



Donnelly Centre
for Cellular + Biomolecular Research
UNIVERSITY OF TORONTO



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DONNELLY CENTRE 2016 ANNUAL REPORT



In the past year, our researchers made discoveries that have the potential to improve lives. They also continued to reap prestigious awards and win competitive funding for their research, as well as train the next generation of researchers. None of this would have been possible without the generous founding support from our donor Terrence Donnelly and others who donated gifts to support our science.

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OUR DISCOVERIES PAVE THE WAY FOR BETTER UNDERSTANDING AND TREATMENT OF DISEASE



Ben Blencowe's team helps uncover one protein's sweeping influence on **autism**. The finding opens the door to further research that could lead to earlier diagnosis and treatment.

Photo: Sabine Cordes

One Protein's Sweeping Influence on Autism Revealed

By Jovana Drinjakovic

As many as a third of autism cases could be explained by a scarcity of a single protein in the brain, Toronto scientists have revealed. The findings provide a unique opportunity to develop treatments for a disorder that is rooted in a motley crew of genetic faults. Researchers induced autistic-like behaviour in mice by lowering the levels of a protein, called nSR100 (also known as SRRM4),

which is important for normal brain development. The study, published on December 15, 2016, in the journal *Molecular Cell*, builds on the teams' previous work which showed that the nSR100 protein was reduced in the brains of autistic people.

The teams were led by Professors **Benjamin Blencowe** of the University of Toronto's Donnelly Centre and **Sabine Cordes** of the

Department of Molecular Genetics and Sinai Health System's Lunenfeld-Tanenbaum Research Institute.

"We previously reported an association between nSR100 protein levels and autism. But this time we show that reduced levels of this protein could really be causative—that's a big deal. Just by reducing the nSR100 levels by 50 per cent, we observe hallmarks of autistic behaviour," said Cordes.

The data also suggest that nSR100 acts as a hub that channels diverse molecular miscues which contribute to autism.

Known best for altered social behaviours, the degree of which can vary tremendously, autism is a common neurological disorder affecting more than one per cent of the population. While its origins are genetic, the specific causes are known in only a fraction of cases that fall into the autism spectrum disorder (ASD). For the majority of people diagnosed with ASD, the reasons behind their disorder remain unknown.

The U of T study provides evidence for the sweeping influence that nSR100 protein has on social behaviour and other features of autism. In the brain, nSR100 acts as a key regulator of alternative splicing—a process that generates a remarkable diversity of proteins, the building blocks of cells.

Proteins are encoded in the DNA sequence of the genes, but the useful instructions are broken up and separated by non-coding DNA. During alternative splicing, non-coding spacers are spliced out and protein-coding segments are brought together to make a finished protein template. But the order in which the coding instructions are stitched together can change so that a single gene can spawn a variety of proteins. This way, cells can expand their protein toolbox to vastly outstrip the number of genes. It's no surprise then,

that alternative splicing is especially pronounced in the brain, where the mushrooming protein diversity is thought to be the driving force behind the brain's astonishing complexity.

Blencowe's team previously discovered nSR100 and had shown that it is diminished in the brains of many autistic people. This finding suggested that autism could, in part, stem from an accumulation of incorrectly spliced proteins in brain cells. This could then lead to mistakes in brain wiring and autistic behaviour further down the road.

A major value of the nSR100 deficient mouse is that it can explain other causes of autism and how they impact neurobiology by converging on the nSR100 protein

This time, the teams decided to test head-on if nSR100 scarcity can indeed cause autism. To do this, **Mathieu Quesnel-Vallieres**, a graduate student jointly supervised by Blencowe and Cordes, created a mutant mouse that lacks nSR100 in order to study its behaviour.

The researchers were amazed to find that reducing nSR100 protein levels only by half was enough to trigger the behavioural hallmarks of autism, including avoidance of social interactions and heightened sensitivity to noise. The nSR100 mutant mice also shared many other features of autism with human patients, such as changes in alternative splicing and brain wiring.

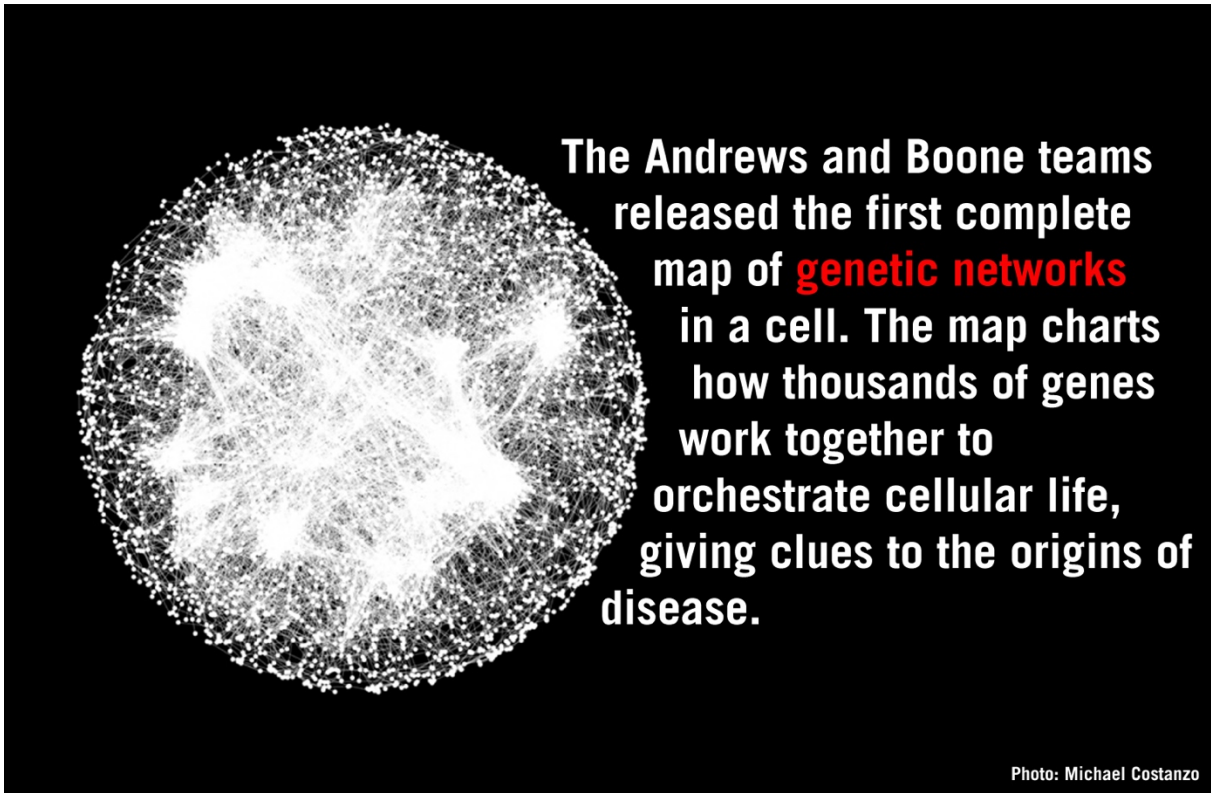
Working with graduate student **Zahra Dargaei** and Professor **Melanie Woodin** in the Department of Cell and Systems Biology at the

University of Toronto, and with Dr. **Manuel Irimia** at the Centre for Genomic Regulation in Barcelona, the researchers were also able to show that nSR100 levels are linked to neuronal activity. “If you have an increase in neuronal activity, which is the case in many forms of autism, the nSR100-controlled alternative splicing program is disrupted and this likely underlies autistic behaviour,” said Quesnel-Vallieres. “A major value of the nSR100 deficient mouse is that it can explain other causes of autism and how they impact neurobiology by converging on the nSR100 protein”, said

Blencowe, who is also a professor in U of T's Department of Molecular Genetics. “Our mouse model will also serve as a useful testing ground for small molecules that have potential to reverse nSR100 deficiency in autism,” he added.

“Instead of focusing on individual mutations linked to autism, it's much more powerful to identify regulatory hubs like nSR100. In the future, if you turned this protein up a little bit in autistic patients, you might be able to improve some of the behavioural deficits” said Cordes.

Instead of focusing on individual mutations linked to autism, it's much more powerful to identify regulatory hubs like nSR100. In the future, if you turned this protein up a little bit in autistic patients, you might be able to improve some of the behavioural deficits



The Andrews and Boone teams released the first complete map of **genetic networks** in a cell. The map charts how thousands of genes work together to orchestrate cellular life, giving clues to the origins of disease.

Photo: Michael Costanzo

Landmark Map Reveals the Genetic Wiring of Cellular Life

By Jovana Drinjakovic

Donnelly Centre researchers have created the first map that shows the global genetic interaction network of a cell. It begins to explain how thousands of genes coordinate with one another to orchestrate cellular life. The study was led by U of T Professors **Brenda Andrews** and **Charles Boone**, and Professor **Chad Myers** of the University of Minnesota-Twin Cities. It opens the door to a new way of exploring how genes contribute to disease, with a potential for developing finely-tuned therapies. The findings are published in the journal *Science* on September 23, 2016.

“We’ve created a reference guide for how to chart genetic interactions in a cell. We can now tell what kind of properties to look for in searching for highly connected genes in human genetic networks with the potential to impact genetic diseases,” said Dr. **Michael Costanzo**, a Research Associate in the Boone lab and one of the researchers who spearheaded the study.

The study took 15 years to complete and adds to Andrews’ rich scientific legacy for which she was awarded a Companion of the Order of

Canada – the highest civilian honour in the country.

Just as societies in the world are organized from countries down to local communities, the genes in cells operate in hierarchical networks to organize cellular life. If we are to understand what 20,000 human genes do, we must first find out how they are connected to each other.

Studies in yeast cells first showed the need to look farther than a gene's individual effect to understand its role. With 6,000 genes, many of which are also found in humans, yeast cells are relatively simple but powerful stand-ins for human cells. Over a decade ago, an international consortium of scientists first deleted every yeast gene, one by one. They were surprised to find that only one in five were essential for survival. It wasn't until the last year that advances in gene editing technology allowed scientists to tackle the equivalent question in human cells. It revealed the same answer: a mere fraction of genes are essential in human cells too.

These findings suggested most genes are "buffered" to protect the cells from mutations and environmental stresses. To understand how this buffering works, scientists had to ask if cells can survive upon losing more than one gene at a time, and they had to test millions of gene pairs. Andrews, Boone and Myers led the pioneering work in yeast cells by deleting two genes at a time, in all possible pairwise combinations, to find gene pairs that are essential for survival. This called for custom-built robots and a state-of-the-art automated pipeline to analyse almost all of the mind-blowing 18 million different combinations.

The yeast map identified genes that work together in a cell. It shows how, if a gene function is lost, there's another gene in the genome to fill its role. Consider a bicycle

analogy: a wheel is akin to an essential gene – without it, you couldn't ride the bike. Front brakes? Well, as long as the back brakes are working, you might be able to get by. But if you were to lose both sets of brakes, you are heading for trouble. Geneticists would say that front and back brakes are "synthetic lethal," meaning that losing both, but neither by themselves, spells doom. Synthetic lethal gene pairs are relatively rare, but because they tend to control the same process in the cell, they reveal important information about genes we don't know much about – for example, scientists can predict what an unexplored gene does in the cell, simply based on its genetic interaction patterns.

We can now tell what kind of properties to look for in searching for highly connected genes in human genetic networks with the potential to impact genetic diseases

It's becoming increasingly clear that human genes also have one or more functional backups. So instead of searching for single genes underlying diseases, we could instead be looking for gene pairs. That is a huge challenge because it means examining about 200 million possible gene pairs in the human genome for association with a disease.

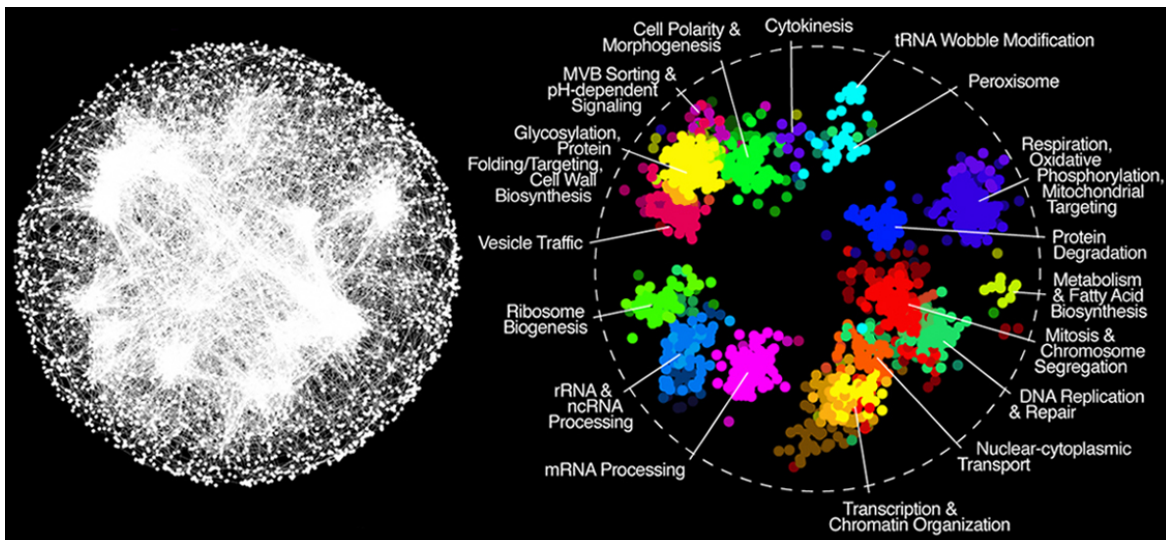
Fortunately, with the know-how from the yeast map, researchers can now begin to map genetic interactions in human cells, and even expand it to different cell types. Together with whole-genome sequences and health parameters measured by new personal devices, it should finally become possible to find combinations of genes that underlie human physiology and disease.

“Without our many years of genetic network analysis with yeast, you wouldn’t have known the extent to which genetic interactions drive cellular life or how to begin mapping a global genetic network in human cells. We have tested the method to completion in a model system to provide the proof of principle for how to approach this problem in human cells. There’s no doubt it will work and generate a wealth of new information,” said Boone, who is also a professor in U of T’s molecular genetics department, a Senior Fellow and a co-director of the Genetic Networks program at the Canadian Institute for Advanced Research (CIFAR) and holds Canada Research Chair in Proteomics, Bioinformatics and Functional Genomics.

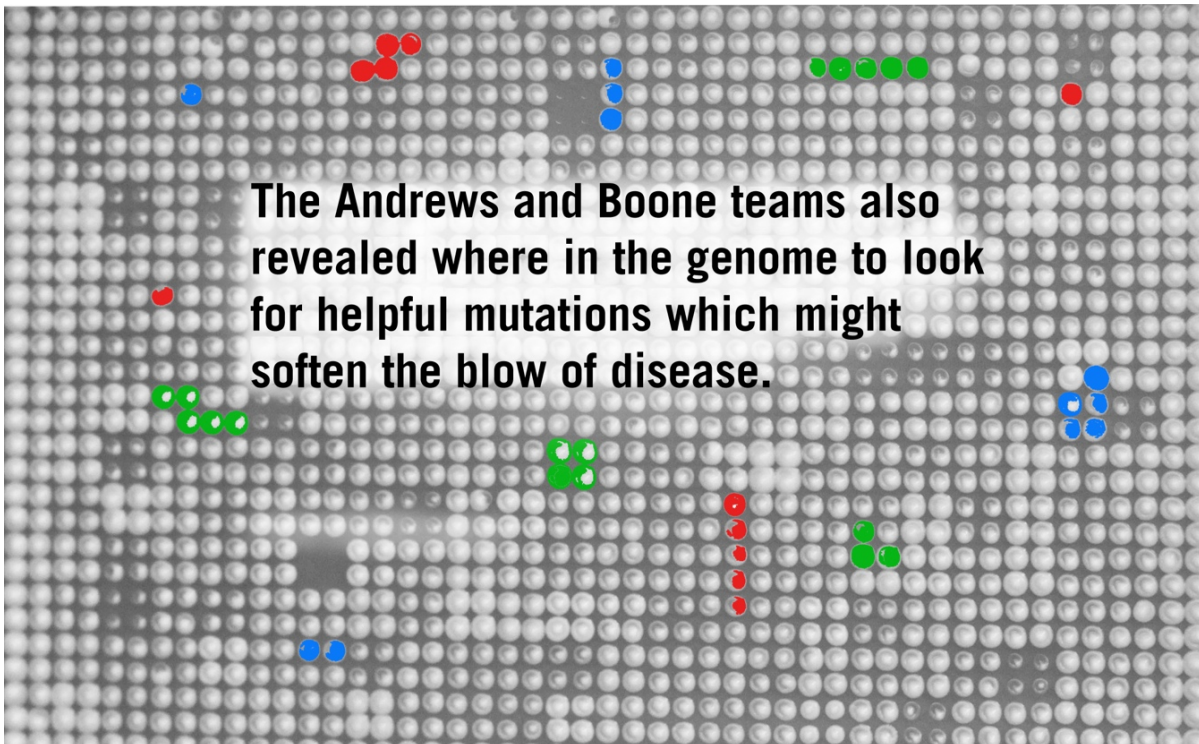
The concept of synthetic lethality is already changing cancer treatment because of its potential to identify drug targets that exist only in tumour cells. Cancer cells differ from normal cells in that they have scrambled

genomes, littered with mutations. They’re like a bicycle without a set of brakes. If scientists could find the highly vulnerable back-up genes in cancer, they could target specific drugs at them to destroy only the cells that are sick, leaving the healthy ones untouched.

We have tested the method to completion in a model system to provide the proof of principle for how to approach this problem in human cells



Yeast genes (circles) sharing similar patterns of genetic interactions are connected in a global network. Genetic interaction patterns cluster genes into major biological processes, mapping a functional wiring diagram of the cell. It allows scientists to predict gene function based on interaction profile.



Why Bad Genes Aren't Always Bad News

By Jovana Drinjakovic

We usually think of mutations as errors in our genes that will make us sick. But not all errors are bad, and some can even cancel out the fallout of those mutations known to cause disease. While little has been known about this process — called genetic suppression — that will soon change as Donnelly Centre researchers uncover the general rules behind it.

Teams led by Professors **Brenda Andrews**, **Charles Boone** and **Frederick Roth**, of the Donnelly Centre and the Department of Molecular Genetics, in collaboration with Professor Chad Myers, of the University of Minnesota-Twin Cities, have compiled the first comprehensive set of suppressive

mutations in a cell, as reported in *Science* today. The four researchers are members of the Genetic Networks program of the Canadian Institute for Advanced Research. Their findings could help explain how suppressive mutations combine with disease-causing mutations to soften the blow or even prevent disease.

This curious bit of biology has only come to light as more healthy people have had their genomes sequenced. Among them are a few extremely lucky folks who remain healthy despite carrying catastrophic mutations that cause debilitating disorders, such as Cystic Fibrosis or Fanconi anemia.

How could this be?

“We don’t really understand why some people with damaging mutations get the disease and some don’t. Some of this could be due to environment, but a lot of could be due to the presence of other mutations that are suppressing the effects of the first mutation,” said Roth, who is also a Senior Scientist at Sinai Health System’s Lunenfeld-Tanenbaum Research Institute.

Imagine being stuck in a room with a broken thermostat and it’s getting too hot. To cool down, you could fix the thermostat—or you could just break a window. Genetic suppression essentially “breaks the window” to keep cells healthy despite damaging mutations. And it opens a new way of understanding, and maybe even treating, genetic disorders.

“If we know the genes in which these suppressive mutations occur, then we can understand how they relate to the disease-causing genes and that may guide future drug development,” said Dr. **Jolanda van Leeuwen**, a postdoctoral fellow in the Boone lab and one of the scientists who spearheaded the work.

But finding these mutations is not easy; it’s a proverbial needle in the haystack. A suppressive mutation could, in theory, be any one of the hundreds of thousands of misspellings in the DNA, scattered across the 20,000 human genes, which make every genome unique. To test them all would be impractical.

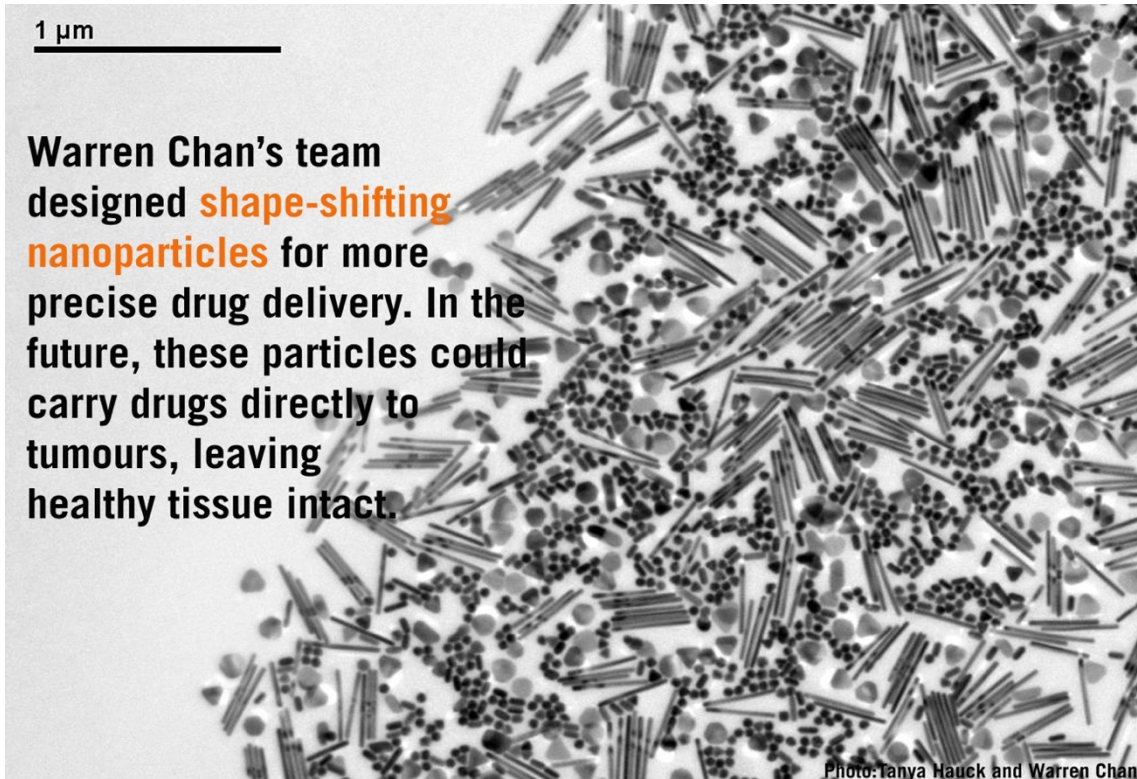
“A study like this has never been done on a global scale. And since it is not possible to do these experiments in humans, we used yeast as a model organism, in which we can know exactly how mutations affect the cell’s health,” said Van Leeuwen. With only 6,000 genes, yeast cells are a simpler version of our

own, yet the same basic rules of genetics apply to both.

The teams took a two-pronged approach. On the one hand, they analyzed all published data on known suppressive relationships between yeast genes. While informative, these results were inevitably skewed towards the most popular genes — the ones that scientists have already studied in detail. Which is why Van Leeuwen and colleagues also carried out an unbiased analysis by measuring how well the cells grew when they carried a damaging mutation on its own, or in combination with another mutation. Because harmful mutations slow down cell growth, any improvement in growth rate was thanks to the suppressive mutation in a second gene. These experiments revealed hundreds of suppressor mutations for the known damaging mutations.

Importantly, regardless of the approach, the data point to the same conclusion. To find suppressor genes, we often don’t need to look far from the genes with damaging mutations. These genes tend to have similar roles in the cell — either because their protein products are physically located in the same place, or because they work in the same molecular pathway.

“We’ve uncovered fundamental principles of genetic suppression and show that damaging mutations and their suppressors are generally found in genes that are functionally related. Instead of looking for a needle in the haystack, we can now narrow down our focus when searching for suppressors of genetic disorders in humans. We’ve gone from a search area spanning 20,000 genes to hundreds, or even dozens. That’s a big step forward,” said Boone.



Warren Chan's team designed **shape-shifting nanoparticles** for more precise drug delivery. In the future, these particles could carry drugs directly to tumours, leaving healthy tissue intact.

Shape-shifting Engineered Nanoparticles for Delivering Cancer Drugs to Tumours

By Marit Mitchell

Chemotherapy isn't supposed to make your hair fall out — it's supposed to kill cancer cells. A new molecular delivery system created at U of T could help ensure that chemotherapy drugs get to their target while minimizing collateral damage.

Many cancer drugs target fast-growing cells. Injected into a patient, they swirl around in the bloodstream acting on fast-growing cells wherever they find them. That includes tumours, but unfortunately also hair follicles, the lining of your digestive system, and your skin.

Professor **Warren Chan**, an investigator in the Donnelly Centre, and also affiliated with the Institute for Biomaterials and Biomedical Engineering and the Departments of Chemical Engineering and Applied Chemistry and Materials Science and Engineering, has spent the last decade figuring out how to deliver chemotherapy drugs into tumours — and nowhere else. Now his lab has designed a set of nanoparticles attached to strands of DNA that can change shape to gain access to diseased tissue.

“Your body is basically a series of compartments,” says Chan. “Think of it as a

giant house with rooms inside. We're trying to figure out how to get something that's outside, into one specific room. One has to develop a map and a system that can move through the house where each path to the final room may have different restrictions such as height and width."

One thing we know about cancer: no two tumours are identical. Early-stage breast cancer, for example, may react differently to a given treatment than pancreatic cancer, or even breast cancer at a more advanced stage. Which particles can get inside which tumours depends on multiple factors such as the particle's size, shape and surface chemistry. Chan and his research group have studied how these factors dictate the delivery of small molecules and nanotechnologies to tumours, and have now designed a targeted molecular delivery system that uses modular nanoparticles whose shape, size and chemistry can be altered by the presence of specific DNA sequences.

"We're making shape-changing nanoparticles," says Chan. "They're a series of building blocks, kind of like a LEGO set." The component pieces can be built into many shapes, with binding sites exposed or hidden. They are designed to respond to biological molecules by changing shape, like a key fitting into a lock.

These shape-shifters are made of minuscule chunks of metal with strands of DNA attached to them. Chan envisions that the nanoparticles will float around harmlessly in the blood stream, until a DNA strand binds to a sequence of DNA known to be a marker for cancer. When this happens, the particle changes shape, then carries out its function: it can target the cancer cells, expose a drug molecule to the cancerous cell, tag the cancerous cells with a signal molecule, or

whatever task Chan's team has designed the nanoparticle to carry out. Their work was published this week in the leading journal *Science*.

"We were inspired by the ability of proteins to alter their conformation — they somehow figure out how to alleviate all these delivery issues inside the body," says Chan. "Using this idea, we thought, 'Can we engineer a nanoparticle to function like a protein, but one that can be programmed outside the body with medical capabilities?'"

Applying nanotechnology and materials science to medicine, and particularly to targeted drug delivery, is still a relatively new concept, but one Chan sees as full of promise. The real problem is how to deliver enough of the nanoparticles directly to the cancer to produce an effective treatment.

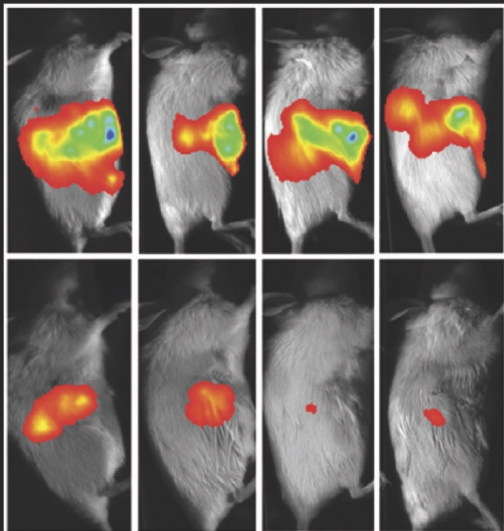
"Here's how we look at these problems: it's like you're going to Vancouver from Toronto, but no one tells you how to get there, no one gives you a map, or a plane ticket, or a car — that's where we are in this field," he says.

"The idea of targeting drugs to tumours is like figuring out how to go to Vancouver. It's a simple concept, but to get there isn't simple if not enough information is provided."

"We've only scratched the surface of how nanotechnology 'delivery' works in the body, so now we're continuing to explore different details of why and how tumours and other organs allow or block certain things from getting in," adds Chan.

He and his group plan to apply the delivery system they've designed toward personalized nanomedicine — further tailoring their particles to deliver drugs to your precise type of tumour, and nowhere else.

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



Using gene editing and custom antibody design, the Moffat and Sidhu teams created a tailored drug that works against **pancreatic cancer**.

Their technology can be extended to a wide range of cancers to rapidly yield new and more precise candidate drugs.

Donnelly Researchers Rapidly Identify New Drug Target and Develop Antibodies to Kill Pancreatic Cancer Cells

By Jef Ekins

Researchers at the University of Toronto have developed a process that dramatically cuts the amount of time it takes to create new cancer treatments. Using a breakthrough technology, their study, published this week in *Nature Medicine*, identified a new potential drug target in a class of pancreatic cancer, and unveiled a new treatment option that exploits genetic faults to destroy cancer cells.

Professors **Jason Moffat** and **Sachdev Sidhu** from the Donnelly Centre and the department of molecular genetics, along with Professor

Stephane Angers from the Leslie Dan Faculty of Pharmacy, made this discovery using the cutting-edge CRISPR-Cas9 genome editing technology.

Using this revolutionary tool, the teams probed the function of every single gene expressed by pancreatic cancer cells to determine that one of the receptors (Frizzled-5) is essential for the growth of mutant pancreatic cancer cells. Normally, the signaling pathways activated by Frizzled-5 tell cells when to divide, what types of cells to

become, and when they should die. When mutated or deregulated, however, they can initiate tumour growth.

"This is the first time that we are able to identify bona fide genetic weaknesses in cancer cells that we can target with drugs, which will not harm healthy tissue," said Moffat.

Having identified the key role that the Frizzled-5 receptor plays in promoting pancreatic cancer growth, the team rapidly developed an antibody drug to inhibit the growth of these cells. The study showed that the antibody proved highly effective in killing the cancer cells in patient-derived samples and shrank tumours in mice without damaging the surrounding healthy cells.

Leveraging the Donnelly Centre's state-of-the-art platform for custom antibody design, the team was able to create a targeted antibody in months – a fraction of the time it would normally take to develop a safe and effective treatment for a specific cancer.

"Our technology allows us to quickly develop a drug that's tailored to a particular kind of cancer and ready to be tested on people. In this study we show that the approach works for a type of pancreatic cancer, but this is only the tip of the iceberg," said Sidhu.

As part of this study, the team also explored the role of this receptor in colorectal cancer, a form of cancer that shares common features with pancreatic cancer. The results of this study indicate that Frizzled-5 may be a factor across multiple cancer types, broadening the potential use of anti-Frizzled-5 antibodies as a targeted cancer therapy.

"Ultimately, this study revealed genetic vulnerabilities in pancreatic cancer cells that could be exploited through the development of new targeted antibodies to inhibit tumor growth," said Angers. "By targeting the exact

signaling circuit activated in these tumors, these rapidly developed antibodies have shown considerable promise as a cancer treatment. Moreover, the state-of-the-art antibody development platform developed at U of T is a transformational leap forward in our ability to rapidly create exciting new treatments to combat various cancers."

Our technology allows us to quickly develop a drug that's tailored to a particular kind of cancer and ready to be tested on people. In this study we show that the approach works for a type of pancreatic cancer, but this is only the tip of the iceberg

OUR RESEARCHERS CONTINUE TO RECEIVE THE HIGHEST ACCOLADES



Professor Brenda Andrews Awarded Companion of the Order of Canada

By Jovana Drinjakovic

Professor **Brenda Andrews**, Director of the Donnelly Centre, has been awarded the Order of Canada. Andrews was named a Companion of the Order – 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,” the Governor General’s office said in its citation. “It feels incredible to be awarded this honour, given all the other people who have been honoured by the Companion of the Order of Canada. I am humbled,” Andrews said last year.

Governor General **David Johnston** also gave the honours to U of T President **Meric Gertler** and several faculty members, whose appointments were announced on December 30 last year.

“Brenda Andrews has moved Canada to the forefront of large-scale genetic studies. Her research has illuminated how diseases are influenced by interactions among entire networks of genes. The innovative techniques she has developed for analyzing these interactions have been adopted by scientists around the world and are helping researchers respond to complex hereditary diseases,” the Governor General’s office said on its website. Andrews, who is also a professor in the Department of Molecular Genetics, is a Fellow of the Royal Society of Canada, a Senior Fellow of the Canadian Institute for Advanced Research and holds the Charles H. Best Chair of Medical Research at U of T. Andrews’ more recent awards also include:

- JJ Berry Smith Doctoral Supervision Award, School of Graduate Studies, University of Toronto, 2013 (inaugural award)
- The Emil Christian Hansen Award for Microbiology, The Carlsberg Foundation, Copenhagen (with Charles Boone), 2013
- Fellow, American Academy of Microbiology, 2012
- Fellow of the American Association for the Advancement of Science, 2011
- Ira Herskowitz Award, Genetics Society of America, 2010

After completing her PhD in molecular biology and biochemistry with Dr. **Paul Sadowski** at U of T, Andrews obtained her postdoctoral training in genetics with Dr. **Ira Herskowitz** at the University of California, San Francisco

(UCSF). Andrews returned to U of T as an Assistant Professor in the Department of Medical Genetics to start her own research group and was elected Chair of Department in 1999.

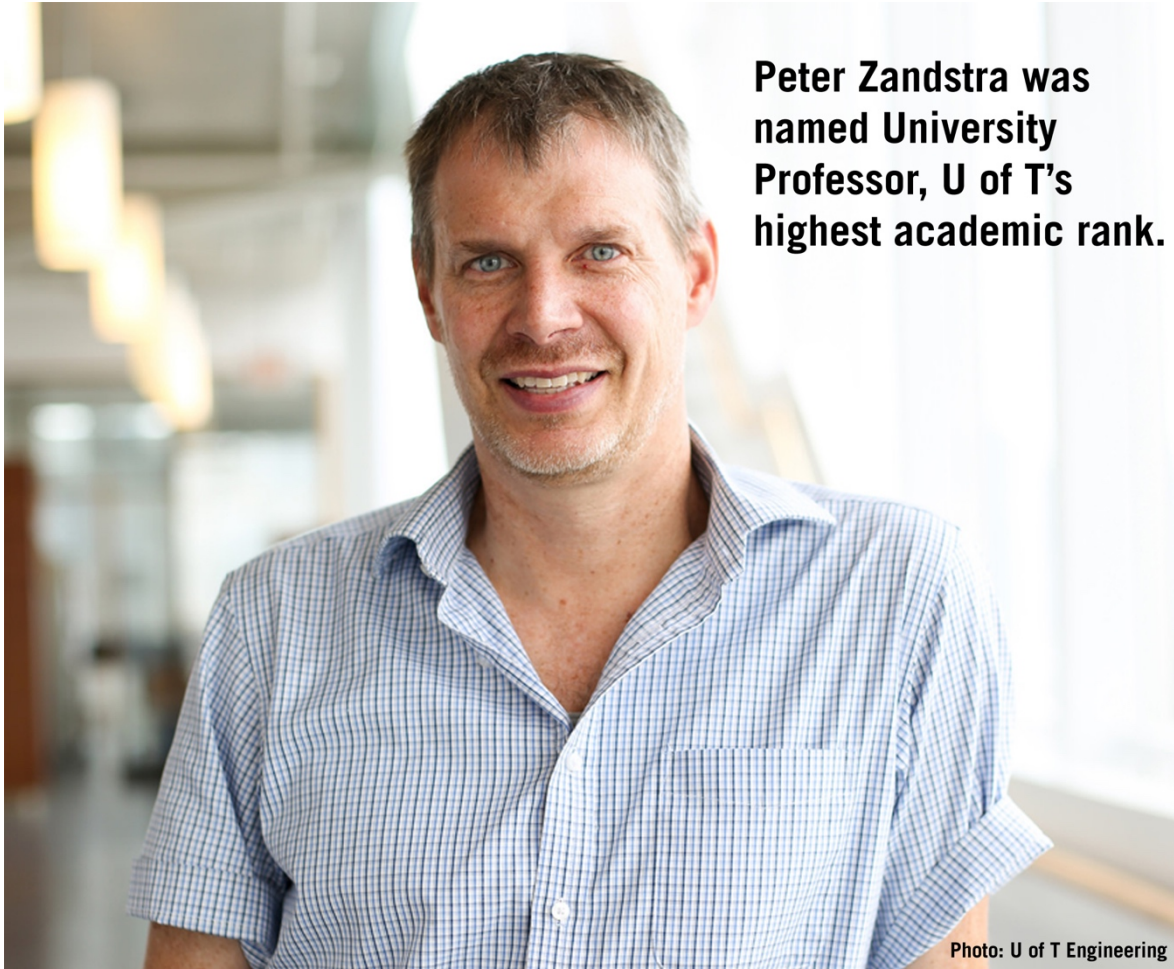
Around this time, Andrews began to collaborate with Professor **Charles Boone** to lay the backbones of the emerging field of genetic networks that aims to understand how genes work co-operatively, rather than as single players, to determine cells’ health and behaviour.

Many of the problems at the cutting edge of modern biology are too vast for a single group to tackle. The collaborative nature of the Donnelly Centre lets us pull together as a team to address these new frontiers

When the 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. The Centre houses 35 research investigators and over 500 staff and trainees who work side by side in an open-concept space to tackle some of the biggest questions in biology.

As a firm supporter of collaborative research, Andrews continues to work with Boone and other scientists to drive innovation in large-scale genetics and computational methods.

“Many of the problems at the cutting edge of modern biology are too vast for a single group to tackle. The collaborative nature of the Donnelly Centre lets us pull together as a team to address these new frontiers,” says Andrews.



Peter Zandstra was named University Professor, U of T's highest academic rank.

Photo: U of T Engineering

Peter Zandstra Named University Professor, U of T's Highest Academic Rank

By Carolyn Farrell

Peter Zandstra, professor in the Donnelly Centre and Institute of Biomaterials & Biomedical Engineering, and Canada Research Chair in Stem Cell Bioengineering, has been appointed to the rank of University Professor. This is U of T's highest academic rank, recognizing unusual scholarly achievement and pre-eminence in a particular field of knowledge. The number of such

appointments is limited to two per cent of the University's tenured faculty.

Zandstra is a pioneer in the field of stem cell bioengineering, an area that applies engineering principles to stem cell biology. His research focuses on understanding how complex communication networks between stem cells and their progeny influence self-renewal and differentiation, and how this

information can be applied to the design of novel technologies capable of controlling cell fate. Zandstra's work has advanced our understanding of stem cell developmental processes and led to the development of cutting-edge technologies for the growth and differentiation of stem cells. Direct applications of his work include tissue and cellular engineering, gene therapy and organ transplantation.

"On behalf of all colleagues at the Donnelly Centre I congratulate Peter Zandstra on this highly deserved honour, " said Professor **Brenda Andrews**, Director of the Donnelly Centre. "His visionary ideas into how genes and cells are organized as a network in a complex system have moved forward not only the field of stem cell biology but biomedical sciences as a whole."

Beyond his own research, Zandstra has led several successful collaborative endeavours to advance bioengineering and biomedicine. He serves as Chief Scientific Officer of the Centre for Commercialization of Regenerative Medicine, which recently received \$20 million from the Canadian government, matched by \$20 million from GE Healthcare, to establish and operate the Centre for Advanced Therapeutic Cell Technologies. Zandstra is also the Executive Director of Medicine by Design, which received \$114 million from the Canada First Research Excellence Fund – the largest grant in U of T's history.

Zandstra has made outstanding contributions to bioengineering education, working with University Professor Michael Sefton, also at the Donnelly Centre, to lay the foundation for U of T's undergraduate Bioengineering program. He designed and taught BME 496: Cellular Engineering, a fourth-year course which is now a core part of the Engineering

Science curriculum, and implemented a new graduate course in this area, BME 1453: Cell and Tissue Engineering. Zandstra also played a key role in the development of the Bioengineering minor, for which he served as director.

"Peter Zandstra has made exceptional contributions to bioengineering, both through his own research and through his leadership in developing and directing large-scale multidisciplinary research collaborations," said Dean **Cristina Amon**. "It is in large part due to his efforts that Canada is gaining a reputation as a leader in stem cell technologies. I congratulate him on this richly-deserved honour."

Peter's visionary ideas into how genes and cells are organized as a network in a complex system have moved forward not only the field of stem cell biology but biomedical sciences as a whole

Zandstra has received several prestigious awards for his research, including the University of Toronto McLean Award, the Premier's Research Excellence Award, the NSERC E.W.R. Steacie Memorial Fellowship and the John Simon Guggenheim Memorial Foundation Fellowship. Zandstra is a fellow of the American Institute for Medical and Biological Engineering, the American Association for the Advancement of Science and the Royal Society of Canada. In 2013 he received the Till and McCulloch Award from the Stem Cell Network.

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



Michael Sefton Received Lifetime Achievement Award from the Tissue Engineering & Regenerative Medicine International Society

By Luke Ng

University of Toronto biomedical engineering University Professor **Michael Sefton** (Donnelly Centre, Institute of Biomaterials & Biomedical Engineering, Department of Chemical Engineering) has been named this year's recipient of the Lifetime Achievement Award from the Tissue Engineering & Regenerative Medicine International Society (TERMIS). The award, issued by the organization's Americas

chapter, recognizes his immense contributions to the fields of tissue engineering and regenerative medicine. Sefton joins an elite list of renowned recipients, including MIT professor of chemical engineering Robert Langer and founding director of the University of Pittsburgh's McGowan Institute for Regenerative Medicine, Alan Russell.

Sefton has made significant contributions to research advances in biomaterials, biomedical engineering and regenerative medicine. He was one of the first to combine living cells with polymers, effectively launching the field now now called tissue engineering. Recently, his lab has created biomaterials that actively promote the growth of blood vessels — such materials accelerate wound healing and support the development of lab-grown tissues. Among his numerous awards and accolades, Sefton received the European Society for Biomaterials International Award in April, the Terumo Global Science Prize in January and was named last year to the U.S. National Institute of Medicine. He holds the title of University Professor, the highest academic rank at the University of Toronto, reserved for less than two per cent of tenured faculty.

A leader in his professional community, he served as president of the U.S. Society for Biomaterials in 2005 and has spearheaded several programs to advance the field. From 1999 to 2005, Sefton was director of the Institute of Biomaterials & Biomedical Engineering (IBBME) leading its development into one of the top institutes of its kind in North America.

“This is a terrific recognition of Michael’s outstanding efforts throughout his career in advancing the field of tissue engineering,” said IBBME director and Donnelly Centre researcher Professor **Christopher Yip**.

Sefton was presented with the award at the 2016 TERMIS-AM conference which took place from December 11 to 14 in San Diego, California.

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

*This is a terrific recognition
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Molly Shoichet Elected Foreign Member of the U.S. National Academy of Engineering.

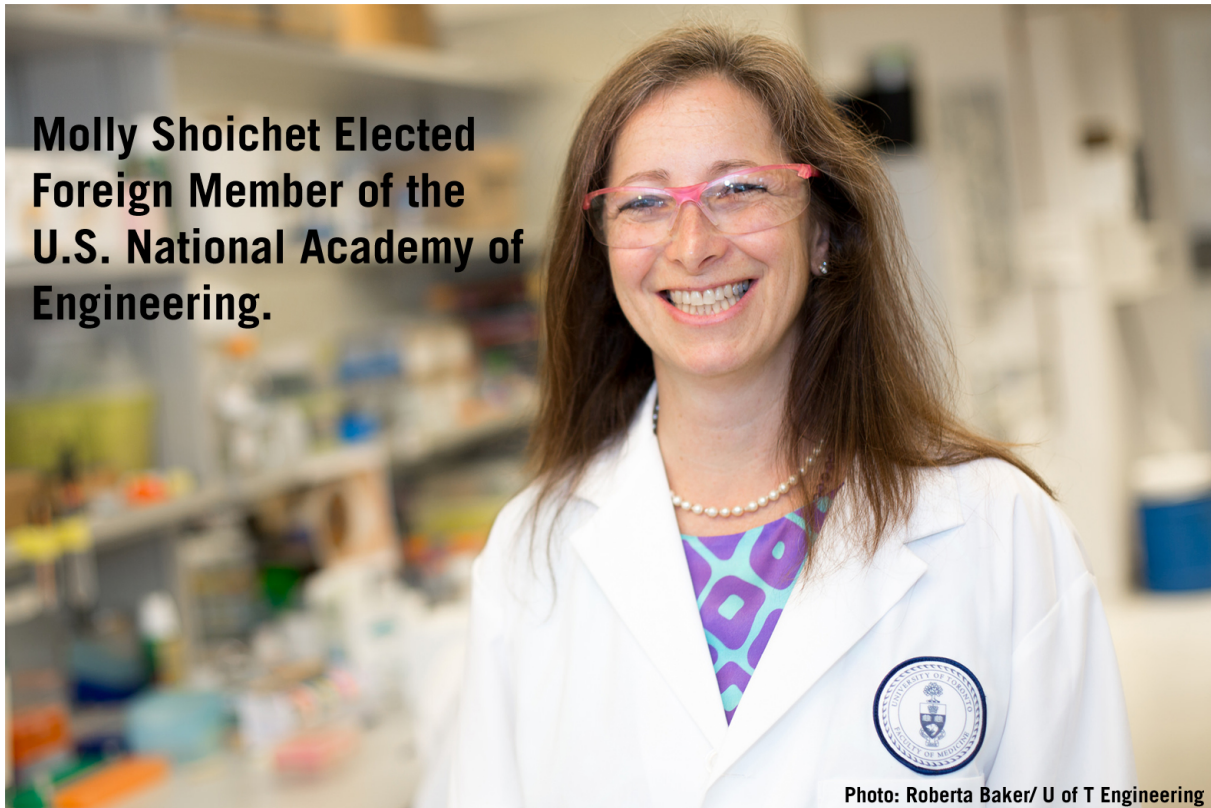


Photo: Roberta Baker/ U of T Engineering

Professor Molly Shoichet Elected as Foreign Member of the U.S. National Academy of Engineering

By Carolyn Farrell and Nina Haikara

University Professor **Molly Shoichet**, who is also a researcher at the Donnelly Centre and a professor in U of T's Institute for Biomaterials and Biomedical Engineering (IBBME) and in the Department of Chemical Engineering and Applied Chemistry (ChemE), has been elected as a Foreign Member of the U.S. National Academy of Engineering (NAE).

Founded in 1964, the NAE provides engineering leadership in service to the United States and globally. Members of the

NAE rank among the world's most accomplished engineers. Shoichet is among only four Canadians inducted to the academy this year.

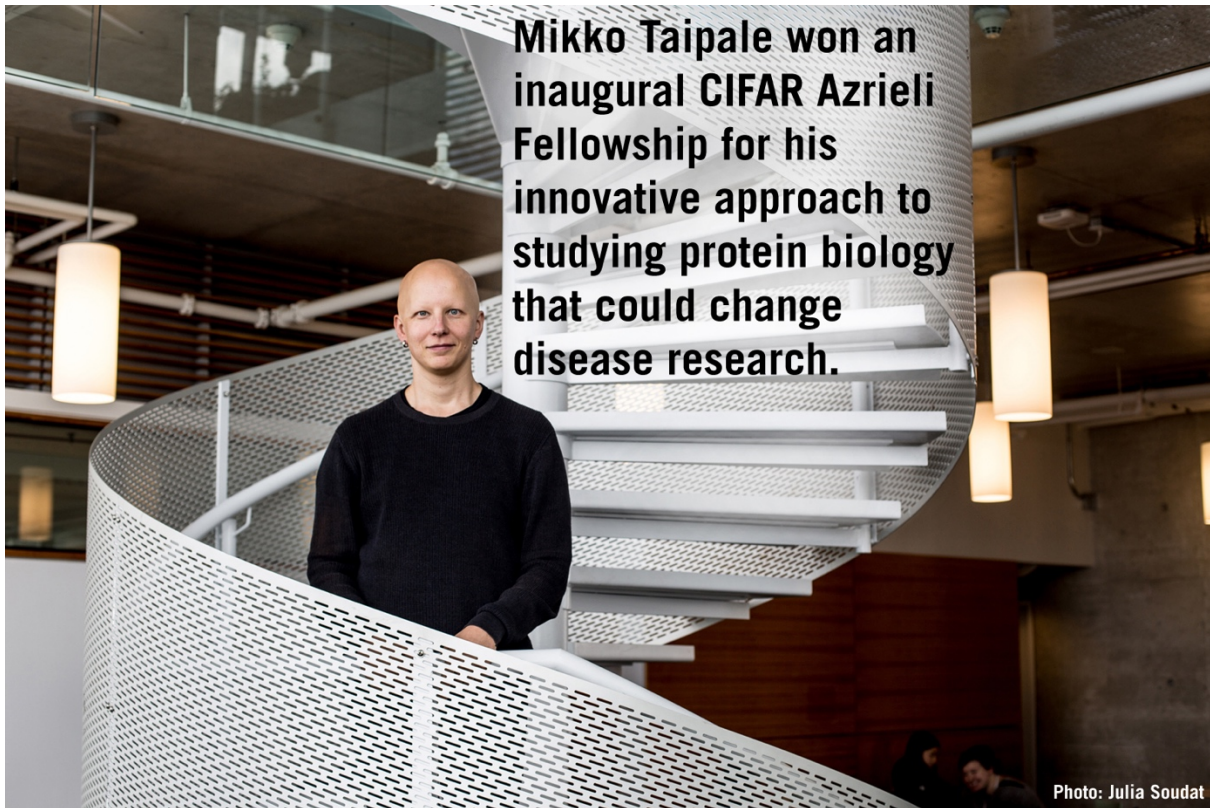
An internationally recognized expert in tissue engineering and regenerative medicine, Shoichet holds the Canada Research Chair in Tissue Engineering. Her research focuses on using stem cells, biocompatible polymers and lab-grown tissues to develop new treatments for cancer, blindness, stroke and other

degenerative conditions. Her research has resulted more than 400 papers, 32 patents and three spin-off companies.

Shoichet is the only person to be elected a fellow of Canada's three national academies: the Royal Society of Canada, the Canadian Academy of Engineering and the Canadian Academy of Health Sciences. She is a fellow of the American Association for the Advancement of Science and the American Institute for Medical and Biological Engineering and an International Fellow of Tissue Engineering and Regenerative Medicine. In 2015 she was named the L'Oréal-UNESCO For Women in Science

North American laureate and listed as one of Chatelaine Magazine's Women of the Year.

In 2014, Shoichet was appointed senior advisor on science and engineering engagement to U of T President Meric Gertler. Among her many science outreach activities, she founded the groundbreaking initiative Research2Reality, which uses digital media to engage and educate the public on the cutting-edge research performed in Canada. Shoichet received the 2015 Fleming Medal and Citation from the Royal Canadian Institute in recognition of her outstanding contributions to the public understanding of science.



Finding Diseases for Already Existing Drugs

By Jovana Drinjakovic

“I have the second best job in the world. The first is being an astronaut,” says **Mikko Taipale**, an assistant professor of molecular genetics at the University of Toronto’s Donnelly Centre. With his feet firmly planted on the ground, Taipale is finding cures for genetic diseases.

Taipale, 39, has won an inaugural \$100,000 CIFAR-Azrieli Fellowship. The award was given to 18 scholars worldwide, who are less than five years into their first academic appointments, by the Canadian Institute for Advanced Research (CIFAR). Among other

winners are U of T professors Natalie Bau (economics) and Luyi Yang (physics).

“This group of phenomenal young investigators is the future of research,” said CIFAR President and CEO **Alan Bernstein** in the institute’s announcement.

Taipale joined the Donnelly Centre in 2014 after a post-doctoral fellowship in the lab of Professor Susan Lindquist at the Whitehead Institute for Biomedical Research and MIT, where he studied how proteins – the end products of genes – fold into three-dimensional molecular machines. At

Donnelly, he has expanded his research to a number of cellular processes that ensure proteins are properly made and working, in order to understand what makes cells healthy and how changes in protein biology cause disease.

One of Taipale's projects sets out to investigate rare and debilitating – but often overlooked – disorders.

“We want to democratize research in rare diseases because most of them are completely neglected. Developing a new drug costs \$1.2 billion and you cannot recover those costs if you only treat thousands, or even hundreds of patients in some cases,” says Taipale.

A rare genetic disease occurs when a particular gene is mutated so that the protein it encodes no longer works. For example, mutations that impede the function of proteins encoded by the genes CFTR or dystrophin will cause cystic fibrosis and muscular dystrophy, respectively. Such harmful mutations run through family trees but only wreak havoc in a small number of people. That's because we carry two copies for every gene, one inherited from each parent. If one copy of a gene is broken, its harmful effects are masked by the other working copy of the gene. It's only when someone inherits both bad versions of the gene that they get sick.

Unlike complex diseases such as cancer, which are caused by mutations in many genes, rare diseases are an easier problem to solve. If you could find a way to restore the broken gene's function, you might be able to alleviate symptoms or cure the disease altogether. Still, a relatively small patient population means that the pharmaceutical industry has little incentive to invest in these diseases.

But what if drugs already existed? What if they lurked among thousands of compounds that have already been approved or are being developed for other conditions?

“We're trying to completely change the way in which we study rare genetic diseases. Traditionally, these diseases are studied one at a time with multiple methods, and we want to study one thousand diseases all at once, with one or two methods” says Taipale.

To do this, he has a collection of 1000 mutant proteins – each carrying a mutation known to cause a genetic disease. The plan is to run a battery of tests on these damaged proteins, side-by-side with their healthy counterparts.

“These experiments will help us understand the underlying molecular causes of disease. Then we can use FDA-approved drugs to fix the damaged proteins. We are trying to find a disease for a drug and not a drug for a disease,” says Taipale.

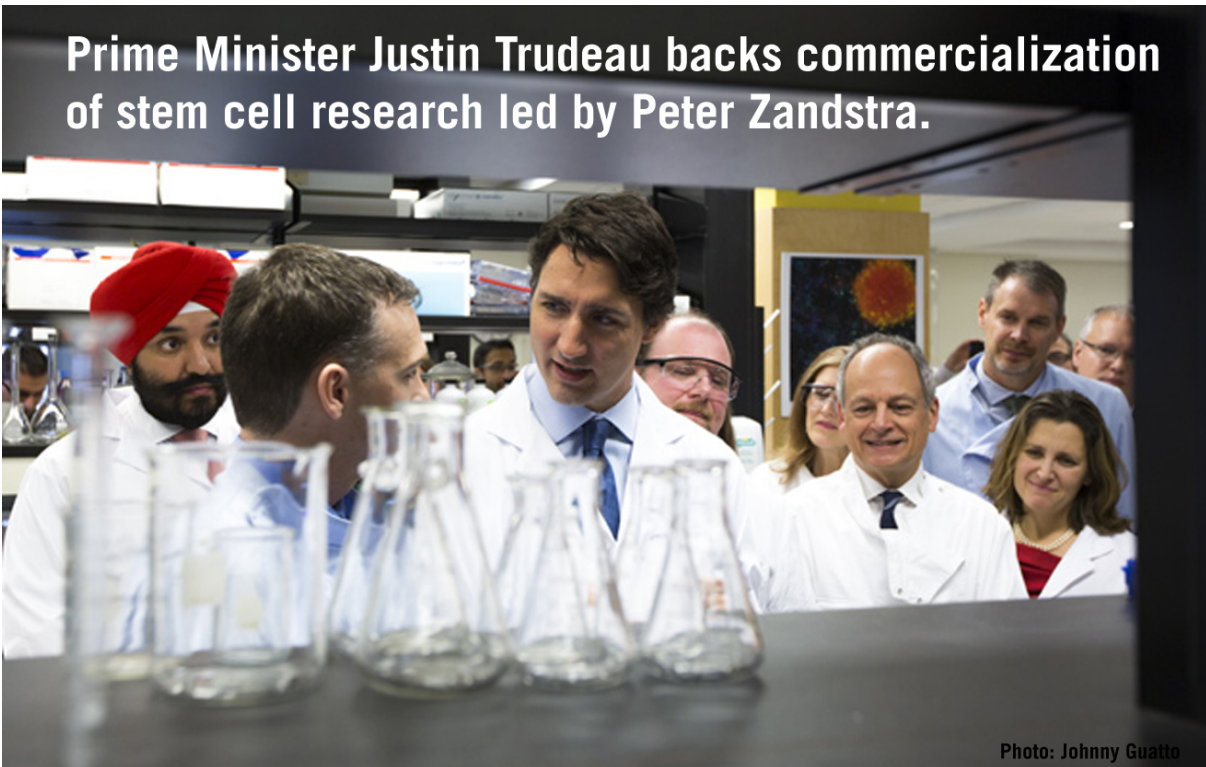
Taipale cites an example of lonafarnib, a failed cancer drug that was repurposed to treat progeria – an extremely rare condition where aging is accelerated so much that patients die of old-age complications in their teens. The drug works by reigning in the rogue progerin protein, which is the underlying cause of the disease.

“Even if you hadn't known anything about the molecular biology of progerin, and done a screen with FDA-approved drugs and drugs in clinical trials, you probably would have found the same compound. I have a hard time believing that out of 7000 rare diseases this would be the only one that has an existing drug that could work. Maybe we'll be able to make a difference for one of these 1000 diseases that we study, but I have no idea which disease it will be,” said Taipale.

OTHER NOTABLE AWARDS

- **Mikko Taipale** was named the Canada Research Chair in Functional Proteomics and Proteostasis.
- **Penney Gilbert** was awarded the Canada Research Chair in Endogenous Repair.
- **Warren Chan** was named a U of T Distinguished Professor.
- **Michael Sefton** was awarded the Global Science Prize from the Terumo Foundation for Life Sciences and Arts in Japan and the International Award from the European Society for Biomaterials.
- **Molly Shoichet** won the Till & McCulloh Award for her contribution to global stem cell research.
- **Igor Stagljär** was awarded the Zdravko Lorkovic Plaque for outstanding contributions to biology, the highest accolade given by the Croatian Biological Society.
- **Brendan Frey** received the Invention of the Year award from U of T.
- **Peter Zandstra** won the Scale-Up and Manufacturing of Cell-Based Therapies Award from Engineering Conferences International.

WE ARE APPLYING OUR DISCOVERIES TO IMPROVE HEALTH



Prime Minister Justin Trudeau Backs Commercialization of Stem Cell Research Led by Peter Zandstra

By Alan Christie, with files from Tyler Irving

Regenerative medicine is the way of the future for Canadian health care, Prime Minister **Justin Trudeau** said, and two new initiatives are helping strengthen the commitment of U of T and its partners to stem cell research and manufacturing.

Trudeau announced at the MaRS Discovery District on Jan. 13 that the federal government will give a \$20 million grant to the Centre for Commercialization of

Regenerative Medicine (CCRM) to establish and operate a new Centre for Advanced Therapeutic Cell Technologies.

At the same time, **Vivek Goel**, vice-president, research and innovation at U of T, announced that Professor **Peter Zandstra**, a principal investigator in the Donnelly Centre and Chief Scientific Officer for the CCRM, has become the inaugural director of Medicine by Design.

The CCRM is the commercial arm of Medicine by Design, a program created last year through a \$114 million grant from the federal government.

Regenerative medicine is the future. Not only is it the future, it's a branch of medicine that Canada and the province of Ontario are actually quite good at.

Trudeau toured two CCRM labs at the Banting Institute with Zandstra, U of T President **Meric Gertler** and **Michael May**, the president and CEO of CCRM, along with **Navdeep Bains**, Minister of Innovation, Science and Economic Development, and **Chrystia Freeland**, Minister of International Trade and MP for University-Rosedale. The group then moved across College St. to MaRS, which will become the new home of the CCRM later this year.

The Prime Minister said he has “great respect” for scientists involved in stem cell research, not only because of what they are doing for the health of Canadians but how “they are pushing the frontiers of science and innovation.”

The bottom line, he said, is that “we must do more to prevent diseases” and the collaboration between public institutions like U of T and its partner hospitals, the private sector and government is crucial in “accelerating the development” of stem cell manufacturing technologies.

GE Healthcare is also committing \$20 million to the new centre. **Kieran Murphy**, CEO of GE Healthcare’s life sciences business, said in a news release that “it is increasingly clear that cell therapies and regenerative medicine will transform health care globally, but successful

industrialization is now crucial to widespread adoption”.

“This new centre,” Murphy said, “will enable us to work with cell therapy companies to push beyond existing technical limits and problem-solve. Toronto’s concentrated and collaborative clinical infrastructure, combined with the strong guidance of the internationally-renowned CCRM, make it an ideal location for the centre.”

It is expected that the global market for cell-based therapies will surpass \$20 billion U.S. by 2025. The main targets for cell-based therapies are cancer, heart disease, neurodegenerative diseases, musculoskeletal disorder and autoimmune diseases.

Trudeau noted that the new centre will be the first in the world to use a collaborative approach between research institutions and industry to solve cell therapy manufacturing challenges. He said the centre will create jobs, strengthen Canada’s knowledge economy and position Ontario as a global hub for the cell therapy industry.

“Regenerative medicine is the future,” Trudeau said. “Not only is it the future, it's a branch of medicine that Canada and the province of Ontario are actually quite good at.”

Zandstra is a professor in U of T's Donnelly Centre and in the Institute of Biomaterials & Biomedical Engineering, holds the Canada Research Chair in Stem Cell Bioengineering. He told U of T News he is thrilled to be the executive director of Medicine by Design. “But the big news today is the funding of the new centre. We are very thankful” for the government’s commitment.

Cristina Amon, dean of the Faculty of Applied Science & Engineering, said Zandstra’s “collaborative efforts with partner hospitals and his leadership in regenerative medicine is

an outstanding example of how U of T engineers are addressing some of the world's most pressing health challenges.”

The mandate of Medicine by Design is to undertake transformative research and clinical translation in regenerative medicine, enhance capability in synthetic biology and computational biology and foster translation, commercialization and clinical impacts.

It was formed as a result of the University of Toronto's success in the Canada First Research Excellence Fund (CFREF). The \$114 million will be spread over seven years, and will allow U of T and its partners to build on years of support for U of T's regenerative medicine researchers from federal granting councils, the Canada Foundation for Innovation and support from the Canada Research Chairs and Canada Excellence Research Chairs programs.

Zandstra will lead and provide over-all scientific direction to the Medicine by Design initiative. May, CEO of the CCRM, said the new centre is a “significant milestone” in the fight to find cures for diseases and to create companies that will bring those cures to the marketplace.

And he reminded everyone that the incredible advances in stem cell therapy and its application “trace back to the discovery of stem cells 65 years ago” by U of T scientists James Till and Ernest McCulloch.

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



Professor Peter Zandstra with Prime Minister Justin Trudeau (Johnny Guatto)

Students from the Wheeler lab brought their custom built device for quick detection of measles and rubella to a Kenyan refugee camp, offering free and accurate tests to those in need.



Photo: Ryan Fobel

Hacking Health Care in a Refugee Camp

By Marit Mitchell & Sean Bettam

They hadn't even been at the refugee camp a whole day when the first of only two power adapters blew up.

Researchers **Ryan Fobel**, his brother **Christian Fobel**, **Alphonsus Ng** and **Julian Lamanna** had been feverishly working toward this day for months. They'd pulled all-nighters, designed, redesigned and debugged circuits, mixed reagents and buffers, put out literal fires, built their portable lab, taken it apart and built it again. They and their lab mates were still

making changes the night before boarding the plane.

Now the four members of Professor **Aaron Wheeler's** Microfluidics Lab — collectively dubbed the "Away Team" — were finally on the ground in a four-room hospital in Kakuma, a camp in remote northwestern Kenya. They were ready to test that their group's portable lab-on-a-chip could handle running 600 laboratory-quality tests for measles and rubella in less than three weeks.

Vaccine-preventable diseases, such as measles and rubella, have long been a threat in the developing world due to low vaccination rates — in 2014 measles killed 115,000 children, and rubella infection among pregnant women can cause fetal death or congenital defects. Diagnostic tests for both measles and rubella must be very sensitive, and are therefore usually conducted in remote, centralized labs — not much help if you are a pregnant woman in a refugee camp. The Away Team had no time or equipment to waste. They'd only brought two transformers, and one was now smoking in the corner of their makeshift lab — without the transformers, they couldn't plug their 110-volt MR Boxes into the 220-volt sockets in Kenya. "It made us nervous," says Ryan. "We had a backup, but we weren't expecting to need it on the first day."

With no Plan B, the Away Team was forced to become true health-care hackers, testing the limits of what lab-based research can deliver in the field.

Our aim was to build a generic instrument that you can recalibrate on the fly—a true lab on a chip

A grand challenge

Wheeler doesn't back away from the seemingly impossible. A professor in the University of Toronto's Donnelly Centre, Department of Chemistry and Institute for Biomaterials & Biomedical Engineering (IBBME), he and his research group are international leaders in the field of microfluidics.

Wheeler and his lab are particularly known for their contributions to "digital microfluidics," a technique used to move, split, recombine and mix miniscule droplets all on a tiny "chip." The chip is made using some of the same methods for making computer chips, the droplets are controlled by applying electrical signals to different electrodes.

This lab-on-a-chip technology allows Wheeler and his students to shrink diagnostic tests that once required rooms full of laboratory equipment down to the size of a credit card.

In 2014, the Wheeler Lab landed a grant from Grand Challenges Canada, in addition to funding from the Natural Sciences and Engineering Research Council, to create the world's first lab-quality field-deployable diagnostic test for measles and rubella viruses using only finger-prick amounts of blood, and test it in Kenya.

"Our aim was to build a generic instrument that you can recalibrate on the fly—a true lab on a chip," says Wheeler. "We use a lot of the tools that makers and hackers are using: 3D-printed components, ink-jet printed electronics, all of our software and hardware is open source. We built in all this flexibility and we needed to validate it in an unpredictable environment."

The Wheeler Lab dubbed their hackable diagnostic platform the MR Box, pronounced "mister box," because it tests for measles and rubella, M and R.

To execute on this international deployment, the group teamed up with the Centers for Disease Control and Prevention (CDC) in Atlanta, and the International Rescue Committee (IRC), a non-governmental humanitarian organization delivering aid in Kakuma. Working with the CDC and IRC, the team made plans to take their MR Boxes to



Christian Fobel, Alphonsus Ng, and Julian Lamanna running blood tests on the MR box instruments in their temporary lab in one of the Kakuma health clinics (Ryan Fobel)

Kakuma at the same time as a massive public measles and rubella immunization campaign. They set an ambitious schedule for themselves. They would test 75 children and 75 caregivers — mothers, community members, etc. — four times each, for a total of 600 individual tests in less than three weeks.

Screening for both diseases separately, they would first test the caregivers, who were expected to have been previously vaccinated and therefore have measles and rubella antibodies. In a second round of tests two weeks later, they would test the children that had been vaccinated, since the antibodies produced in response to vaccination mimic an infectious response.

The study was designed to evaluate their tool's capabilities for both monitoring the rate of vaccine coverage and for identifying disease outbreaks. This would leave them with two days to visit the Kenyan Medical Research Institute (KEMRI) national laboratory in Nairobi, the institution that would test their samples and validate their lab-on-a-chip technology — or not — before returning to Toronto.

Clock is ticking

One week into the three-week field trial, the Away Team was waiting for the remaining samples. Even down to one transformer, all four MR Boxes had held up and they had

successfully run 300 tests on blood samples from the caregivers and children.

Now public health workers were starting to collect samples from the children after they'd been vaccinated, but these wouldn't be available to test until the final two days of their testing window. To finish the remaining tests in just two days, they would need to have all four MR Boxes running — they couldn't afford to have a single thing break.

It takes a village to test a village

While the Away Team was sweating in Kakuma, a tight-knit crew of at least nine post-doctoral fellows, graduate students and undergrads were back in Toronto, hustling to solve problems as they arose — early in the trip, they had to manufacture and ship a jug of their custom assay solution with a special UN flight after the Away Team's container leaked on the way over. PhD candidate **Darius Rackus** was leading the crew. Over the course of improving their platform in preparation for Kenya, Rackus estimates that the group fabricated more than 1,000 chips themselves on campus.

"This is by far the biggest test of our system that we've ever attempted," said Rackus. "And more than that, we've got this motley crew of researchers out in the field with this healthcare device we've built from scratch — we're really pushing what we can do as academics."

Back in the field, it was time for the Away Team to push through the final 48 hours of testing — with half of their tests still to run. They needed to have all four MR Boxes hold up and run at full capacity in order to get through the remaining 300 tests.

Ryan's mind cast back to the night before they boarded their flight to Kenya, when he and Christian had been frantically trying to

redesign a circuit that kept going up in flames. They knew then that without having that circuit board working, the team could only run two machines at a time.

"We got to the very last component we were testing, and we said, 'If it isn't this thing, we don't know what it is,'" said Christian.

They got the circuit working and three weeks later in Kakuma, their hustle was paying off. All four MR Boxes cooperated through that last 48 hours and the Away Team successfully ran the final 300 tests.

"If we hadn't fixed it, I don't think we would have finished," said Lamanna.

This is by far the biggest test of our system that we've ever attempted. We're really pushing what we can do as academics

Gold standard

Exhausted but elated, the Away Team left the refugee camp and set out on the long and bumpy road back to Nairobi to deliver their samples to KEMRI.

Not only does KEMRI handle all diagnostics for Kenya, it's also the destination for high-reliability tests from five neighbouring countries. Expecting a state-of-the-art robotic instrument capable of handling an extremely high volume of tests, the Away Team was shocked to find two people at a lab bench, processing tests by hand.

"We were very impressed with the quality of the staff, but to see how limited the resources are that they have to work with, knowing that all the surrounding countries are sending their samples there...it was sobering," said Christian.

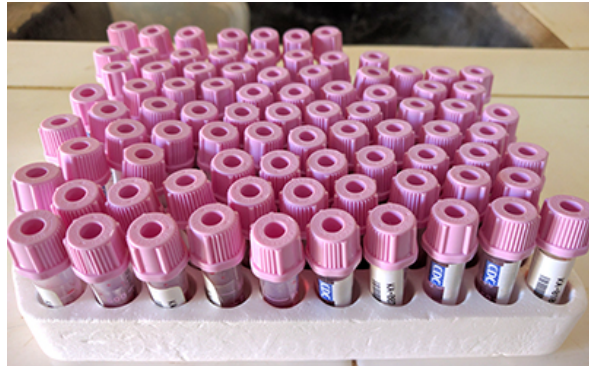
The KEMRI lab currently processes approximately 2,400 samples in a year. The MR Box can handle the same number in a month. “We realized that for around \$1,000, our hacked-together platform could potentially improve this lab that’s serving half a continent,” said Wheeler. “Even a modest investment could make a big difference in this institutional setting.”

Force of will

“If you had told me four years ago that we were going to process two tests for two diseases for 150 people in the span of three weeks, I would have said it was impossible,” said Wheeler. “The only way to make this happen was to have this core group of 15 people, from young undergrads through post-docs, working together. This happened organically because this group wanted it to happen so badly.”

With all 600 tests now awaiting comparison against KEMRI’s results, the Wheeler Lab is reunited and working on the next challenge: introducing more automation into their platform.

“What we really want is to make the instruments so robust that you can hand them off to locals, who can jump on a motorbike and ride miles into the bush and operate them by themselves off solar power,” said Wheeler. Don’t think they won’t do it.



Blood sample collection tubes representing about half of those collected during the study. (Credit: Ryan Fobel)

If you had told me four years ago that we were going to process two tests for two diseases for 150 people in the span of three weeks, I would have said it was impossible

The Northern Biologics Inc startup, co-founded by Sachdev Sidhu and Jason Moffat, acquired Mosaic Biomedicals SL to enable further development of a new anti-cancer drug, expected to enter clinical trials in 2017.



Northern Biologics to Develop New Cancer Drug for Clinical Trial

By Versant Ventures and Northern Biologics

Northern Biologics Inc. announced on December 19, 2016, that it merged with Mosaic Biomedicals SL in a deal that will enable and accelerate the development of MSC-1, a humanized antibody expected to begin clinical trials in several cancerous tumor types in 2017, with multiple study sites planned in Europe and North America. MSC-1 is a first-in-class antibody that targets leukemia inhibitory factor (LIF), a pleiotropic cytokine that is overexpressed in certain solid

tumors. LIF promotes cancer progression by regulating the tumor microenvironment and by inducing self-renewal in tumor-initiating cells.

Joan Seoane, Ph.D., a co-founder of Mosaic and director of translational research at the Vall d'Hebron Institute of Oncology within the Vall d'Hebron University Hospital, Barcelona, led pioneering work on the role of LIF in oncogenesis, and the discovery of MSC-1. Versant Ventures has expanded its series A

commitment to Northern Biologics and Celgene Corp. has exercised an option to acquire certain rights to the MSC-1 program under its existing agreement with Northern Biologics. Following the transactions, Northern Biologics

has full funding for the early clinical development of MSC-1, in addition to its preclinical portfolio of therapeutic antibodies. Dr. Seoane has joined Northern Biologics' board of directors, and Mosaic co-founder **José Baselga**, M.D., Ph.D., will serve as chair and senior medical advisor to the scientific advisory board (SAB). **Guido Magni**, M.D., Ph.D., a partner at Versant Ventures and former global head of the medical science department of Roche Pharmaceuticals, joined the SAB as a lead clinical advisor.

"I'm pleased to welcome Dr. Seoane to the board of Northern Biologics and excited for Dr. Baselga and Dr. Magni to lead our SAB efforts," said **Brad Bolzon**, Ph.D., chair of the board and managing director at Versant Ventures. "This deal, along with additional financing, is a critical step in building Northern into a world-class oncology company that can deliver new therapies for patients with difficult-to-treat cancers."

Northern Biologics also announced that it recruited Robert Wasserman, M.D., to serve as Chief Medical Officer and to lead the clinical development of MSC-1. Dr. Wasserman previously was vice president, global therapeutic area head of oncology at Covance Inc.

His clinical training took place at the University of Pennsylvania School of Medicine and the Children's Hospital of Philadelphia, and he has held senior translational and clinical development roles at Merck, Novartis and Roche.

"I'm very pleased to welcome Bob Wasserman to our leadership team," said **Stefan Larson**, Ph.D., chief executive officer of Northern Biologics. "We look forward to developing

This deal, along with additional financing, is a critical step in building Northern into a world-class oncology company that can deliver new therapies for patients with difficult-to-treat cancers

MSC-1 as a new approach to meeting the needs of cancer patients."

Northern Biologics was launched in June 2014 by Blueline Bioscience, a Canadian biotechnology incubator backed by venture capital firm Versant Ventures, in partnership with the University of Toronto and University Health Network's Princess Margaret Cancer Centre. Headquartered in the MaRS Discovery District of Toronto, the company is developing a portfolio of antibody-based therapeutics for oncology and fibrosis.

OUR SCIENTISTS CONTINUE TO RAISE COMPETITIVE FUNDING FOR THEIR RESEARCH



Donnelly Teams Sweep National Funding Grants

By Jovana Drinjakovic

Five Donnelly Centre teams have won Genome Canada's Disruptive Innovation in Genomics grants in support of research projects totalling more than \$6 million. The competition was set to boost development of technologies that have a potential to transform and speed up the commercialization of biomedical discovery.

Professors **Sachdev Sidhu** and **Igor Stagljar** received advanced Phase Two grants — the sole two grants awarded in Ontario — to further advance their technologies for the study of disease-related proteins. Stagljar was also awarded an early stage grant, along with Professors **Charlie Boone**, **Jason Moffat** and

Andrew Emili for proposals that tackle how genes and proteins work together in human cells.

The awarded projects will advance our understanding of genetic and protein networks. Genes code for proteins, which make up our cells and do most of the work in them. But no protein acts alone, and it is when these molecular interactions are disrupted that disease occurs. The trick is then to find the Achilles Heel of the disease and target it selectively in a way that does not harm healthy cells and tissues.

Recent advances in genomic technologies have allowed scientists to hunt for genetic causes of diseases faster than ever before. With Genome Canada's support, these Donnelly teams will develop new ways of finding precise molecular antidotes to target diseases, including cancer.

Boone and Moffat teams, in collaboration with Professor Brenda Andrews' group, will use the genome editing CRISPR technology to hunt for genes in cancer cells that help tumours evade available treatments. Working together with Sidhu, they will create selective, protein-based compounds to block the molecules that give cancer its competitive edge in order to stall its growth. These compounds can then be further developed to be tested on patients, together with already available drugs, as combination therapies.

With previous funding from Genome Canada, Sidhu and Moffat have already established a platform for generating protein-based drugs to target disease proteins found at the cell's surface. In less than six years, they have created hundreds of anti-cancer compounds, and many of these have been licensed or partnered with the pharmaceutical industry through the University of Toronto's Centre for Commercialization of Antibodies and

Biologics (CCAB), which was co-founded by Sidhu and Moffat in 2014. Several of these compounds are on track to reach the clinic as early as 2018. The current grant will allow Sidhu to expand the strategy to also include proteins that are found inside cells.

Stagljar's team will tackle membrane proteins, which are tucked inside a layer that surrounds each cell and its inner compartments, and which are often mutated in cancer and many other diseases. The researchers will expand their technology for detecting membrane protein interactions to include every type of human cell. This will then allow them to identify those interactions that only occur in a disease state and screen for compounds that selectively block them in search of new treatments - an approach that was already shown to work for the most common type of lung cancer.

The awarding of Phase Two grants was conditional on the researchers securing two thirds of total project costs from external sources. Both Sidhu and Stagljar have raised the funds through their start-up companies, Ubiquitech and Protein Network Sciences, respectively, with Stagljar also securing support from Genentech, a pharmaceutical giant based in San Francisco.

To gain a thorough view of each protein's whereabouts in cells, Emili's team will build a new sub-microscopic imaging technology for studying each and every one of the many millions of individual protein molecules in human cells and tissues in unprecedented detail. This will allow scientists to understand how biological systems work at the molecular level and will provide clinicians with a tool to diagnose diseases like cancer faster and more accurately.



Michael Sefton won \$1.1M from JDRF for type 1 diabetes research.

Photo: Neil Ta

Michael Sefton receives \$1.1M from JDRF for type 1 diabetes research

By Luke Ng

University of Toronto professor **Michael Sefton** (Donnelly Centre, Institute of Biomaterials & Biomedical Engineering, Department of Chemical Engineering) has been presented with a major research award from international diabetes foundation JDRF to advance treatment research for type 1 diabetes (T1D).

The funding, valued at approximately \$1.1 million (\$845,135 USD), supports a three-year study at the University of Toronto’s Institute of Biomaterials & Biomedical Engineering (IBBME) to explore an experimental treatment that involves transplanting healthy pancreatic cells into patients living with the disease. Once successfully

implanted, these cells can then produce insulin to help regulate blood glucose levels.

Though promising, these cells — known as pancreatic islet cells— are fragile, and current transplantation sites such as the abdominal cavity and liver are “hostile” environments that can increase the likelihood of rejection.

Sefton and his team are investigating whether transplanting islet cells under the skin will improve the cells’ survival.

“The skin is a less hostile site for islets and has clinical advantages of being more accessible than current sites and possibly be even safer for patients,” said Sefton, who holds appointments in

U of T's Department of Chemical Engineering & Applied Chemistry and IBBME. "However, one of the challenges of using the skin as a transplant site is that it has relatively few blood vessels."

Sefton, a world-renowned tissue engineering pioneer, plans to apply his team's expertise to creating a "pre-vascularized" environment rich in blood vessels under the skin to ensure the survival of the insulin-producing cells before transplantation takes place.

"The goal is to enable islet cell transplantation under the skin in a retrievable, 'device-less,' physiologically integrated, and scalable implant site," said Sefton. "The goal of this strategy is better control of blood glucose and reduced complications, leading to more widely available treatment for those living with this disease."

"Islet transplantation is a promising approach to treatment that also minimizes the risk of serious complications that affect those who live with T1D," said **Dave Prowten**, president and CEO of JDRF Canada. "We are proud to support Dr. Sefton and his team as they work to uncover new ways to make this treatment more readily available for people living with T1D."

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

The goal of this strategy is better control of blood glucose and reduced complications, leading to more widely available treatment for those living with this disease



New Funding to Fast-track Breakthroughs in Stem Cell Research

By Jovana Drinjakovic

Donnelly Centre teams have netted the competitive Medicine by Design grants for research projects that range from overcoming blindness, to shedding light on brain repair and finding new ways to make blood. The \$27 million investment will be shared over three years between 20 University of Toronto teams, five of which are led by Donnelly Centre researchers.

The awards champion teamwork among experts from different fields, including molecular geneticists, computational biologists, engineers and clinicians, aimed at expanding our knowledge of stem cell biology

and translating it into practical use. Among the Donnelly Centre team leaders are University Professors **Michael Sefton** and **Molly Shoichet**, and Professors **Cindi Morshead**, **Gary Bader** and **Jason Moffat**. Stem cells hold great potential for making replacement tissues thanks to their ability to turn into any cell type. Scientists hope to harness this potential to treat injury and disease. The Shoichet team has taken on blindness: the team is creating replacement retinal cells to stave off vision loss due to age-related macular degeneration. They are investigating how best to grow and transplant

cone photoreceptors, the cells responsible for central vision.

In addition to growing transplant cells in a dish, it may also be possible to coax our own stem cells to repair damage from within. All major organs have stem cells that drive tissue maintenance and repair, but this process is slow and not geared to replacing entire organs. The Sefton team is investigating a possibility of tricking the body's muscle stem cells to form entire muscles in order to replace tissue lost to trauma or surgery. They are using "living" scaffolds, created in the lab from biomaterials that spur blood vessel growth, as a surface for the stem cells to grow on and form a functional muscle.

Even the brain, previously thought to be incapable of regeneration, has its stock of stem cells. The Morshead team is investigating whether brain stem cells could be used to repair damage caused by stroke. Gary Bader and colleagues are taking a computational approach to map genetic circuits that control how stem cells form the most complex organ in the body, in order to

shed light on the fundamental processes in brain development, disease and aging. These insights will pave the way for future drug-discovery and cell-based repair therapies.

Jason Moffat's team will use the grant to create a roadmap for turning human stem cells into blood stem cells, which reside in the bone marrow and make blood. A greater understanding of this process should make it possible to create blood stem cells directly from patients' tissue and deal in one stroke with the challenge of finding a suitable bone marrow donor and immune rejection.

Medicine by Design was created last summer after the federal government gave the University of Toronto the largest single research award in its history – \$114 million – to accelerate research in regenerative medicine. It is led by Peter Zandstra, a University Professor in U of T's Donnelly Centre and Institute of Biomaterials & Biomedical Engineering and the Canada Research Chair in Stem Cell Bioengineering.



Amy Caudy and Gary Bader are on the **Cancer Stem Cell Dream Team that was awarded \$11.7M from SU2C to fight childhood and adult brain cancer.**

Donnelly Researchers Gary Bader and Amy Caudy Take on Brain Cancer

By Jovana Drinjakovic

Donnelly Centre researchers Drs. **Gary Bader** and **Amy Caudy** to fight childhood and adult brain cancers as part of an interdisciplinary research team, it was announced this month. The Cancer Stem Cell Dream Team is led by Drs. Peter Dirks, from the Hospital for Sick Children (SickKids) in Toronto, and Samuel Weiss, of the University of Calgary.

Backed by the Stand Up to Cancer Canada (SU2C) initiative, the team will gather detailed biological profiles on brain cancer stem cells (BCSCs) that drive cancer occurrence. The researchers will catalogue any changes in the cells' genetic code, as well

as in epigenetic programming that controls gene activity.

At the Donnelly Centre, Caudy's team will further analyze how these cells metabolize nutrients, while Bader's team of computational biologists will make sense of the vast amount of data that will be generated by the consortium. Critically, these new insights are expected to lead to tangible advances in drug development in the hope of extending the lives of patients who currently have few options.

Despite advances in cancer care, brain tumours remain the most difficult to treat. The

average survival for glioblastoma, the most common form, is entrenched at just 15 months following diagnosis. To gain a deeper understanding of the disease, the researchers will examine cancer stem cells from 70 patients. Most of these tumours are of the glioblastoma type, with a smaller portion of ependymoma, the third most common childhood cancer, with a similarly poor outcome.

“We want to collect an unprecedented amount of information on patient tumour stem cells and integrate all the data together. The goal is to come up with a list of molecular networks that are acting in these cells that could be attacked by drugs,” says Bader, who is also a professor in U of T’s Department of Molecular Genetics and an associate member of the Lunenfeld-Tanenbaum Research Institute at Mount Sinai Hospital in Toronto.



Professor Gary Bader (Calvin Thomas)

This approach was previously successful when Bader and colleagues from SickKids integrated different types of data for ependymoma and identified a weakness - a drug target - in a patient’s tumour. Having

found the right drug that only killed the tumour cells, the doctors were able to successfully treat two patients. A part of the Dream Team’s funding will be to kick start a clinical trial for this drug in the hope of it becoming the first treatment for ependymoma.

Cancer stem cells are like the stem cells’ evil twins. Normally, the stem cells help our bodies grow and repair, due to their ability to turn into any cell type. But they can also go haywire to become cancer stem cells, locked in an eternal state of proliferation. Instead of making useful cell types, such as brain or blood cells, cancer stem cells fuel tumour growth.

The goal is to come up with a list of molecular networks that are acting in these cells that could be attacked by drugs

Changes in cell state are driven by sweeping shifts in epigenetic marks – these are chemical tags that reside near the genes and act as on/off switches. Scientists think that cancer stem cells arise from errors in epigenetic marks that ramp up those genes that favour cell division. A big part of the team's effort will be to decipher the epigenetic programming in tumour stem cells.

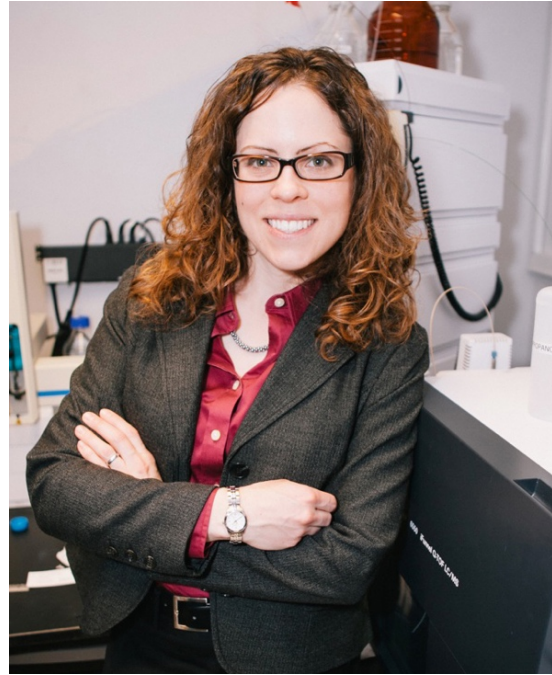
In particular, Caudy’s team will home in on a metabolite called 2-hydroxyglutarate (2HG) that can reset epigenetic marks to push cells into a state where they divide more. While high levels of 2HG have been linked to glioblastoma, as well as to other types of cancer, it seems that cells have several different ways to stockpile the chemical. Thanks to new technology developed in

collaboration with Dr. Adam Rosebrock, Caudy will be able to measure precise amounts of 2HG in the BCSCs in search of its sources.

“I think we’ll learn many basic things about cancer, and I hope that we may be able to find better drug targets. Right now for we have so little to offer these children with glioblastoma,” says Caudy, also a professor in the Department of Molecular Genetics.

The drug discovery arm of the project is fast-tracked through the Structural Genomics Consortium (SGC), a Toronto-based public-private partnership that facilitates collaboration between the pharmaceutical industry and academic research labs.

The team’s research is supported by \$11.7 million, funded by Stand Up To Cancer Canada, Genome Canada, the Canadian Institutes of Health Research, the Cancer Stem Cell Consortium and the Ontario Institute for Cancer Research (OICR). OICR will also provide up to \$1.2 million for clinical trials in Ontario.



Professor Amy Caudy (Calvin Thomas)

I think we’ll learn many basic things about cancer, and I hope that we may be able to find better drug targets. Right now for we have so little to offer these children with glioblastoma

Fritz Roth is on the team that won \$75M from the American Heart Association to find cures for heart disease.



Professor Frederick Roth Among Those Awarded \$75M to Find Cures for Heart Disease

By Jovana Drinjakovic

University of Toronto Professor **Frederick Roth** is part of a team that has been awarded the One Brave Idea Research Award. The five-year, \$75 million award from the American Heart Association (AHA), Verily Life Sciences (formerly Google Life Sciences) and AstraZeneca will support collaborative research among clinicians, biologists and computational scientists towards better diagnosis and finding cures for coronary heart disease (CHD).

Roth is a professor of molecular genetics and computer science and a researcher at the University of Toronto's Donnelly Centre for Cellular and Biomolecular Research as well as a Senior Scientist at Sinai Health System's Lunenfeld-Tanenbaum Research Institute. Despite progress in medicine, heart disease remains the leading cause of death in the world, including in Canada and the U.S. This is partly because we still lack the ability to detect heart disease before much of the damage to the patient has occurred. By

marrying wearable technology that collects unprecedented amounts of personal data with DNA sequencing and advanced computational analysis, the researchers hope to get ahead of the disease.

The interdisciplinary team, selected from hundreds of applicants, will be led by Dr. **Calum MacRae**, of Brigham and Women's Hospital (BWH) and Harvard Medical School in Boston, to uncover "the causes of heart disease, including previously unrecognized signals marking the transition from wellness to the earliest, yet still largely invisible stages of disease," said **Nancy Brown**, chief executive officer of the American Heart Association.

By combining computational and experimental strategies, we would like to help identify traits that are early predictors of coronary heart disease

Roth, who holds a Canada Excellence Research Chair and also co-directs the Canadian Institute for Advanced Research Program in Genetic Networks, leads a research team carrying out computational biology and large-scale genetic assays. His team will bring to the table innovative data analysis and the latest advances in next-generation sequencing applications to help drive progress towards personalized medicine for CHD.

"By combining computational and experimental strategies, we would like to help

identify traits that are early predictors of CHD. These traits may in turn identify the genes that impact CHD outcomes alone or in combination. My lab is systematically testing the consequences of genetic differences, or variants, in human disease genes. By building "look-up tables" of harmful variants before a patient's genome is sequenced, we can more immediately take appropriate therapeutic measures, even before we see the standard symptoms of disease," said Roth.

"I am thrilled that Fritz Roth is part of this significant multidisciplinary effort. Roth's cutting-edge research, both as a geneticist and a computational scientist, will help drive forward the search for the molecular roots of heart disease," said Professor **Brenda Andrews**, Director of the Donnelly Centre.

In addition to Roth's lab at U of T, other members of the team also include research groups from Harvard, Boston University, MIT, Stanford University and Northeastern University.

"Alone, each of our organizations has helped to transform our understanding of coronary artery disease. Yet, for all the success we have had, there has been no legacy of resources upon which to continue building," said MacRae in a statement issued by the BWH. "Our project will create a global consortium to support programs from idea conception to clinical realization, and establish a lasting resource for future research endeavors in cardiovascular and other chronic disease."

The AHA, Verily and AstraZeneca launched One Brave Idea in January 2016 as the largest one-time award to a single team to find a cure to end CHD and its consequences.

WE ARE BUILDING PARTNERSHIPS ACROSS THE GLOBE



Croatian president **Kolinda Grabar-Kitarovic** toured the Donnelly Centre while visiting U of T to build partnership between the university and Croatian institutions.

Photo: Johnny Guatto

Croatian President Visits U of T, Tours Lab and Meets Students

By Geoffrey Vendeville

Croatia's first female president toured the laboratory of a University of Toronto molecular biologist Tuesday, making time to chat and snap selfies with local Croatian students.

Kolinda Grabar-Kitarović was shown around the lab of Professor **Igor Stagljär**, a renowned researcher and biochemist at the Donnelly Centre. The purpose of her visit was to foster partnerships with the University of Zagreb and

other Croatian institutions – a mission Stagljär shares.

“I’m trying to really push the boundary of collaborations between these two universities so that we have a steady exchange of students and ideas that will lead to some cool discoveries one day,” Stagljär said.

Grabar-Kitarović also met with philanthropist Terrence Donnelly after whom U of

T's Donnelly Centre for Cellular and Biomolecular Research is named.

Stagljar, who graduated from the University of Zagreb and earned a PhD in Switzerland before joining U of T's departments of biochemistry and molecular genetics in 2005, said he was flattered that his home country's head of state wanted to visit his lab.

"How many times do you get the chance to welcome the president of a country in your lab? We're thrilled, very happy. It means we're also doing great research," Stagljar said

Grabar-Kitarović was "extremely excited by the world-class research and teaching ongoing at the University of Toronto," said Ted Sargent, U of T's VP International, adding that she was aware of the "seminal contributions" to science made by Stagljar and **Mladen Vranic**, the renowned diabetes researcher and professor emeritus.

At one point during the lab tour, Grabar-Kitarović donned a white coat and learned to stain a protein gel with the help of Stagljar.

Afterward, she and her entourage – including the Croatian ambassador to Canada – went to Simcoe Hall, where they chatted with 20 Croatian students majoring in a variety of subjects, from architecture to international relations. In a candid talk about Croatia's growing pains since independence and the challenges she faced in office, she said her country would benefit from closer ties with universities such as U of T.

"We need your knowledge, we need your experience, and I will hope you will consider how to forge closer connections with your peers in Croatia," she said.

Her remarks hit home with **Veronika Salamun**, a third-year architecture student and the president of the U of T Croatian Student Association.

"You want to know that you could have potential to grow in Croatia," she told U of T News. "It felt really amazing to meet with a female role model."

Iva Dadic, a master's student in civil engineering who came to U of T more than a year ago, said she was happy to come face-to-face with the president of her native country. "I never met the president back home – I guess I had to go to Canada," she joked.

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

We need your knowledge, we need your experience, and I will hope you will consider how to forge closer connections with your peers in Croatia

WE ARE RAISING A NEW GENERATION OF OUTSTANDING RESEARCHERS



Untangling Blood Complexity Nets Wendy Qiao Donnelly Thesis Prize

By Jovana Drinjakovic

When Wendy Qiao moved across the globe to join Professor Peter Zandstra's lab in the Donnelly Centre, she couldn't have known that, six years later, her research would net her one of the biggest student honor in the institute – the Donnelly Thesis Prize. Now, with the award under her belt and an exciting

job in the pharmaceutical industry, Qiao looks back on her career choices that have one thing in common - a zest for solving difficult problems.

Congratulations on winning the Donnelly Thesis Prize! After years of hard work, how does it feel to know that your thesis got

recognized in this way?

It is certainly a nice way to conclude my academic career. I feel honoured and inspired to continue my journey in bioengineering.

What made you decide to join the Zandstra lab in the first place?

I did my undergrad in biomedical engineering at the University of Auckland in New Zealand. The program was focused on engineering and computational science. I was becoming more interested in computational biology at that time. At the end my undergrad, I felt the need to learn some biology in order to have a career in computational biology. That's why I was looking for an opportunity to work on a computational side of things in a biology lab. Peter's group was one of the few that was well set up for both experimental and computational work - integrating mathematical modelling with stem cell biology. I thought that was a really good environment to be in.

How did your coding and maths skills help expand our understanding of stem cell biology?

My project focused on blood stem cells. They are the origin of all types of blood cells and play an important role in blood generation. Different types of blood cells in our body all talk to each other, such that mature blood cells talk to blood stem cells and control how the stem cells decide which cells to turn into. It is a very dynamic process in a mixed system. My thesis is the beginning of untangling and understanding this process.

This sounds really complicated. How did you go about it?

We broke the problem into separate chunks and developed strategies to understand this complexity at three levels. First, we looked at

the population level – in this mixed system of cells, what are the relative proportions of different cells? Then, we investigated inter-cellular communication – how these different cells signal to blood stem cells. Finally, we looked at the intra-cellular level how blood stem cells integrate all these signals from their environment to make their decisions of which cell type to turn into.

The Zandstra lab is at the forefront of stem cell research. What was it like to work in such an environment?

Peter is a visionary mentor and he likes to see the big picture. For instance, stem cells reside and function in a microenvironment. At any point, their cell fate decision is the result of many factors. When people study stem cell fate regulation, they tend to focus on one aspect at a time. Peter had a different approach early on, in that if we are to understand stem cell biology, we need to look at the system as a whole. Now, more and more researchers are beginning to take into account global regulation in a complex system.

The Donnelly Centre is houses researchers in many different fields. Was it helpful to have such diverse colleagues under the same roof?

Definitely! When I joined Peter's lab, I was new to the type of data and modeling that I was working with. I would literally just go up to Drs. Gary Bader and Quaid Morris' floor in the Donnelly Centre and knock on their doors to ask questions. It would have been a lot harder at the beginning of my thesis without their help. Bader and Morris also ended up being my thesis advisors, as well as collaborators.

You have since become a highly sought-after collaborator, authoring six publications during your PhD.

Yes, the strategies we developed to understand blood stem cells can also be applied to other systems. I worked directly with Dr. Martin Bornhauser from Dresden University in Germany on untangling interactions between cells in the bone marrow and breast cancer, Dr. Michael Rendl from Mount Sinai Hospital in New York on hair follicle research, and also indirectly with Drs. Freda Miller and David Kaplan, of the Hospital for Sick Children in Toronto, on applying my models on brain stem cells. These collaborations have taught me the “big picture” thinking, and how to transfer scientific concepts and techniques from one field to another.

You now work as a computational scientist in a pharmaceutical company. What made you decide to switch gears and how did your training set you up for this job?

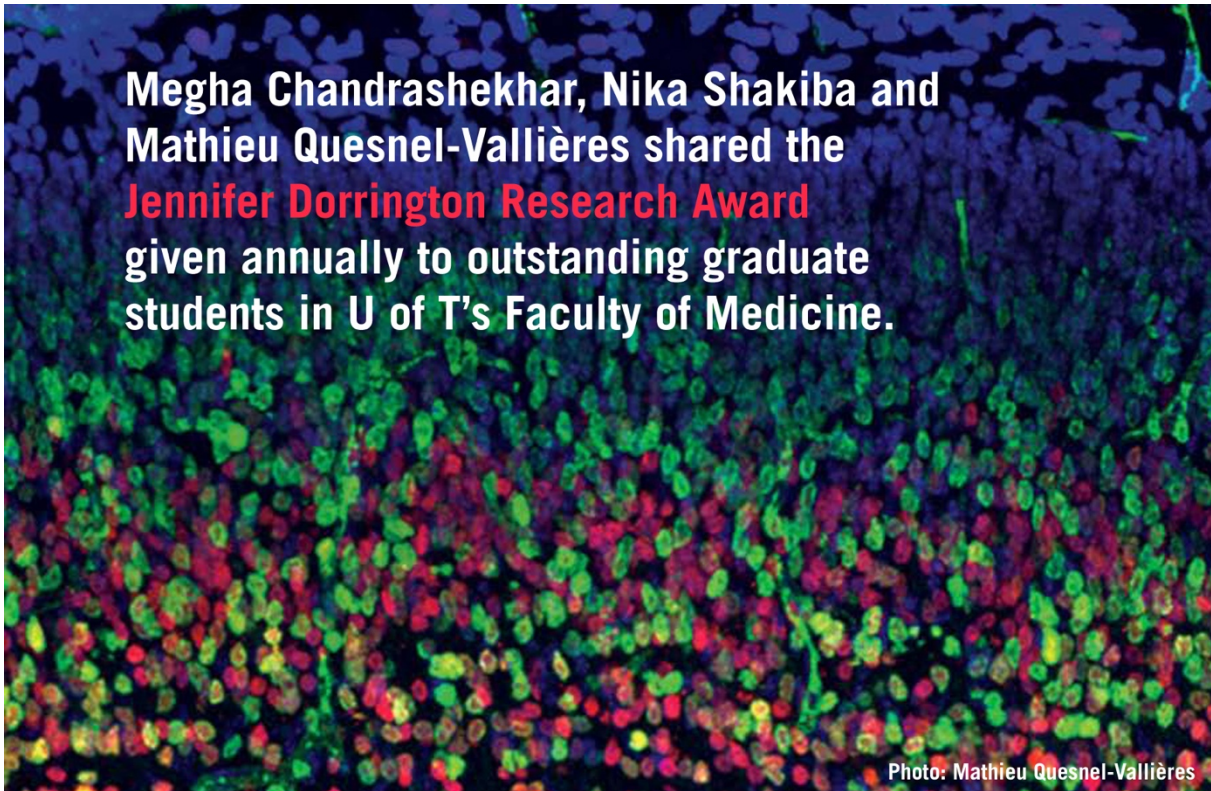
Although I enjoyed exploratory research in an academic setting, I also feel excited when my work has practical application. While I was still doing my PhD, I did an internship with Merrimack Pharmaceuticals that specializes in cancer research. That’s when I first had the taste of modeling patients’ responses to drugs based on their biological data, and I enjoyed

it. I now work with them on understanding how the immune system and cancer cells talk to each other, and so my PhD project was a good foundation for what I am doing now.

Do you have any advice for budding scientists who are just embarking on their PhDs?

Yes, absolutely. There are three main lessons that I have learnt from my PhD training, which I would like to share. Academically, pursuing a PhD takes a lot of hard work, dedication and persistence. Being self-motivated and focused can help you get through hard times. Scientifically, to improve the impact of your work and advance your career, I found it helpful to always have a big picture in mind and think about how your work may be used in other fields, since many concepts and technologies are transferable across fields. Speaking about career, my experience is that I had a lot of freedom on deciding my research direction, so that I had opportunities of steering the direction of my research in a way to build my scientific and technical knowledge needed to get an industry position in a different field from my PhD research. My advice would be to think about what you want to do after PhD training early and plan accordingly when you are still doing PhD.

Pursuing a PhD takes a lot of hard work, dedication and persistence. Being self-motivated and focused can help you get through hard times.



Jennifer Dorrington Award Winners Announced

By Jovana Drinjakovic

When **Megha Chandrashekhar's** PhD research featured on the pages of *Maclean's* and *The Atlantic*, she had every reason to be proud. Not only was her new approach of tackling cancer published in a leading scientific journal, it also reached the public curious to know if cancer will ever be beaten.

Chandrashekhar, along with **Nika Shakiba** and **Mathieu Quesnel-Vallières**, is this year's winner of the Jennifer Dorrington Graduate Research Award. From discoveries in cancer, to autism, to stem cells, these young scientists have already made tremendous contributions in their fields. They are highly deserving of the Dorrington award that

recognizes research excellence and that will further propel them towards fulfilling careers in science.

Meet this year's recipients:

MEGHA CHANDRASHEKHAR

Chandrashekhar joined U of T's Department of Molecular Genetics after obtaining a Bachelor's in Technology from VIT University in Vellore, India, where she ranked fourth in the department, followed by a Master's degree at Queens University in Kingston, Ontario. She decided to join Professor Jason Moffat's group at the Donnelly Centre to help develop

new technology that could revolutionize cancer research and had spectacular success. The reason why cancer treatment is so harrowing is that the current drugs destroy both the cancer and the neighboring healthy tissue. Chandrashekhar wanted to find genes that are only required in cancer cells, so that they could be used as drug targets to selectively attack the disease.



Megha Chandrashekhar

Using the latest gene editing technology, known as CRISPR, Chandrashekhar sifted through the genomes of five different cancer cell lines to find distinct sets of genes that keep each of them alive. These sets of genes also reflect each cancer's unique vulnerability, its Achilles Heel, that could be targeted by specific drugs. Chandrashekhar's pioneering study paves the way for future research that will speed up the discovery of better and more precise treatments.

Chandrashekhar may well be leading these efforts, as she plans to stay in the field after graduating next year. "I feel extremely honored and appreciative for receiving this significant award. Recognition of my work for

this award boosts my confidence and provides further motivation to pursue research in this field," says Chandrashekhar.

Recognition of my work for this award boosts my confidence and provides further motivation to pursue research in this field

MATHIEU QUESNEL-VALLIERES

After obtaining Bachelor's and Master's degrees from the University of Montreal, Mathieu Quesnel-Vallières joined U of T's Department of Molecular Genetics to study molecular processes that shape the brain during development, and in his research, he uncovered molecular roots of autism spectrum disorder (ASD).

The focus of Quesnel-Vallières' research was a cellular process called alternative splicing (AS). AS expands the protein catalogue in cells that underpins the enormous complexity of brain structures. Jointly co-supervised by Professors Ben Blencowe, of the Donnelly Centre, and Sabine Cordes, of Mount Sinai Hospital's Lunenfeld-Tanenbaum Research Institute, who are world leaders in the study of AS and brain development, respectively, Quesnel-Vallières had the best of both worlds in which to hone his research skills.

During his PhD, Quesnel-Vallières created a powerful tool – a mouse lacking an AS regulator, the gene called nSR100. Using sophisticated genetics, he was able to switch off nSR100 in different parts of the brain, and at different times, to ask precise questions about its role.

This revealed that mice with disrupted

nSR100 function had impaired protein diversity and wiring defects in their brains. Crucially, another study, that Quesnel-Vallières was part of, found that people with ASD had less nSR100 in their brains, suggesting that nSR100 is crucial for normal brain development.

Quesnel-Vallières findings mark a step toward a unified view of the disorder notorious for its mishmash of genetic causes, with hundreds of genes believed to contribute to ASD. nSR100 now offers a glimpse of hope as a rare, robust molecule that could be used to diagnose ASD early, and even develop treatments for it.



Mathieu Quesnel-Vallières

Expecting to graduate this summer, Quesnel-Vallières, is preparing for the next chapter in his career. “I am presently interviewing in academic laboratories in the United States and in Switzerland for a post-doc position that would allow me to extend my expertise in RNA biology and neuroscience. The Dorrington Award will definitely help me build a strong application when I have to compete with

candidates from all over the world for a postdoctoral fellowship later this year,” says Quesnel-Vallières.

The Dorrington Award will definitely help me build a strong application when I have to compete with candidates from all over the world for a postdoctoral fellowship

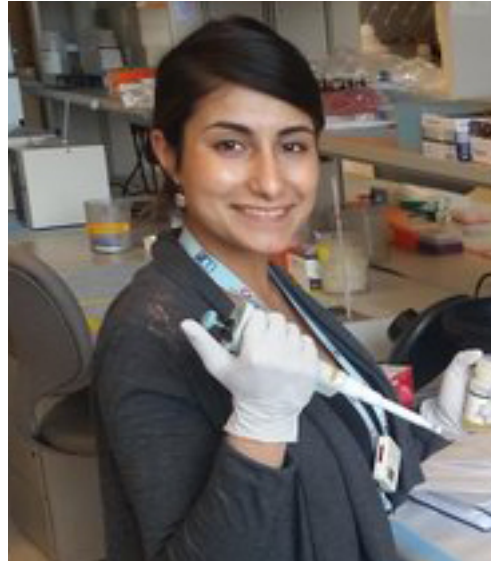
NIKA SHAKIBA

Having graduated at the top of her class in Engineering Science at U of T, Nika Shakiba was a rare kind of new graduate – one that is both highly competent in the lab and able to do complicated number crunching. These skills enabled her to break new ground in stem cell research, which she has been carrying out in Professor Peter Zandstra’s group, at the Donnelly Centre, and in the Institute of Biomaterials and Biomedical Engineering. Shakiba has been building a better understanding of stem cells, which can turn into any cell type and hold great promise for regenerative medicine. A decade ago it became possible to convert, or reprogram, adult cells, such as skin cells, into stem cells – these are called induced pluripotent stem cells (iPSCs). iPSCs not only skirt the controversial sourcing of stem cells from embryos, but they could also be used to make genetically identical, patient-specific cells for clinical use. But reprogramming takes weeks, and scientists still do not fully understand it. This has ultimately hampered their ability to generate iPSCs reliably and in clinically useful amounts.

Shakiba has been applying her skills in cell biology and mathematical modelling to dissect the course of reprogramming. Not all cells follow the same route to becoming stem cells due to inherent stochastic processes. Shakiba has been cataloguing all the different reprogramming paths, and she will use these data to computationally predict a chain of events that will turn any given cell into a stem cell. Her work, expected to be published soon, will provide valuable insights into how to control cell production for clinical use. In the meantime, Shakiba has already identified a key molecule that can be used to more quickly fish out the valuable iPSCs from a blend of cells in a dish.

With one year left before graduating, Shakiba's plan is to become a Professor in Biomedical Engineering, and she believes that the Dorrington award will help her achieve this goal. "This award will enable me to focus on my scientific training. It provides support and motivation to continue to develop my passion for science both in the lab and outside the lab through various outreach activities. The Jennifer Dorrington Award is a generous reminder of the importance of pursuing our dreams, which is enabled by the support of our academic community," says Shakiba.

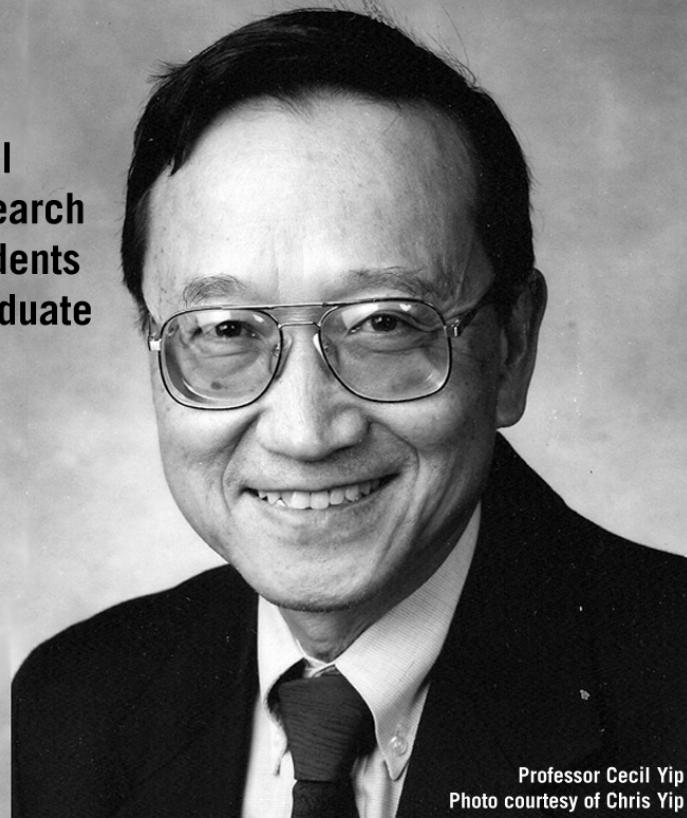
The award was established by the Dorrington family in 2006 as a tribute to Dr. Jennifer Dorrington, who was a professor in the Banting and Best Department of Medical Research. Dorrington's pioneering research greatly advanced our understanding of reproductive biology and ovarian cancer.



Nika Shakiba

The Jennifer Dorrington Award is a generous reminder of the importance of pursuing our dreams, which is enabled by the support of our academic community

The Cecil Yip Doctoral Research Award that recognizes the potential of interdisciplinary research was awarded to 10 students in their first year of graduate study.



Professor Cecil Yip
Photo courtesy of Chris Yip

Winners of the Cecil Yip Doctoral Research Award Announced

By Jovana Drinjakovic

This year's awardees include 10 students, from the University of Toronto's departments of molecular genetics, computer sciences, chemistry and biomedical engineering (IBBME), who are doing their doctoral research in the Donnelly Centre, it was announced by Professors **Brenda Andrews**, Director of the Centre and **Christopher Yip**, Director of IBBME and the Chair of the Yip Doctoral Award Committee.

The award recognizes outstanding students at the very start of their doctorate degrees who

pursue inter-disciplinary research to address fundamental questions in biomedicine.

"It was both challenging and exciting for the committee to rank and review the applicants for these awards. The breadth of the proposed projects and the caliber of the applicants really reflected the outstanding interdisciplinary research in the Donnelly, and how it is attracting top graduate students to the University of Toronto," said Professor Yip. Advances in genomic technologies have allowed scientists to get a holistic view of

molecular changes that occur in cells when, say, a gene is mutated, in order to understand how genes, and their protein products, orchestrate cellular life. **Thuy Nguyen** (Boone lab) is investigating how different combinations of gene losses affect cell survival to shed light on previously unexplored genetic interactions, whereas **Benjamin Piette** (Taipale lab) is mapping protein interactions that control a key cellular process, during which proteins are folded into three-dimensional molecular machines.

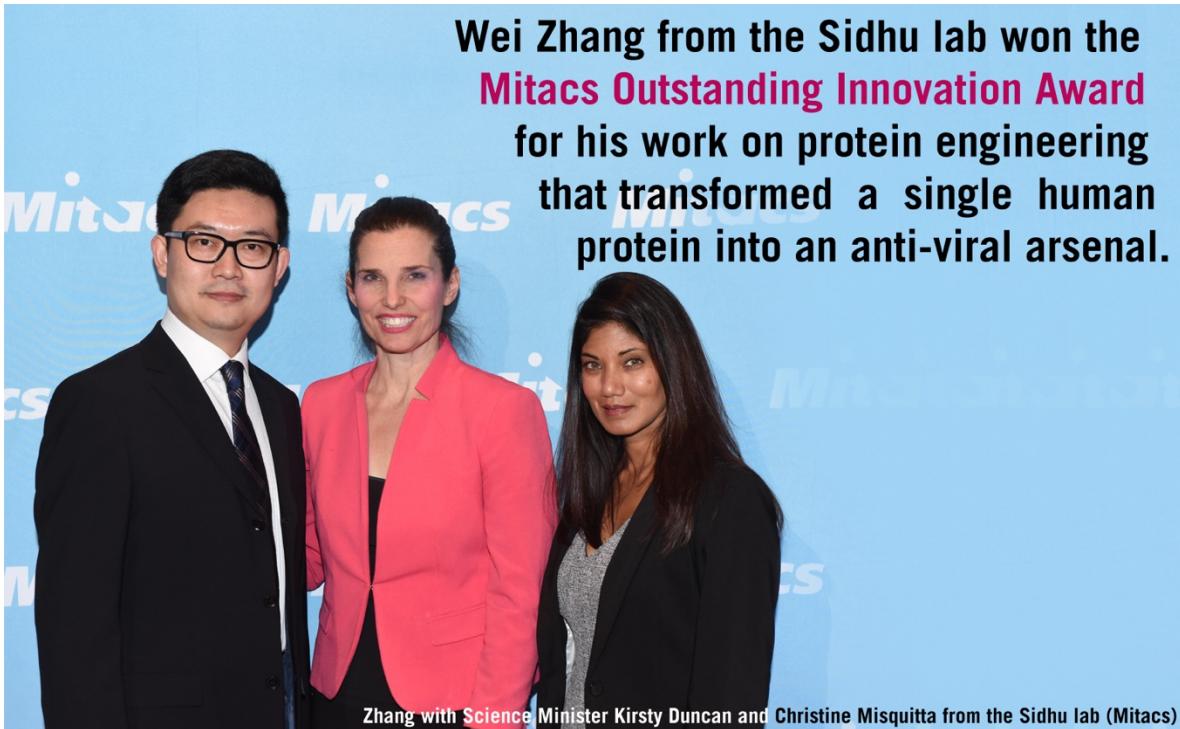
Yutong Ma (Caudy lab) is analyzing cell's metabolic networks to gain insight into some of the most basic biochemical processes that power our cells. And **Margot Lautens** (Fraser & Caudy labs) is studying metabolic networks that operate under low oxygen in search of drug targets that could be used to attack parasitic worms without causing side-effects to human hosts.

Being able to model a disease in a dish — by growing cells from a tissue stricken by the disease — lets scientists not only get to the molecular roots of the condition, but also to test drugs in search of potential treatments. In order to speed up progress in understanding some of the most debilitating diseases, **James Morrissey-Scoot** (Gilbert Lab) will develop a recipe for growing muscle cells from patients with Duchenne muscular dystrophy, whereas **Laura Smith** (Shoichet lab) will use biomaterials to create three-dimensional scaffolds, on which she hopes to grow the elusive glioblastoma cells, taken from the most deadly type of brain cancer for which there is no treatment yet available.

Ben Ouyang (Chan lab) is tackling cancer by researching if nanoparticles can be used to poison the tumour's immediate environment in order to stall its growth. And **Jeff Wintersinger** (Morris lab) is developing

advanced machine learning to backtrack the genetic evolution of cancer and find exact genetic changes that helped a particular cancer metastasize or become drug-resistant. Progress in biology and medicine is increasingly driven by advances in computational sciences that yield new ways of analyzing the growing amount of data. **Chris Cremer** (Morris lab) is developing machine learning algorithms to automate the analysis of patients' medical records in order to be able to predict patient health in the future. And **Nil Sahin** (Andrews and Morris Labs) is teaching computers how to spot the slightest differences between millions of cells that carry single, or combinations of, genetic mutations to shed light on how genes regulate cellular events.

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.



Donnelly Researcher Receives Outstanding Innovation Award

By Jovana Drinjakovic

As a protein engineer, Dr. **Wei Zhang** gives old molecules new tricks. And now, he's transformed a single human protein into a virus-crushing arsenal that could lead to long-sought treatments for deadly infections.

This week, Zhang received the Mitacs Award for Outstanding Innovation, for his work on creating molecular antidotes against viruses that cause Middle East Respiratory Syndrome (MERS) and Crimean-Congo Hemorrhagic Fever (Congo Fever). His patent-pending research was crucial to the launch of a new Toronto-based company called Ubiquitech, which will further commercialize his work so it can be used in a clinical setting.

As a postdoctoral research fellow in Professor **Jason Moffat**'s group in the Donnelly Centre,

Zhang already holds a competitive Elevate Fellowship from Mitacs, a nonprofit which supports innovation across public and private sectors. The fellowship enabled Zhang to start thinking about commercializing his research through a collaboration with the Centre for Commercialization of Antibodies and Biologics (CCAB), the industry partner for his fellowship, located at the U of T.

"Wei has done a phenomenal job of applying a cutting-edge new technology to the pressing issue of emerging pathogenic viruses. It's a great example of how an investment by Canada in basic research and talented young scientists can lead to real impacts on human health," says Dr. **Sachdev Sidhu**, CEO of CCAB.

After completing a doctorate with a U of T Professor **Daniel Durocher**, Zhang joined Moffat and Sidhu's labs to learn the ropes of protein engineering. The two teams had previously developed a powerful technology to quickly create synthetic proteins that could be used as research reagents, or developed further into drugs.

Although Zhang's work revolves around a single protein, called ubiquitin, its applications are far-reaching. Named after its pervasive presence in every cell on earth, ubiquitin works by attaching to other proteins to help relay signals telling the cell to grow or fight infections, for example. Encoded by genes, proteins do most of the work in the cell. They are built from amino acids, which are stitched together based on the DNA blueprint. Using molecular tricks, scientists can change how a protein behaves by changing its DNA sequence.

And so, through subtle tweaks, Zhang has turned a lone, naturally occurring ubiquitin into a set of tools—synthetic ubiquitin variants (UbV)—which allow him to manipulate the proteins that ubiquitin normally binds to. For example, a ubiquitin variant may spur the activity of the other protein, or it may take it out of action completely. But each variant has a unique target, allowing Zhang to control protein activity with unrivalled precision.

Being able to thwart a protein is particularly useful when dealing with harmful molecules, like those made by bacteria and viruses, for example.

“Ubiquitin-dependent signalling is important in the immune response, and a lot of viruses encode proteins that bind human ubiquitin, which allows them to topple the body's defense mechanism. One of them is MERS, a respiratory virus similar to SARS that caused

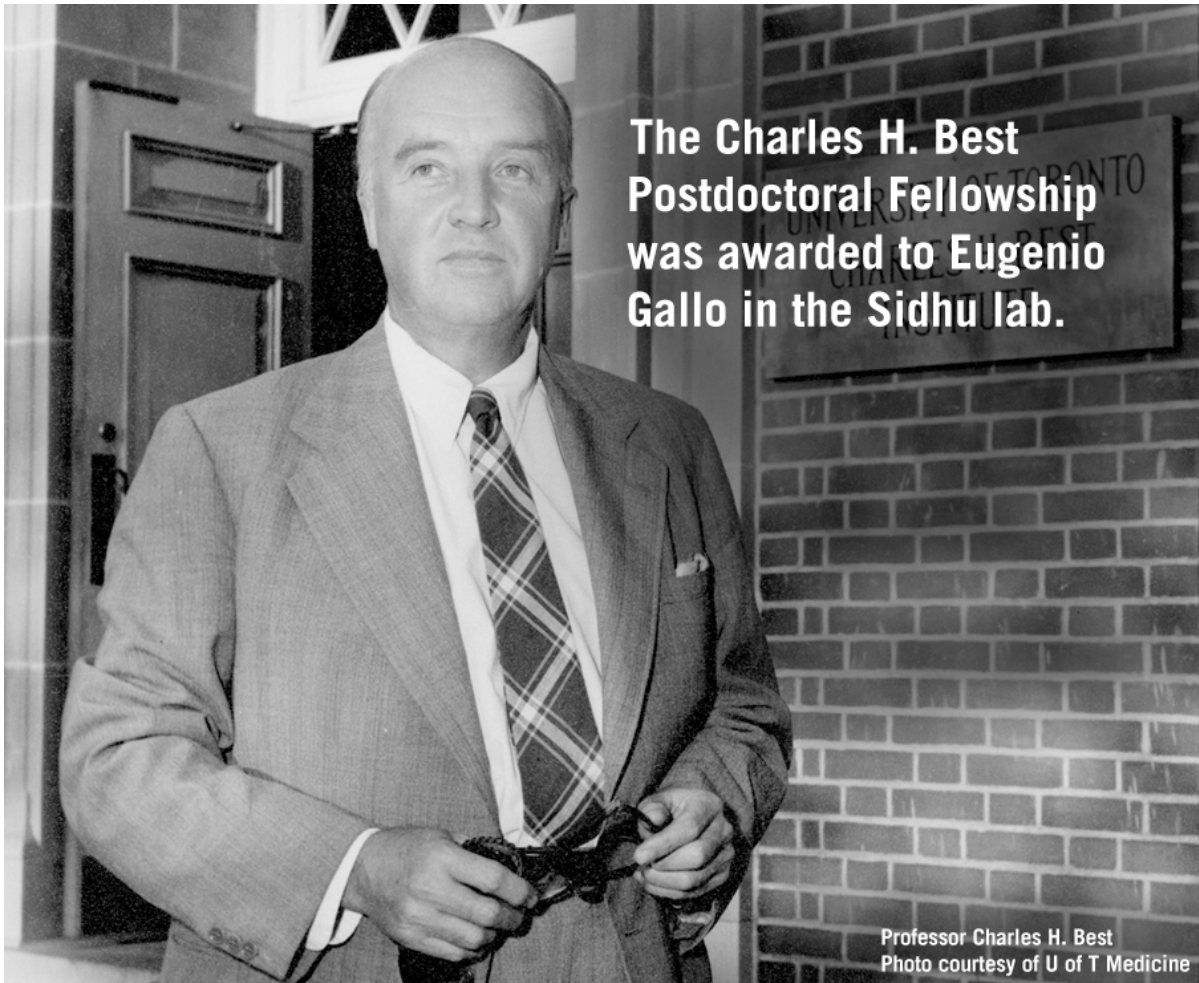
a global epidemic in 2002. 14 years later, nothing has come out of clinical trials. While vaccines are being developed for many viruses, there is no treatment in sight for people who are infected,” says Zhang.

MERS emerged in Saudi Arabia in 2012, and it kills almost 40 per cent of those who become infected, making it even more dangerous than SARS. Zhang has engineered a ubiquitin variant which blocks MERS' ability to evade the immune response. “When we treat the cells infected with MERS with the ubiquitin variant, we can kill the virus in two days,” says Zhang.

Wei has fully captured the potential of protein engineering technology with his research. He is poised to turn basic science into applications that could help people

The list of anti-viral ubiquitins could become long. Zhang has already created a variant that's effective against Congo Fever virus, which causes internal bleeding and kills almost half of those infected. But what's most exciting about Zhang's approach is that it can be applied to any viral protein that binds ubiquitin. “We are able to quickly—in less than one month—generate inhibitors for any ubiquitin-binding proteins in the virus,” says Zhang. This means that Zhang's work could also be applied to viruses such as SARS, Zika, and Ebola, as well as to preventing viral damage to food crops and animals.

“Wei has fully captured the potential of protein engineering technology with his research. He is poised to turn basic science into applications that could help people,” says Moffat.



Winner of the Charles H. Best Fellowship Announced

By Jovana Drinjakovic

Dr. **Eugenio Gallo** has been awarded this year's Charles H. Best Postdoctoral Fellowship, it was announced by Professor Brenda Andrews, the Director of the Donnelly Centre, and by The Charles H. Best Fellowship Committee. Gallo has joined Professor **Sachdev Sidhu's** group at the Donnelly Centre, where he uses advanced protein engineering to find new ways to attack cancer.

"Eugenio has been a fantastic addition to the group. Aside from his excellence in science, he is one of the most enthusiastic and personable scientists I have had the pleasure to work with," said Sidhu.

Gallo is working on a group of proteins called integrins that regulate how cells communicate with their environment. If this process breaks down, it can lead to cancer. Protruding on

both sides of the cell's outer layer, integrins play two important roles. First, they act as anchors, pinning a cell down in its place, and loosening their grip when a cell needs to move. They also serve as communications channels between the outside world and the cell's interior, passing on the messages that can switch genes on or off. Should this transmission go off course, it could turn a normal cell into a cancer cell, able to divide uncontrollably and move into other parts of the body. Scientists believe they can stop this from happening by engineering molecules that shut down the haywire integrins.

With a strong track record in cancer biology and protein engineering, Gallo is up for the task. During his postdoc, Gallo will first chart out how integrins contribute to cancer in the first place. To do this, he will develop synthetic antibodies, which act as protein neutralizers, against several cancer-associated integrins in human cells. Antibodies are molecules that stick to proteins and can change their functions, typically blocking a part of the protein that, for example, senses a signal from the environment. Usually collected from animals, in a process that can take months, antibodies are precious and hard to get. But with the help of the animal-free, phage-display technology, pioneered in the Sidhu lab for custom antibody design and production, Gallo will be able to quickly compile a toolkit containing hundreds of antibodies to understand how different integrins work in normal and cancer cells.

Gallo's research comes at a time when antibody-based drugs, also called biologics, are gaining popularity as a new generation of cancer treatments. Because antibodies recognize and bind to individual proteins with needle-like precision, antibody-based

treatments usually have fewer side effects compared to the blanket approach of chemotherapy. In addition to making a trove of sought-after research reagents, Gallo's work could also lead to the discovery of new anti-cancer drug candidates.

This rare opportunity of applying a cutting-edge antibody engineering technology toward developing new therapeutics, which Sidhu's team is internationally recognized for, is precisely what attracted Gallo to join the group.

"I am immensely grateful for having the opportunity of having joined the group due to its highly collaborative and innovative environment," said Gallo.

We thank The Charles H. Best Foundation on 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.

Eugenio has been a fantastic addition to the group. Aside from his excellence in science, he is one of the most enthusiastic and personable scientists I have had the pleasure to work with

INSPIRING THE NEXT GENERATION OF RESEARCHERS



In 2016, Donnelly Centre hosted visits from more than 100 students from Toronto highschools. During these visits, the students had a chance to speak with our researchers and learn about their work, as well as get a hands-on experience with basic methods in molecular biology. We showed them genetically modified yeast, worms and fish that our scientists use to understand how biology works. They also saw some of the latest instruments that are the cornerstone of genomics research, such as DNA sequencing

machines and robots that handle thousands of experiments each day for large scale studies in genetics. None of this would have been possible without our fantastic graduate students and postdocs who take the time away from their research to help as outreach demonstrators!

Also, thanks to Dr. **Christine Misquitta**, Donnelly Centre again took part in Bring Our Children to Work Day, an annual U of T event and Science Rendezvous, the largest celebration of science in the country.



Bring Our Children to Work Day in the Donnelly Centre



Donnelly Centre booth at Science Rendezvous

SELECT MEDIA HIGHLIGHTS

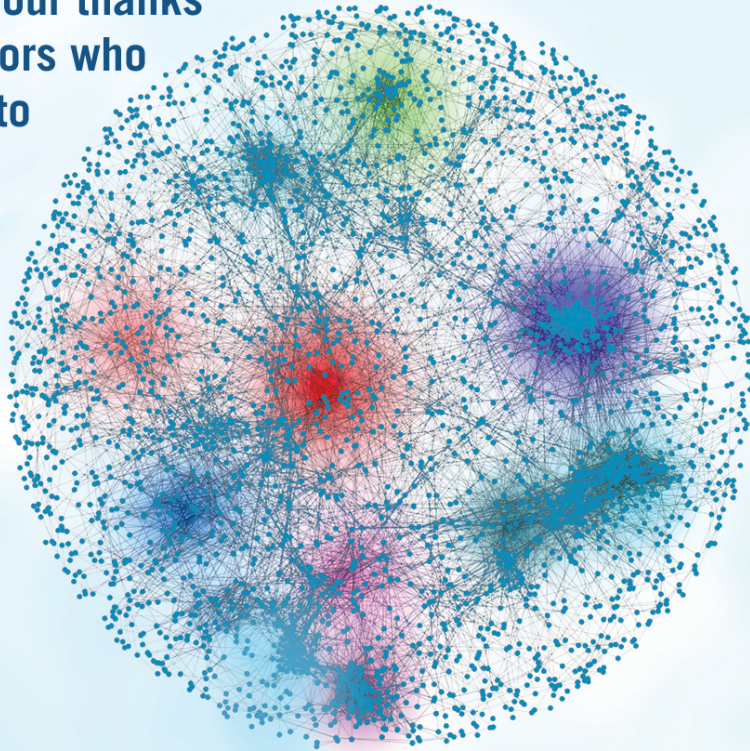
In 2016, our discoveries reached a broad audience by being featured in print and online media. Here's a selection of some of the highlights:

- Introverted mice reveal clues to large swath of autism cases - *The Globe and Mail*
- Lacking a single protein may be the cause of 1 in 3 autism cases: Canadian research - *Global News*
- Cause of one third of all autism cases may have been discovered by scientists - *The Independent*
- Autism: Scientists May Be Able To Explain A Third Of All Cases – *The Huffington Post*
- Shortage of a Protein Linked to Autism in Mice - *The Scientist*
- Mapping the perfect wine and cheese pairings - using data science - *BBC News*
- Looking for the best wine and cheese pairings? There's an app for that - *CBC News*
- How to throw the ultimate wine-and-cheese party using the miracle of data - *The Washington Post*
- New approach to Ebola, SARS leads to research award - *Toronto Star*
- Mutation vs. Mutation - *The Scientist*
- Why Some Genetic Miscues Are Helpful - *Quanta Magazine*
- Scientist using big data against heart disease wins \$75 million award - *STAT News*
- Giant Genetic Map Shows Life's Hidden Links - *Quanta Magazine*
- Five Ways Yeast Will Help Save Lives - *Discover Magazine*
- It Took 15 Years to Map Every Gene Interaction in a Yeast Cell - *Motherboard|VICE*
- Why scientific breakthroughs take time to move from lab to bedside - *Toronto Star*
- Discovery Could Help Deliver Protein Drugs - *Forbes*
- How artificial intelligence could transform the medical world - *Toronto Star*
- Peek Into the Weird and Wonderful Age of AI - *WIRED*
- How shapeshifting nanoparticles could deliver drugs to tumours - *Wired UK*

**TO REMAIN AT THE CUTTING EDGE, OUR RESEARCHERS REQUIRE
CONSISTENT SUPPORT THAT RISES ABOVE POLITICAL TRENDS OR
A CHANGING ECONOMY**

**We wish to express our thanks
to the following donors who
made gifts in 2016 to
advance our work:**

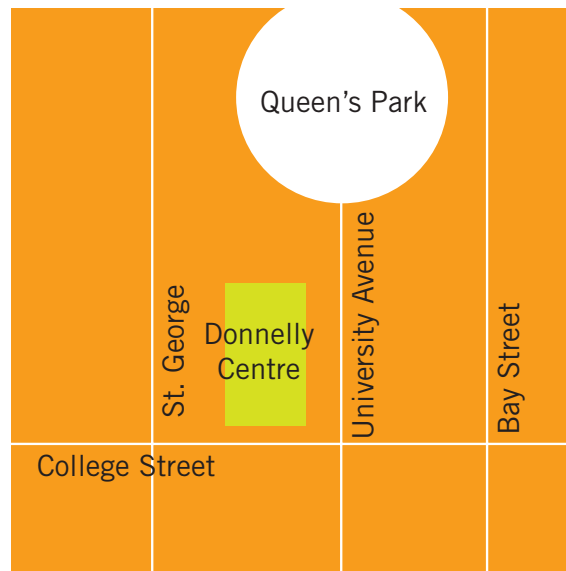
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THANKS EVERYONE FOR A GREAT 2016!

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