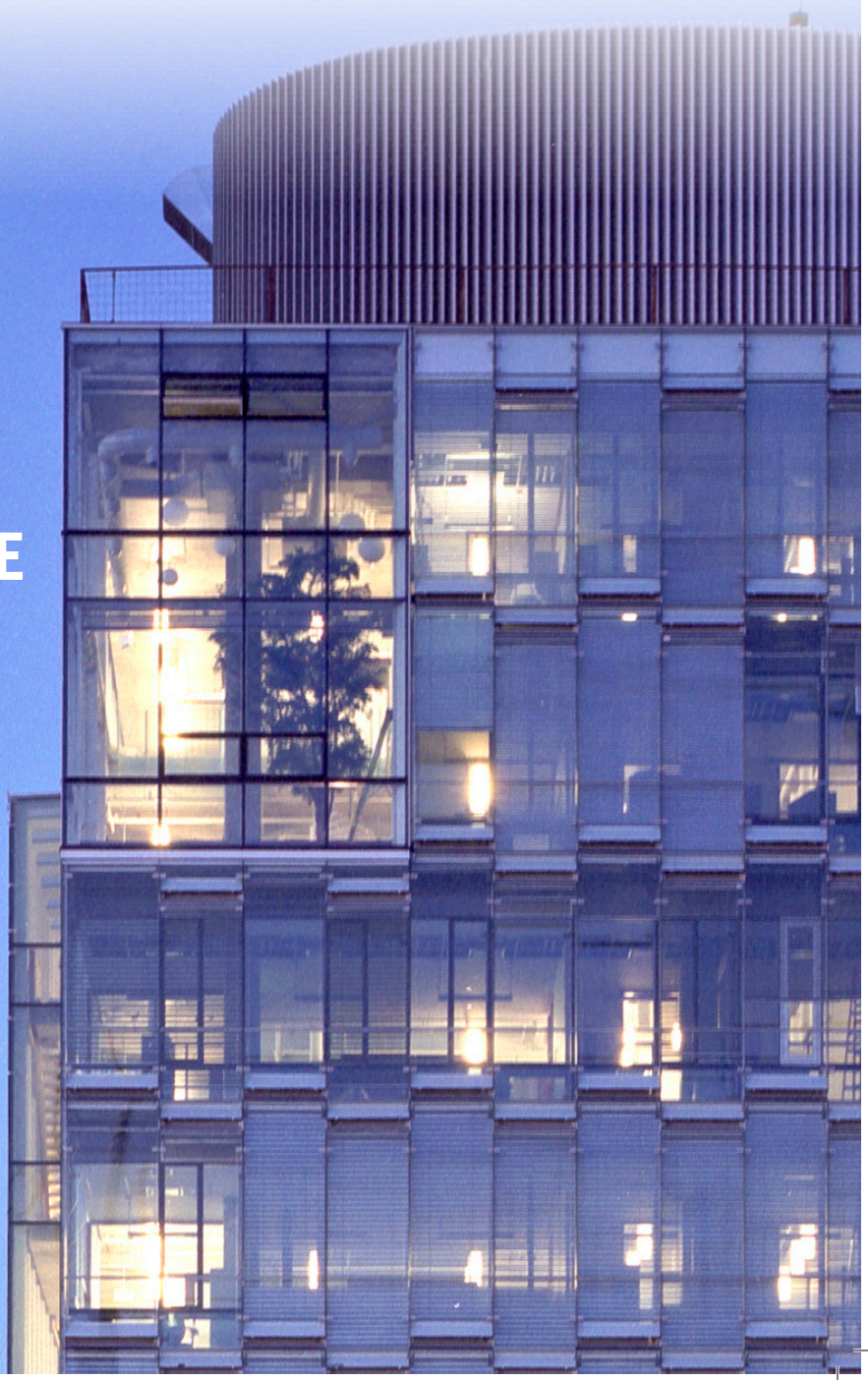
Donnelly Centre
for Cellular + Biomolecular Research
UNIVERSITY OF TORONTO

UNIVERSITY OF
TORONTO

DONNELLY CENTRE ANNUAL REPORT 2017



Founded in 2005, Donnelly Centre for Cellular and Biomolecular Research is an interdisciplinary biomedical research institute at the University of Toronto.

With this report, we would like to extend a warm thank you to our visionary donor Terrence Donnelly on another generous gift which will ensure that Donnelly Centre researchers continue to unlock secrets of the living world and make discoveries that have the potential to improve lives.

Table of Contents:

OUR RESEARCHERS GLEANED NEW INSIGHTS THAT COULD IMPROVE LIVES AND HEALTH FOR ALL CANADIANS

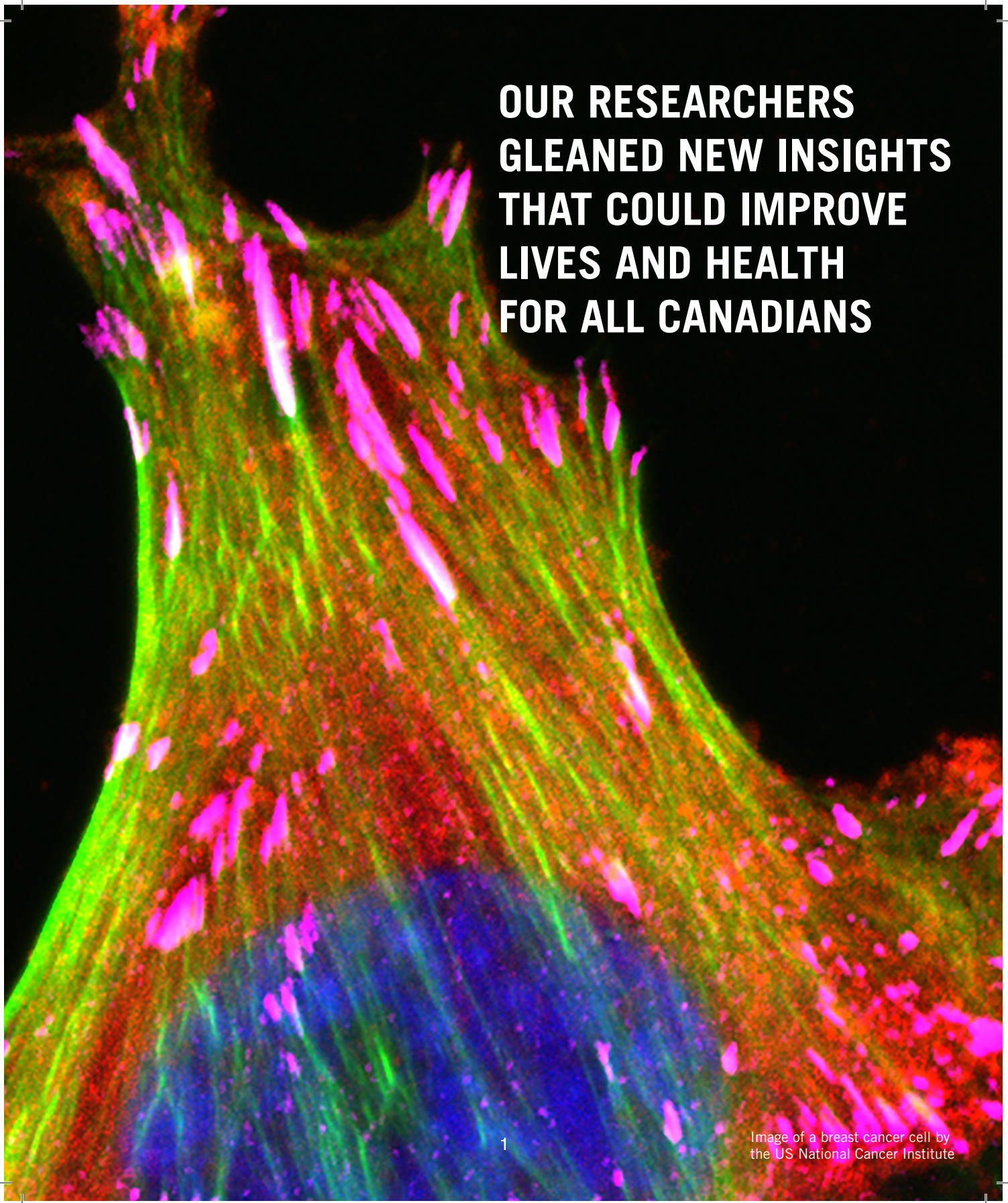


Image of a breast cancer cell by the US National Cancer Institute

Deep Learning Helps Scientists Keep Track of Cell's Inner Parts

By Jovana Drinjakovic
May 2, 2017.

Scientists have developed a deep learning algorithm that can track proteins, to help reveal what makes cells healthy and what goes wrong in disease.

"We can learn so much by looking at images of cells: how does the protein look under normal conditions and do they look different in cells that carry genetic mutations or when we expose cells to drugs or other chemical reagents? People have tried to manually assess what's going on with their data but that takes a lot of time," says **Benjamin Grys**, a graduate student in molecular genetics and a co-author on the study.

Dubbed DeepLoc, the algorithm can recognize patterns in the cell made by proteins better and much faster than the human eye or previous computer vision-based approaches. In the cover story of this month's issue of *Molecular Systems Biology*, teams led by Professors **Brenda Andrews** and **Charles Boone** of the Donnelly Centre for Cellular and Biomolecular Research and Department of Molecular Genetics, also describe DeepLoc's ability to process images from other labs, illustrating its potential for wider use.

From self-driving cars to computers that can diagnose cancer, artificial intelligence (AI) is shaping the world in ways that are hard to predict, but for cell

biologists, the change could not come soon enough. Thanks to new and fully automated microscopes, scientists can collect reams of data faster than they can analyze it.

"Deep learning will ultimately bring the timescale of this analysis down to the same timescale as the experiments"

"Right now, it only takes days to weeks to acquire images of cells and months to years to analyze them. Deep learning will ultimately bring the timescale of this analysis down to the same timescale as the experiments," says **Oren Kraus**, a lead co-author on the paper and a graduate student co-supervised by Andrews and Professor **Brendan Frey** of the Donnelly Centre and the Department of Electrical and Computer Engineering. Andrews, Boone and Frey are also Senior Fellows at the Canadian Institute for Advanced Research.

Similar to other types of AI, in which computers learn to recognize patterns in data, DeepLoc was trained to recognize diverse shapes made by glowing proteins—labeled a fluorescent tag that makes them visible—in cells. But unlike computer vision that requires detailed instructions, DeepLoc learns directly from image pixel data, making it more accurate and faster.

Grys and Kraus trained DeepLoc on the teams' previously published data that shows an area in the cell occupied by more than 4,000 yeast proteins—three quarters of all proteins in yeast. This dataset remains the most complete map showing exact position for a vast majority of proteins in any cell. When it was first released in 2015, the analysis was done with a complex computer vision and machine learning pipeline that took months to complete. DeepLoc crunched the data in a matter of hours.

DeepLoc was able to spot subtle differences between similar images. The initial analysis identified 15 different classes of proteins, each representing distinct neighbourhoods in the cell; DeepLoc identified 22 classes. It was also able to sort cells whose shape changed due to a hormone treatment, a task that the previous pipeline couldn't complete. Grys and Kraus were able to quickly retrain DeepLoc with images that differed from the original training set, showing that it can be used to process data from other labs. They hope that others in the field, where looking at images by eye is still the norm, will adopt their method.

"Someone with some coding experience could implement our method. All they would have to do is feed in the image training set that we've provided and supplement this with their own data. It takes only an hour or less to retrain DeepLoc and then begin your analysis," says Grys.

In addition to sharing DeepLoc with the research community, Kraus is working with **Jimmy Ba** to commercialize the method through a new start-up, Phenomic AI. Ba is a graduate student of AI pioneer **Geoffrey Hinton**, a retired U of T professor and Chief Scientific Adviser of the newly established Vector Institute. Their goal is to analyse cell image-based data for pharmaceutical companies.

"In an image based drug screen, you can actually figure out how the drugs are affecting different cells based on how they look rather than some simplified parameters such as live/dead or cell size. This way you can extract a lot more information about cell state form these screens. We hope to make the early drug discovery process all the more accurate by finding more subtle effects of chemical compounds," says Kraus.

Scientists Enlist Engineered Protein to Battle MERS Virus

By Jovana Drinjakovic
May 19, 2017.

In June 2012, a 60 year-old man with flu-like symptoms walked into a private hospital in Jeddah, Saudi Arabia. Two weeks later, he died from multiple organ failure, becoming the first victim of a mysterious virus that came to be known as Middle East Respiratory Syndrome or MERS.

The World Health Organization (WHO) has identified MERS as an urgent threat with no vaccine or treatment in sight. This could change thanks to a new anti-viral tool, developed by University of Toronto researchers.

Writing in the journal *PLoS Pathogens*, the team led by Professor **Sachdev Sidhu**, of the Donnelly Centre for Cellular and Biomolecular Research and Department of Molecular Genetics, describe how they turned ubiquitin, a staple protein in every cell, into a drug capable of thwarting MERS in cultured human cells. Because the technology can be applied to a wide range of pathogens, it could become a game-changer in anti-viral therapeutics with implications for human health and the farming industry.

"Vaccines are important for prevention, but there is a great need for anti-viral medicines to treat people who have become infected," says Dr. **Wei Zhang**, a postdoctoral research fellow in Sidhu's lab who did most of the work on the study.

MERS is similar to SARS, the virus that killed almost

800 people in a 2002 global epidemic. Both kill upwards of a third of people infected and, like many viruses, emerged from animals—bats and camels in the case of MERS—after mutating into a form capable of infecting human cells. Although MERS has so far been detected in 27 countries since the first case emerged in 2012, the outbreak has largely been contained within Saudi Arabia, according to the WHO.

"Viruses have evolved proteins that allow them to hijack host proteins. We can now devise strategies to prevent this from happening"

Like many viruses, MERS works by hijacking the ubiquitin system in human cells composed of hundreds of proteins that rely on ubiquitin to keep the cells alive and well. Upon infection, viral enzymes alter ubiquitin pathways in a way that allows the virus to evade the immune defense while multiplying and destroying the host tissue as it spreads in the body. "Viruses have evolved proteins that allow them to hijack host proteins. We can now devise strategies to prevent this from happening," says Zhang.

Zhang and colleagues engineered the human ubiquitin protein into a new form that paralyses a key MERS enzyme, stopping the virus from replicating. These synthetic ubiquitin variants act quickly, completely eliminating MERS from cells in a dish within 24 hours.

The researchers also created UbVs that blocks the Crimean-Congo virus, the cause of a haemorrhagic fever that kills about 40 per cent of those infected. And they're designed to only target only the virus — hopefully minimizing side effects in any future drug.

But before these engineered proteins can be developed into medicine, researchers first must find a way to deliver them into the right part of the body. For this, Zhang and Sidhu are working with Dr. **Roman Melnyk**, a biochemist in The Hospital for Sick Children in Toronto and a world expert in protein delivery.

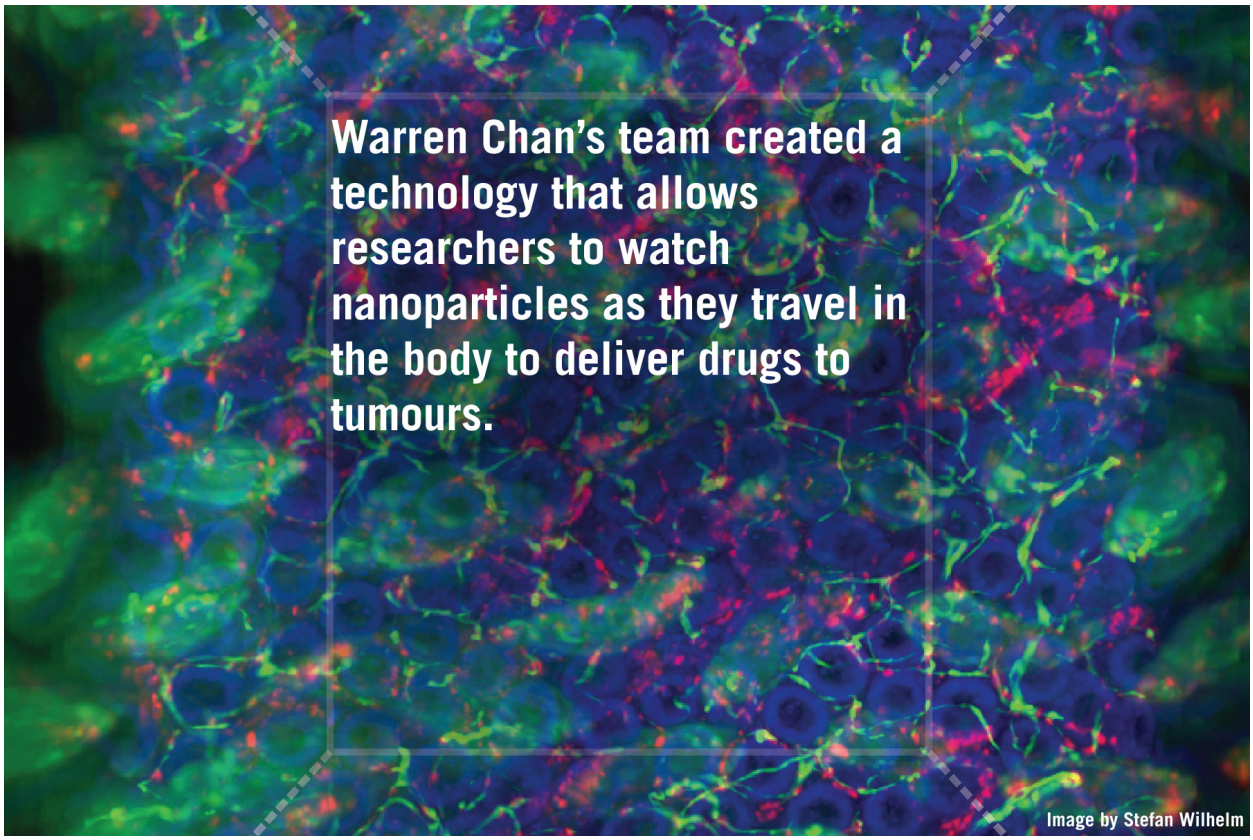
The team is also investigating the possibility of finding drugs that work in a similar manner but can already cross the cell membrane.

It is likely that the proteins will be tested first in plants and animals where regulatory approvals are less strict than they are for human drugs. "We are also working on an engineered ubiquitin that targets a corn virus responsible for destroying large swaths of corn fields in North America, with colleagues in Manitoba," says Zhang.

In the meantime, Zhang will continue to improve delivery of his designer proteins to human cells that target not only MERS but also other viruses. He hopes others will follow suit.

"With our tool, we can quickly generate anti-viral medicine and we hope that our method will inspire other researchers to try it out against diverse pathogens," says Zhang.

The study was done in collaboration with Professor Marjolein Kikkert, of Leiden University Medical Centre in The Netherlands and Professor Brian Mark at the University of Manitoba.



Targeting Tumours: Researchers Investigate Biological Barriers to Nanomedicine Delivery

By Heidi Singer
August 9, 2017.

For cancer patients, understanding the odds of a treatment's success can be bewildering. The same drug, applied to the same type of cancer, might be fully successful on one person's tumour and do nothing for another one. Physicians are often unable to explain why.

Now, University of Toronto engineers are beginning to understand one of the reasons. **Abdullah Syed** and **Shrey Sindhwani**, both PhD candidates at U of T's Institute of Biomaterials & Biomedical Engineering (IBBME) and their colleagues have created a technology to watch nanoparticles traveling into tumours — revealing barriers that prevent their delivery to targets and the variability between cancers.

"The biggest thing we've noticed is that nanoparticles face multiple challenges posed by the tumour itself on their way to cancer cells," says Sindhwani, an MD-PhD student in the Integrated Nanotechnology & Biomedical Sciences Laboratory of Professor **Warren Chan** at the Donnelly Centre for Cellular and Biomolecular Research and IBBME. Syed and Sindhwani co-published their findings online June 22, and on the cover of the *Journal of the American Chemical Society*. "So the treatment might work for a while — or worse, there's just enough of the drug

for the cancer to develop resistance. This could be prevented if we can figure out the ways in which these barriers stop delivery and distribution of the drug throughout the cancer."

Tiny "nanoparticles" offer great hope for the treatment of cancer and other disease because of their potential to deliver drugs to targeted areas in the body, allowing more precise treatments with fewer side effects. But so far the technology hasn't lived up to its promise, due to delivery and penetration problems.

"Once we understand barriers that don't allow drugs to reach their disease site, we can start knocking them down and improving patient health"

To dismantle this roadblock, the two graduate students searched for a way to better view the particle's journey inside tumours. They discovered that the tough-to-see particles could be illuminated by scattering light off their surfaces.

"The sensitivity of our imaging is about 1.4 millionfold higher," says Syed. "First, we make the tissue transparent, then we use the signal coming from the particles to locate them. We shine a light on the particles and it scatters the light. We capture this scattering light to learn the precise location of the nanoparticles."

It was already understood that nanoparticles were failing to accumulate in tumours, thanks to a meta-analysis of the field done by Chan's group. But the researchers have developed technologies to look at nanoparticle distribution in 3D, which provides a much fuller picture of how the particles are interacting with the rest of the tumour biology. "The goal is to use this technology to gather knowledge for developing mathematical principles of nanoparticle distribution in cancer, similar to the way principles exist for understanding the function of the heart," says Syed.

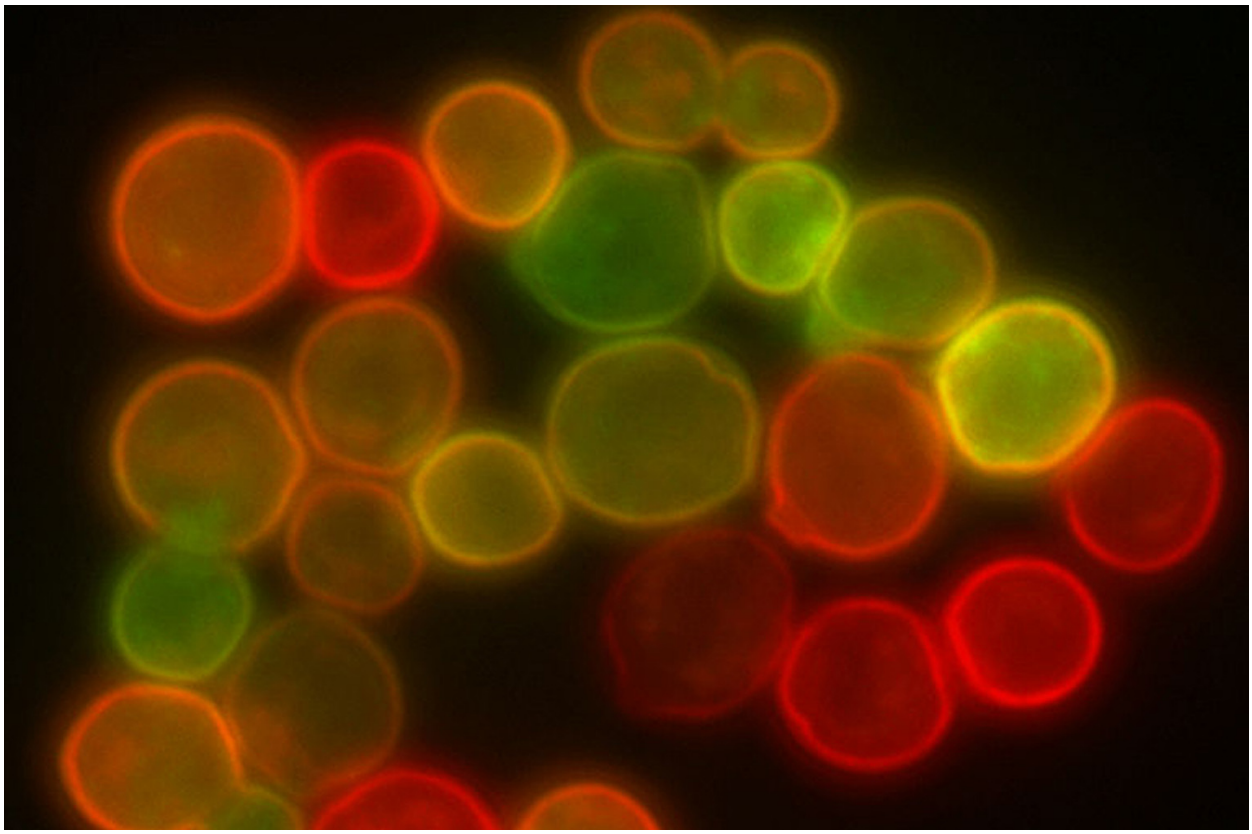
And because each tumour is unique, this technology and knowledge base should help future scientists to understand the barriers to drug delivery on a personalized basis, and to develop custom treatments.

The next step is to understand what in cancer's biology stops particles from fully penetrating tumours — and then to develop ways to bypass cancer's defences.

But the technology is also useful for diseases other than cancer. With the help of Professor Jennifer Gommerman, an researcher in the Department of Immunology who studies multiple sclerosis (MS), Syed and Sindhwani captured 3D images of lesions in a mouse model mimicking MS using nanoparticles.

"This is going to be very valuable to anyone trying to understand disease or the organ system more deeply," says Sindhwani. "And once we understand barriers that don't allow drugs to reach their disease site, we can start knocking them down and improving patient health" adds Syed.

This story first appeared in *U of T medicine News*.



Baker's Yeast Helps Researchers Find New Medicines

By Jovana Drinjakovic
July 17, 2017.

A team of Canadian, US and Japanese scientists turned to baker's yeast in a hunt for better drugs.

One of the hardest parts in drug discovery is pinning down how a medicine actually works in the body. It took nearly 100 years to uncover the molecular target of aspirin, but even with cutting-edge technology, it can take years to untangle how drugs interfere with cells. And yet, to develop medicines that target disease effectively and are safe —with no side effects—these molecular insights are key.

Now a new method developed by Donnelly Centre researchers and international collaborators has the potential to accelerate target discovery with help from yeast cells, which are a simpler version of human cells but far better known at the molecular level.

Teams led by Professors **Charles Boone**, a professor of molecular genetics in U of T's Donnelly Centre for Cellular and Biomolecular Research, **Chad Myers**, of the University of Minnesota-Twin Cities, and Professors **Minoru Yoshida** and **Hiroyuki Osada**, from the RIKEN Centre for Sustainable Resource Science in Japan, developed a new chemical genetics approach to link a drug to a cellular process it acts on.

Boone and Myers are also fellows at the Canadian Institute for Advanced Research, where Boone is a Senior Fellow and co-Director of the Genetics Networks program.

The study, published on July 17 in the journal *Nature Chemical Biology*, tested how nearly 14,000 compounds, hundreds of which were previously unexplored, affect basic cellular processes to alert drug makers towards chemicals that are most likely to target a particular disease. The data pointed to ~1000 chemicals, many of which are natural products derived from soil microbes, as a rich source of potential medicines against a range of diseases, from infections, to Alzheimer's and cancer.

"It's long been thought that natural products are more functionally diverse, that they can do more things than purely synthetized compounds and that certainly seems to be true from our data"

Despite modern technology, drug discovery still largely rests on guesswork. To find a drug that, say, kills cancer cells, scientists sift through libraries containing thousands of chemical compounds, the majority of which will have no effect at all.

"There are many different types of libraries to choose from. A lot of the time you choose a library based on its availability or its cost, not any sort of functional information, and so it becomes a shot in the dark," says **Jeff Piotrowski**, a lead author on the paper who was a postdoctoral fellow in both the Yoshida and Boone labs and now works at the Boston biotechnology company, Yumanity Therapeutics, which uses yeast cells to find drugs for neurodegenerative diseases.

With their chemical genetics platform, Piotrowski and colleagues were able to show which parts of the cell are targeted by thousands of compounds from seven different libraries, six of which have been extensively explored and include collections from the U.S. National Cancer Institute, the National Institute of Health and the pharmaceutical company Glaxo-Smith-Kline. The seventh and largest collection, from RIKEN in Japan, harbors thousands of virtually unexplored natural products from soil microbes.

Yeasts are currently the only living organism in which scientists have a good handle on the basic cellular processes, such as DNA replication and repair, energy production, and transport of cargo molecules, allowing them to link a drug to a particular bioprocess.

"By annotating these libraries, we can tell which library targets which bioprocess in the cell. It gives us a head start on linking a compound to a target, which is perhaps the most challenging part of drug discovery," says Piotrowski.

The data revealed, for example, that the RIKEN library contains compounds that act in many different ways: from microbe-fighting chemicals that could be used to treat infections, to drugs that target cellular trafficking that is implicated in Alzheimer's and Parkinson's diseases, to those that interfere with cell replication and might be used against cancer. In fact, the RIKEN library turned out to have many novel compounds with anticancer potential.

"It's long been thought that natural products are more functionally diverse, that they can do more things than purely synthetized compounds and that certainly seems to be true from our data," says Boone.

And because natural compounds were shaped by evolution to act on living organisms, they are better candidates for future medicines than synthetic compounds that often do not even get into the cells. It' not surprising then that from aspirin to penicillin, to the blockbuster cancer drug taxol, some of our best medicines we have come from nature.

The data also revealed chemicals that influence more than one process in the cell. These compounds are more likely to cause side effects and are best avoided. "With our map, we can see these promiscuous

compounds earlier and focus on the good ones," says Piotrowski.

The study was possible thanks to an earlier work by Boone, Myers, and Professor **Brenda Andrews,** the director of the Donnelly Centre, that mapped out how thousands of genes interact with each other to drive fundamental processes in the cell. The basic premise here was that removing one gene might not do anything because there's a backup system in place, but removing two genes leads to a profound effect. It's a bit like playing pick-up sticks where removing one stick at a time has no effect, but removing two together brings the pile down, or makes it stronger.

Instead of looking at double mutants, the present study measured how single mutants combined with drugs to influence the cells' wellbeing. This then allowed researchers to identify which bioprocess is affected by a particular drug, thereby identifying the drug's mode of action. The beauty of the system employed by this international, multidisciplinary research team was that it integrates all genes within the same assay to assess the behavior of the entire genome in response to a particular drug in one experiment.

The Best Place to Treat Type 1 Diabetes Might be Just Under Your Skin

By Luke Ng
August 15, 2017.

A group of U of T researchers have demonstrated that the space under our skin might be an optimal location to treat type 1 diabetes (T1D).

The new study, led by researchers from the Donnelly Centre for Cellular and Biomolecular Research and the Institute of Biomaterials & Biomedical Engineering (IBBME), involved transplanting healthy pancreatic cells under the skin to produce insulin for blood glucose regulation.

"The skin has the advantage of being readily accessible," said **Michael Sefton**, University Professor and senior researcher of the study published today in the *Proceedings of the National Academy of Sciences* (PNAS). "It is also presents fewer hazards than other transplantation sites."

In persons with T1D, insulin-producing beta cells, located in regions of the pancreas known as pancreatic islets, are damaged. Implanting healthy new cells could restore insulin function, but it's hard to get them in the right place.

"Pancreatic islets are scattered throughout the pancreas in between other pancreatic cells that secrete digestive enzymes," said **Alexander Vlahos**, the lead author of this study and a PhD candidate

in IBBME. “This makes it impractical to try and deliver islets to the pancreas: you would most likely be delivering it to a region of the pancreas that is secreting these enzymes.”

Other sites such as the abdominal cavity and liver aren’t much better: they are considered “hostile” environments that can damage the new cells, resulting in loss of function.

“The accessible location of the skin makes islet transplantation a lot more manageable, especially if the patient responds negatively to the donor cells,” said Vlahos. “The space under the skin has a large area so that it can support many islets, which is necessary for this approach.”

Vlahos pursued the idea of transplanting pancreatic islets under the skin because the current method of implanting into the liver requires too many donor cells.

“You need to overshoot the quantity of islets when injecting into the liver because you lose about 60 per cent of the transplanted cells within the first 48 hours,” said Vlahos. “That amount of islets requires two to three donors for each recipient.”

In his tests, Vlahos injected healthy pancreatic islets under the skin and found that normal blood sugar levels could be restored within 21 days, provided he created blood vessels at the same time. When the islet transplants were removed, glucose levels returned to diabetic levels.

However, Vlahos believes that these results mark only the beginning of a bigger picture.

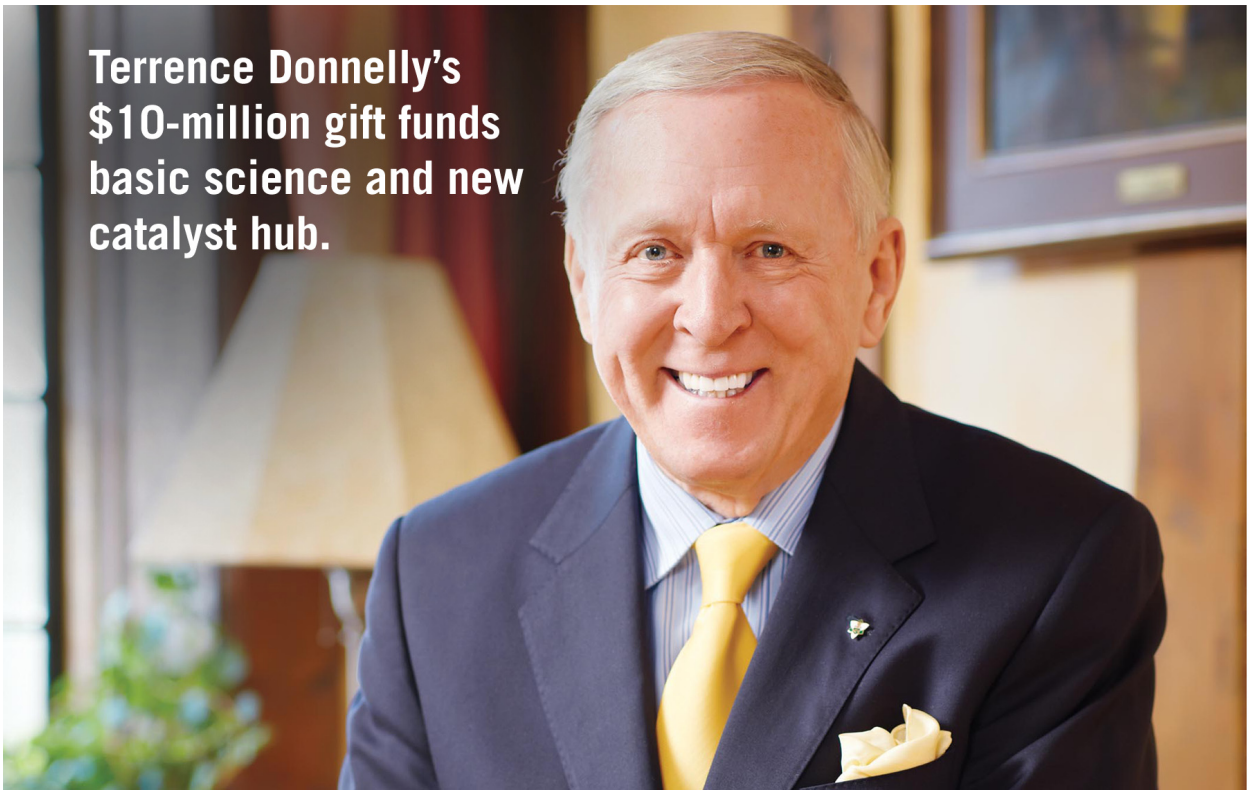
“Pancreatic islets comprise approximately one per cent of the pancreas, but require 15 to 20 per cent of the blood flow to the organ,” said Vlahos. “We needed to ensure adequate blood flow to the islets in order for this to work.”

“The next phase of our research will involve engineering the blood vessel network first and then injecting fewer islets into the already vascularized tissue ,” said Sefton. “A well-vascularized environment will allow more of the cells to survive and function within the host, reducing the need for multiple donors per patient.”

Earlier results of this work provided the basis for a successful proposal for $1.1 million from international diabetes foundation JDRF to support the next phase of this research.

“The accessible location of the skin makes islet transplantation a lot more manageable, especially if the patient responds negatively to the donor cells”


THANKS TO OUR GENEROUS DONOR, TERRENCE DONNELLY, AND COMPETITIVE RESEARCH GRANTS, OUR RESEARCHERS CONTINUE TO ADDRESS BIG QUESTIONS IN BIOLOGY



Terrence Donnelly's $10-Million Gift Funds Basic Science, New Catalyst Hub

By Anjali Baichwal
October 17, 2017.

Terrence Donnelly has made a $10-million gift to fund basic science at U of T and create a "catalyst hub" for scientists at the Donnelly Centre for Cellular and Biomolecular Research. The donation is Donnelly's third major commitment to U of T, and completes an arc of strategic giving that boosts U of T's capacity and reputation as an international leader in research and teaching in health care and basic science.

Donnelly is one of U of T's most generous donors, whose visionary philanthropy has had deep impact in the basic sciences. His initial investment commitment in 2002 helped build U of T's Donnelly Centre, a 13-storey powerhouse of scientific discovery, with world-class researchers working at the intersection of biology, computer science, engineering, chemistry and pharmacy.

In 2011, he made another transformational gift to help build the Terrence Donnelly Health Sciences Complex at U of T Mississauga, which houses the Mississauga Academy of Medicine, and where 54 new undergraduate medical students are admitted every year, graduating 216 new doctors each cohort.

His latest gift to the Donnelly Centre follows his belief that fundamental research is the best way for researchers to work together from a variety of fields to decipher the biology behind the world's most devastating diseases.

"We need basic research to eliminate disease," says Donnelly. "To do that we have to have a constant stream of educated Canadians and people from around the world to keep pushing the envelope in research. That's what led me to my third part of this gift."

"More research is needed to discover the causes of disease and to learn how we can prevent people from getting sick. Basic research is the only way we will be able to achieve this"

Donnelly, 83, says he has been blessed with good health his whole life. "It's the greatest treasure anyone can have," he says. As a result, he has dedicated his philanthropy to helping those, who through no fault of their own, have not been fortunate to enjoy the same.

"This latest gift is to enhance the capacity of the Donnelly Centre to recruit top researchers from around the world, who have the ability to make a contribution in the struggle to eliminate diseases that plague mankind," says Donnelly. "My goal is to try, with my limited resources and whatever time I have, to make a difference in the lives of people who do not have good health."

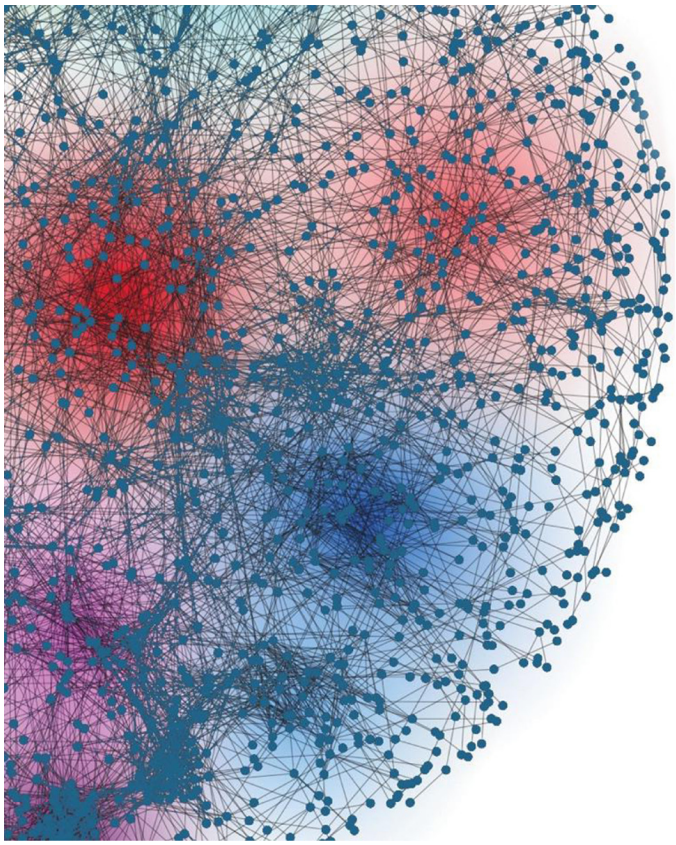
Brenda Andrews, the director of the Donnelly Centre, says Donnelly was also compelled to make this latest gift by the progress and success the Donnelly Centre has enjoyed over the past 10 years. "Donnelly Centre research has attracted a fair amount of attention from various private sector partners and biotech industries," she says. "That success means that we are at a point where some of our platforms are mature enough that we need more room to accommodate even more research activity."

Accordingly, Donnelly's gift will help relocate some of the Donnelly Centre's existing platforms and activities to a new space where they can forge even stronger links to industry. "This additional space will allow scientists from companies to intermingle with scientists from the academic side of the research program," says Andrews. "This will help us catalyze innovation and provide our students with hands-on experience with the biotechnology sector."

Donnelly's gift will also establish a fund within the Donnelly Centre that the director can use – unrestricted – to support the top priorities of the Centre. Andrews says this is a remarkable aspect of the gift because it provides freedom for the Donnelly Centre and its scientists to decide what research directions it wants to follow. "This kind of funding, particularly in today's granting environment, is something that will really help us stay at the leading edge of research and enhance our ability to attract the most sought-after trainees and scientists in the world."

Those researchers are quite familiar with their benefactor. In fact, Donnelly knows nearly all of them by face, if not by name. That's because Donnelly is a regular visitor to the Centre, avidly seeking out scientists and students to learn more about their research. "He's an integral part of the centre, and he's very interested in talking to any student, fellows, to find out what they're doing," says Andrews. "It's very inspiring for the students and researchers to see his enthusiasm and interest in their research and in basic science."

Donnelly says supporting research at the Donnelly Centre is the best investment he's ever made in his life. "I am very proud of what the Donnelly Centre researchers have done in the past 10 years and excited about what they'll do in the coming decades," he says. "More research is needed to discover the causes of disease and to learn how we can prevent people from getting sick. Basic research is the only way we will be able to achieve this. I believe my investments will not only transform health care but inspire others who have the opportunity to do the same."



Collaborative research led by Brenda Andrews gets a $2.76M boost from the federal government to help realize the potential of personalized medicine.

Image by Donnelly Centre

New Funding to Help Set the Stage for Personalized Medicine

By Jovana Drinjakovic
October 13, 2017.

An inter-disciplinary team of researchers led by **Brenda Andrews**, University Professor and director of the Donnelly Centre for Cellular and Biomolecular Research, has been awarded funding from the Canada Foundation for Innovation (CFI) for research that may one day allow to predict with confidence a person's risk of disease and tailor treatment based on their genetic makeup. The $2.76 million Innovation Fund grant will go towards building new technology for shedding light on how genes work together as part of a network to influence health of an organism.

"Our goal is to accelerate the important transition from basic cataloguing of genome sequences to functional characterization of genetic variation encoded within individual genomes," says Andrews, who is also a professor in U of T's Department of Molecular Genetics. "The wealth of information that our project will generate will impact our understanding of human cell function and disease and advance strategies for personalized medicine."

Andrews' team brings together U of T experts in diverse areas of genomics and from different research institutes and departments. On the team are Professors **Ben Blencowe**, **Charlie Boone**, **Tim Hughes**, **Jason Moffat** and **Mikko Taipale** from the Donnelly Centre and, as well as Professors **Stephane Angers**,

of the Leslie Dan Faculty of Pharmacy and **Daniel Durocher**, of the Lunenfeld-Tanenbaum Research Institute at Sinai Health System in Toronto. All are also professors in the Department of Molecular Genetics. Through past collaborations, the team members have already developed technologies necessary for generating the first large-scale genetic network in human cells.

"Our goal is to accelerate the important transition from basic cataloguing of genome sequences to functional characterization of genetic variation encoded within individual genomes"

The funding was announced by Kirsty Duncan, federal minister of science, as part of an investment of more than $554 million in infrastructure projects at universities, colleges and research hospitals across Canada, according to a statement from the CFI. Overall, U of T researchers received more than $100 million for projects in diverse areas, from regenerative medicine to neuroscience and astronomy.

So far, research in human genetics has largely focused on collecting genome sequences from thousands of people in search of genetic clues of disease. But to understand how the genome impact health, it is important to study interactions between genes, which can't be gleaned from sequence data alone.

Most diseases, such as cancer or heart disease, are caused by misspellings in dozens or even hundreds of genes, each one contributing ever so slightly to the overall risk and severity of disease. At the same time, no two genomes are the same—each person carries a unique combination of misspellings in their DNA, or genetic variants, which influence health in some way.

"The onslaught of new genome sequence information has revealed a knowledge void – while most diseases are influenced by genetic variation, we do not understand how to properly interpret personal genome sequences to predict what genetic variation is linked to disease," says Andrews. "And we cannot embrace the idea of personalized medicine until we make a new leap in our understanding of human genetics."

To begin to unpick how multiple genes and their variants contribute to disease, Andrews and Boone created the first map of genetic interactions for any cell. They did this by systematically removing gene pairs from yeast cells to find the genes working together to maintain the processes in the cell.

The new funding will go towards establishing a platform for doing similar studies in human cells using the gene editing tool CRISPR. Thanks to Moffat's earlier work, a CRISPR library of "off switches" for every single human gene, is already available in the Donnelly Centre.

Medical implications of a human genetic interaction map are far-reaching. Knowing which genes work together can point to genetic variants that may fine-tune disease severity. These insights could also help develop more precise genetic tests for cancer and other common disease. And in drug discovery, distinct genetic networks of healthy and cancer cells, for example, can reveal drug targets that are unique to cancer, leading to new treatments that would not cause harm to healthy tissue.

The prospect of personalized medicine—where one's genome spells out diseases to come and calls for the right treatment—is poised to become a reality, said Andrews.

Penney Gilbert Leads International Team to Study How Physical Stress Turns on Genes in Stem Cells

By Tyler Irving and Luke Ng
May 27, 2017.

Can you activate a stem cell by squeezing it? A new international collaboration led by Professor **Penney Gilbert** aims to find out.

The researchers will study how muscle stem cells turn genes on and off in response to physical stresses that arise in response to tissue injury. Their results could lead to new treatments for genetic diseases.

"Every cell in the human body has the exact same genetic material, but our hair cells look and act very differently than the cardiac cells that pump our heart because of the way different genes are turned on in distinct cell types," says Gilbert, a principal investigator at the Donnelly Centre for Cellular and Biomolecular Research and a professor in the Institute of Biomaterials & Biomedical Engineering.

However, when the process of turning genes on or off fails, disease often ensues.

While scientists have already uncovered many of the secrets that explain how and when genes are turned on and off, most of them involve 'chemical cascades' of signaling molecules and cell receptors. Much like a Rube Goldberg Machine, where an initiating event

triggers an elaborate series of subsequent actions, these methods can take a long time to achieve the final result. Gilbert and her colleagues believe that faster methods exist. For example, under certain circumstances, physical forces — as opposed to chemical changes — could cause certain genes to become activated or deactivated.

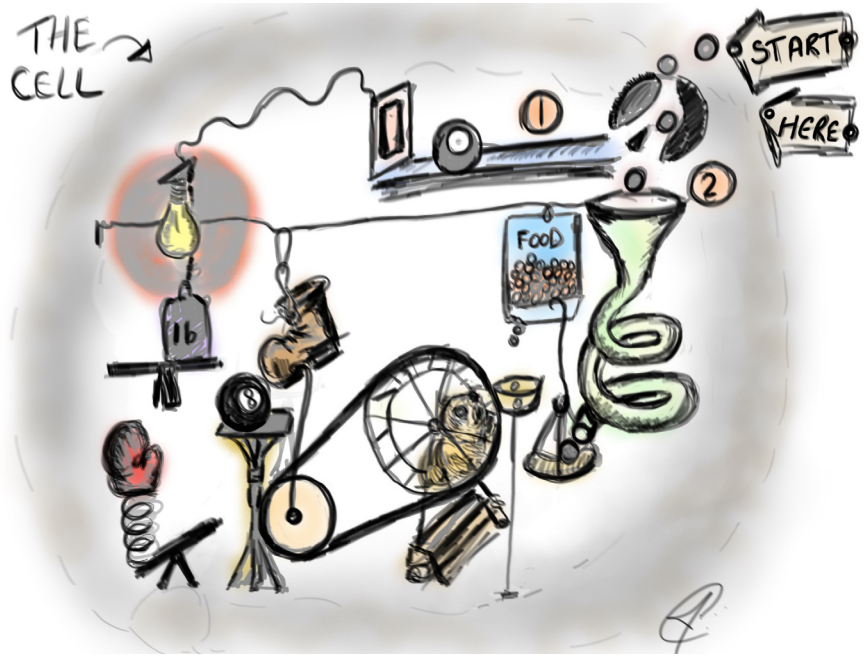
"Muscle stem cells are sprinkled within skeletal muscle tissue, and these tiny cells are first responders when this tissue becomes injured," says Gilbert. "To do their job they transition from having very few genes turned on to all of a sudden turning on lots of genes all at once." The team suspects that the trigger for this transition may be the shear, compressive and tensile stresses experienced as a result of injury to the muscle.

The new partnership is funded by a $1.4 million grant from the Human Frontier Science Program. It brings together Gilbert's expertise in muscle stem cells with advanced methods in biophysics from Professor Timo Betz at the University of Münster, as well as molecular imaging techniques developed by Professor Xavier Darzacq at the University of California, Berkeley. Together the team will comprehensively examine the ways in which muscle stem cells transmit the physical stresses they experience into changes in their DNA and gene expression.

The results of the study could provide scientists with new, non-chemical strategies for turning genes on and off, not only in muscle stem cells, but other cell types as well. This in turn could help treat genetic diseases or other conditions caused when genes fail to turn on or off in the right place or the right time.

"To nail down our idea we must work together since we each bring a different expertise to the table," adds Gilbert. "We are so grateful to HFSP for fundamental research support—they allow scientists the freedom to follow their creativity."

This story first appeared in *IBBME News*.



Much like a Rube Goldberg Machine, genes can turn on and off as a result of a series of chemical cascades downstream of an initiating event (Path 2). HFSP funding will explore whether physical forces can more directly influence gene expression (Path 1). (Maria Abou Chakra)

OUR RESEARCHERS RECEIVED AWARDS AND APPOINTMENTS TO NEW LEADERSHIP POSITIONS

Image by Calvin Thomas

Director Brenda Andrews Named University Professor

By Jovana Drinjakovic
June 5, 2017.

Brenda Andrews, director of the Donnelly Centre for Cellular and Biomolecular Research and Charles H. Best Chair of Medical Research at U of T, has been appointed to the rank of University Professor. It is U of T's highest academic rank that recognizes extraordinary scholarly achievement and pre-eminence in a particular field of knowledge and is usually awarded to no more than two per cent of the tenured faculty.

Andrews is a pioneer in the field of systems biology which aims to understand how biological entities such as cells for example, operate as a whole as opposed to studying their constituent parts in isolation as was done before. This shift was driven by technological advances with Andrews' group at the forefront—the tools developed in the lab have enabled research of cell biology on a previously unimaginable scale with an early adoption of artificial intelligence to help analyse the ensuing vast amounts of data. These studies revealed how thousands of genes work together to orchestrate cellular life and are beginning to shed light on the causes of complex genetic diseases.

In her own research and beyond, Andrews is known for championing collaboration among scientists from diverse fields. When U of T's Faculties of Medicine, Pharmacy and Engineering founded the Donnelly Centre in 2005 as an interdisciplinary hub for the

study of genome biology, Andrews was appointed Director and has been at the helm ever since.

"Brenda's extraordinary contribution to systems biology has propelled the field forward so that we can begin to address the complex relationship between genes and disease"

During this time, the Centre has become internationally recognized as a leading biomedical research institute and continues to attract competitive scientists at all stages of their careers. Before becoming director of the Donnelly Centre, Andrews was Chair of the Department of Medical Genetics (now Molecular Genetics), where she remains a professor, and Chair of Banting & Best Department of Medical Research at U of T.

In 2016, Andrews was named a Companion of the Order of Canada—the highest civilian honour in the country—for her "globally significant research in systems biology and for developing and nurturing prominent scientific communities in molecular genetics".

As a globally renowned scientist, Andrews sits on many review panels, editorial and advisory boards and is the founding editor-in-chief of the journal *Genes|Genomes|Genetics*, an open access journal of the Genetics Society of America. She is a Fellow of the Royal Society of Canada (2005), the American Association for the Advancement of Science (2011) and the American Academy of Microbiology (2012). In 2005, Andrews was the inaugural Director of the Genetic Networks Program of the Canadian Institute For Advanced Research, where she remains a Senior Fellow.

"Brenda's extraordinary contribution to systems biology has propelled the field forward so that we can begin to address the complex relationship between genes and disease," says **Trevor Young**, Dean of the Faculty of Medicine. "Thanks to her leadership in the Donnelly Centre, Toronto has become globally recognized as a leading hub for systems biology research. I congratulate her on this richly-deserved honour."

Andrews' many awards also include Ira Herskowitz Award from the Genetics Society of America (2010), the inaugural JJ Berry Smith Doctoral Supervision Award from U of T (2013), the Emil Christian Hansen Award for Microbiology from the Carlsberg Foundation (2013), and the Jeanne Manery Fisher Memorial Award from the Canadian Society for Molecular Biology (2017).

Ben Blencowe Elected Fellow of Royal Society of Canada

By Jovana Drinjakovic

Professor **Ben Blencowe** has been elected fellow of the Royal Society of Canada (RSC) in recognition of outstanding scientific achievement.

Blencowe, Principal Investigator in the Donnelly Centre for Cellular and Biomolecular Research, is recognized for his pioneering contributions to the understanding of the regulation, function, and evolution of alternative splicing, an essential process by which genes generate vast repertoires of RNA and protein products. His work demonstrated the remarkable complexity of this process, elucidated a sequence code that controls splicing, and revealed programs of alternative splicing with critical roles in animal development and human disease.

"I'm truly honoured to receive this recognition, but it would not have happened without the dedication of an incredibly talented team of postdoctoral fellows, students, technicians and faculty collaborators that have helped drive our research program," said Blencowe, who is also a professor in the University of Toronto's Department of Molecular Genetics. "Our research also would not be where it is without the outstanding and supportive working environment of the Donnelly Centre".

Fellowship in the RSC is one of the highest honours a Canadian researcher can achieve. Founded in 1882, the Society's mission is to recognize scholarly, research and artistic excellence, as well as advise governments and organizations, and promote a culture of knowledge and innovation in Canada and with other national academies around the world.

"Ben is internationally recognized as world-leading in the field of mammalian gene regulation and has helped bring U of T to the forefront of genome biology research," says **Brenda Andrews**, University Professor and director of the Donnelly Centre. "His contributions to both fundamental discovery and technological advancement have greatly expanded our understanding of cellular processes in development and disease. On behalf of the Donnelly Centre, I congratulate him on this richly deserved honour."

Some of Blencowe's key discoveries include how cells interpret the splicing code to make more protein molecules than there are genes in the genome.

He also showed how this amplified molecular diversity acts as a driving force of organismal complexity in the development and evolution of vertebrates, and in particular in the shaping of the staggeringly complex mammalian brain. His team also discovered that alternative splicing controls the process by which stem cells become specialized cells in the body, a finding that has the potential to improve cell manufacturing for regenerative medicine.

Blencowe's team further uncovered how misregulation of alternative splicing during development can lead to neurological disorders such as autism. This research has raised prospects for a new therapeutic strategy for autism, a challenge his group is currently engaged in.

Blencowe holds Banbury Chair in Medical Research and has received several awards for his research excellence, including the Medical Research Council of Canada Scholar Award (1998), Ontario Premier's Research Excellence Award (2000), Canadian Society for Molecular Biosciences (CSMB) Senior Investigator Award (2011), and the NSERC John C. Polanyi Award (awarded by the Governor General of Canada in 2011 for his work on the splicing code). He currently serves on several advisory boards as well as editorial boards of high profile international journals.

"Ben is internationally recognized as world-leading in the field of mammalian gene regulation and has helped bring U of T to the forefront of genome biology research"

Molly Shoichet Named Ontario's First Chief Scientist

By Tyler Irving
November 17, 2017.

University Professor **Molly Shoichet** has been appointed Ontario's Chief Scientist.

"Shoichet is one of the top biomedical scientists in the country, with in-depth knowledge of Ontario's research community," said **Reza Moridi**, Ontario's Minister of Research, Innovation and Science. "As Chief Scientist, she will help us continue a proud tradition of science and research excellence through evidence-based decision making and will open the world to the incredible innovative talent and technologies Ontario has to offer."

Shoichet, a principal investigator in the Donnelly Centre for Cellular and Biomolecular Research and a professor in the Department of Chemical Engineering & Applied Chemistry and the Institute for Biomaterials & Biomedical Engineering, is the first person to hold the new position. Her responsibilities will include working with research hospitals, universities and research institutes to champion high quality science in government and education, help the government make decisions on science-based policy issues and advise the government on how to support future research and innovation projects.

She will also lay the groundwork for the next generation of research and innovation jobs by leading

the development of the best science strategy for the province.

Shoichet holds the Canada Research Chair in Tissue Engineering and is a leading researcher in stem cell transplantation and regenerative medicine. Her lab group is known for its use of materials called hydrogels that surround and protect stem cells when they are injected in the body. These hydrogels help stem cells survive and integrate into tissues, including nervous tissue damaged by stroke, macular degeneration or other diseases.

She has published more than 500 papers, patents and abstracts, and given more than 350 lectures worldwide in regenerative medicine, tissue engineering and drug delivery. She has won numerous awards and scholarships, including the 2017 Killam Prize in Engineering, the 2015 L'Oréal-UNESCO For Women in Science Award for North America and the 2013 Queen Elizabeth II Diamond Jubilee Medal. She is the only person to be a Fellow of Canada's three National Academies, and is both a Foreign Member of the U.S. National Academy of Engineering and a Fellow of the American Association for the Advancement of Science.

Since 2014, Shoichet has served as U of T President **Meric Gertler**'s senior advisor on science and engineering engagement. She is also the co-founder of Research 2 Reality, which uses digital media to communicate cutting-edge research performed in Canada and spark nationwide awareness. In 2015, she received the Fleming Medal and Citation from the Royal Canadian Institute in recognition of her outstanding contributions to science communication.

"Professor Shoichet is internationally renowned for her pioneering research, and for her leadership in engaging citizens in engineering, science and innovation," said **Cristina Amon**, Dean of U of T Engineering and Provostial Advisor on Women in Science, Technology, Engineering and Math (STEM). "On behalf of the Faculty of Applied Science & Engineering, I congratulate her on richly deserved appointment."

This story first appeared in *U of T Engineering News*.

"Professor Shoichet is internationally renowned for her pioneering research, and for her leadership in engaging citizens in engineering, science and innovation"

Christopher Yip Chosen to Head International Partnerships

By Geoffrey Vendeville
March 31, 2017.

Professor **Christopher Yip**, a leading researcher in the field of single-molecule biophysics, has been appointed the University of Toronto's first associate vice-president, international partnerships. He starts a five-year term on July 1 and aims to foster international academic and industry collaborations. He will be reporting to Vice-President, International **Ted Sargent** and Vice-President, Research and Innovation **Vivek Goel**.

Yip brings almost a decade of leadership experience within U of T's Institute of Biomaterials and Biomedical Engineering (IBBME), a team of more than 100 faculty members from engineering, medicine and dentistry who look for innovative solutions to pressing problems at the intersection of health-care and engineering.

"U of T is known for its strengths in a number of different areas," he told U of T News. "Part of my job will be to help enable and grow new emerging areas of impact in the U of T ecosystem."

The benefits of forging new partnerships around the world are multifaceted, he said. "It aids in increasing the profile of the university, the students and the research. It also improves the profile of Canada more broadly."

On large research projects, borders tend to become

blurred.

"Research is borderless," he said. "We will identify how teams can come together on large projects that take full advantage of each institution's strengths."

He added: "It's the opposite of what you see right now around the world, where people are saying 'Let's put more and more borders up and block things.'"

Whether in a lab or administrative position, Yip says his goal is always to support others.

"For me, it's important to provide resources and opportunities to let people drive initiatives, and that's my main focus."

"Research is borderless. We will identify how teams can come together on large projects that take full advantage of each institution's strengths"

Yip joined the university in 1997. He is a faculty member in the department of chemical engineering and applied chemistry, department of biochemistry, IBBME and U of T's Donnelly Centre for Cellular and Biomolecular Research. Located in the Donnelly Centre, his lab research group of post-doctoral, graduate and undergraduate students studies the phenomena that take place at the molecular scale.

"We're developing and applying new ways of understanding how molecules assemble and form structures, and developing new ways of visualizing these processes," he said.

The applications of their research extend to biology, biophysics, nanotechnology and engineering.

In recent years, Yip's lab has hosted students from Singapore and Cuba, and sent U of T students to Asia and Europe. He also facilitated a partnership with the U.S. Department of Energy which led two of his grad students to study at the Sandia National Laboratory in Albuquerque.

"It was very much a two-way street. They learned from us and we learned from them," Yip said.

Yip is the author of more than 90 peer-reviewed publications and four book chapters, and has won a Premier's Research Excellence Award among other academic distinctions. From 2000 to 2010, he held a tier II Canada Research Chair in molecular imaging.

"Our ability to continue to recruit the best scholars and students from around the world hinges on our global reputation," said Professor Goel. "Through the IBBME, Chris has clearly demonstrated the ability to foster collaboration at all levels, bringing together a multidisciplinary community of students, scholars and external partners to support the impact of their research globally."

Professor Sargent said: "Chris Yip, in his leadership, has stimulated and seeded outstanding new team initiatives. He has shown how to bring collaborating researchers together within U of T to put our best foot forward to the world. And he has built global partnerships that leverage and showcase the best U of T has to offer. He is perfectly poised to unite U of T's International and Research and Innovation portfolios into a coherent platform building global partnerships.'

Will he have the stamina for the new position?

His hobby suggests he does. Yip is an avid runner, who has 25 marathons and 25 half-marathons under his belt. His best time completing a marathon was three hours and seven minutes.

This story first appeared in *U of T News*.

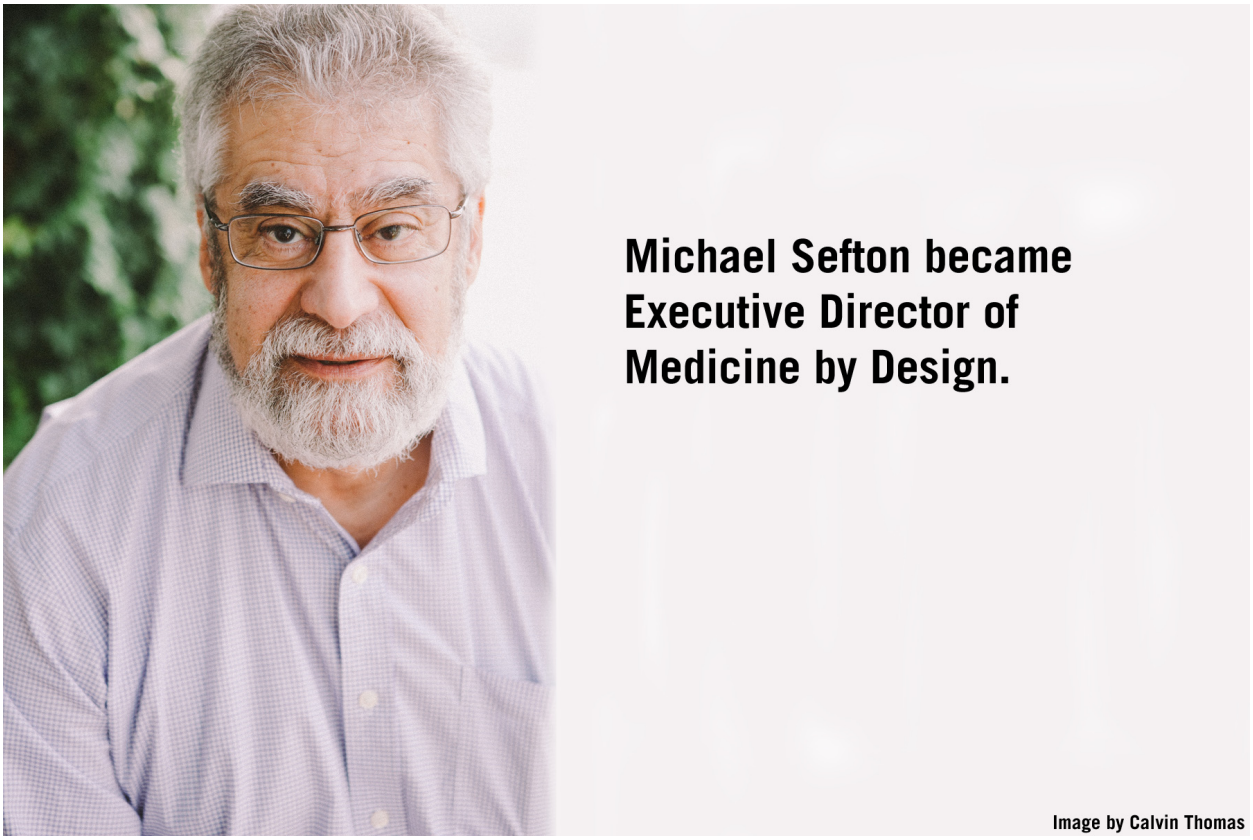


Image by Calvin Thomas

Michael Sefton to Lead Medicine by Design as Executive Director

By Ann Perry
June 29, 2017.

Engineering professor and Donnelly Centre investigator **Michael Sefton** has been appointed executive director of Medicine by Design, a University of Toronto initiative that is accelerating discoveries in regenerative medicine research to improve treatments for conditions such as heart failure, diabetes and stroke. Sefton, a pioneer in tissue engineering and biomaterials, takes over from **Peter Zandstra**, also at the Donnelly Centre, who is stepping down to lead a new school of biomedical engineering at the University of British Columbia.

"Regenerative medicine is a key priority for the University of Toronto, and Medicine by Design is strengthening our position as a global centre of excellence and innovation in this area," said **Vivek Goel**, chair of Medicine by Design's Executive Committee and U of T's vice-president of research and innovation. "Michael is an internationally recognized expert in the field, and I am delighted he has agreed to lead the next phase of Medicine by Design."

Medicine by Design was established in July 2015 with a $114-million grant — the largest single research award in U of T's history — from the federal government's Canada First Research Excellence Fund. The initiative builds on U of T's rich legacy of

contributions to stem cells and regenerative medicine, starting in the early 1960s with the identification of blood stem cells by biophysicist James Till and hematologist Ernest McCulloch.

In its first two years, Medicine by Design has awarded more than $30 million to more than 100 researchers across U of T and its affiliated hospitals through programs that support a robust pipeline of projects from early stage "new ideas" research to clinical translation and commercialization. Its largest award program funds 20 collaborative teams made up of researchers and clinicians with expertise in life and physical sciences, engineering, medicine and computational biology. Sefton leads a team project that is focusing on using novel biomaterials to stimulate skeletal muscle to fix itself, a process known as endogenous repair. Other teams are tackling diabetes, blindness, and liver and inflammatory bowel diseases, as well as advancing basic research at the convergence of disciplines ranging from stem cell to computational biology.

"By bringing together outstanding researchers and clinicians from diverse disciplines and giving them the resources they need to tackle big questions, Medicine by Design offers a remarkable opportunity to do high-impact research that has the potential to advance and even redefine key areas of regenerative medicine," said Sefton, a University Professor, the Michael E. Charles Professor of Chemical Engineering and a faculty member in the Department of Chemical Engineering & Applied Chemistry and the Institute of Biomaterials & Biomedical Engineering.

"I look forward to building on the excellent work Peter has done to foster new collaborations and strategically focus the expertise of our community around critical research and its translation into the clinic."

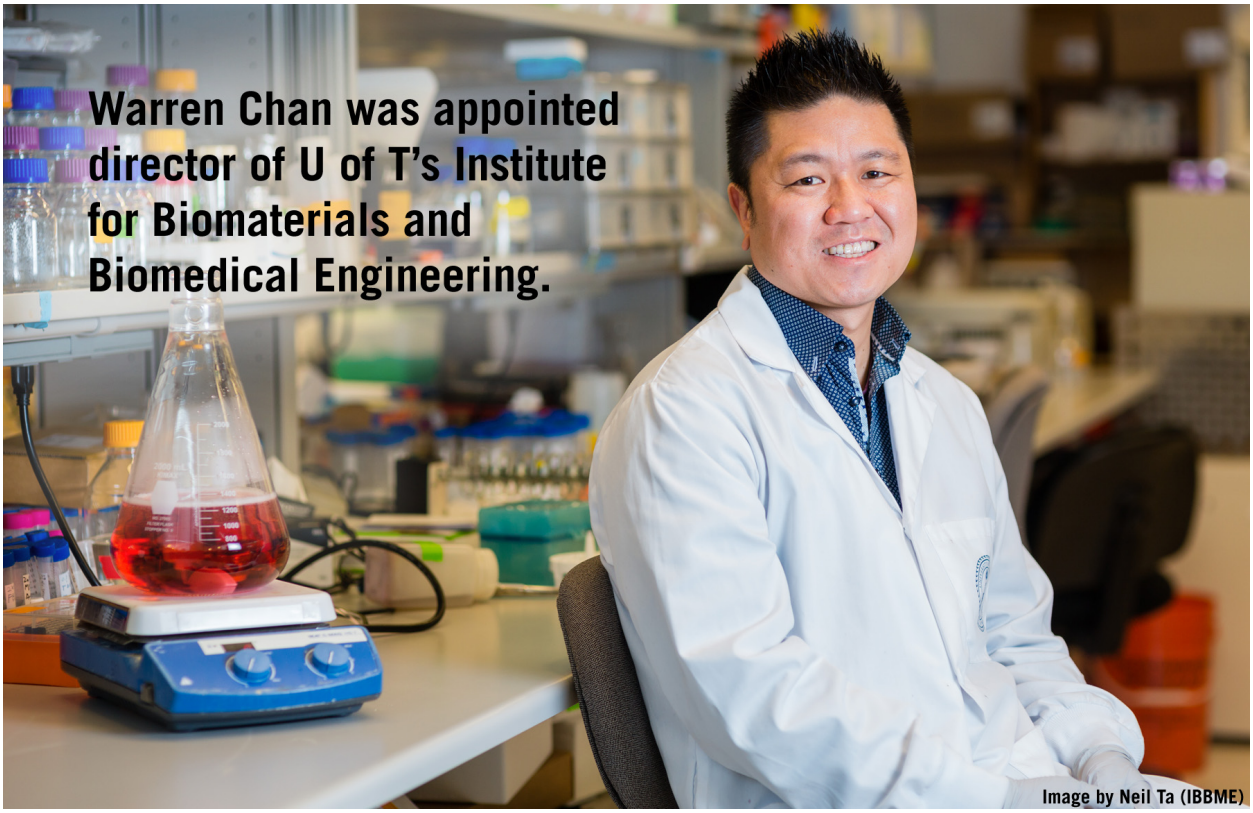
Medicine by Design's other activities include supporting the recruitment of established and emerging researchers to strengthen U of T's capacity in key areas such as synthetic biology and immunoengineering, and working closely with CCRM and industry to identify and advance discoveries with commercialization potential. It is also building international relationships through its Global Speaker Series, as well as its Summer by Design program, a partnership with the Rotman School of Management and CCRM that has brought a dozen PhD students from peer international universities to Toronto this summer for a series of workshops and conferences.

Sefton holds degrees in chemical engineering from the University of Toronto (1971) and the Massachusetts Institute of Technology (1974), and has been at the University of Toronto since 1974. He has been active in the preparation of blood compatible materials through heparinization, the microencapsulation of mammalian cells in synthetic polymers and various strategies for vascularizing tissue constructs.

Sefton has served as director of U of T's Institute of Biomaterials & Biomedical Engineering and as president of the U.S. Society for Biomaterials. He has received numerous awards including the Founders Award of the U.S. Society for Biomaterials, the Killam Prize in Engineering of the Canada Council for the Arts, and the Acta Biomaterialia Gold Medal. He was elected an international member of the U.S. National Academy of Medicine in 2014 and received the Terumo Global Science Prize in 2016.

Sefton's five-year term as Medicine by Design's executive director will begin on July 1, 2017.

This story first appeared on *Medicine by Design News.*



Warren Chan Appointed Director of IBBME

November 20, 2017.

Warren Chan, U of T professor and principal investigator in the Donnelly Centre for Cellular and Biomolecular Research, has been appointed as director of the Institute of Biomaterials & Biomedical Engineering (IBBME) for a five-year term, effective January 1, 2018.

The announcement was made in a joint memo from **Cristina Amon**, dean of the Faculty of Applied Science & Engineering, **Daniel Haas**, dean of the Faculty of Dentistry, and **Trevor Young**, dean of the Faculty of Medicine. Chan joined IBBME as a faculty member in 2002, was promoted to associate professor in 2008 and to full professor in 2012. He is currently the U of T Distinguished Professor of Nanobioengineering, and has been the recipient of the Kabiller International Nanomedicine Award (2015), and the NSERC E. W. Steacie Fellowship (2012). Chan also held the Canada Research Chair in Bionanoengineering from 2006-2016. He has previously served as IBBME's Collaborative Program coordinator from 2008 to 2011 and is currently an associate editor of ACS Nano.

Chan is an internationally recognized, leading researcher in the area of nanoengineering, where he is developing nanotechnology for the diagnosis and treatment of cancer and infectious diseases. He has published 91 peer-reviewed research articles, seven book chapters and a book.

With files from Luke Ng and Faculty of Applied Science & Engineering. This story first appeared on *IBBME News*.

OTHER NOTABLE AWARDS AND APPOINTMENTS

- **Brenda Andrews** was awarded the Jeanne Manery Fisher Memorial Award for scientific accomplishments by the Canadian Society for Molecular Biology and appointed to the governing council of the Canadian Institutes of Health Research.

- **Molly Shoichet** received the Killam Prize for Engineering.

- **Aaron Wheeler** was named Canada Research Chair in Microfluidic Bioanalysis.

- **Gary Bader** was named Ontario Research Chair in Biomarkers of Disease.

- **Tim Hughes** was named John W. Billes Chair of Medical Research.

OUR DISCOVERIES ARE HELPING CREATE NEW TREATMENTS AND IMPROVE DISEASE DIAGNOSIS

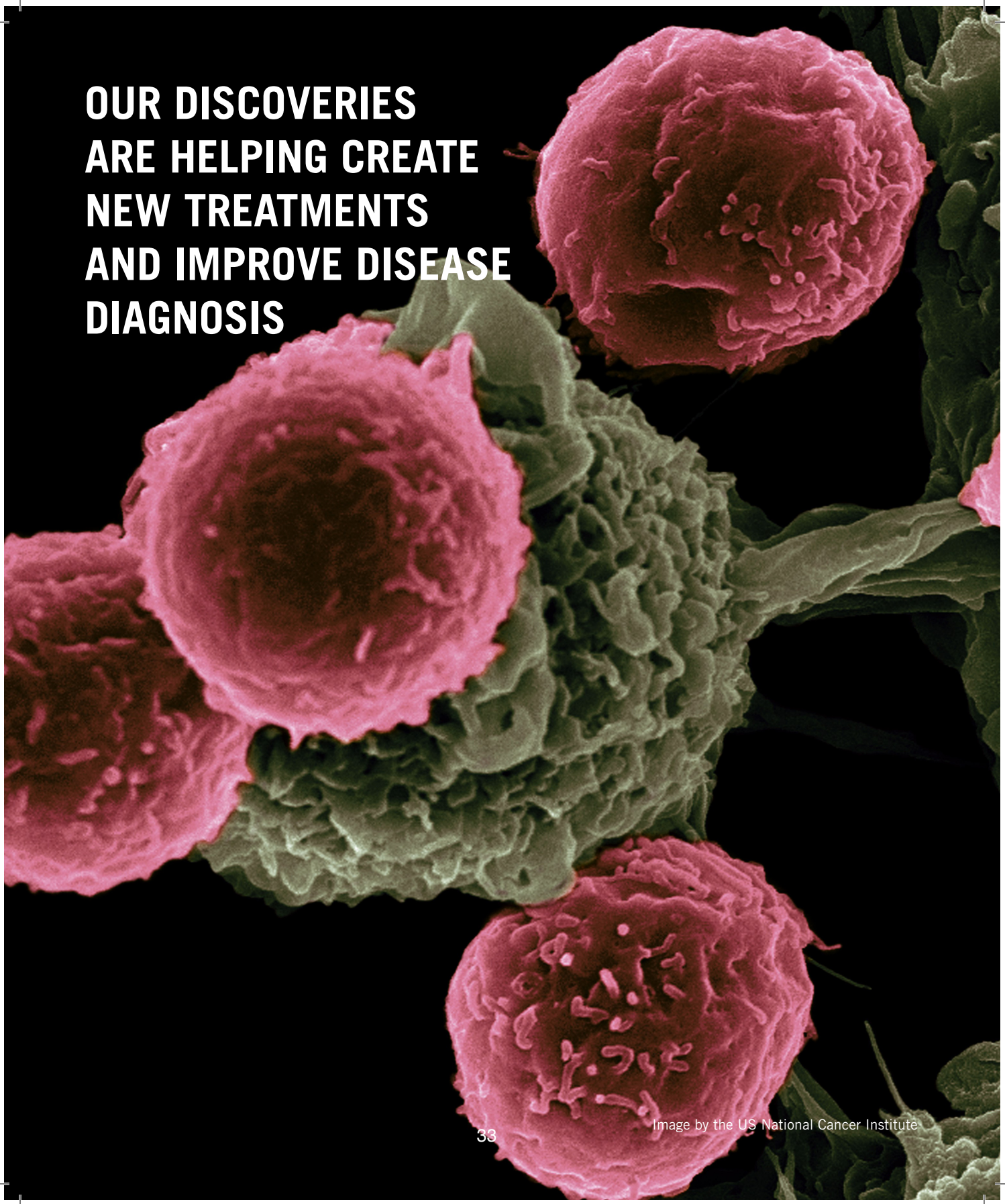


Image by the US National Cancer Institute

New Cancer Immunotherapy Gets US$62-Million Boost Thanks to Donnelly Centre Antibody Engineering Technology

By Jovana Drinjakovic
Dec 26, 2017.

A new therapy that enhances the body's ability to fight cancer has received a $62-million (USD) boost thanks to Donnelly Centre's antibody engineering technology.

Called Myeloid Tuning™, the therapy is designed to boost the body's anti-tumour immunity by removing the cells that normally put brakes on the immune system using engineered antibodies from U of T's Toronto Recombinant Antibody Centre (TRAC).

"Instead of turning on the immune cells directly, you get rid of the cells that are inhibiting the immune cells," says Professor **Sachdev Sidhu**, who co-founded TRAC with Professor **Jason Moffat** as a state-of-the-art antibody engineering platform at the Donnelly Centre for Cellular and Biomolecular Research, where both are faculty members.

Unlike natural antibodies produced by the immune system to fight disease, engineered antibodies can be designed to target any molecule or cell type and are becoming increasingly used in medicine as a new generation of drugs.

The work that led to myeloid tuning started five years

ago as a research collaboration between Sidhu and Moffat, both also professors in U of T's Department of Molecular Genetics, and Professor Max Krummel at the University of California San Francisco (UCSF). Krummel co-invented the first engineered immunotherapy approved in 2011 against skin cancer. Three years later, Sidhu and Krummel co-founded Pionyr Immunotherapeutics in San Francisco to turn their research idea into reality.

"It's an example of how you can go very quickly, within a few years, from basic research to potential clinical applications," says Sidhu.

In recent years, immunotherapy, in which the body's immune system is awakened to destroy tumour cells, has emerged as a highly promising treatment against a range of cancers.

"This is an example of how you can go very quickly, within a few years, from basic research to potential clinical applications"

Last month, Pionyr announced it raised $62 million (USD) from investors bringing its total funding to $72 million (USD) raised in two years to develop myeloid tuning into a form in which it can be tested on patients. The funding boost came on the back of promising proprietary data obtained with antibodies created in Toronto. So far, myeloid tuning has been shown to be effective in multiple mouse tumour models.

Built from the ground up in 2010, TRAC has grown into a sought-after technology platform with more than 50 ongoing collaborations worldwide. Besides

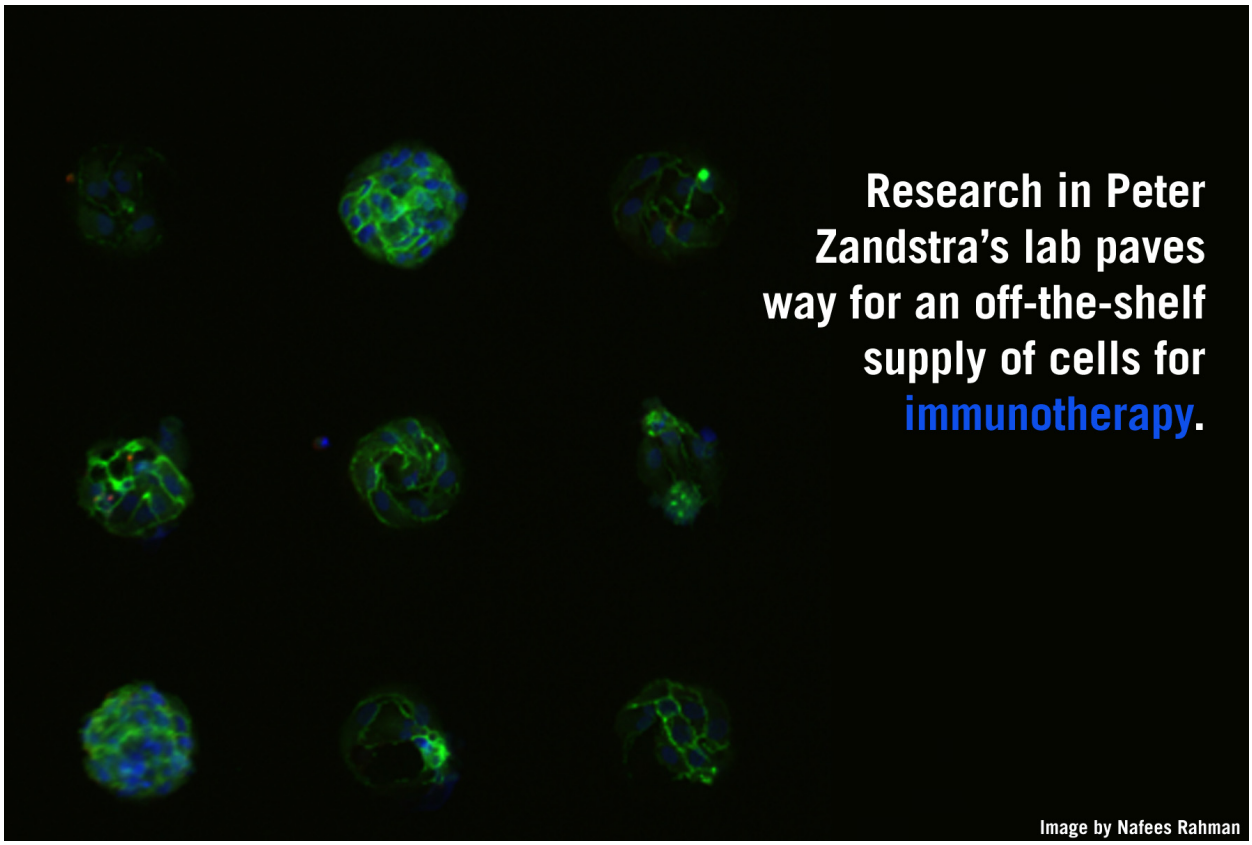
Professors Sachdev Sidhu and Jason Moffat (left to right).

Pionyr, there's also Saksin LifeSciences in India, a startup that is turning TRAC antibodies into new medicines for blindness.

"The TRAC has established itself as a premier protein engineering platform attracting partnerships and significant research funding from industry," says Moffat.

Moffat and Sidhu want to see more new drugs developed in Toronto. That is being made possible thanks to additional support from the visionary philanthropist Terrence Donnelly, whose gift 13 years ago helped found the interdisciplinary biomedical research institute that now bears his name. In October, Donnelly announced a new $10-million gift to support research and innovation. That will enable the Donnelly Centre to soon launch a new hub for biotechnology startups that will accelerate translation of its research discoveries into new therapies.

"Pionyr came out of a similar biotech incubator at UCSF. Imagine what we could do if we had one here. We have thousands of high-quality antibodies that are just sitting there waiting to be turned into new drugs," said Sidhu.



Donnelly Centre Research Paves Way for Off-the-Shelf Supply of Cells for Immunotherapy

By Jovana Drinjakovic
May 25, 2017.

Bioengineering and professional soccer may not have much in common at first glance, but **Nafees Rahman** sees a clear link between the career path he chose and his childhood dream.

"Soccer is a team sport and research is also about a team — you can never do it by yourself," says Rahman, who recently completed his research in the laboratory of Professor **Peter Zandstra** at the University of Toronto's Institute of Biomaterials & Biomedical Engineering and will receive his PhD during June convocation.

Rahman specializes in making new blood from scratch as a potential source of cells for life-saving treatments. Together, he and **Shreya Shukla**, another student from Zandstra's lab who will receive her PhD next month, have developed new technologies that clear some of the barriers to having a limitless source of cells to target cancer and other diseases. Their findings, described in two recent papers published in *Nature Communications* and *Nature Methods* and funded by Medicine by Design and the Ontario Institute for Regenerative Medicine, could lead to new cell therapies for boosting patients' immune systems against disease, and for cancer

which immune cells can be engineered to attack tumours.

"A long-term vision in regenerative medicine is to have a renewable source of cells for therapy," says Zandstra, a University Professor and executive director of Medicine by Design. "Our two papers focused on generating blood and immune cells in the lab that could be used in cancer immunotherapy. Working with our collaborators at U of T, affiliated hospitals and CCRM, we are getting closer to being able to do this."

"Our two papers focused on generating blood and immune cells in the lab that could be used in cancer immunotherapy"

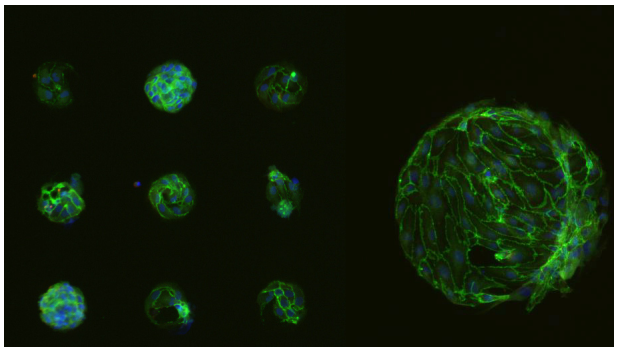
Medicine by Design brings together more than 100 researchers from across U of T and its affiliated hospitals, along with hundreds of post-doctoral fellows and graduate students, in collaborative teams to accelerate breakthroughs in regenerative medicine. With its commercialization partner, CCRM, the initiative is also driving Toronto's regenerative medicine ecosystem and propelling new therapies to market — and ultimately to patients — more quickly.

Researchers around the world are racing to find ways to use stem cells to treat, and even cure, debilitating diseases thanks to their ability to multiply and make all cell types in the body. Naturally occurring stem cells in the bone marrow and cord blood are already being used to bolster the immune systems of patients undergoing cancer treatment that leaves them defenseless against infections. But because the cell grafts come from donors, they are not always available in sufficient supply. Zandstra's lab, located in the Donnelly Centre for Cellular and Biomolecular Research, is trying to solve this problem by engineering ways to produce these cells in the lab.

Working with **Juan Carlos Zúñiga-Pflücker**, a professor at U of T's Department of Immunology and a senior scientist at Sunnybrook Research Institute, the researchers broke down the problem into two areas. First, they found a way to convert pluripotent stem cells — cells that are able to make all the cells in our bodies — into blood progenitor cells, an intermediate state from which all cells in the blood, including immune T cells that fight off infections, are formed. Then they developed new technology for turning blood stem cells into T cells in a way that can be scaled up for clinical use.

"The ultimate goal is to join the two technologies into one pipeline," says Zandstra. This pipeline would make it easier to develop immunotherapy for cancer using T cells engineered to attack tumours, he adds.

Writing in *Nature Communications*, Rahman and colleagues describe how simulating the cells' natural environment during development was key to understanding how blood forms. Instead of spreading the cells evenly across the surface of the dish as usual, Rahman placed them in discrete clusters of different sizes. This allowed him to study how cells talk to each other to influence what kind of blood cells the stem cells turn into. He discovered that larger clusters produced fewer blood cells because the cells secrete a molecule that blocks this process.

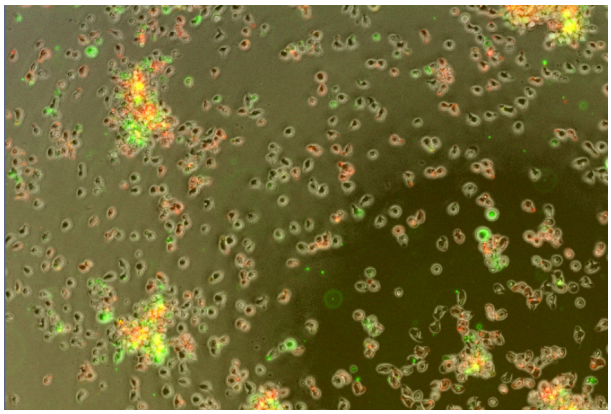


Human stem cell-derived blood progenitor cells grown in small and large clusters (Nafees Rahman).

"The importance of cell-cell communication during embryonic development is key and it was nice to see this phenomenon replicated in the dish," says Rahman. "Just by changing cluster size we were able

to control how many blood cells we get, resulting in a significant improvement in cell yields."

While blood stem cell grafts can rebuild the patient's immune system, it takes roughly a year for the immune T cells to appear and start working, leaving the patient vulnerable to life-threatening infections. Shukla's goal was to protect patients faster.



Blood stem cells morphing into immature immune cells, marked with red and green fluorescent proteins (Shreya Shukla).

"Our idea was to use blood stem cells to produce T cells in the lab that we can then transplant into patients," says Shukla.

But producing immune cells has been hampered by uncertainty over the conditions and ingredients that are required, limiting their potential as medicine.

To overcome this challenge, Shukla identified essential components that are needed to spur the blood stem cells to become T cells. As described in the *Nature Methods* paper, the new technology consists of precisely-defined ingredients and can be scaled up for industrial production.

When injected into mice, the lab-grown T cells can rebuild the immune system in one month, far more quickly than what it takes for the blood stem cells to mature inside the body. If the same is true in humans, it could have immediate applications in cell transplantation.

"With our approach, you could move the field to where you have universal, off-the-shelf T cells which could be used in many applications, including cancer immunotherapy," says Shukla. "You could start with blood or pluripotent stem cells, engineer them to recognize tumours and then turn these into T cells that would rapidly reconstitute the patient's immune system with cancer-fighting cells."

"This would get around the problem of the current immunotherapy approach that uses the patients' own T cells. There can be manufacturing problems with that because there is a lot of variability between different patients' T cells," says Shukla.

Shukla is currently testing the technology at a California biotechnology company, where she is doing a six-month internship through the Natural Sciences and Engineering Research Council of Canada's Create M3 program.

Rahman, too, has swapped an academic lab for a job in biotechnology. Earlier this year, he joined Neurona Therapeutics, a San Francisco startup that aims to generate human stem cell-derived nerve cells for the treatment of epilepsy.

Having played soccer competitively all his life, he is also looking for a team.

"The plan is definitely to play soccer in San Francisco but only for fun," Rahman says. "My focus now is on learning how to develop stem cell-based therapy going from early discovery in the lab to treating patients."

This story first appeared in *Medicine by Design News*.

Igor Stagljar Launches Startup to Help Find New Smart Drugs

By Chris Sorensen
April 24, 2017.

Igor Stagljar likens the process of commercializing his ground-breaking research into cell membrane proteins – which has yielded hundreds of new targets for drug-makers seeking cures for cancer and other deadly diseases – to building a highly automated Tesla factory.

But there's a key difference: ProteinNetwork Therapeutix will be based here in Canada, not south of the border.

Stagljar, a principal investigator in the Donnelly Centre for Cellular and Biomolecular Research and a U of T professor of biochemistry and molecular genetics, initially considered setting up his new venture in Silicon Valley. But he and business partner Ivan Plavec ultimately decided Toronto was a better option.

"The technology is here and the know-how is here," says Stagljar, citing U of T's large pool of research talent and a growing cluster of venture capital investors on or near the university's downtown campus. "Maybe some people from my lab will even go to work for the company." U of T is at the centre of Canada's largest concentration of hospitals, research institutes and business incubators. That includes 10 accelerators run by the university itself. Many of the

technologies being developed here are increasingly being spun off into life sciences startups, with nine such ventures being launched in the past three years alone.

Plavec, who lives in the San Francisco Bay Area, and has already been involved with a successful biotech startup there, says Canada's favourable corporate tax rates were also a factor. He also cited last year's opening of Johnson & Johnson's JLABS life sciences incubator in partnership with U of T, as evidence of growing U.S. interest in Toronto's booming startup scene.

"There are approximately 500 diseases that can be tackled with this technology"

Helping to seal the deal: a $1 million grant from CQDM's Quantum Leap program. The grant, co-funded by the Brain Canada Foundation, targets research with "very high potential impact" within the biopharmaceutical industry. It's only the second time the program has funded a Canadian researcher. The other was U of T's Andrei Yudin, a professor of chemistry.

Stagljar's research certainly qualifies as having a potentially big commercial impact.

With the help of his 17-person lab, he developed a new genetic technique that allows researchers to map the interactions between proteins in a cell's membrane, a process previously made difficult because of the proteins' fragile, transitory states. The interactions play a key role in determining whether a cell stays healthy or becomes diseased, and are therefore of huge interest to pharmaceutical companies seeking a new generation of precision drugs to cure deadly diseases like cancer.

"There's about 500 proteins that we know of nested in the cellular membranes that are involved in the onset of various human diseases," says Stagljar, citing cancer, Parkinson's, Alzheimer's, hypertension, diabetes, cardiovascular disease and even migraines. "There are approximately 500 diseases that can be tackled with this technology."

But studying protein interactions in the lab is not the same as systematically evaluating them on a commercial scale. So Stagljar is in the process of retooling his laboratory at the Donnelly Centre, tapping a local Ontario company to design and build robotics that can handle hundreds of screens per day.

Everything should be up and running within the next 12 months. Stagljar's focus at U of T will be on "druggable" membrane proteins related to three types of cancer: lung, breast and pancreatic. His company, meanwhile, will use similar technology and equipment to focus on other diseases in partnership with pharmaceutical partners.

"We're already leading very serious talks with well-known drug companies," Stagljar says. "Two out of the five biggest pharmaceutical companies are interested in our technology."

How long until ProteinNetwork expects to see results?

"I think in the next two or three years, we will learn about new drug targets, which, when neutralized by drugs, would lead to cures for these cancers," says Stagljar. "But before these drugs would appear in clinics is a long process, from nine to 12 years.

"Our focus right now is to build a high-throughput, high-grade technology for biomedical research."

This story first appeared in *U of T News*.

Gary Bader's Team Helps International Group of Researchers Discover 72 New Genetic Variants that Predispose to Breast Cancer

October 23, 2017.

University of Toronto researchers have helped identify 72 new genetic variants that contribute to the risk of developing breast cancer as part of a major international collaboration involving hundreds of researchers worldwide.

The studies, reported today in the journals *Nature* and *Nature Genetics*, identified 72 common variants that predispose to breast cancer. Among these genetic regions, some are specifically associated with either estrogen receptor-positive (ER+) or estrogen receptor-negative (ER-) breast cancer – the subset of cases that do not respond to hormonal therapies, such as the drug tamoxifen.

The findings are the result of work by the OncoArray Consortium, a huge endeavour involving 550 researchers from about 300 different institutions in six continents. In total, they analyzed genetic data from 275,000 women, of whom 146,000 had been diagnosed with breast cancer.

"These new variants substantially expand the number of genes and pathways that are involved in breast cancer development, and these represent multiple new avenues of research to learn how to treat breast cancer," says **Gary Bader**, a professor at the Donnelly Centre for Cellular and Biomolecular Research and the department of molecular genetics,

whose research group was among five U of T teams involved in the study.

Bader's group was instrumental in identifying new pathways involved in breast cancer and making the discovery that ER+ and ER- breast cancers are linked to different pathways, supporting the idea that these cancers are genetically distinct diseases and therefore need to be thought of differently by researchers.

Breast cancer is caused by complex interactions between a large number of genetic variants and the environment. The inherited component of breast cancer risk is due to a combination of rare variants in genes such as BRCA1 and BRCA2 that confer a high risk of the disease, and many more common genetic variants that each confers only a small risk. The newly identified risk regions nearly double the numbers that are already known, thereby bringing the number of known common variants associated with breast cancer to around 180.

The risk variants identified in the two studies are common: While some are carried by one woman in 100, others are carried by more than half of all women. Individually, the risks conferred by each variant are modest. But because they are common and their effects multiply together, the combined effect is considerable. These findings will help improve risk prediction. The researchers believe these differences may be sufficient to change practice, such as in how women at different risks are screened.

"Using data from genomic studies, combined with information on other known risk factors, will allow better breast cancer risk assessment, therefore helping to identify a small but meaningful proportion of women at high risk of breast cancer," says Professor Jacques Simard from the Genomic Centre of the CHU de Québec-Université Laval Research Centre in Québec City, who was one of the co-leading investigators on the project.

"These women may benefit from more intensive screening, starting at a younger age, or can be offered screening by magnetic resonance imaging (MRI), which is more sensitive, allowing early detection and prevention of the disease. At the same time, this personalized information will also be useful to adapt screening modalities for women at substantially lower risk," says Simard.

"These new variants represent multiple new avenues of research to learn how to treat breast cancer"

The major advance of the study was that a large amount of genomic information was used to better link genetic variants to the genes they act on. Identified as single misspellings in the DNA code, variants are scattered across the genome and often fall outside the gene-coding regions. To find a gene that is affected by any given variant, researchers would typically home in on a gene that is located closest to the variant – a difficult task when there are many genes to choose from, as is often the case.

But here, data about transcription factor binding – proteins that bind the DNA at specific sites to switch genes on and off – as well as epigenetics data that tell researchers how accessible DNA is to transcription factors, were taken into account to better predict which gene should be linked to which breast cancer-associated variant.

Despite this leap in our understanding of the genetic risks of breast cancer, Bader says that the data still can't explain most of breast cancer cases and are not yet widely useful for population screening. The current study looked at common variants and to explain more of breast cancer risk, researchers will need to consider rare mutations as well as how different genes interact to influence each other's effect on disease.

The research was funded by Genome Canada, Genome Quebec, Canadian Institutes of Health Research, Quebec Breast Cancer Foundation, Cancer Research UK, National Cancer Institute USA and the European Union Horizon 2020 program.

THROUGH DIVERSE ACADEMIC AND INDUSTRY PARTNERSHIPS OUR RESEARCH IS HAVING A WIDER IMPACT

Road Less Traveled - Donnelly Labs Tackle Neglected Parasitic Diseases

By Jovana Drinjakovic
April 10, 2017.

Parasites nearly killed her grandmother, and now **Samantha Del Borrello** is striking back.

Del Borrello is a graduate student investigating new ways of attacking parasites. She says her "nonna's" childhood in 1940s rural Italy was plagued by intestinal worms that ravaged her health to the point doctors thought she would die.

"It is crazy to think that I may not be here because of a parasite, and now I am working on preventing the parasites from hurting people. It's kind of cool," says Del Borrello, a PhD candidate in the University of Toronto's Donnelly Centre for Cellular and Biomolecular Research and the Department of Molecular Genetics.

Internal parasites, which infect the gut, lungs and liver, may not be a major health concern in the developed world, but globally they affect close to two billion people.

Gut worms infect 880 million children, according to the World Health Organization. Parasitic infections are rampant in the poorest areas, caused by nematode worms like roundworms, whipworms and hookworms. Untreated, these infections typically cause anemia and lethargy, or even death. Children

are most vulnerable.

"Drugs already exist for some parasite infections but resistance is always evolving — we need new ways to attack these complex creatures," says **Andrew Fraser**, a professor in the Donnelly Centre, and Del Borrello's PhD supervisor.

Professor Andrew Fraser

Growing drug resistance comes at a time when the pharmaceutical industry has little incentive to invest in solving health problems that affect poor people who cannot afford treatment.

One way forward is for academic labs to work with pharmaceutical companies to identify promising drugs. Fraser's work with Janssen, a branch of the pharmaceutical giant Johnson & Johnson, is one example of this kind of collaboration.

Peter Roy, who is also a professor in the Donnelly Centre, says there is also potential for the agriculture industry to play a role in developing new treatments.

"Most of the meat we eat has been treated with anthelmintics, drugs that kill parasitic worms," says Roy. "If novel anthelmintics are shown to be useful for cows and sheep, then they might become therapies for humans."

Fraser and Roy, who are also both appointed to the Department of Molecular Genetics, lead research into identifying new anti-parasitic drugs. As their main tool, the researchers are relying on a harmless type of worm called *C. elegans*, which is also widely used in labs. Unlike parasites, which live inside a body, lab worms grow on a dish and are easy to work with.

Many parasites make their way to places in the body where there is little oxygen to breathe. In order to survive, they switch to a type of metabolism that's not fueled by oxygen.

Normally, lab worms need oxygen to live. But Del Borrello and PhD candidate **Margot Lautens** found a way to trick the lab worm into behaving like a parasite, deep inside the gut. Using drugs, they turned off the worm's ability to use oxygen, forcing the worm to use parasite-like metabolism. This allowed researchers to study quirky parasite biology in an animal right in front of them.

"The way worms survive in low oxygen is extremely unusual, humans don't use this process at all. That's the key. It means that if we can target this unusual

"Drugs already exist for some parasite infections but resistance is always evolving — we need new ways to attack these complex creatures"

metabolic pathway, we should be able to kill the worms without having any impact on the human host," says Fraser.

Using a different strategy, Roy's team has already uncovered a treasure trove of potential anti-parasitic compounds. Two years ago, postdoctoral fellow **Andrew Burns** was part of a team that uncovered 275 chemical compounds that killed *C. elegans*. These worm active compounds, dubbed wactives, were then tested on fish and human cells to identify which ones could potentially harm the host.

Professor Peter Roy

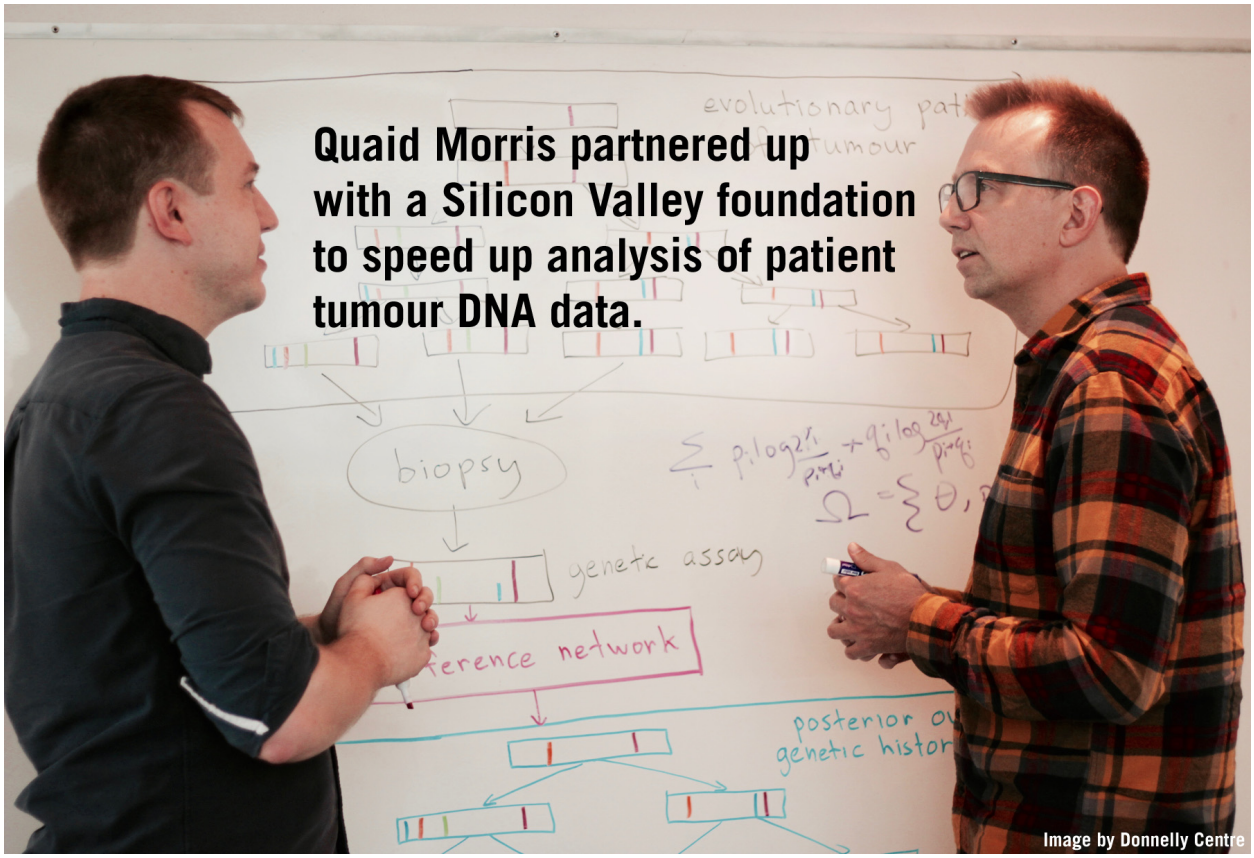
That team is now teasing apart how wactives work. A new study in *PLOS Neglected Tropical Diseases* describes how a compound called wact-86 works by blocking an important enzyme in the worm. The next step is to explore whether wactives can clear parasitic infections in larger animals.

Another potential avenue is to work with a pharmaceutical company from the start. To do this, Fraser is working with BIO Ventures for Global Health (BVGH), a Seattle-based non-profit that boosts research in neglected tropical diseases through partnerships between academic labs and the pharmaceutical industry.

The organization, among other roles, helps academia and industry share reagents, says **Ujwal Sheth**, Associate Director at BVGH.

Last month, Fraser signed a deal with Janssen, granting his team rights to the company's drug collection—a potential chemical gold mine with 80,000 diverse compounds. If they find a medicinally promising compound, Janssen could decide take it on, said Sheth. Or, the BVGH could help connect Fraser with other partners with capacity to develop new medicines, she added.

"The best anthelminthic drug today, ivermectin, was developed in the 1970s as a partnership between an academic lab and a major pharmaceutical company. It's a great cooperative model to help solve these huge global health problems," said Fraser.



Parntership to Speed up Analysis of Patient Tumour DNA Data

By Jovana Drinjakovic
December 11, 2017.

University of Toronto computational scientists have received new funding to develop faster and more accurate algorithms that can keep track of how tumours change over time in a bid to improve diagnosis and treatment.

Teams led by Professor **Quaid Morris**, of the Donnelly Centre for Cellular and Biomolecular Research, and **David Duvenaud**, of the Department of Computer Science, received a boost for their research that aims to drastically cut down—from weeks to seconds—the time it takes to build a tumour's "family tree" from its DNA sequence data in order to learn how the cancer has evolved and how it may respond to treatment.

Both Morris and Duvenaud are also members of the recently founded Vector Institute for artificial intelligence, launched with the support from U of T.

"We anticipate that tumour evolution data are going to be used clinically, but one of the main barriers to clinical use is computation time which can take days and sometimes weeks," says Morris, who is also a professor in the Departments of Computer Science and Molecular Genetics. "But you can't wait a couple of weeks for the software to run before making decisions about treatment, prognosis or even

diagnosis."

The $200,000 USD grant, which was awarded by the NVIDIA Foundation and the Silicon Valley Community Foundation, will go towards building a faster version of the artificial intelligence-powered software previously developed by Morris' team. The algorithm works by scanning billions of DNA changes, or mutations, which have accumulated in tumours, to piece together an evolutionary history of a patient's cancer.

"We anticipate that tumour evolution data are going to be used clinically, but one of the main barriers to clinical use is computation time which can take days and sometimes weeks"

As cancer begins to grow, its cells mutate much faster than the healthy ones, and in doing so acquire new qualities that allow them to spread and wreak havoc in the body. But not all mutations that are present in a tumour drive its growth—many are mere passengers, side-effects of the high mutation rate and therefore clinically irrelevant.

As mutations make their mark on cancer, researchers like Morris and Duvenaud can use tumour DNA sequence data to figure out which mutations came earlier and which ones came later in order to identify the ones responsible for the disease. This research could help tailor treatment and predict patient outcome as well as open new avenues for drug discovery.

Lots can also be learned from knowing the type of mutations and where in the tumour's genome they accumulate in.

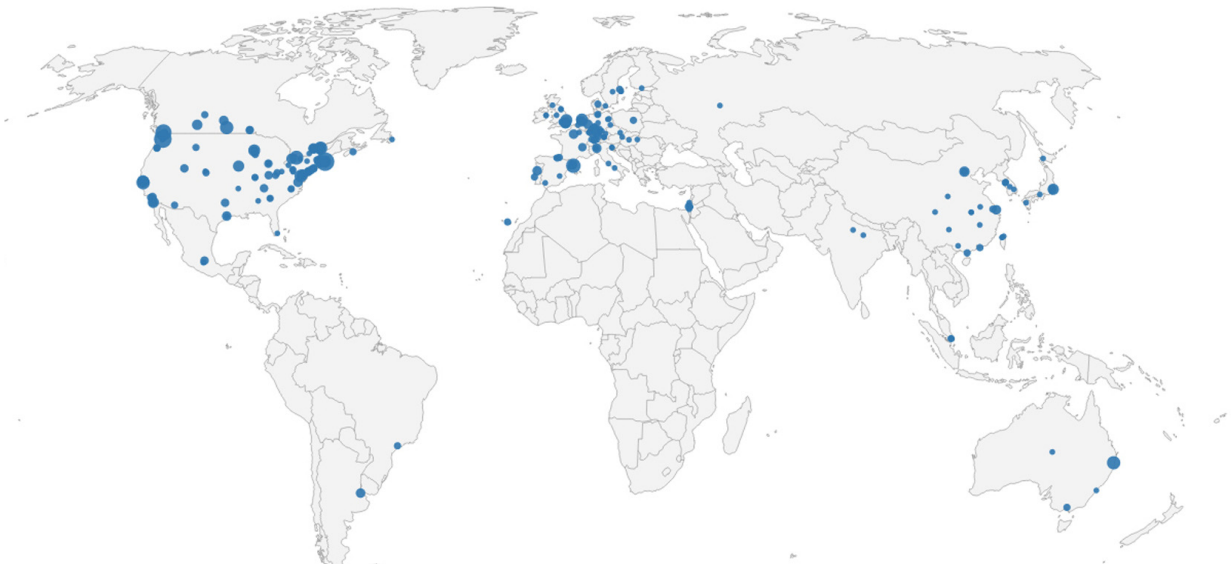
"Mutations accumulate differently in a breast tumour than in a liver tumour for example," says Morris. "And types of mutations are different. Mutations caused by UV light in skin cancer are distinct from mutations caused by smoking that accumulate in lung cancer."

These types of analyses could also reveal a cancer's cell of origin, which is currently difficult to do for patients who learn they have cancer only after it has spread.

To speed up data analysis, Morris and Duvenaud plan to build a parallel computing platform using multiple graphics-processing units (GPUs), a much faster type of computer hardware. Having first found major use in video games, GPUs have since become an essential component of deep learning, a form of artificial intelligence in which computers learn to recognize patterns from a large amount of data.

Nvidia Foundation is a philanthropic arm of NVIDIA, a technology company that makes some of the top GPUs on the market. In addition to Morris and Duvenaud's teams, a team of researchers from the University of California in San Diego also received funding from the foundation, which has been supporting cancer research since 2011.

IN 2017, OUR RESEARCHERS PUBLISHED 193 STUDIES WITH COLLEAGUES AT HOME AND ALL OVER THE WORLD



The map shows where in the world our collaborators work and with whom we co-published papers during the past year.

For an interactive map, please go to:

bit.ly/CollaborationMap

A SPOTLIGHT ON SOME OF OUR AWARD-WINNING GRADUATE STUDENTS

Hong Han Wins Donnelly Thesis Prize

By Jovana Drinjakovic
April 21, 2017.

When **Hong Han** left her home in China for a university degree in Canada, she was hoping the move would broaden her horizons. 10 years later, with high profile research papers and a host of awards under her belt, she has made contributions to science few of her peers can match.

Han is the recipient of the Donnelly Centre Thesis Prize, awarded annually to a doctoral student, working in a Donnelly Centre lab, whose completed thesis has achieved the highest standards of quality, originality and research significance.

"We are delighted that Hong Han has received the Donnelly Thesis Award for her outstanding PhD thesis on alternative splicing regulatory networks that control cell fate," it was said in a letter from the prize selection committee. This year's committee was chaired by **Jason Moffat** and counts **William Ryu**, **Quaid Morris**, **Andrew Fraser** and **Julie Audet** as members. All are principal investigators in the Donnelly Centre and professors in the University of Toronto.

During her PhD, Han was jointly supervised by **Benjamin Blencowe** and Moffat, both professors in the Donnelly Centre and U of T's Department of Molecular Genetics.

"I am very grateful and honoured to receive this prestigious award. I owe my success to my supervisors,

committee members as well as everyone else who provided support, encouragement and help along the way. The open and shared environment in Blencowe and Moffat labs in the Donnelly Centre has made it a fantastic place for collaboration, without which I would not have been able to make this amount of progress," says Han.

"U of T and MoGen had the great graduate program offering the opportunity to work in the Donnelly Centre with some of the most renowned researchers in the field"

Han studied a process in the cell called alternative splicing (AS), whereby genetic messages that code for proteins are reshuffled and stitched together such that a single gene can code for more than one protein. In this way, AS works to expand the protein repertoire in the cell so that it surpasses the number of available genes. Given than cells are mainly made from proteins, which also do most of the work in them, it's in part thanks to AS that we have a vast range of different cell types in the body—from nerve cells that transmit information in the brain to beating heart cells that pump the blood. And when AS goes awry, this can lead to neurological conditions such as autism, but also to cancer and other diseases. It's not surprising then that understanding the rules of AS is opening new opportunities for diagnosis and treatment.

Han was only half way through her PhD when she made a discovery that has implications for regenerative medicine. Working with stem cells— immature, embryo-like cells that can make all cells in the body—she discovered a previously underappreciated role for AS in maintaining the stem cells' potential to generate all other cell types. She showed that the way stem cells switch from this early, immature state to becoming a differentiated cell, such as a nerve cell for example, is by dialing down an AS program that's controlled by proteins called MBNL1 and MBNL2. Han also showed that silencing the activity of MBNL1 and MBNL2 in differentiated cells can accelerate a process referred to as 'reprogramming', whereby differentiated cells can be transformed into stem cells. The findings were published in *Nature* in 2013, with Han as the lead author, and opened the door to a more efficient way of creating stem cells for research and therapeutic applications.

More recently, Han developed a new technology called SPAR-Seq that allows her to monitor dozens of AS and gene expression events occurring in cells at the same time. The method, published earlier this year in the journal *Molecular Cell*, has attracted a number of collaborations in Canada and abroad.

Continuing her work in the Donnelly Centre as a Home Research Fellow, supported by a fellowship endowed by the family of Robert Bertram Home, Han is currently using the SPAR-Seq platform to search for genes and drugs that can correct autism-related AS errors in nerve cells in the hope of finding a potential splicing-directed drug for autistic patients. With Moffat and Blencowe, Han is also working on another project that aims to identify biomarkers for diagnosis of neurological conditions and cancer by analyzing cell surface protein variants generated by AS.

Born and raised in the coastal city of Dalian, in north east China, Han decided to move to Canada to study biology in the University of British Columbia where living by the ocean reminded her of home. After graduating with distinction, Han's desire to pursue a PhD in functional genomics was sparked by the arrival of new technologies that transformed biological research. Toronto, she said, was an obvious choice.

"I found that U of T and MoGen (Department of Molecular Genetics) had the great graduate program offering the opportunity to work in the Donnelly Centre with some of the most renowned researchers in the field," says Han.

During her time in the Donnelly Centre, Han has won a number of awards, including two Jennifer Dorrington Research Awards, awarded to outstanding students in the Faculty of Medicine, three U of T Open Fellowships and three Ontario Graduate Scholarships.

Meet Stanley Wai-Kwong Ng, Yonatan Lipsitz and Samuel Lambert, winners of the 2017 Jennifer Dorrington Doctoral Research Award, awarded annually to outstanding graduate students in U of T's Faculty of Medicine.

Trio Wins Jennifer Dorrington Graduate Research Award

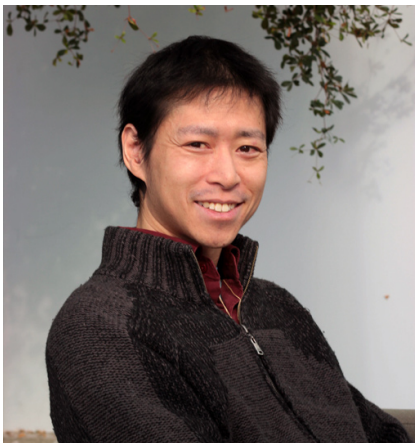
By Jovana Drinjakovic
February 7, 2017.

It's not often that a graduate student develops a diagnostic test, which can accurately predict outcome in patients with leukemia, and which could soon become a staple tool in the clinic. But then again, **Stanley Wai-Kwong Ng** is not an ordinary student. A graduate of computer and electrical engineering, Ng came into cancer research as a novice— and took it by storm. Along with **Yonatan Lipsitz** and **Samuel Lambert**, Ng is a recipient of the 2017 Jennifer Dorrington Doctoral Research Award, awarded annually to outstanding students in the Donnelly Centre for Cellular and Biomolecular Research who are enrolled in the graduate program in U of T's Faculty of Medicine.

"It's an honour to receive this award. I read that Dr. Dorrington died of cancer, so this award is very meaningful to me as my primary motivation for contributing to cancer research is to directly impact and improve patient survival," says Ng, who joined University Professor **Peter Zandstra**'s group after graduating from McMaster University four years ago.

Ng's background in machine learning equipped him with the know-how for detecting subtle patterns in big data. This allowed him to effectively apply a statistical learning algorithm to derive a formula and develop an assay that can rapidly—within 24 to 48 hours—predict clinical outcome in patients with acute myeloid leukemia (AML). Based on gene expression profiling of rare leukemia stem cells (LSC)

in patient blood or bone marrow, the test, known as the LSC17 score, estimates precision prognosis, including overall survival, time to relapse, and how likely the patient is to respond to drugs. Because AML is an aggressive blood cancer that progresses quickly, patients usually start chemotherapy soon after diagnosis, while typically waiting several weeks before tests results come back to reveal patient risk and help doctors decide on the best course of further treatment.



Stanley Wai-Kwong Ng

Ng's work, which was done in close collaboration with Drs. **John Dick**, **Jean Wang**, and **Mark Minden** at the Princess Margaret (PM) Cancer Centre, could vastly cut the time it takes to accurately rank patients according to their risk, and choose the right treatment, early in the disease. It also netted the team a high-profile research paper in a prestigious journal *Nature*, with Ng as a lead author.

Within a few years, clinicians may start using the test that Ng helped develop. To make this happen, Ng has put in place a computational workflow and helped to implement the LSC17 assay in the advanced molecular diagnostics lab at PM to calculate individual patient risk scores. A clinical trial is being planned, which could start as early as the end of the year, while testing of LSC17 may also extend to other centres in Canada and abroad. While he plans to continue working in cancer research by securing a postdoctoral position some time next year, Ng's ongoing efforts will include working closely with the clinic to maximize successful clinical integration of the LSC17 score. "I want to make sure that what I helped to create works in the real world and is helping patients," says Ng.

Like Ng, Lipsitz came to biomedical research from another field. After graduating in chemical engineering from McGill University, Lipsitz was interested in applying his chemical processing knowledge to some of the key challenges in regenerative medicine—production of large quantities of human cells for future cell therapies.

Lipsitz is also a member of the Zandstra lab, where scientists have been developing new technologies aimed at bringing stem cell discoveries to patients. Stem cells are pluripotent, which means that they can give rise to any cell type in the body, and could be used to create replacement tissues and organs to treat a host of diseases. However, scaling up laboratory science to efficiently grow the billions of cells required to treat large patient populations poses unique challenges.

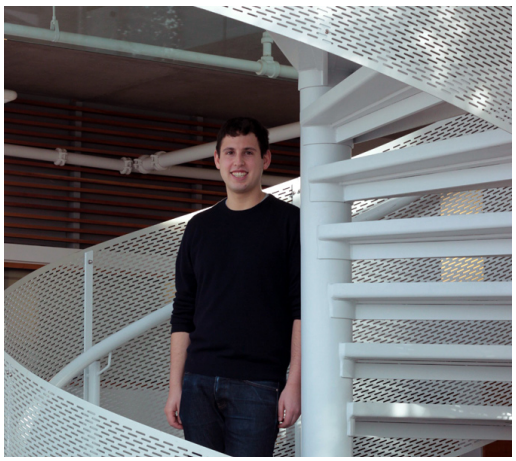
Yonatan Lipsitz

"Peter's lab applies core chemical engineering to biological systems using cutting-edge technologies to overcome the challenges of the scale up process. For example, we are engineering pluripotent stem cells to boost their ability to expand in manufacturing systems," says Lipsitz.
For Lipsitz, who joined the Zandstra lab five years

ago, the timing could not have been better. The last few years have seen a push in Canada and Toronto towards translation of stem cell science into therapies, in which Zandstra plays a key role as co-founder of the Centre for Commercialization of Regenerative Medicine and director of U of T's Medicine by Design.

"I am very excited about seeing these therapies curing patients," says Lipsitz who is eyeing a career in the biotech sector after completing his PhD. "I want to be part of making cell therapies accessible to patients". Lipsitz is already becoming involved in the regenerative medicine community in Toronto. Last month, he and a team of U of T scientists and entrepreneurs identified key bottlenecks in stem cell commercialization and presented their findings to a panel of industry experts.

While the focus of Ng and Lipsitz's research has been to improve patients' lives, Lambert has been grappling with a more fundamental question in biology, at the core of understanding life in all its forms.



Samuel Lambert

After graduating in biology from the University of Guelph, Lambert joined Professor **Timothy Hughes**' group, which is among world-leading in studying how cells read the genome. Each cell in the human body contains the exact same genetic information, yet brain cells are very different from heart cells, which are again different from, say, cells that make up the liver. What makes one cell different from another is a set of genes that is switched on at any given time. In fact, all biological processes, from intricate patterning of butterfly wings to foetal development, are underpinned by the right genes being switched on in the right cells at the right time. When this process breaks down, it can lead to disease.

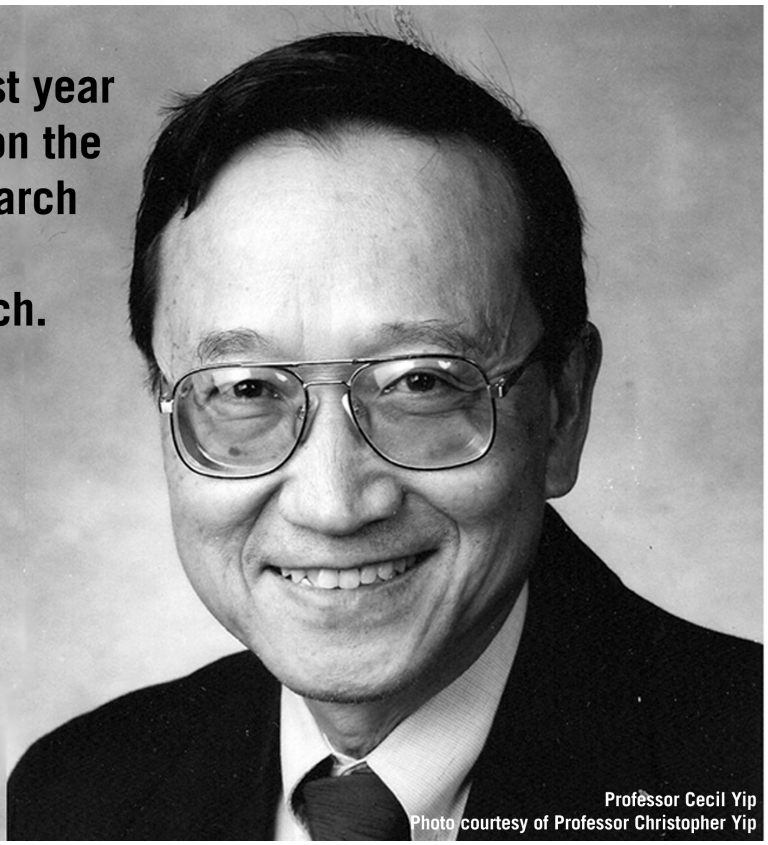
During his PhD, Lambert has been studying proteins called transcription factors (TFs), which bind DNA to turn genes on or off. TFs do this by triggering or halting, respectively, the transcription of genes' sequences into instructions for making proteins, the building blocks of life. TFs recognize specific landing sequences in the DNA, and Lambert's project focused on finding the diversity of sites for TFs in different organisms. Contrary to previous thinking, Lambert found that similar TFs from closely related species often recognize different sites in DNA. He then showed that the same is true across the tree of life suggesting that TF binding differences may be part of the driving force behind evolution.

This is Lambert's second Dorrington Award, having first received it while he was a Master's student. "With the generous support from the Dorrington family, I continued my research in what I think is one of the most fascinating questions in biology. The hope is that if we can understand how cells normally perform these functions we'd have a better clue at how to fix it when it goes awry in disease," says Lambert.

Expecting to graduate in less than five years from starting his PhD, Lambert is planning his next move. "For my postdoc, I would like to join a lab where I can combine what I've learned about gene transcription in my PhD with human genetics to better predict our risk for disease," he says.

The award was established by the Dorrington family in 2006 as a tribute to Dr. Jennifer Dorrington, who was a professor in the Banting and Best Department of Medical Research. Dorrington's pioneering research greatly advanced our understanding of reproductive biology and ovarian cancer.

Ten students in their first year of graduate research won the Cecil Yip Doctoral Research Award in support of interdisciplinary research.



Professor Cecil Yip
Photo courtesy of Professor Christopher Yip

Meet Winners of 2017 Cecil Yip Doctoral Research Award

By Jovana Drinjakovic
August 17, 2017.

Ten PhD candidates who come from diverse training backgrounds, and are enrolled in different U of T graduate programs, have been awarded the Cecil Yip Doctoral Research Award, the award committee has announced. The prestigious award is given annually to first year graduate students who do their doctoral research in the Donnelly Centre and whose proposed projects extend beyond traditional scientific field boundaries. This year's successful candidates come from three U of T departments: Molecular Genetics (MoGen), Chemical Engineering and Applied Chemistry (ChemE) and the Institute of Biomaterials and Biomedical Engineering (IBBME).

"This year's candidates exemplified the unique interdisciplinary environment and collaborative culture of the Donnelly Centre. The diverse backgrounds of the candidates, ranging from biology to engineering and philosophy, and, in some cases, extensive industrial experience, demonstrates how the Donnelly Centre attracts those who are keen to work in areas outside of their comfort zone on some of the most challenging questions in biomedicine," says Professor **Christopher Yip**, Associate Vice-President of International Partnerships and Chair of the Yip Doctoral Award Committee.

Research at the intersection of biology and engineering has the potential to develop new methods for delivering drugs precisely when and where they are needed in order to target cancer for example, or spur on tissue regeneration to heal damage or injury. Mr. **Benjamin Kingston** (IBBME), Ms. **Jessica Ngai** (ChemE) and Mr. **Wayne Ngo** (IBBME) in the Chan lab are studying how tiny nanoparticles can be better engineered to deliver cancer drugs directly into tumours to avoid the all-out toxic assault on the body that comes with chemotherapy.

The diverse backgrounds of the candidates demonstrates how the Donnelly Centre attracts those who are keen to work in areas outside of their comfort zone on some of the most challenging questions in biomedicine

To heal nerves damaged by high levels of glucose in the blood, which can cause diabetic patients to lose all feeling in arms and legs, Ms. **Alaura Androschuk** (IBBME, Sefton) is investigating if a biomaterial, previously discovered by the lab to promote healing of the muscle, can also drive nerve repair.

Investigating cellular processes in easy-to-study organisms such as yeast and worms can reveal insights that apply to all animals but would be very hard to study in humans. To understand how cells change with age, Mr. **Clarence Hue Lok Yeung** (Mogen, Andrews and Boone) is investigating complex genetic networks that drive the aging process in yeast cells. And Mr. **Daniel Merritt** (Mogen, van der Kooy lab) is taking advantage of nematode worms as a model system for understanding the molecular basis of how animals detect smell.

One of the biggest outstanding questions in biology is how cells interpret the genetic information encoded in the DNA and its RNA copies that contain the blueprint for making proteins, the building blocks of life. The so-called RNA binding proteins (RBPs) play an important role by ensuring that an RNA message is correctly prepared before being translated into a protein, but it remains unclear how the RBPs recognize the countless RNA molecules and act on them appropriately. Mr. **Alexander Sasse** (Mogen, Morris) and Ms. **Kaitlin Laverty** (Mogen, Hughes and Morris) are tackling this problem by developing advanced computational models for predicting which RBPs bind which RNA molecules.

Proteins make up our cells and do most of the work in them by interacting with each other to carry out cellular processes. When proteins go awry—cease to interact with their normal partners and/or acquire new alliances—that's when diseases occur. Two of this years' Yip award winners are studying rules behind protein interaction to gain a deeper insight into basic cell biology and mechanisms of disease: Mr. **Dmitri Segal** (Mogen, Taipale) is uncovering binding partners for the 14-3-3- family of "scaffolding" proteins that interact with hundreds of diverse proteins to facilitate molecular events in the cell, whereas Mr. **Greg Martyn** (Mogen, Sidhu) is focusing on the family of SH2 proteins that are involved in a number of diseases, including cancer. Martyn will engineer SH2 superbinders, or protein fragments that bind so strongly to the SH2 proteins that they can be used to manipulate their function and as such used in research and drug development.

The award was established as a tribute to Professor **Cecil Yip**, who was the former Vice-Dean, Research in the Faculty of Medicine and a key player in both the ideology and eventual realization of the Donnelly Centre as an interdisciplinary institute at the forefront of biomedical research.

A SPOTLIGHT ON SOME OF OUR POSTDOCTORAL FELLOWS MAKING THEIR MARK ON CANCER RESEARCH

Meet Jingwen Song, the 2017 Charles H. Best Fellow

By Jovana Drinjakovic
May 24, 2017.

Jingwen Song has won the flagship postdoctoral award in the Donnelly Centre for Cellular and Biomolecular Research. The decision to award Song the Charles H. Best Fellowship was based on academic merit and strength of research proposal.

"The Best award will help me to stay motivated and confident to reach my ultimate goal which is to become a Principal Investigator," says Song.

Song joined University Professor **Jack Greenblatt**'s laboratory earlier this year, after completing graduate studies at McGill University in Montreal.

"Jingwen Song is a very important addition to our group. Her Ph.D. research with Professor Stephane Richard at McGill was impressive, and I expect Jingwen to greatly expand the scope of what we can accomplish," says Greenblatt, a University Professor with appointments in the Donnelly Centre and Department of Molecular Genetics.

During her postdoctoral training, Song will study how genes eventually become protein molecules that make up the cells and do most of the work in them. Once a gene is switched on, its DNA sequence

is copied into an intermediate RNA molecule that serves as a protein template. Song's research will shed light on the molecular processes ensuring that the RNA is made properly. When this goes awry, it can lead to cancer and other diseases.

In particular, Song will focus on two related proteins called RPRD1A and RPRD1B that help make the RNA. Very little is known about these proteins, but abnormally high levels of RPRD1B in 85 per cent of human tumours—including lung, liver, breast and colon— hint at its importance in cancer.

Proteins work by forming alliances with other proteins and Song will identify partners of RPRD1A and RPRD1B in cells with a new technology she is developing. She will also look for drugs that can dial down the two proteins and that could help battle cancer in the future.

"I really like science and enjoy the process of facing and solving the problems," says Song.

Song came to Canada seven years ago after completing an undergraduate degree in biology in Zheng Zhou, her hometown in central China. Following a Master's degree in Professor Barry Posner's group at McGill, she joined Professor Stephane Richard's team for a PhD, also at McGill. During this time, Song first began to explore the link between RNA biology and cancer and won several graduate student awards for her work.

"While I was at McGill, I had heard a lot about Professor Greenblatt because his research is related to what I was doing for my PhD. I had also heard about the Donnelly Centre as being an open collaborative environment with advanced facilities and I am very happy to be here," says Song.

We thank The Charles H. Best Foundation for their continued support for this award. The Fellowship was established in the honor of Charles H. Best, who had only just graduated from university when he co-discovered insulin with Frederick Banting in 1921 in Toronto.

"During my PhD at McGill, I had heard a lot about the Donnelly Centre as an open collaborative environment with advanced facilities and I am very happy to be here"

Wei Zhang Wins Prestigious Cancer Research Award

By Jovana Drinjakovic
October 10, 2017.

When **Wei Zhang** was a graduate student in a research hospital lab, he would encounter cancer patients going through therapy, knowing all too well the damage the treatment was causing to their bodies. "The patient's body is crushed by the drugs, which work by mutating the DNA causing the cancerous cells to die, but normal cells also suffer," says Zhang. Ten years on, Zhang is in a position where he can help develop therapies that target cancer more precisely and are kinder on the patient.

And an award from the Cancer Research Society will help him reach this goal.

Zhang, a senior post-doctoral fellow in the labs of Professors **Sachdev Sidhu** and **Jason Moffat**, of the University of Toronto's Donnelly Centre for Cellular and Biomolecualr Research and Department of Molecular Genetics, has won this year's Cancer Research Society/BMO Bank of Montreal Scholarship for the Next Generation of Scientists. The award supports early young investigators by providing CAD 120K in research funding, once they have obtained a faculty position at a Canadian research institution.

"Wei Zhang has all the attributes of a great scientist and mentor: creativity, perseverance, collegiality and the patience to deal with both peers and trainees,"

says Sidhu, who is also Chief Scientific Officer of the Centre for Commercialization of Antibodies and Biologics and Senior Investigator at the Ontario Institute for Cancer Research. "I am confident he will make a great principal investigator and Canada will be fortunate to retain him in our midst."

The award is expected to help Zhang's application for a faculty position stand out in a fiercely competitive job market and secure research funds in the future.

"With protein engineering, we can create new molecules that have the potential for cancer therapy.

"The award means that I proved to the selection committee of a university that I can attract competitive funding as a principal investigator," says Zhang, who last year won the Mitacs award for Outstanding Innovation for creating proteins capable of destroying the deadly viruses behind the Middle East Respiratory Syndrome (MERS) and Congo-Crimean fever.

Zhang grew up in China and obtained a bachelor's degree in Beijing. He then moved to Canada and received a master's degree from Toronto's York University and a PhD from U of T where he studied DNA damage and repair in the lab of Professor Daniel Durocher at the Sinai Health System's Lunenfeld-Tanenbaum Research Institute. It was during his PhD that Zhang realized that DNA damage could be a way in to target cancer cells more precisely without harming healthy tissue.

Healthy cells have two main systems in place to fix breaks in the DNA that can be caused by radiation or chemicals, for example. In cancer cells, however, one of these repair machineries is often disabled by mutations, leaving them uniquely vulnerable to drugs that block the remaining repair system.

That the approach works was shown by PARP (poly ADP ribose polymerase) inhibitors, new drugs that selectively block one DNA repair machinery to only kill the cancer cells without causing widespread side-effects.

With hundreds of proteins involved in DNA repair, any one of them is a potential drug target. Zhang's plan is to use protein engineering skills that he obtained in the Sidhu and Moffat labs to create new tools to selectively target different parts of the DNA repair machinery.

Protein are complex molecules composed of different parts that do different things in the cell. Most research tools work like a power cut, where they block an entire protein instead of switching off just one light. This all-or-nothing type of intervention can cause side-effects that precise therapies could avoid.

"There is an urgent need for tool molecules, which can be generated using protein engineering, to probe the molecular processes driving DNA repair with unprecedented precision," says Zhang.

Zhang's initial focus will be on the so-called UBZ4 domain proteins, named after the part of the molecule with which they contact other proteins, and which are often mutated in people with Fanconi anemia, a rare inherited disease.

Calm and self-effacing, Zhang also harbors an unmistakable resolve to advance cancer research and to ultimately help patients.

"With protein engineering, we can create a new molecule that can do what we want it to do—for example to bind its partner much more strongly than the natural protein," says Zhang. "And I want to use these proteins as tools to generate molecules that have the potential for cancer therapy."

THROUGH YOUTH OUTREACH WE ARE SPARKING CURIOSITY AND A LOVE OF SCIENCE AMONG OUR YOUNGEST CITIZENS

Image by Lisa Ngo

Donnelly Centre 2017 Youth Science Outreach

By Jovana Drinjakovic
December 23, 2017.

This year, our visitors included grade 8 students, from the **Father Serra** primary school, who spent a day at the Centre learning about cells, tissues and living beings. Starting with baker's yeast, we explained how this simple organism—which consists of only one cell—can teach us a lot about human cells. This is because both humans and yeasts evolved from the same ancestral cell that lived 100 million years ago which makes our cells broadly similar to yeast cells. Moving on to tissues, our visitors saw stem cells growing in a dish and learned how, with clever tricks, these cells can be coaxed to become, say, eye or heart tissue which scientists hope to one day use as replacement body parts to treat injury and disease. Finally, tiny worms crawling in a dish served as an example of a multicellular animal — and one that scientists in the Donnelly Centre and around the world use as a research tool to figure out how genes work.

Later in the year, our friends from the **Dragon Academy** high school came for seminars on muscle repair and microfluidics.

We believe that science is for everyone, regardless of gender or background, and we are thrilled to have

Dragon Academy students and teachers with members of the Wheeler lab who demonstrated their microfluidics device that had been used to detect infectios disease in rural Africa (Lisa Ngo).

had the opporunity to welcome students from the **Canadian Association for Girls in Science** and the **Visions of Science Network Learning** and look forwad to having more events together.

In April, it was time for the annual **Bring Our Children to Work** (BOCW) day, open to children in grades 4-7 of U of T employees. The organizer Christine Misquitta and Donnelly Centre graduate students and postdoctoral fellows who acted as demonstrators talked about ongoing research at the Centre, showed the kids how to extract their own DNA and tickled their brains by asking them to decipher a message written in the DNA code.

In May, we took our experiments outside for **ScienceRendezvous**, the annual nation-wide celebration of science. At U of T, the event takes place along St. George Street which becomes packed with booths from diverse U of T departments and its research hospitals. To mark the 150th anniversary of Canada, the goal was to highlight how Canadian science and its scientists made their mark on the world. Our booth featured, among others, an experiment that measures how much sugar there is in various foods and drinks to help raise a better understanding of how to keep heathy and stave off diabetes which is only treatable thanks to the discovery of insulin, made at U of T almost a century ago.

BOCW participants extracting their own DNA from cheek cells (Christine Misquitta).

Passerbys taking part in science activities at the Donnelly Centre booth during Science Rendezvous

In the fall, instead of welcoming visitors at the centre, it was us who went on the road. We joined colleagues from SickKids and Mount Sinai for a mini science fair in the **Lincoln M. Alexander** secondary school in Mississauga organized by the school's science teacher and U of T alum Ms. Dao Tran. We brought yeasts, flies and fish larvae as examples of organisms that our scientists study in order to understand how cells work and break down during disease. Tahani Baakdah, our talented graduate student brought her needlework—yes needlework! Tahani crochets stem cells, neurons and brains to explain her research to kids!

"Thank you for your generosity in sharing the time, the passion for science, the knowledge and the resources. Conversations are more science-rich because of their interactions with you and your resources" - Ms. Dao Tran, science teacher, L.M. Alexander Secondary School

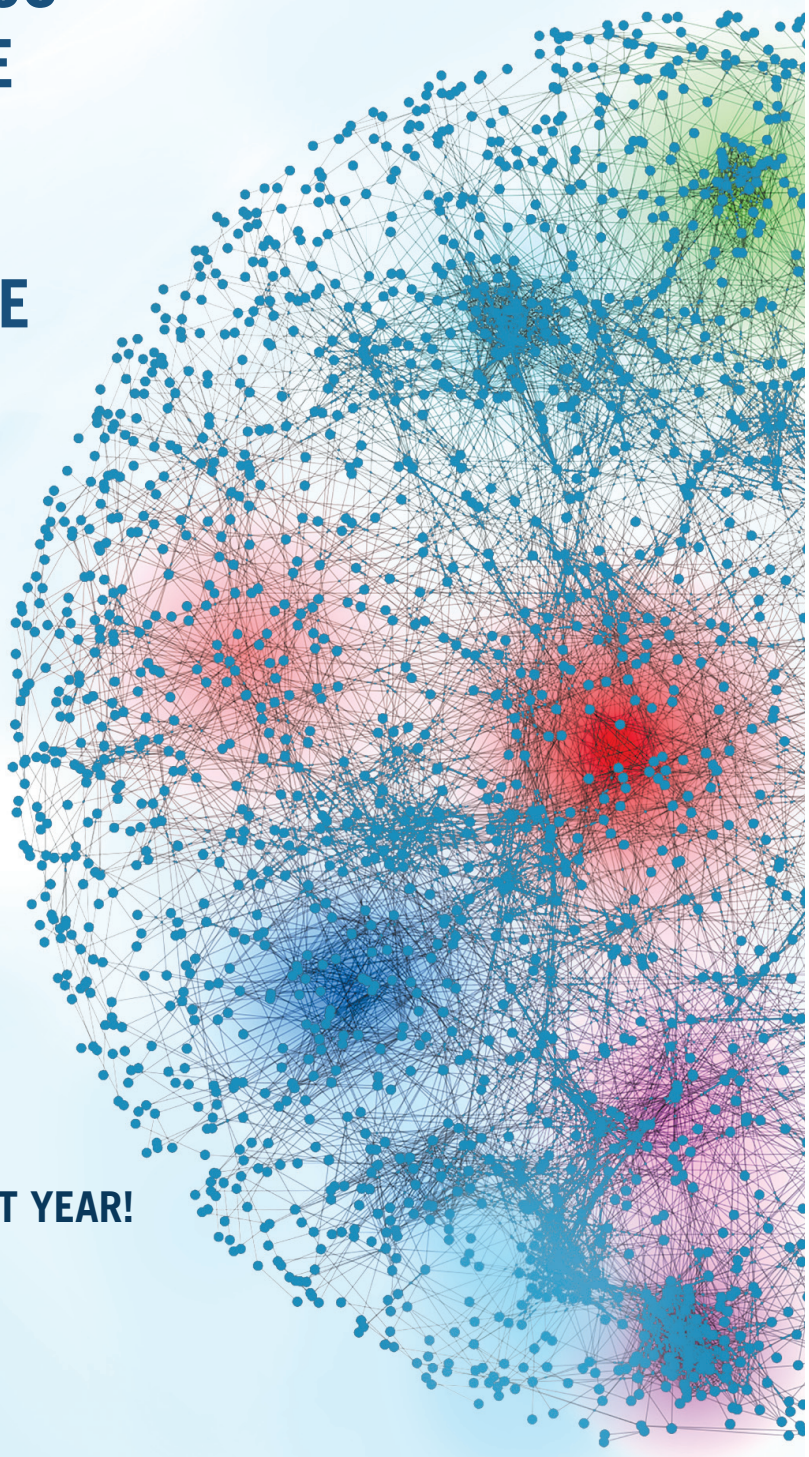
Our props for a science fair at the Lincoln M. Alexander Secodnary School in Mississagua.

SELECT MEDIA HIGHLIGHTS

During the past year, some of our researchers and their discoveries reached a wider audience by being featured in print and online media. Here is a selection of some of the highlights:

- Quaid Morris gave interview to CBC Radio One's Metro Morning on how artificial intelligence can shape medicine
- Sachdev Sidhu was interviewd for CBC Radio 1's The Current about the high cost of drugs for rare genetic diseases
- Andy Fraser was a guest on CTV Toronto's Knight in the Morning
- Igor Stagljar was featured on Croatian national TV about his discovery involving a class of proteins that regulate cancer growth
- Major research collaboration finds new genetic markers for breast-cancer risk - *The Globe and Mail*
- Breast cancer breakthrough as study uncovers new genetic variants that increase risk - *The Guardian*
- Personalized cancer plans the future of fighting disease - *Toronto Star*
- How the discovery of stem cells revolutionized medicine - *The Globe and Mail*
- Prestigious Killam Prize for engineering awarded to female scientist second year in a row - *CBC News*
- A Killam Prize winner's top 5 ideas for getting more women in STEM - *CTV News*
- In this lab, researchers work to reverse degenerative disease and gender discrimination - *The Times of Israel*
- Could Absence of NSR100 protein in Brain Cells Explain Autism? - *AutisMag*
- What Kind of Mutant Are You? - *Research 2 Reality*
- We Don't Understand Life… But We're Trying - *Research 2 Reality*
- Finally, a way to halt Canada's 'brain drain' - *The Globe and Mail*
- Indo-Canadian venture radicalises drug research - *Hindustan Times*
- Ontario appoints first chief scientist to 'make government smarter' - *CBC News*
- Pionyr Immunotherapeutics gains meaty $62M series B - *FierceBiotech*
- CCAB: bridging Canadian academic R&D with the biotherapeutics economy - *Canadian Innovation News*

WE WISH TO EXPRESS OUR THANKS TO THE FOLLOWING DONORS WHO MADE GIFTS IN 2017 TO ADVANCE OUR WORK:



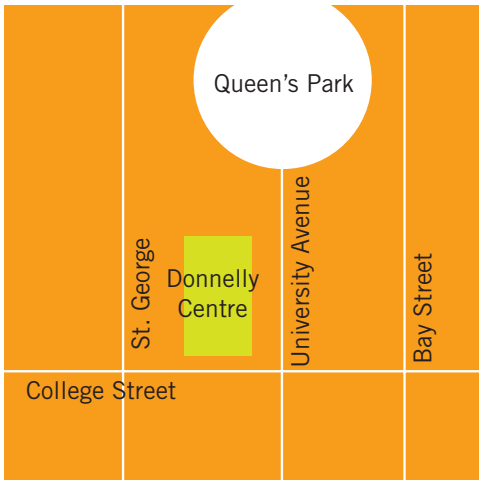
Terrence Donnelly

Glenna Duff
The Charles H. Best Foundation
NVIDIA Foundation
Anonymous

THANKS EVERYONE FOR A GREAT YEAR!

Please visit our website:

www.thedonnellycentre.utoronto.ca



Donnelly Centre, University of Toronto

160 College Street | Toronto, ON M5S 3E1 | T: 416.978.8861 | F: 416.978.8287

www.thedonnellycentre.utoronto.ca

Donnelly Centre
for Cellular + Biomolecular Research

UNIVERSITY OF TORONTO