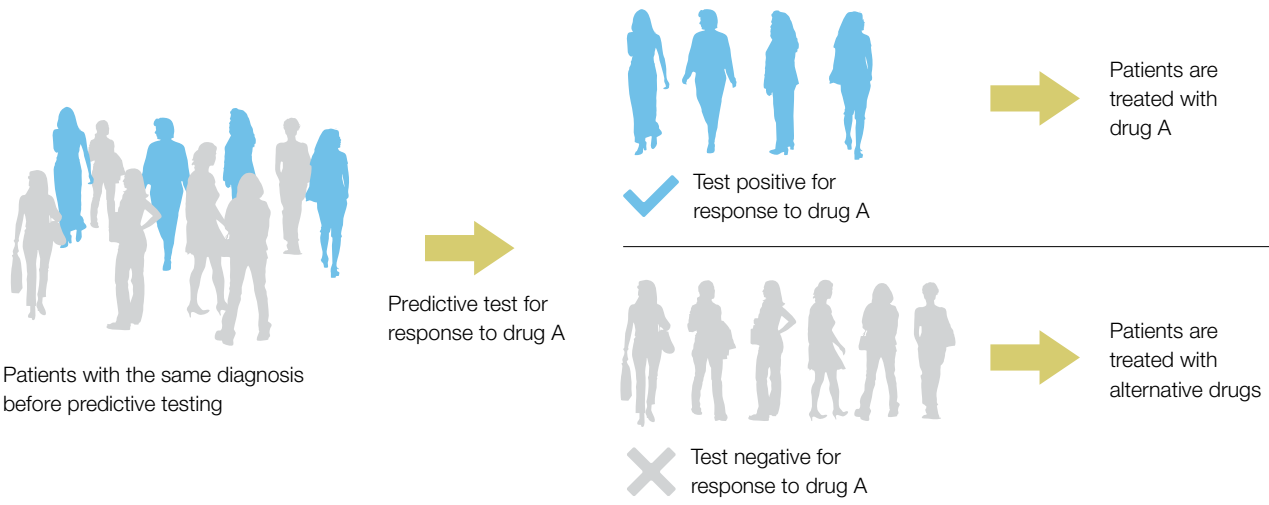
The use of anthracyclines in adjuvant chemotherapy in early breast cancer prior to metastasis is now very common, especially in North America and Europe. Despite their documented value and widespread use, Bartlett believes that there are drawbacks to giving them to every patient. "There is no doubt that anthracyclines prevent relapse in some patients as the studies have shown, but we also must keep in mind that these are cytotoxic drugs that can have serious side effects," he explains. "The big question now becomes who benefits from anthracyclines and who can safely forgo their use."

In 2000, Bartlett and his collaborators began a series of projects to try to identify biomarkers of anthracycline benefit. They also worked to show that a diagnostic test based on these markers could identify whether or not a woman would benefit from anthracycline use. "We were able to identify a robust diagnostic test that could be delivered in a local hospital pathology lab with the same sort of quality assurance procedures that are currently used, for example, in HER2 testing for Herceptin," explains Bartlett.

DEFINITIONS

- **CMF**
  Cyclophosphamide Methotrexate Fluorouracil (CMF) is a form of chemotherapy comprising cyclophosphamide, methotrexate and 5-fluorouracil.
- **Adjuvant therapy**
  Treatments designed to prevent cancer from returning.

PREDICTIVE TEST FOR RESPONSE TO DRUG



Dr. John Bartlett and his team are developing a biomarker that will be able to predict whether or not a patient would benefit from anthracycline use. This will allow those patients who would not benefit to safely forgo anthracyclines and avoid the potentially serious associated side effects.

Dr. John Bartlett is Director of OICR's Transformative Pathology Program, Professor, Laboratory Medicine and Pathobiology, University of Toronto and Honorary Professor, College of Medicine and Veterinary Medicine, The University of Edinburgh.

The movement of the biomarker into clinical use took another step forward when Bartlett presented his research findings to the European Breast Cancer Conference in March 2014. There he spoke during a practice change session about using the test in cases where taxanes are not going to be used in treatment. "This meeting was a good opportunity to start talking with clinicians and establish a better understanding of what needs to be done so that this test can find its way into hospital pathology labs," says Bartlett. "Personalized medicine is not just about new treatments, but also using the treatments we currently have in a better way," says Bartlett. "By giving anthracyclines to only those women who will benefit I believe we could make a significant positive impact on adjuvant therapy in early breast cancer and improve the lives of patients."

FACTS ABOUT BREAST CANCER

Breast cancer is the most commonly diagnosed cancer in Canadian women over the age of 20.

It is estimated that 23,800 Canadian women and 200 Canadian men were diagnosed with breast cancer in 2013.

Breast cancer deaths have decreased by 42 per cent since their peak in 1986 due to earlier detection, advances in screening and improved treatments.

Bartlett and his team gathered tissue samples from five different clinical trials in Belgium, Canada, Denmark, England and Wales, and Scotland and performed a retrospective meta-analysis. Through this study the researchers were able to show that there is a benefit to using this biomarker when planning treatment of early breast cancer. "Looking back at this clinical trial data provided us with Level 1 evidence that this test is useful in stratifying patients based upon anthracycline benefit. I believe that this is one of the first times that this type of evidence has been produced in a retrospective predictive biomarker analysis," says Bartlett.

/// Personalized medicine is not just about new treatments, but also using the treatments we currently have in a better way. ///

Now that the scientific foundation has been laid the researchers have turned their attention to moving the test into clinical use, which in some ways can be more challenging than the initial research. "One of the difficulties in biomarker development is that medical practice changes as the research is ongoing. Specific to our case is that taxanes have become common in adjuvant breast cancer therapy," says Bartlett. "The anthracycline marker is currently being tested in a prospective clinical trial. This will be a first step towards the possibility of changing medical practice for women who are receiving taxanes as part of their treatment." ●

About personalized medicine

In cancer, personalized medicine is used to help patients and clinicians select the therapy with the best chance of success based upon the genomic profile of the patient's disease. Choosing the right therapy is important not just because it will provide the most benefit, but also because it rules out those that would be of no use, allowing patients to avoid unnecessary negative side effects. One of the central tools in practicing personalized cancer medicine are the diagnostic tests that give doctors the information they need to formulate the best treatment plan for their patients.

The data challenge

Researchers from the Ontario Institute for Cancer Research and the University of California Santa Cruz (UCSC) have developed a crowd-sourced approach to solving a big problem with big data.

In November 2013 the ICGC-TCGA DREAM Somatic Mutation Calling Challenge was announced. It was organized in collaboration with Sage Bionetworks and IBM's Dialogue on Reverse Engineering Assessment and Methods (DREAM) and is supported by the world's two largest cancer genome sequencing initiatives – the International Cancer Genome Consortium (ICGC) and The Cancer Genome Atlas (TCGA).

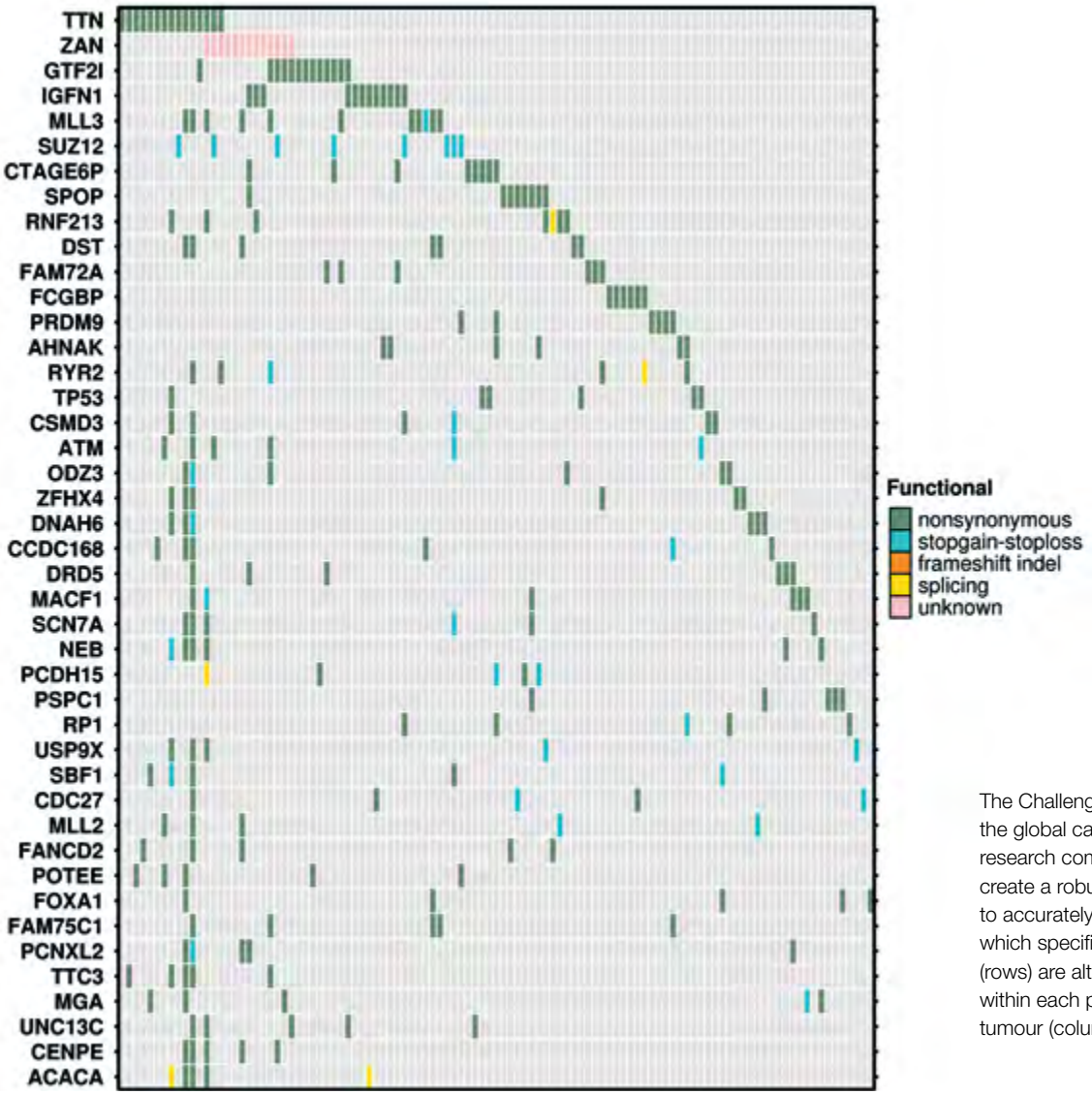
The Challenge asks teams of scientists to create the best algorithms to predict cancer-induced mutations found using whole genome sequencing data. The amount of data produced through whole genome sequencing is enormous and cancer researchers have to identify the most important parts. The Challenge seeks solutions that will better find single nucleotide variations and breakpoints in DNA.

"While literally hundreds of millions of dollars have been committed to sequencing cancer genomes, the best ways to extract clinically and biologically important information from them remain unknown," says Dr. Paul Boutros.

Current studies in predicting cancer-related mutations only agree on as little as one third of their findings. The organizers of the Challenge

DEFINITION

- **Algorithms**
  An algorithm is a set of steps that are followed to solve a mathematical problem or to complete a computer process.



The Challenge is helping the global cancer research community create a robust way to accurately predict which specific genes (rows) are altered within each patient's tumour (columns).

The ICGC-TCGA DREAM Somatic Mutation Calling Challenge aims to improve the algorithms used to analyze genomes by having teams from around the world develop competing methods, from which the most effective will be chosen for further use. This will help advance next-generation sequencing into routine clinical use.

Dr. Paul Boutros is the Challenge Lead and a Principal Investigator, OICR's Informatics and Bio-computing Program.

hope the winning algorithms can help advance next-generation sequencing technology into routine clinical use. It could be used to customize cancer treatments based upon a patient's genetic profile. It is envisioned that the best algorithms resulting from the Challenge will become the gold standard for the analysis of sequenced cancer genomes. Soon after the Challenge concludes the winning algorithms will be put to work on the ICGC-TCGA Whole Genome Pan-Cancer Project, which will involve the sequencing and analysis of more than 10,000 genomes.

"My team will be reanalyzing tens of thousands of genomes stored at the CGHub repository using the winning algorithms from this Challenge," says Challenge Scientific Advisory and UCSC Professor Dr. Josh Stuart. "I believe competition-based assessment will become standard for big-data projects, and believe this Challenge is setting the trend."

Teams will be given access to the raw DNA sequencing data of 10 pairs of genomes comprising both normal and cancer samples. Five of the pairs will be from prostate cancer patients and five will be from those with pancreatic cancer. Access to the raw DNA data will be coordinated through the ICGC's Data Access Compliance Office to ensure legal, ethical and regulatory standards are met.

The Challenge has attracted researchers from around the world and they are already providing results. "Challenge participants have completed analysis of our first tumour and although it's early we are starting to see some interesting results. To date 333 teams have registered to study these tumours and they have performed 948 separate analyses," explains Boutros. "As far as we know this makes these the most analyzed cancer genomes in the world."

This analysis was performed using an *in silico* method that saw mutations added to the genomic data of healthy human cell lines. Teams were then asked to find the mutations using what they thought were the best computational methods. Part of the advantage of the Challenge's model is that even mistakes have value. "The primary goal of the Challenge is to identify the best methods for performing analysis of genomic data and sharing these tools with the research community, but there is definitely value in the submissions of all teams," says Boutros. "We will be able to look at the methods that didn't work as well and apply these lessons to our work. Running a challenge lets the community learn together."

Sponsorship from Google has provided cloud-computing credits to participants. This means that groups that do not have access to the type of computing power necessary for this work can perform their analyses virtually.

In July 2014, the organizers will take the candidate mutations predicted by the teams and validate them using an independent sequencing platform. This validation will take place at OICR in Boutros' lab. He will not take part in the competition. The organizers are estimating that teams will identify at least 5,000 candidate mutations. Using the validation data they will rank the predicted mutations based upon their sensitivity, specificity and balanced accuracy, as well as other factors to determine the winning algorithms.

In keeping with the Challenge's openness the algorithms will be made available for other researchers to use and a partnership has been formed with Nature Publishing Group for publication of the best work through standard peer-review channels. Boutros says, "So far the Challenge has proven to be a great way to work and unlock the potential when we empower the best in the world with a way to work together. We expect to use this model in the future to move our field forward." ●

The Global Alliance for Genomics and Health

The Global Alliance for Genomics and Health is an international coalition that formed in 2013 to enable the responsible sharing of genomic and clinical data.

The Alliance is made up of more than 200 organizations including healthcare providers, research funders, research institutes, disease advocacy groups and life science and information technology companies, including OICR. Peter Goodhand, Executive Director of the Alliance, discusses where the Alliance is now and what it plans to do next.

What led to the creation of the Global Alliance for Genomics and Health?

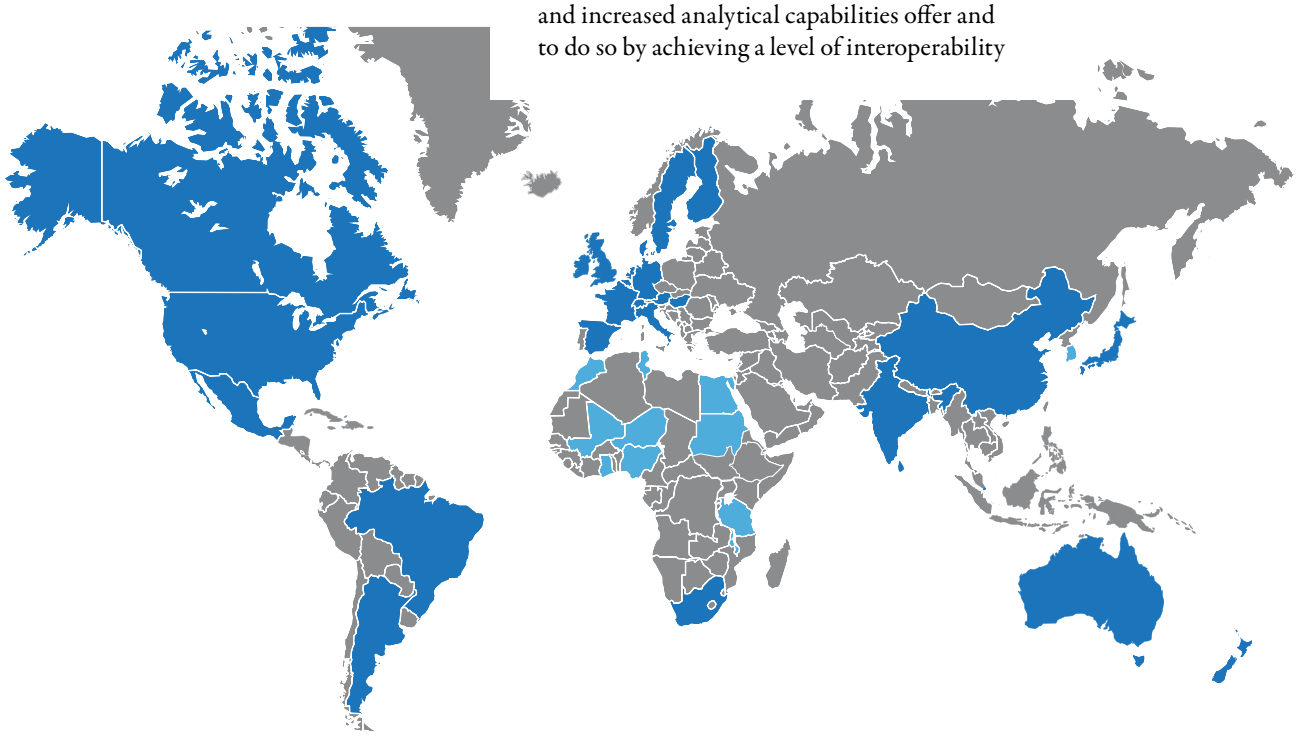
There was a growing realization amongst genomic researchers that due to the very significant reduction in sequencing costs, they were going to have the opportunity to generate more data than they had ever been able to generate before. There was also a realization that if they didn't organize and prepare properly for this in a collective way, they would never be able to deal with and use these massive amounts of data to their full potential.

At the same time, there was recognition that distributed computing and high-performance computing offered the solution to the problem of big data, providing an opportunity to organize and analyze data in such a way that would be meaningful in the clinical environment and could actually impact genomic medicine, not just research.

What is the goal of the Global Alliance?

The goal is to improve human health by realizing the potential that reduced sequencing costs and increased analytical capabilities offer and to do so by achieving a level of interoperability

Countries participating in the Global Alliance for Genomics and Health.



The Global Alliance for Genomics and Health will create common standards to organize and analyze genomic data so it can be more easily shared between researchers around the world. This will allow researchers to tackle larger, more complex projects and find new solutions to improve human health.

Peter Goodhand is Executive Director of the Global Alliance for Genomics and Health.

between the data regardless of which country it is generated in or which disease state it is focused on. These data can be used to find solutions in areas like rare diseases, drug responses to cancer or subtle differences in common diseases.

/// "We are not just looking at this from a research perspective nor are we looking at it solely from a clinical environment and hoping that it somehow connects to the research. We are also looking at regulatory, ethics, social and legal implications in different environments." ///

What is the Global Alliance doing differently than other organizations working with genomic and health data?

The Global Alliance is truly global in that it does not focus on a single country, continent, or region and we are working hard to achieve an even greater global presence to address and resolve broader issues of geographic boundaries and cultural context. The Alliance crosses all disease states, so it is not focused solely on cancer, rare or infectious diseases. We are a multi-sector partnership that includes research funders, research institutes, academic medical centres, patient and disease advocacy groups, private sector companies and professional associations. It is that combination of global reach, cross-disease focus and the breadth of the sectors that are participating in the Global Alliance that is the strongest differentiator from all other initiatives.

The structured approach we have taken to address all aspects of the big data opportunity is also unique. This is a very integrated approach on a global scale to a rapidly evolving ecosystem.

Why is this approach necessary?

Let me give you an analogy. As the user of a smart phone you expect to have the ability to communicate with anyone else with a phone wherever you are in the world, not just the people with your specific device or on your local network. There is a level of technical interoperability that exists in the wireless communication sector where the technical aspects have been organized to the point where we don't notice them. And there is also a trusted business relationship between your own carrier and the carrier wherever you happen to be travelling.

To achieve global interoperability and sharing of genomic and health data in a responsible way, we need to have the same level of technical interoperability and trusted relationships that we see in telecommunications. There are many technical things in our everyday lives that we take for granted and we need to find that same level of controlled, responsible access to data regardless of where you are. That is what will allow us to realize the potential of genomics.

What has kept researchers and institutions from doing this before now?

It is not that it hasn't been done before – many institutions have already started. A great example of sharing data is the International Cancer Genome Consortium. There are many examples, with a limited number of participants or around a particular disease state. And so rather than start everything from scratch, we aim to really leverage all the great work and initiatives that have already started and find ways of adding value and global reach.

How many partner organizations would the Global Alliance like to see involved?

What is important isn't how many there are, it is how they are involved. What we are looking for is active, engaged participation, with people contributing their knowledge, data and expertise, and also showing a willingness to implement changes or new approaches that come out of the Alliance. We want to ensure they reflect the breadth of the Alliance's potential and we expect to create even stronger collaborations within the Alliance.

What progress has been made so far?

The genesis of the Alliance was a White Paper that was written in early 2013 where we cast the general direction in which we'd move. It was refined and then widely circulated in June 2013 with the support of 73 organizations. Since then we have managed to more than double the number of partner organizations, including many private sector companies and significantly increase the number of countries in which we have a presence. We have also seen a marked increase in active participation from organizations and individuals including having now established an effective Steering Committee and four active Working Groups that are starting to engage with their stakeholders. Moreover, the Alliance's deliverables have been identified and there is a work plan in place with specific deliverables for each work area; we are now starting to form task teams that will deliver on these objectives.

Have you seen any resistance from researchers or institutions that may not want to share data?

I couldn't say we've had resistance but what people have appropriately been doing is asking us questions about how we are approaching responsible data sharing or clarifying the ways we would do it. People initially may have thought that we were creating one giant data repository – in fact, that is not the intent. The Alliance will not store, operate or compute on data; that work will be done by partner organizations in trusted relationships. So I think what we saw was actually in the form of very appropriate questions and people wanting to define exactly what we were doing and what we weren't doing – and so far most people have been happy with the answers we've provided.

How are you working to ensure data is secure and patient information is kept safe?

Each one of our partner organizations currently has their own methods of securing data and protecting patient confidentiality. We will be looking to enhance that current level of security by communicating best practices for data security and at the same time increase the opportunity to share data. It is an absolute prerequisite for people who are willing to share data that they can see and demonstrate that data is secure and that privacy is respected.

What are the next steps for the Global Alliance?

The first and biggest next step is to deliver on the plans of our working groups. While we do that, we want to continue to build the organization, increase participation, and clarify our governance and membership. But the absolute next step is to ensure that we achieve our first year deliverables. To make this happen we need to leverage the excellent core team that is in place at OICR, and the other host sites in the U.S. and U.K. and secure a strong base of funding. We are off to a great start and have a tremendous opportunity ahead of us. •

200+ GLOBAL ALLIANCE PARTNERS

Global Alliance partners include:

1. Universities and research institutes
2. Academic medical centres and health systems
3. Disease advocacy organizations and patient groups
4. Consortia and professional societies
5. Funders and agencies
6. Life science and information technology companies

Tobacco control – the world's first health treaty

Cancer is a disease that places an immense burden on humanity, with wide-ranging health, societal and economic impacts.

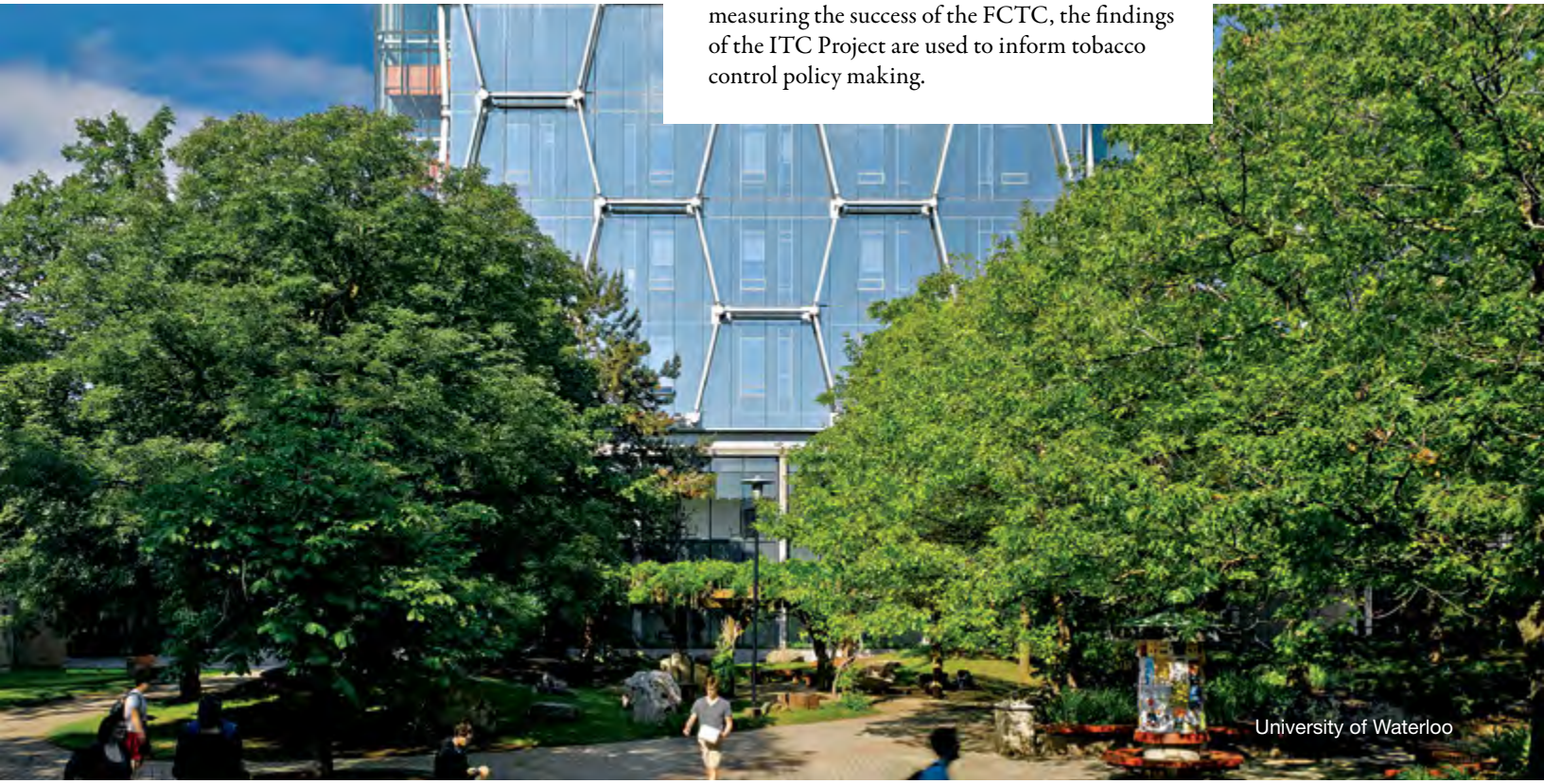
While cancer is a complex disease that can be difficult to fully understand, there are some clear actions people can take to try to prevent it, including eating well, drinking alcohol in moderation, exercising daily, and most of all, not smoking.

Tobacco use is the leading cause of cancer worldwide. It is also the number one source of preventable death and disease, projected to kill one billion people in the 21st century. In 2003 the World Health Organization responded to this global problem with the adoption of the Framework Convention on Tobacco Control (FCTC), the world's first health treaty. The FCTC calls for policies such as pictorial warning labels, advertising restrictions, smoke-free laws and bans on flavourings.

Is the treaty working? Measuring the impact of the FCTC is the job of a team of more than 100 researchers known as the International Tobacco Control Policy Evaluation Project (ITC Project), led by Dr. Geoffrey Fong of the University of Waterloo. Fong and his colleagues conduct sophisticated longitudinal cohort surveys of representative samples of tobacco users and non-users in 22 countries to measure the impact of FCTC policies. These surveys allow the ITC Project team to see how well tobacco control policies have been implemented and if they have changed levels of tobacco use. In addition to measuring the success of the FCTC, the findings of the ITC Project are used to inform tobacco control policy making.

According to the World Health Organization:

- Tobacco kills more than six million people every year worldwide;
- That number will increase to more than eight million by 2030;
- 80 per cent of these deaths will be in the developing world.



University of Waterloo

One of the main planks of tobacco control policy is to educate tobacco users to better understand the health risks of tobacco use. This information can be conveyed through mass media campaigns, health care providers and other channels, but placing health warning labels on tobacco packaging has proven to be one of the most effective. Article 11 of the FCTC is designed to compel signatory nations to use this valuable tool to reduce tobacco use.

/// On May 31, 2013 Fong was honoured with a World Health Organization World No Tobacco Day Award, an annual award that recognizes world leaders in advancing tobacco control. ///

Although Canada signed the FCTC in 2003 it did not need Article 11 to nudge lawmakers into mandating pictorial health warning labels on tobacco packaging – laws requiring them were already in place since 2001. Fong notes that since the 1997 Tobacco Act already restricted tobacco advertising in Canada the warnings had even more impact. "The regulations around tobacco advertising left packaging as one of the last places that producers could convey their brand to consumers," he explains. "Packaging is of particular importance to tobacco companies as cigarettes are a badge product, meaning that they signify to others what kind of person you are."

In 1994 Canada was the first country to require black and white text warning labels on the top of cigarette packages and in 2001 was the first country to introduce pictorial warning labels. These pictorial warnings are now part of the Article 11 guidelines and must cover the top of the package as well as 50 per cent of the front and back panels.

A number of studies across different countries – many of them conducted by the ITC Project – have demonstrated the effectiveness of pictorial warnings. In a recent ITC study, for example, the 2001 pictorial warnings in Canada were estimated to have decreased smoking rates by 12 to 20 per cent. Fong is pleased to see evidence of the success of pictorial warning labels, but notes that, like any message, warning labels lose effectiveness over time. "Our research shows that there is a message fatigue effect that reduces the effectiveness of these labels as smokers grow used to them," he says. Fong and his colleagues recommended in a November 2013 report that the government follow the Article 11 guidelines to rotate and refresh the guidelines every two to three years. New pictorial warnings were introduced in Canada in 2012 and improved with the addition of a 'quitline' toll-free number and website, amongst other changes.

In China, ITC Project researchers study a very different tobacco control landscape. The government-owned Chinese National Tobacco Company holds a 97 per cent share of the Chinese tobacco market and seven to 10 per cent of Chinese tax revenue is from the tobacco trade. China is home to about 300 million smokers (one-third of the world's smokers), and about 1 million Chinese people die each year due to smoking-related causes, losing on average about 15 years of life.

"Despite the pressing need to reduce smoking rates, our study of China found that it has fallen well short of its commitments under the FCTC due to very weak policies in a number of areas including health warning labels," says Fong. "Furthermore, we found that Chinese smokers have the lowest level of awareness of the negative effects of smoking and the second-lowest awareness of the hazard of second-hand smoke of the 19 countries for which we had data at the time."

In November 2008, China and the other signatories of the FCTC agreed on guidelines for the implementation of Article 11, but one month before this China introduced warnings that would not have met the Article 11 Guidelines, which called for pictorial warnings.

"The text-only warnings covered 30 per cent of the package, not the 50 per cent called for under the guidelines," says Fong. "Instead of multiple messages, the two Chinese warnings were essentially the same: One warned that 'smoking harms your health', the other stated that 'quitting smoking reduces your harm.'" The warnings were repeated on the back of the package, but they were in English, which of course is a foreign language to the 1.3 billion people in China. It took four years to change the English warning to Chinese.

The ITC Project report on China found that these text-only warnings went generally unnoticed by smokers and that the labels made only eight per cent of smokers think about the harmful effects of smoking 'a lot'. The ITC China team also conducted an experimental study that showed the superiority of adding vivid images to text warnings. "Our evaluation found that the warning labels in use in China only satisfy one of nine

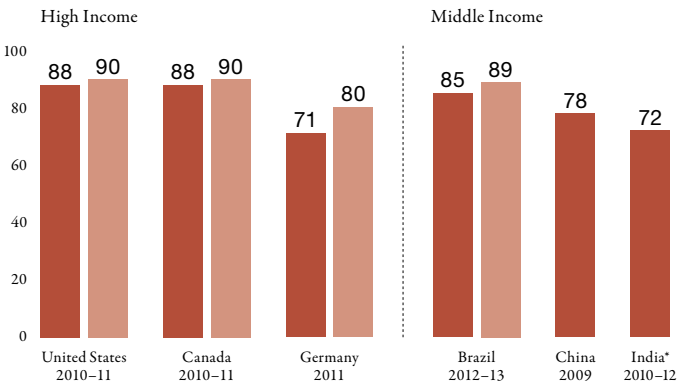
The ITC Project

The 22 countries studied by the ITC Project represent more than half the world's population and 70 per cent of its tobacco users and reach across every continent (except for Antarctica). These include high income countries such as Canada, United States, United Kingdom, France, middle-income countries such as Brazil, Mexico, China, and India, and lower-income countries such as Bangladesh, Kenya, and Zambia.

The ITC Project is determining the effectiveness of tobacco control policies around the world. These policies are key to reducing the impact of tobacco use worldwide, which is the single leading cause of cancer. By identifying best practices and informing further policymaking, the ITC project aims to improve tobacco control and public health.

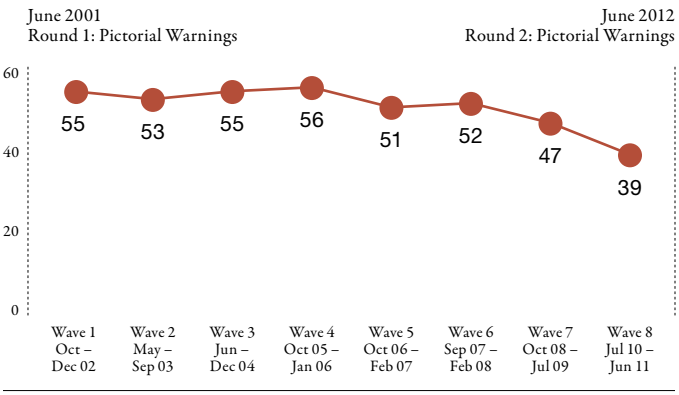
Dr. Geoffrey Fong is Professor in the Department of Psychology and the School of Public Health and Health Systems at the University of Waterloo, Chief Principal Investigator and Founder of the International Tobacco Control (ITC) Policy Evaluation Project and Principal Investigator, OICR.

Percentage of smokers who "agree" or "strongly agree" that if they had to do it over again, they would not have started smoking, by country, showing that the vast majority of smokers simply do not want to be smokers



*For India, dual tobacco users (those tobacco users who reported smoking both cigarettes and bidis) were also included in the analysis.

Impact of health warnings on Canadian smokers' perceptions and behaviours in the last month, by wave, showing the need to refresh the warnings



Article 11 guidelines. It is clear that a great deal of work needs to be done in this area," says Fong.

Comparing the state of tobacco packaging regulations in Canada and China could make one think that the former has achieved all it can in this respect. However that isn't necessarily the case. "A big part of what the ITC Project is about is taking the lessons learned in one country and using them to benefit populations worldwide," says Fong. "Canada was once the most progressive country when it came to tobacco packaging laws, but now I believe it is time for us to look to Australia which required plain (non-branded) packaging for cigarettes beginning in December 2012. Other countries are also considering this strategy."

Controlling the use of tobacco may seem like an insurmountable challenge, but Fong says that when compared to other public health problems, such as obesity, the fight against tobacco use has an advantage – simplicity. "Obesity is a very serious issue in public health right now, but it is driven by many different factors such as diet, lifestyle and a person's genetic makeup, so there is no easy solution to the issue. With tobacco the answer is obvious. We need to help smokers quit and prevent others, especially youth, from starting in the first place. It is the goal of the ITC Project to gather the evidence and inform governments and health stakeholders about what works and what doesn't. We hope to contribute to strong evidence-based approaches to reduce the tragedy and to use the best tools to achieve this." ●

If you're looking to quit smoking, call 1-877-513-5333 in Ontario for free help by phone.

Finding the source of cancer

In 1994, the lab of Dr. John Dick made a trailblazing discovery that changed the way researchers view the onset of cancer.

Dick and his team discovered the presence of the leukemic stem cell, an important piece of the puzzle in understanding the science behind cancer stem cells. Cancer stem cells arise out of normal stem cells due to significant changes in the DNA sequences that regulate the cell. Because of their persistence and ability to reproduce, these stem cells, which are the root cause of the cancer, must first be targeted.

In the past year, Dick's lab has made two major stem cell breakthroughs related to their role in acute myeloid leukemia (AML) and colorectal cancer. AML is a blood cancer that originates with stem cells in the bone marrow. In most cases, AML is diagnosed only after the disease is fully developed, as there are no detectable changes in the blood at an earlier stage. How the disease develops in its early stages is not well understood.

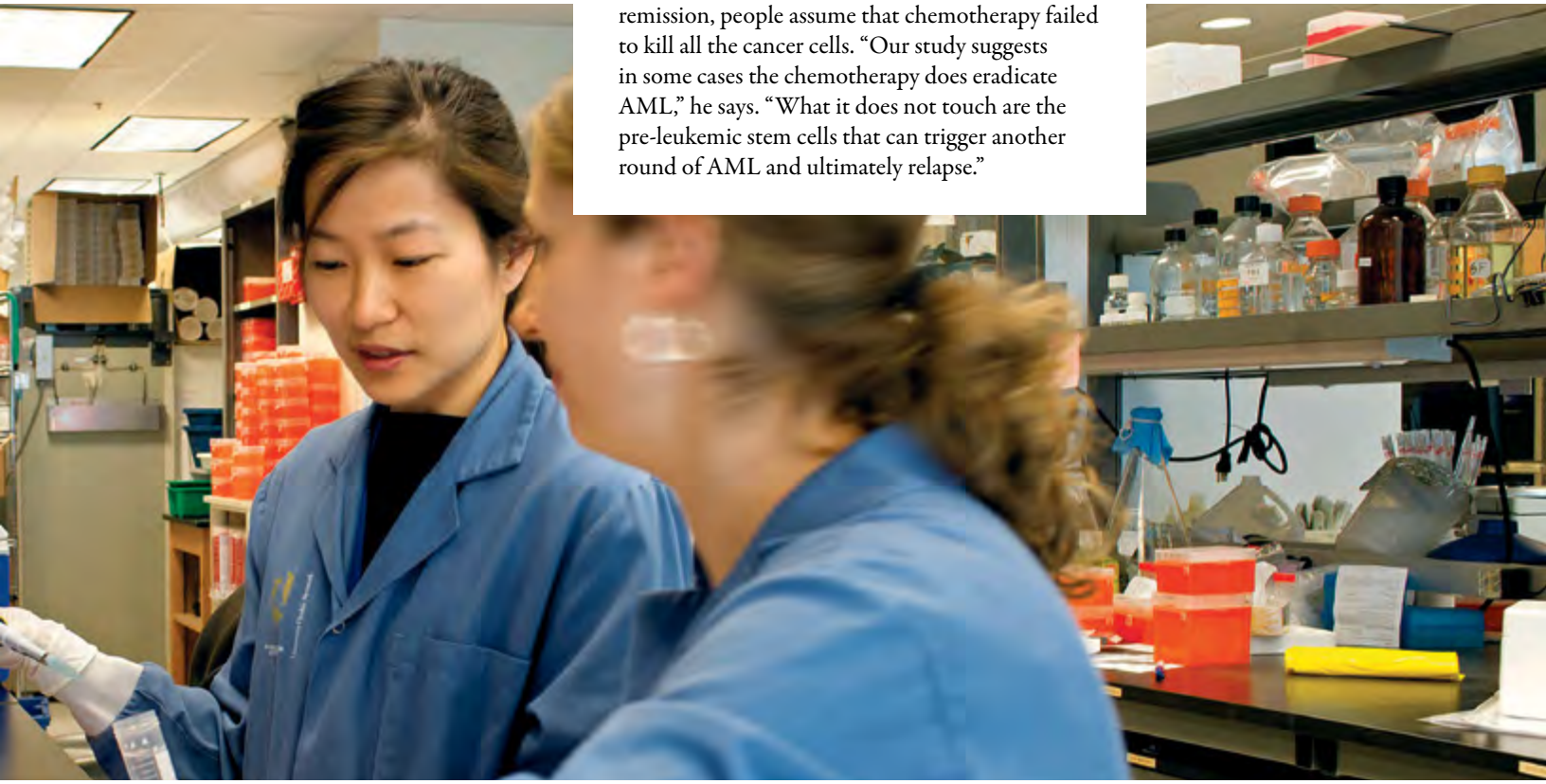
Dick's lab successfully identified a pre-leukemic hematopoietic stem cell that could be the source of leukemia stem cells in AML, as well as the cause of relapse in patients due to its evasion of therapy.

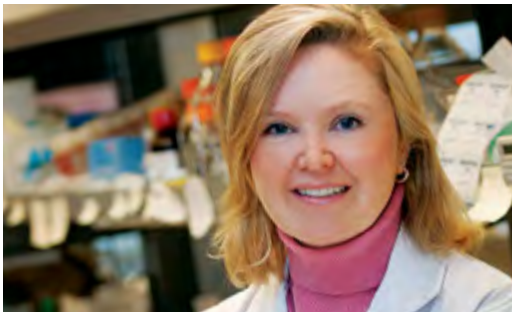
"In about 25 per cent of AML patients, a mutation of the DNMT3a gene causes pre-leukemic stem cells to slowly take over the blood system," says Dick. "These cells survive chemotherapy and can eventually acquire additional mutations, and relapse."

When a patient relapses after a period of remission, people assume that chemotherapy failed to kill all the cancer cells. "Our study suggests in some cases the chemotherapy does eradicate AML," he says. "What it does not touch are the pre-leukemic stem cells that can trigger another round of AML and ultimately relapse."

DEFINITIONS

- **Stem cells vs. cancer stem cells** Stem cells are cells that can reproduce themselves and give rise to other kinds of cells. Cancer stem cells are closely related to normal stem cells and will share many of the behaviors and features of those normal stem cells, but often in a distorted way.





Researchers this year in Dick's lab identified a pre-leukemic stem cell that, if detected and properly targeted, could be used to stop the disease early, when it is easier to treat.

Dr. John Dick is Director of OICR's Cancer Stem Cell Program, Senior Scientist, Princess Margaret Cancer Centre, University Health Network and Professor, Department of Molecular Genetics, University of Toronto.

Dr. Catherine O'Brien is Assistant Professor, Department of Surgery, University Health Network and Scientist, Ontario Cancer Institute.

"This discovery could potentially lead to accelerated drug development to specifically target the DNMT3a gene," Dick says. "If they can target the gene or stem cell at an early stage, the disease could be more receptive to targeted therapies and easier to treat."

This collaborative project was awarded funding from the California Institute for Regenerative Medicine and the Cancer Stem Cell Consortium (CSCC), whose partners include the Canada Foundation for Innovation, the Canadian Institutes of Health Research, Genome Canada and OICR, jointly held a competition which resulted in the award of funds to the collaborative project. "OICR's genome and bioinformatics teams were essential in creating a 100 leukemia gene detection panel and in generating the needed mutation data to complete the study," says Dick. "This was instrumental to the discovery."

The findings should also give researchers the motivation to look for pre-leukemic stem cells in AML patients with other mutations and in a wide variety of other cancers. "We know what causes the pre-leukemic stem cells, but have yet to determine what causes the DNMT3a gene to mutate," he says.

A different stem cell phenomenon was discovered in another of Dick's projects, on colorectal cancer: it identified a gene called BMI-1 that controls self-renewal in colon cancer stem cells.

Dr. Catherine O'Brien, a cancer surgeon-scientist, who has worked with Dick in colorectal cancer research and is now leading this effort in her own lab, describes the work they did. "We already knew that the BMI-1 gene regulates how intestinal stem cells work and that 65 per cent of patients have the biomarker," she says. "Based on the gene's role in self-renewal of normal intestinal stem cells, a key process that ensures stem cells are never lost in a tissue, we asked whether or not it would have a role in cancer cells."

The team found that reducing the expression of BMI-1 decreased tumour growth, proving its key role in supporting the tumour. "Once the BMI-1 pathway was blocked, the stem cells were unable to self-renew, resulting in long-term and irreversible halt in tumour growth." In other words, the cancer was permanently shut down.

"Once the discovery was made, our main interest was whether or not this gene could be targeted with a drug," says O'Brien. "We partnered with a small biotech company from the U.S. (PTC Therapeutics) to see if using a drug to target BMI-1 would have an effect on tumour growth." This work is ongoing.

This research also led to something a little more complex in O'Brien's lab. "We have evidence that our stem cells are very plastic and that this plasticity allows a non-stem cell to become a stem cell and vice versa, which affects tumour growth," she says.

"We have found that we can't just target the initiating cell, because the non-initiating cells can become initiating cells. What we've seen is that one of the ways that BMI-1 is working is through preventing that plasticity."

O'Brien believes that drugs that inhibit the BMI-1 gene can be used in combination with conventional therapy to successfully treat colorectal cancer.

"This is just one of a new class of drugs that we'll be seeing more and more," she says. ●

DEFINITIONS (CNTD)

- **Colorectal cancer** Cancer that develops in the colon (the longest part of the large intestine) and/or the rectum (the last several inches of the large intestine before the anus).
- **Hematopoietic stem cell** An immature cell that can develop into all types of blood cells, including white blood cells, red blood cells and platelets.
- **Biomarker** A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.
- **Conventional therapy** Treatment that is widely accepted and used by most healthcare professionals (e.g., chemotherapy).

Improving the treatment of prostate cancer

Imagine a world in which prostate cancer could be treated in just a one-day outpatient procedure.

With current technologies, including advanced screening and diagnostic tools, this world is increasingly becoming a reality for some patients diagnosed with certain types of cancer. Prostate cancer is one of them.

The last 30 years have seen a dramatic increase in awareness and screening for prostate cancer. The number of men who are cured of the disease when it is found early has increased. In general, it is a slow-growing disease that often appears later in life; but if it's not monitored, tumours can grow and become difficult or impossible to treat.

Dr. John Trachtenberg, the lead clinician of a Phase I trial testing a device to help manage prostate cancer, is hoping the technology he is working on will bring much needed change to the field. "One of the biggest problems with current prostate cancer treatment is that it is ridiculously morbid for the type of disease it is today," he says. "In Western countries where regular screening takes place, about 60 to 80 per cent of patients are found to have low-volume, low-grade disease with low risk. In many cases systemic therapies like chemotherapy are simply not needed."

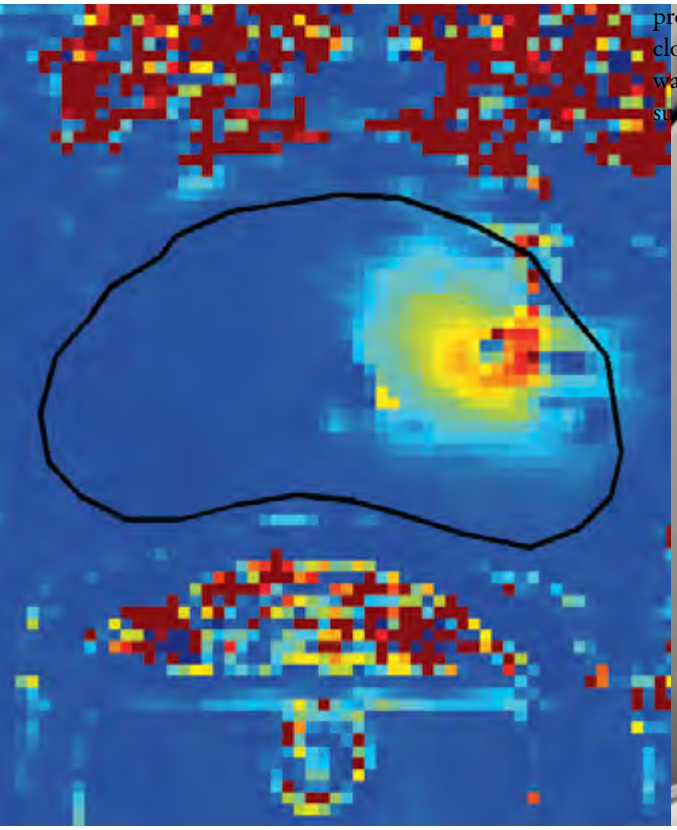
Trachtenberg says various North American trials have all come to the same conclusion. A randomized controlled trial called PIVOT conducted between 1994 and 2002 studied 731 patients who either underwent radical prostatectomy or had nothing done and were closely observed instead. After 12 years, there was no observable difference in the disease-specific survival rate.

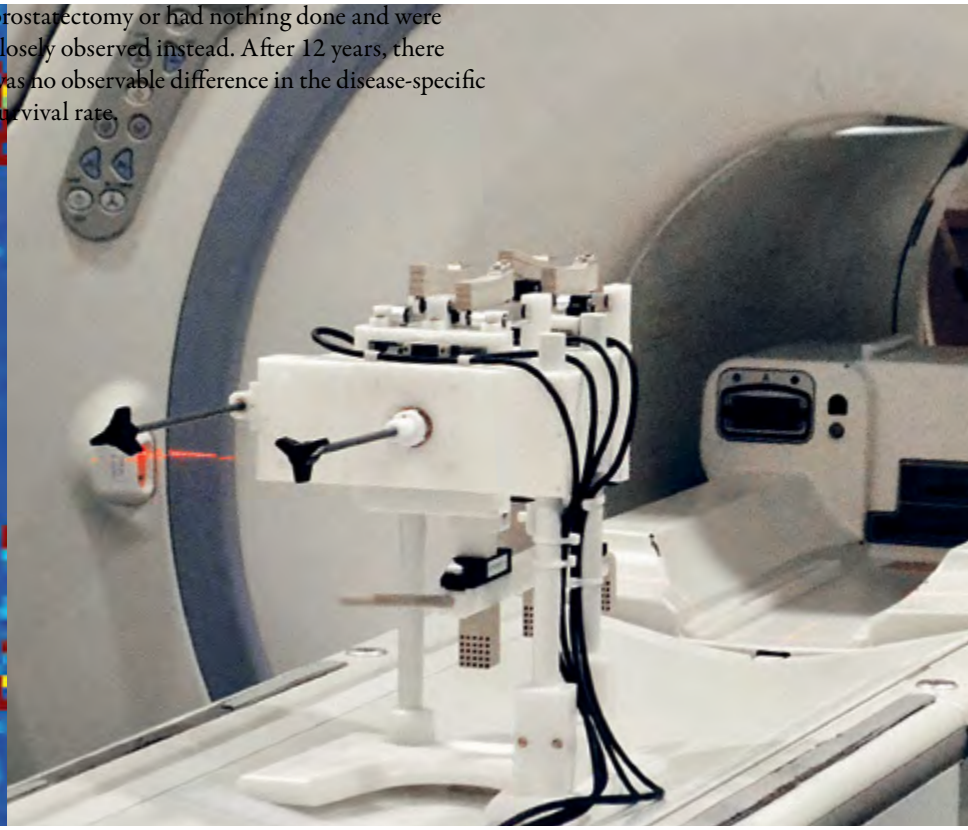
DEFINITIONS

- **PIVOT**
  The Prostate Cancer Intervention Versus Observation Trial.
- **Prostatectomy**
  Surgery to remove the prostate gland.
- **MRI**
  Magnetic resonance imaging – A procedure in which radio waves and a powerful magnet linked to a computer are used to create detailed pictures of areas inside the body.
- **Metastatic disease**
  The spread of a cancer from one organ or part to another non-adjacent organ or part.

Left: An image of the prostate, outlined in black as it is being treated with focal ablation.

Right: The focal ablation device on an MRI machine.





The clinical trial Trachtenberg is conducting will allow prostate cancer to be treated with a minor outpatient procedure, preserving the length and quality of life of people being treated for prostate cancer.

Dr. John Trachtenberg is the Fleck Tanenbaum Chair of Prostatic Disease, Professor of Surgery, University of Toronto and Director, Prostate Centre, Princess Margaret Cancer Centre.

Dr. Aaron Fenster is Director, OICR's Imaging Translation Program, Co-Director, OICR's Smarter Imaging Program, Director and Scientist, Imaging Research Laboratories, Robarts Research Institute, Western University.

University Health Network

Robarts Research Institute, Western University

Facts

- Prostate cancer is the most common cancer in men;
- It kills about 40,000 to 50,000 men per year in North America alone;
- Over 90 per cent of prostate cancers are curable if detected and treated at their earliest stages.

"Studies like PIVOT have shown that while there's not a big difference in survival, there is a difference in the side effects," says Trachtenberg. "Eighty per cent of men become impotent and 20 per cent suffer incontinence after treatment – and these are only the most common side effects."

His hope was to develop a less invasive treatment that would have a better balance of oncologic efficacy versus quality of life. "To do this, we brought together a variety of newer treatments and discoveries of the day into a treatment option," he says. "MRI can show you where the tumour is and can give you an idea of how aggressive it is."

A concept Trachtenberg and his team use is the index lesion, which is the largest site of a tumour and the most conspicuous site of tumour seen by multiple sequences of an MRI. "MRI allows you to see the largest tumour. Usually there are four or five tumours of variable sizes, but there's always a larger one. About 85 per cent of local progression comes from this tumour or index lesion and if found early enough and treated, could preclude the presence of local progression and maybe metastatic disease, just like a colonoscopy does today."

Once the tumour is found with imaging and diagnostic tools, Trachtenberg uses a state-of-the-art robotic device that delivers focal ablation to remove the index lesion. "Once a biopsy has been done to prove that the tumour is the site of highly proliferated cancer cells, it is then ablated and coagulated completely," he says. "By using magnetic resonance phase shift you can see within one degree centigrade the area that you are coagulating versus the area that you need to preserve."

"Right next to the tumour are often the nerves that control erection and continence, and the urethra. We can avoid those areas by differentiating between the heat in the tumour that is being coagulated and the normal temperature of the functional sites next to it."

In collaboration with Dr. Aaron Fenster in London, Trachtenberg and his team have treated more than 50 patients. "Not a single person has had any significant side effects," he says. "There have been no reports of impotence or incontinence three weeks after treatment. Because the laser is placed by a series of needles through the perineum there is often bruising and mild painful urination for some time, but compared to other options this is mild."

Dr. Jeremy Cepek, a recent PhD graduate in Fenster's group is currently working on a second-generation device that will have improvements in needle angulation and other technical limitations that came up in the trial. Cepek says, "Rather than doing freehand needle insertion we have come up with a stable platform that can precisely align the needle to the point we want to hit, through whatever trajectory we want. We can design a treatment plan and then execute that plan exactly." (For more on Jeremy Cepek, please see page 37).

Trachtenberg's approach is simple. "It is true that when we treat only the most aggressive portion of the tumour, we leave some tumours behind," he says. "We believe the small tumours that aren't seen by MRI are not important because they are very slow growing. I'd argue that quality of life is much more important to these patients."

Trachtenberg believes prostate cancer is not that different from other cancers such as breast and thyroid that are being consistently over treated. This technology could have great impact across the board. •

Tailoring treatment for prostate cancer

Finding the right treatment for prostate cancer remains difficult: some prostate cancers grow slowly and don't cause harm, while others grow quickly and are life threatening. How can doctors better tailor treatment to their patients and monitor their progression more precisely?

In April 2013, OICR's High Impact Clinical Trials (HICT) Program joined Janssen Inc. to address this problem and increase translational research in prostate cancer, particularly castration-resistant prostate cancer. With $1 million from Janssen, the HICT Program funded three peer-reviewed translational research projects, leveraging Ontario's expertise in genomics, circulating tumour cells and molecular imaging to test novel biospecimen and imaging biomarkers. Projects now underway at sites in Hamilton, London, Ottawa and Toronto are looking to better understand prostate cancer through the validation of miRNA signatures to predict which patients will develop resistance to hormone therapy sooner, the testing of new imaging and fluid biomarkers and of new molecular imaging strategies.

Building on the success of the first collaboration, Janssen recently provided an additional $500,000 in funding to the project. These funds will be used to develop an additional one or two translational research projects linked to multi-centre trials evaluating additional tumour-based biomarkers for aggressive prostate cancers.

"This collaboration between OICR and Janssen represents a significant opportunity to support important research that will benefit prostate cancer patients," said Dr. Richard K. Plante, Medical Director – Oncology/Nephrology at Janssen. "The nature of the partnership has provided a unique framework through which future research opportunities across a number of research and academic institutions can be sustained, given Janssen's long term focus in genitourinary oncology and long-term portfolio commitment to advanced prostate cancer."

"This program has really demonstrated how OICR's existing networks and activities can be used to create a strong partnership with industry and support excellent research in areas of mutual interest," said Dr. Janet Dancey, Director of OICR's High Impact Clinical Trials Program. "This type of collaboration makes for better research, and ultimately leads to better opportunities for patients." •

What is castration-resistant prostate cancer?

Castration-resistant prostate cancer is an aggressive form of prostate cancer that has become resistant to hormone therapy, usually one to three years after the start of therapy.

Finding ways to better predict which patients with prostate cancer will develop resistance to hormone therapy sooner, doctors can better tailor treatment to patients and monitor their progression more precisely. This improved treatment will have fewer side effects. The partnership helps to facilitate our goal.

Dr. Janet Dancey is Director, NCIC Clinical Trials Group, Director, OICR's High Impact Clinical Trials Program, Scientific Director, Canadian Cancer Clinical Trials Network and Chair, Experimental Therapeutics Network, Cancer Care Ontario.

Accelerating national research initiatives in ovarian cancer

New partnerships between organizations and biobanks could be the key to accelerating research in ovarian cancer. If researchers can find the samples they need in a timely manner and with minimal restrictions, it will not only progress their projects, but in turn lead to more breakthroughs in the treatment of the disease.

This year the Ontario Tumour Bank (OTB) and the Canadian Ovarian Cancer Experimental Unified Resource (COEUR) joined together to further ovarian cancer research across Canada. Dr. John Bartlett, Provincial Principal Investigator of OTB and Monique Albert, Director of OTB announced that OICR has signed on as a partner to contribute ovarian tumour samples to COUER through OTB.

The new partnership creates obligations and benefits for OICR. "The main benefit is in knowing that our samples are being put towards a valuable resource that is going to drive forward ovarian research," says Albert. "Any researcher at OICR working on ovarian cancer projects can gain access to these samples at no charge. If they put in an application and their project qualifies, the COEUR program will release samples to them."

Albert mentions another positive to the partnership. "Any researcher who generates data from these samples is obligated to return the results and data to the main COEUR project. Down the road this pool of data will grow and meta-analyses can be conducted to see if there is something bigger that can come out of this." The Terry Fox Research Institute has set aside $5 million for five years so that the COEUR program could work to acquire a large number of ovarian cancer samples. The goal is to acquire samples from 2,000 patients.

"With the broad spectrum of ovarian cancer samples, there will be sufficient cases to meet the demands of any given ovarian research project," she says. "The first five years of the COEUR program have been primarily dedicated to establishing the bank, including governance, infrastructure, and acquisition of samples. The next five years will be dedicated to maintaining the bank and leveraging the data that is returned from partners."

Albert believes that the partnership with COEUR is helping OTB further its efforts to create a culture of biobankers in Canada. "We work very closely with other biobanks across Canada to try and develop better standards and raise awareness of biobanking. Our goal is to impress upon researchers the value of accessing samples from a biobank as it allows them to access what they need to further their research. Participating in COEUR is reinforcing that this is the position we're taking." ●

DEFINITION

- **COEUR**
  COEUR is a consortium of 35 leading ovarian cancer experts from across Canada, 15 of whom are based in Ontario. With funding of $5 million from the Terry Fox Research Institute and the Canadian Partnership Against Cancer, it is the largest Canadian research consortium dedicated to ovarian cancer.

The partnership between OTB and COEUR will create a culture of biobankers in Canada and will benefit ovarian cancer researchers who now have easy access to tissue samples.

Monique Albert is Director, Ontario Tumour Bank.

Improving clinical trials in Canada

There has been growing concern over the past decade that academic clinical trials in Canada are under threat. In 2010, in a major report on the state of Canadian clinical trials, the Canadian Cancer Research Alliance recognized this trend, noting that clinical trials activity was rapidly shifting from academia to industry.

Academic clinical trials are an important part of any robust healthcare system, answering questions of public good that may not be of interest in for-profit research environments. Among the report's recommendations was a pan-Canadian approach that would support academic clinical trials infrastructure and increase recruitment.

The Canadian Cancer Clinical Trials Network (3CTN) was created in April 2013 to tackle this problem head on, improving the efficiency and quality of academic trials in Canada. OICR was named the central coordinating hub and secretariat of 3CTN. Dr. Janet Dancey leads 3CTN and OICR is collaborating with the NCIC Clinical Trials Group and the Network of Networks to function as the 3CTN Coordinating Centre.

"Ultimately, better clinical trials benefit everyone, including patients, researchers, clinicians, governments and funders," said Dancey. "We are committed to revitalizing the clinical trials community and ensuring we have the right environment to design and conduct the best academic cancer trials in Canada."

Over the past year 3CTN has engaged and collaborated with key stakeholders across Canada to build support for the Network and launched its business plan, which was approved by an international panel in April 2014. Now 3CTN will begin to establish itself by designating Network Regional Cancer Centres and Network Cancer Centres through an application process. These centres, located across the country, will serve as hubs for the delivery of 3CTN programs to other cancer centres in their regions. 3CTN will also be working with funders during this period to ensure the required resources are in place.

Ultimately the goal is to give more people access to better trials and to increase collaboration on trials across Canada. "Canadians have benefited from this country's outstanding history of successful academic cancer clinical trials for many years," said Dancey. "The Canadian Cancer Clinical Trials Network is key to ensuring that legacy continues." •

Canadi li i l
Tri ls Network

ABOUT 3CTN

The Canadian Cancer Clinical Trials Network (3CTN) is a pan-Canadian initiative created to improve the efficiency and quality of academic clinical trials in Canada. The network consists of teams at cancer treatment centres and hospitals that will provide support and coordination to enable sites to increase their capacity and capability to conduct academic trials.

The Canadian Cancer Clinical Trials Network was created to improve the efficiency and quality of academic clinical trials in Canada. Over the next few years it aims to increase collaboration between existing clinical trial centres, giving Canadians more access to better academic cancer trials.

Back row, left to right:
Sajna Baboo, Data Coordinator; Saher Lalani, Financial Analyst; Nicole Fraser, Administrative Assistant; Kay Friel, Director, 3CTN Operations.

Front row, left to right:
Dr. Janet Dancey, Scientific Director, 3CTN; Diana Kato, Project Manager; Karen Arts, Director, 3CTN Initiatives.

ICGC Portal

In order to answer important questions in cancer research, scientists must have access to high quality data that will allow them to carry out their projects successfully in a timely manner. For genomics researchers tackling today's large scale research projects, having access to data on cancer genes and mutations collected is essential.

Forty-nine cancer genome projects are currently submitting data to the International Cancer Genome Consortium (ICGC) Data Coordination Centre, hosted at OICR, and the data they submit can be now be accessed even more easily because of the new ICGC Data Portal, unveiled at the ICGC's 8th scientific workshop in Toronto in October 2013. The new ICGC Data Portal was developed by OICR's software engineering team led by Dr. Vincent Ferretti, Principal Investigator, and was designed to simplify the process of contributing data for researchers and to add relevant features.

Using the simplified search functions, researchers can now explore more kinds of data. "Previously, researchers could select their criteria and get a list of observations such as DNA mutations," says Ferretti. "In the new portal, we can now provide relevant statistics based on these observations. We have centrally annotated all mutations, displaying which mutations belong to a certain gene and where in the gene they can be found."

Graphics and visualization were given priority in the latest release as well. "We have included diagrams, bar charts and other images to help visualize results quickly," says Ferretti. "A genome viewer used to browse exactly where the mutations occur in a given tumour type was also included."

Reaction to the portal since its unveiling in October has been very positive. "Since the last ICGC scientific workshop we have received many offers to collaborate," says Ferretti. One of the most significant is the National Cancer Institute's (NCI) new Genomics Data Commons Portal in collaboration with the University of Chicago. The new portal, which is currently under construction, will allow authorized users access to existing and new genomic data from the NCI in a secure and regulatory-compliant fashion.

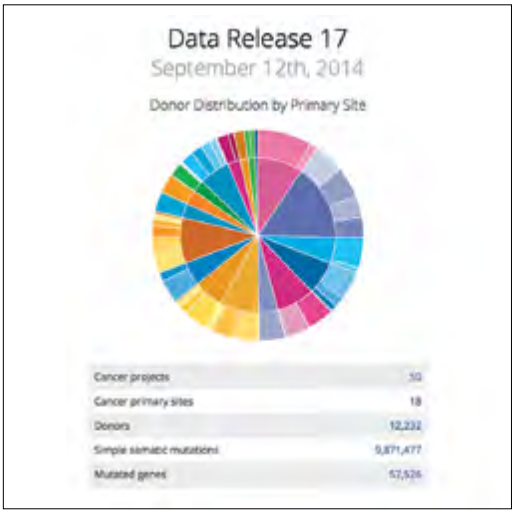
The ICGC Data Portal, for which Ferretti took over the direction two years ago, has a team of seven software engineers and bioinformaticians. "Projects of this magnitude take time, especially with such a small team," he says. "In many ways this release is only the first step. There are many more features and tools that we'd like to add in future releases."

Since the portal is a tool for exploring data, Ferretti would like to see the next versions include more for direct analysis of the data that could manipulate and compare results of queries and integrate new annotations like pathways and new data types such as gene expression and copy number variation. "Until then, researchers can download the ICGC data and run their own tools," he says. "They can use the portal to determine what data is available for a given project or type of donor."

Ferretti also sees potential for the portal to be used in clinical research. "If a clinician could look up a mutation that was being studied in a given clinical trial and found out that it could be targeted for treatment with a specific drug, this would have direct benefit to patients." There are many ways the portal can be further developed and used to better cancer research and its potential for growth is staggering. ●

DEFINITIONS

- **ICGC**
  International Cancer Genome Consortium (ICGC) is a voluntary scientific organization that provides a forum for collaboration among the world's leading cancer and genomic researchers. Its purpose is to coordinate large-scale cancer genome studies in tumours from 50 cancer types and/or subtypes that are of main importance across the globe. As of today, 71 large-scale cancer genome projects are currently participating in the ICGC.
- **DCC**
  The Data Coordination Centre (DCC) located at OICR, is where ICGC data is collected and housed. The DCC team then annotates the data before releasing it to the wider research community.



The new ICGC Data Portal gives researchers better accessibility to the data they need, which could help to fast-track their research. Its improved capabilities have seen extremely positive feedback that has resulted in multiple requests for collaboration with OICR.

Using better data to improve care for patients

Researchers in OICR's Health Services Research (HSR) Program are on the front lines of cancer research, observing how cancer treatment is implemented in Ontario and using that knowledge to develop improved treatment strategies for patients.

Colon cancer is a highly treatable cancer if detected and treated early. In 2007, Ontario set up the ColonCancerCheck screening program to increase participation in colon cancer screening. The HSR team monitored the successful roll out of this program and used its research findings to increase participation through physician-linked invitations and improved correspondence. They found that the ColonCancerCheck program increased the number of people participating in initial screening, but almost 30 per cent of patients with a positive screen did not follow up on the results.

HSR investigators are now researching why this occurs, speaking to physicians and patients to identify common barriers, performing a systemic review to identify new interventions and setting up a randomized intervention study.

The team is also looking at ways to improve quality of life for patients undergoing chemotherapy. Nearly 43 per cent of breast and 46 per cent of colon cancer patients who received chemotherapy after surgery visited an emergency room during treatment. The HSR team is now developing a toolkit of resources and a new electronic communication tool to give patients resources and knowledge needed to better manage their treatment. These will be assessed in a randomized trial. "By keeping patients out of the emergency room we can improve their safety and quality of life while reducing unnecessary healthcare costs," says Earle.

The team will be using similar research techniques to explore methods to improve pain management for cancer patients. "We've observed that one third of cancer patients who reported high pain scores while undergoing treatment had no evidence of either initiation or change in their pain medication," says Earle. "This research can help patients undergoing treatment better manage their symptoms."

They will also be looking at ways to improve chronic disease management and outcomes for the nearly half a million Ontarians who currently have a personal history of cancer. Several studies have shown that patients with conditions such as diabetes have worse outcomes for those conditions if they have also had a history of cancer. Investigators are now using administrative data in population-based cohorts of patients with diabetes and cancer to explore the effect of diabetes on the quality of cancer care and to evaluate the impact of a cancer diagnosis on the quality of diabetes care.

One of the flagship programs of the Health Services Research Program is the Ontario Cancer Data Linkage Project (cd-link), a data-release program that allows approved researchers at academic institutions in Ontario direct access to cancer treatment data from anywhere in the province, while also respecting patients' privacy.

To date, the program has received more than 40 requests from academic researchers, clinician scientists and postdoctoral fellows, for projects including the impact of adherence to HER2 testing, treatment and monitoring guidelines in early state breast cancer, phase-specific and lifetime costs of cancer in Ontario and the effect of adjuvant hormonal treatment on bone health in older breast cancer survivors. It has been so successful that plans were recently announced to expand this approach to other disease types and to accommodate researchers outside of Ontario. "cd-link brings the creativity of the wider research community to bear on the data as opposed to just a few people," says Earle. "If we can identify which treatment strategies are superior to others," says Earle, "it helps us make treatment better for everyone in the future." •

DEFINITIONS

- **cd-link**
  cd-link is a data release program whereby administrative datasets relevant to cancer health services research, such as the Ontario Cancer Registry and Ontario Health Insurance Plan claims are linked, de-identified and, with the protections of a comprehensive Data Use Agreement, provided directly to researchers.
- **Health Services Research Program**
  The Health Services Research Program is a joint venture of OICR and Cancer Care Ontario. The Program's overall objective is to enhance Ontario's capacity to do research that informs health policy, optimizes the delivery of cancer care and maximizes the benefits of the province's cancer discovery program.

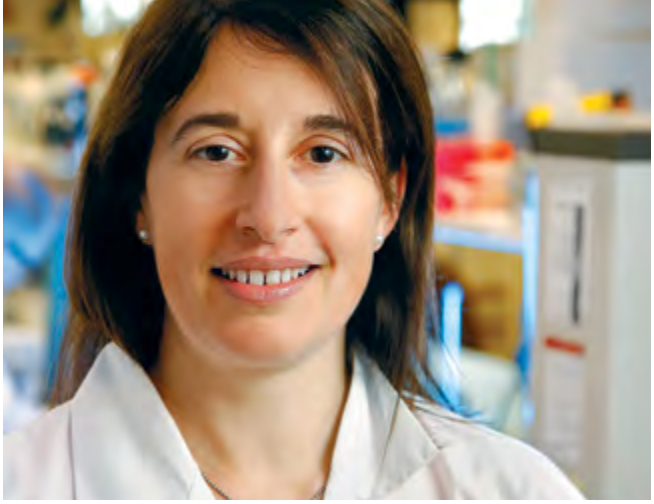
The Health Services Research Program answers the most important health services questions facing cancer control in Ontario by increasing research data infrastructure, developing methodologies to use these data for economic evaluation and coordinating knowledge translation efforts.

Dr. Craig Earle is Director of OICR's Health Research Services Program, a Medical Oncologist at Sunnybrook's Odette Cancer Centre and a Senior Scientist at the Institute for Clinical Evaluative Sciences.

THE NEXT GENERATION

THE NEXT GENERATION

Carolina Ilkow



Cancer cells grow rapidly, but have a fatal flaw. Like a building constructed hastily without proper care, they are structurally weaker than regular cells. This makes them a prime target for viruses, which when specially designed by researchers, can enter and destroy cancer cells while leaving the much stronger normal cells intact.

Dr. Carolina Ilkow is fascinated by viruses and their potential to help cancer patients. Originally from Argentina, Ilkow came to Canada to complete a PhD at the University of Alberta, where she first developed an interest in working with viruses. When she finished her degree she found she wanted to do something that would have a direct impact in the clinic. She joined the lab of Dr. John Bell in Ottawa as a postdoctoral fellow, where she remains today.

She is working to better understand the role of oncolytic viruses in treating pancreatic cancer. Ilkow studies the interaction of viruses, tumours and the environment in which tumours grow. In particular she focuses on cancer-associated fibroblasts, which encourage tumour growth and metastasis. These fibroblasts can form into stroma, and in some tumours, like pancreatic and breast, they make up a huge part of the tumour. Stroma provides the matrix on which tumour can grow, and in the cases of some common chemotherapies act as barriers that prevent treatments from getting into the tumour.

Ilkow's recent findings, then, were welcome news for researchers developing viruses to treat cancer. She found that that stromal cells actually aid in the delivery of oncolytic virus therapies, helping a virus to replicate when given to a patient to treat cancer. That's the complete opposite effect than with chemotherapy. In effect, the stroma acts as a staging ground where the virus can replicate when attacking the weaker cancerous cells.

"So far what we've found is that indeed the interaction between cancer-associated fibroblasts and cancer cells is positive for oncolytic viruses, so they enhance or help the virus to replicate in the tumour and to kill cancer cells," says Ilkow. "We found that we can target these cells with oncolytic viruses and the presence of these cells is beneficial for the virus to replicate and to be effective in killing the cancer cells."

This finding was the first of its kind and opens up new avenues for deploying more oncolytic therapies.

"The fact that we started studying cancer-associated fibroblasts and the role of these cells with oncolytic viruses, no one else has done it so far. We saw the challenge and tried something different. It is very important to think in that way. I don't like to do things that have been done, I like to do something new and something that will contribute to change."

Ilkow's research showed that stroma, which has been a barrier for the successful delivery of chemotherapy, actually aids in the delivery of virus-based therapies. This opens up new opportunities in the development of new oncolytic treatments for cancer.

Ilkow says that she has always been extremely passionate about science. Growing up in Buenos Aires she was performing dissections and reading scientific books from a very young age. Nonetheless she thinks her career so far has been unexpected and challenging in the best possible way.

"Sometimes it is not easy to do science. You have a lot of experiments and a lot of things don't work. You have an idea but you cannot find a way to prove it. But that is also what is most fascinating about this job. I go home and I'm cooking and I'm still thinking about the experiment that I'm doing the next day. I can't disconnect from my work, but I love what I do so much it is amazing. No other job would challenge you as much as science does."

The next steps are to work on the development of more viral therapies that will take advantage of her recent findings. She would like to first develop or engineer a new oncolytic virus that would more effective in treating pancreatic cancer. She is also interested in narrowing the gap between translational and basic sciences, something that she feels her work in Bell's lab has encouraged.

"I think it is really important that here in our lab we have the opportunity to interact with doctors and patients all the time. Those things help keep us focused as researchers, seeing the reality and what you are working for. In terms of pancreatic cancer and tailoring oncolytic viruses, there is not a lot out there for patients now. What motivates me most is to improve the therapy for at least that tumour type and hopefully expand to other tumour types from there." •

Paul Krzyzanowski

The gene signatures Krzyzanowski is mapping will help to detect esophageal cancer earlier, when it can be much more easily treated.

Understanding the inner-workings of any complex system can be challenging, but Dr. Paul Krzyzanowski has always been interested in finding ways to do exactly that. He has always liked to take things apart to understand how they are constructed and how they work. In his early years, he remembers disassembling radios and computers to satisfy his curiosity.

Today he's studying considerably more complex systems. Working with Dr. Lincoln Stein as a postdoctoral fellow in the Informatics and Biocomputing Program, he's mapping gene signatures that will help to detect esophageal cancer earlier. While still a rare form of cancer, patients are often diagnosed with esophageal cancer when they begin to complain of trouble swallowing. At this point the treatment options are limited, as it means that the cancer has already advanced far enough to make surgery difficult and risky.

Yet physicians know that there is a path that leads to the development of esophageal cancer. People who have chronic heartburn have a higher than normal chance of developing a condition known as Barrett's Esophagus. People with Barrett's Esophagus in turn have a higher risk of developing esophageal cancer. By monitoring these earlier ailments and testing patients periodically for cancer, physicians would be able to find and treat esophageal cancer when it is just a few millimeters in size, and still highly curable.

"As long as you detect esophageal cancer early enough, there are procedures to remove it, some as simple as having melanoma removed on the skin. But these options work well when you detect cancer at it's smallest," says Krzyzanowski.

"To do this, we are looking at whether about 100 genes are mutated or not in a patient's tumour DNA, and use knowledge of how those genes work together to score how different a patient's cells are from what we normally expect. We think we'll be able to score whether a patient with Barrett's Esophagus is travelling down that path to cancer well in advance, giving patients and physicians ample time for treatment."

The challenge, as with early detection with any type of cancer, is to find DNA from a small amount of cancer cells amongst many healthy cells. But it is that complexity that drew Krzyzanowski to the project. "We're looking for a needle in a haystack," he says. "But the goal of this project is to be able to leverage all the genomics technologies available and identify the best technical way to spot mutations in a speck of cancer from an entire background of normal cells and create a new way to help patients."

While today Krzyzanowski publishes scientific papers, his publishing career actually began in high school. There he produced an underground newspaper that became so popular amongst his classmates and teachers that the school came to a standstill on mornings when it was published. "Only 1 in 4 lockers received the paper, encouraging everyone to ignore their classes and find copies to reproduce. It really went viral – back in 1996", laughs Krzyzanowski. It was so popular, in fact, that it almost got him expelled from school (his principal later only reprimanded him for his misuse of the school photocopier to print the newspaper).

As an undergraduate he became very interested in many of the majors offered, but he gravitated to biosciences. "Biology was a mysterious area where there was always an exception to the rule. It's complicated. When you assume that the same things work the same way in different organisms, you often find out that they don't."

Later in his career he realized that he was less interested in looking at biology from a purely academic viewpoint and more interested in taking new ideas arising in biology and genetics and trying to convert them into knowledge that can actually be used in the clinic.

"Our discoveries aren't going to help people if they remain in journal articles," says Krzyzanowski. "They really need to be translated and incorporated into products and services before they will help improve human health and happiness."

Looking ahead, Krzyzanowski says that he's developed an interest in understanding how to bring together different elements of the research environment to better collaborate and ensure that this translation occurs.

"In science and research, there are so many great ideas that fail for various unscientific reasons. You need to develop the skill to look at all your options and avoid the 80 per cent that won't work right now and focus on the 20 that will. I'd like to be able to do that not just scientifically, but also in problems relating to industry, government, academia and the public."

In the meantime he looks forward to seeing his current project move closer to the clinic. Noting that like most people, he has friends and family with chronic heartburn or Barrett's Esophagus. "You never know, in 20 years someone I know might develop esophageal cancer. If they can have that cancer removed in a morning appointment and go on to live a normal, healthy, life – that would be extremely gratifying. That thought provides a lot of personal motivation to make this project work." ●

THE NEXT GENERATION

Jared Simpson

Simpson designs new methods to turn the sequencing data produced by OICR's genomics projects into meaningful information that can be used by researchers to develop the next generation of cancer diagnostics and treatments.

Dr. Jared Simpson has had an unusual career path for a cancer researcher. He started his schooling in physics, before transferring to computer science. He developed an interest in lighting and rendering and making realistic scenes on a computer, which led to a career in the video game industry. He enjoyed the challenge of the work but soon found he wanted to do something more with his skills.

On the advice of a friend who worked in cancer research, he transferred to the BC Cancer Agency's Michael Smith Genome Sciences Centre, where he was able to put his programming skills to good use – solving big data problems associated with cancer research. That was 2007, when next generation genome sequencers had just been released and were presenting new possibilities for genomics research.

"It was a very exciting time because it was still very early days in the field and working with the new data we had," says Simpson. "There were a lot of challenges working with the scale of the data, and most of the software for the previous generation had to be rewritten. It was a great opportunity for people with a computational background to make an immediate impact on genomics."

Simpson eventually decided to further his skills in the field by completing a PhD, studying under Dr. Richard Durbin at the Sanger Institute in Cambridge, U.K. When he finished he returned to Canada to join OICR as an OICR Fellow in the Informatics and Bio-computing Program.

"I wanted to stay at a research institute. I like the teamwork aspect at an institute like OICR or Sanger, where the institute has a clear focus in what they are doing and everyone is pulling in the same direction. It was about coming to a place where I could stay close to the data generation on the genomics side and also find collaborations. OICR is a great fit for me."

Simpson now uses the computer programming skills he honed developing video games to design new methods of analyzing the sequencing data produced by OICR's genomics projects.

"The amount of data you get from sequencing a tumour is huge – hundreds of gigabytes. To identify what mutations have occurred in the tumour you need very efficient software," explains Simpson. He both designs algorithms and implements them in software, all of which is open source.

But the task isn't as straightforward as it might initially seem. There are only thousands of mutations out of billions of bases in a tumour. "I'm trying to find new methods to improve our ability to find new mutations in tumours. This will hopefully lead to biological insights as to how the cancer developed."

The challenge is amplified by the sheer volume of sequencing that's being done at OICR. "That's for a single tumour, but we're sequencing hundreds to thousands of tumours. The software we develop needs to be able to precisely find mutations and it needs to be computationally efficient enough to run at very large scale."

Does he have any regrets about the circuitous route he's taken to get to his position at OICR? "I took a lot of time to figure out what I wanted to do," he admits. "Some people in high school know they want to be a doctor or an engineer. I didn't." But he definitely thinks it has been a benefit, especially because now in science everything is interdisciplinary. "To work in bioinformatics you need to both understand the biology and you also need very strong computation skills. My current work at OICR really draws on all the experiences I've had."

Simpson hopes to be involved in even larger projects over the next few years as his role at OICR expands. He is already looking ahead to the challenges the next generation of sequencing technology will bring and hopes to once again be on the forefront of those changes. He says there are still things that researchers are not getting out of current sequencing technology, even though it is allowing them to do amazing work. The next technology currently in development is long read, single molecule sequencing, where much longer stretches of DNA are sequenced.

"If we had 100 times longer reads we'd be able to do a lot more with that data. But that also means we are going to have to rewrite a lot of software again." •

Jeremy Cepek

Sometimes solving a complex problem requires looking at it from a different angle. Dr. Jeremy Cepek is a young researcher who has carved his own niche in cancer research by doing just that. Cepek is an engineer who has brought a different perspective to the challenges facing the researchers he works with, and to help find new solutions for patients.

That's what happened shorty after Cepek joined the lab of Dr. Aaron Fenster as a PhD student in 2010. There was an ongoing clinical trial for MRI-guided focal therapy for prostate cancer underway in Toronto, but there were difficulties in trying to guide needles to the patient's prostate within an MRI scanner. "It is very difficult because there's not a lot of room to work and you have to take the patient in and out of the scanner to insert the needle. We wanted to develop something that would help them to do this more accurately and to make it more repeatable." (for more information on the trial, see story on page 27).

The task started with a challenge from Dr. Fenster. "He told me I had to come up with something to make this better for patients. And then I had to, over a couple of years, define the problem and come up with a device."

The result was an improvement in hardware – a more stable platform that allows the needle to be precisely aligned with and guided along a desired path through the tissue. From a patient perspective this means better treatment in less time with fewer side effects. "The aim is to give them the treatment they need without unnecessary side effects, reducing the worry that their cancer is still growing."

Cepek collaborated with the doctors running the trial in Toronto, who liked what he came up with, and modified it to suit their clinical workflow. "Now that we have used it in patients we are getting better at predicting which patients we can and cannot treat with this technique, and increasing our confidence in measuring how good of a job we are doing."

Cepek did not always plan to work in cancer research. As an undergrad he wrote computer code for fluid simulations, eventually completing a Master's degree in computational fluid dynamics. He quickly found it wasn't for him, but was inspired by his supervisor, who allowed him to work very independently. It was that self-directed research that became formative in his future approach. "If you can't change the question, or evolve the question that you are asking, then you may end up asking the wrong question. I think you have to continually have the freedom to evolve your approaches and pursue what is currently the most critical problem."

But he found that the problems he was solving as a mechanical engineer were industrial and really didn't motivate him. "I enjoyed the work but the end point was just not as impactful as I wanted it to be." He heard about a position in Dr. Fenster's lab. "It combined my interests in mechanical engineering and mechatronics with a problem that affects everyone in terms of quality of life. It was in line with my own skills and in an area I wanted to learn more about – imaging. It was a natural, exciting choice for me."

He says he's a little bit of a black sheep in the lab because he's working on device development and mechatronics – something he sees as more of an opportunity than a drawback. Cepek's goal is to continue to do research while also becoming a clinician, a position he hopes he could use to bridge the gap he sees between the engineering and medical worlds. He recently completed his PhD and is now starting medical school. "There are not a lot of engineers in the medical field. The problem is that physicians don't always know what is possible or how to define what they need and they aren't always sure how we can help them."

He's also using the feedback from the trial to develop a second generation of the device, and hopefully prepare for a Phase II trial. "I know that there is such a huge amount of work that still needs to be done. I am far more aware now of the difficulties in solving these problems. But the challenges are really what drive you to develop new and better solutions." •

Cepek developed a new piece of technology that better guides needles used in the treatment of prostate cancer so that patients receive better treatment in less time with fewer side effects.

DEFINITION

- **MRI-guided focal laser ablation**
  Focal laser ablation uses precisely targeted heat to eradicate cancerous cells in the prostate. The heat is delivered through a small needle and guided into the prostate using magnetic resonance imaging (MRI). It is designed to treat a smaller portion of the prostate rather than the whole gland, thus reducing side effects.

FINANCIAL STATEMENTS

Independent Auditors' Report

To the Members of the Ontario Institute for Cancer Research

The accompanying summarized financial statements, which comprise the summarized statement of financial position as at March 31, 2014 and the summarized statements of operations and changes in net assets and cash flows for the year then ended, are derived from the audited financial statements of the Ontario Institute for Cancer Research as at and for the year ended March 31, 2014. We expressed an unqualified audit opinion on those financial statements in our auditors' report dated June 26, 2014.

The summarized financial statements do not contain all the disclosures required by Canadian accounting standards for not-for-profit organizations applied in the preparation of the audited financial statements of the Ontario Institute for Cancer Research. Reading the summarized financial statements, therefore, is not a substitute for reading the audited financial statements of the Ontario Institute for Cancer Research.

Management's responsibility for the summarized financial statements
Management is responsible for the preparation of the summarized financial statements in accordance with Canadian accounting standards for not-for-profit organizations.

Auditors' responsibility
Our responsibility is to express an opinion on the summarized financial statements based on our procedures, which were conducted in accordance with Canadian Auditing Standards 810, "Engagements to Report on Summary Financial Statements".

Opinion
In our opinion, the summarized financial statements derived from the audited financial statements of the Ontario Institute for Cancer Research as at March 31, 2014 and for the year then ended are a fair summary of those financial statements in accordance with Canadian accounting standards for not-for-profit organizations.

Ernst & Young LLP

Chartered Accountants
Licensed Public Accountants
Toronto, Canada
June 26, 2014

A copy of the complete audited financial statements is available upon request.

Statement of Financial Position

Excerpt from the audited financial statements.

	2014	2013
Assets		
Current		
Cash	**$ 11,960,910**	$ 24,472,226
Restricted cash and cash equivalents	**4,909,861**	4,850,219
Accounts receivable	**5,201,041**	4,258,336
Supplies	**519,140**	834,500
Prepaid expenses	**2,062,204**	2,307,201
Current portion of deferred lease expense	**124,848**	124,848
Total current assets	**24,778,004**	36,847,330
Long-term portion of prepaid expenses	**1,171,379**	706,968
Deferred lease expense	**72,830**	197,678
Capital assets, net	**34,291,904**	24,399,183
Note receivable	**378,274**	446,602
	$ 60,692,391	$ 62,597,761
Liabilities, Deferred Contributions and Net Assets		
Liabilities		
Current		
Accounts payable and accrued liabilities	**$ 9,324,479**	$ 9,231,656
Unearned rental revenue	**94,179**	–
Term loan	**390,000**	460,000
Total current liabilities	**9,808,658**	9,691,656
Deferred contributions	**12,245,748**	24,565,111
Deferred capital contributions	**34,291,904**	24,399,183
	56,346,310	58,655,950
Commitments		
Net Assets	**4,346,081**	3,941,811
	$ 60,692,391	$ 62,597,761

Statement of Operations and Changes in Net Assets

Excerpt from the audited financial statements.

Year ended March 31	Cancer Research Program	External Grants Program	2014	2013
Revenue				
Grant from Ministry of Research and Innovation	$ 81,408,185	$ –	$ 81,408,185	$ 84,164,759
Other grants	1,606,809	10,412,874	12,019,683	12,278,681
Rent	1,251,849	–	1,251,849	1,251,703
Fees, workshops and other income	551,674	5,824	557,498	362,507
	$ 84,818,517	$ 10,418,698	$ 95,237,215	$ 98,057,650
Expenses				
Investigator and research support	$ 34,086,512	$ 4,706,548	$ 38,793,060	$ 45,738,098
Salaries and benefits	28,091,339	2,734,390	30,825,729	28,780,329
Amortization of capital assets	7,043,331	1,613,688	8,657,019	8,968,802
Rent, utilities, taxes and building maintenance	6,393,497	–	6,393,497	5,584,500
Maintenance, office and general	4,017,953	298,800	4,316,753	3,731,312
Information system support	1,224,200	206,844	1,431,044	1,798,645
Contracted services	2,502,267	775,668	3,277,935	1,959,784
Professional fees	523,856	3,950	527,806	735,304
Workshops and conferences	275,969	10,541	286,510	337,764
Marketing and communications	255,323	68,269	323,592	280,572
	$ 84,414,247	$ 10,418,698	$ 94,832,945	$ 97,915,110
Excess of revenue over expenses	404,270	–	404,270	142,540
Net assets, beginning of year	3,941,811	–	3,941,811	3,799,271
Net assets, end of year	$ 4,346,081	$ –	$ 4,346,081	$ 3,941,811

Statement of Cash Flows

Excerpt from the audited financial statements.

Year ended March 31		2014		2013
Operating Activities				
Excess of revenue over expenses	**$**	**404,270**	$	142,540
Add items not involving cash				
Amortization		**8,657,019**		8,968,802
Decrease in deferred lease expense		**124,848**		124,848
		9,186,137		9,236,190
Changes in non-cash balances related to operations				
Restricted cash and cash equivalents		**(59,642)**		(575,219)
Accounts receivable		**(942,705)**		315,409
Supplies		**315,360**		(104,754)
Prepaid expenses		**(219,414)**		17,862
Accounts payable and accrued liabilities		**92,823**		(1,468,445)
Unearned rental revenue		**94,179**		(4,255)
Deferred contributions (net)		**(2,426,642)**		11,350,123
Cash provided by operating activities	**$**	**6,040,096**	$	18,766,911
Investing Activities				
Purchase of capital assets		**(18,817,072)**		(7,943,592)
Proceeds on disposal of capital assets		**267,332**		638,067
Repayment of note receivable		**68,328**		37,894
Cash used in investing activities	**$**	**(18,481,412)**	$	(7,267,631)
Financing Activities				
Repayment of term loan		**(70,000)**		(40,000)
Cash used in financing activities		**(70,000)**		(40,000)
Net increase (decrease) in cash during the year		**(12,511,316)**		11,459,280
Cash, beginning of year		**24,472,226**		13,012,946
Cash, end of year	**$**	**11,960,910**	$	24,472,226

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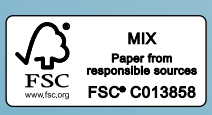

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(13 tons of wood)

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