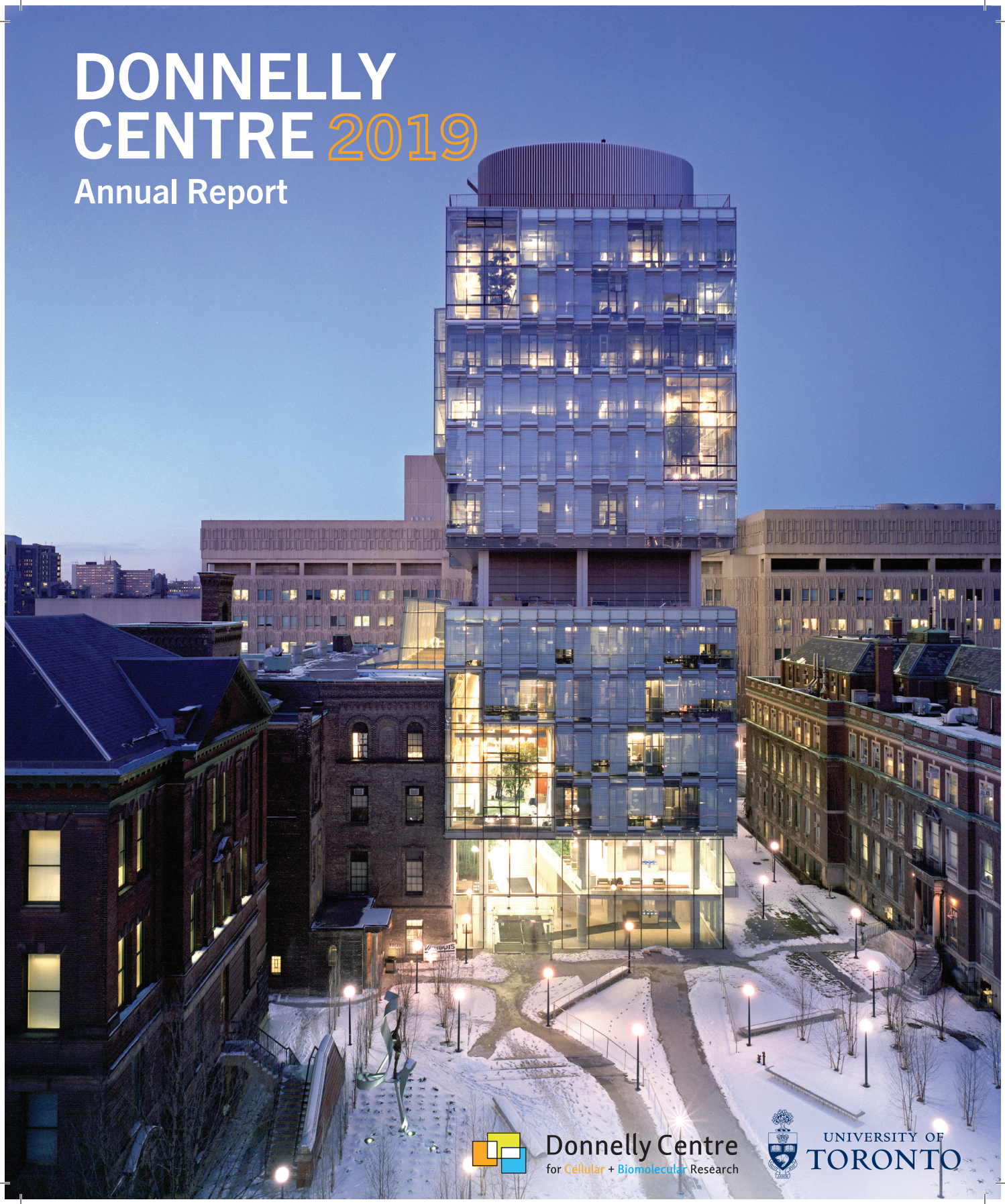
DONNELLY CENTRE 2019

Annual Report



Donnelly Centre
for Cellular + Biomolecular Research

UNIVERSITY OF TORONTO

Founded in 2005 at the University of Toronto, Donnelly Centre for Cellular and Biomolecular Research is an interdisciplinary research institute where scientists make discoveries to improve health.

With this report, we bring you a selection of stories about Donnelly Centre science and other accomplishments by our principal investigators and trainees. We also extend our warm thanks to Terrence Donnelly, whose gift helped found the Centre, and whose ongoing support, along with that of other benefactors, ensures that it remains a leading hub for biomedical research.

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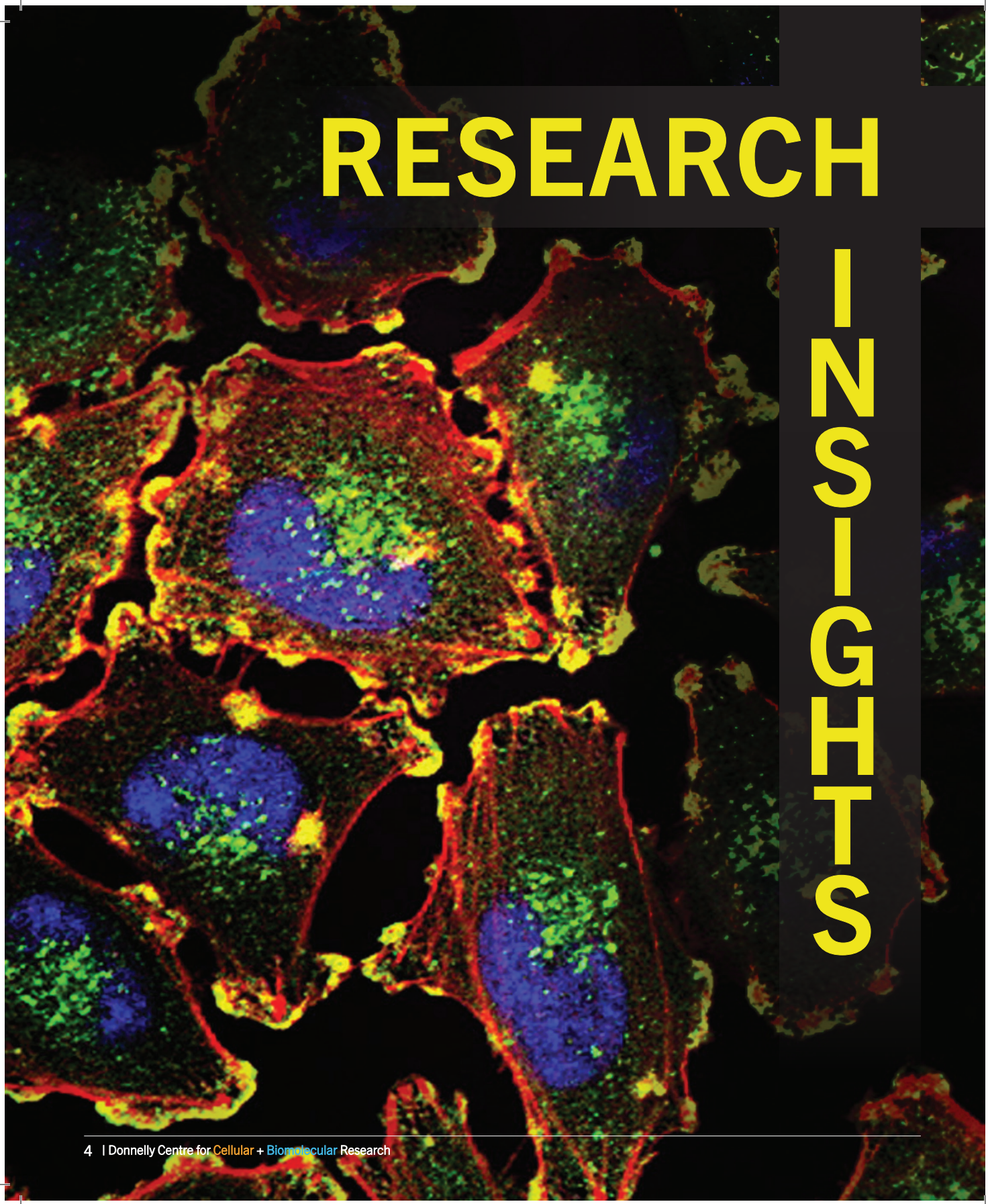
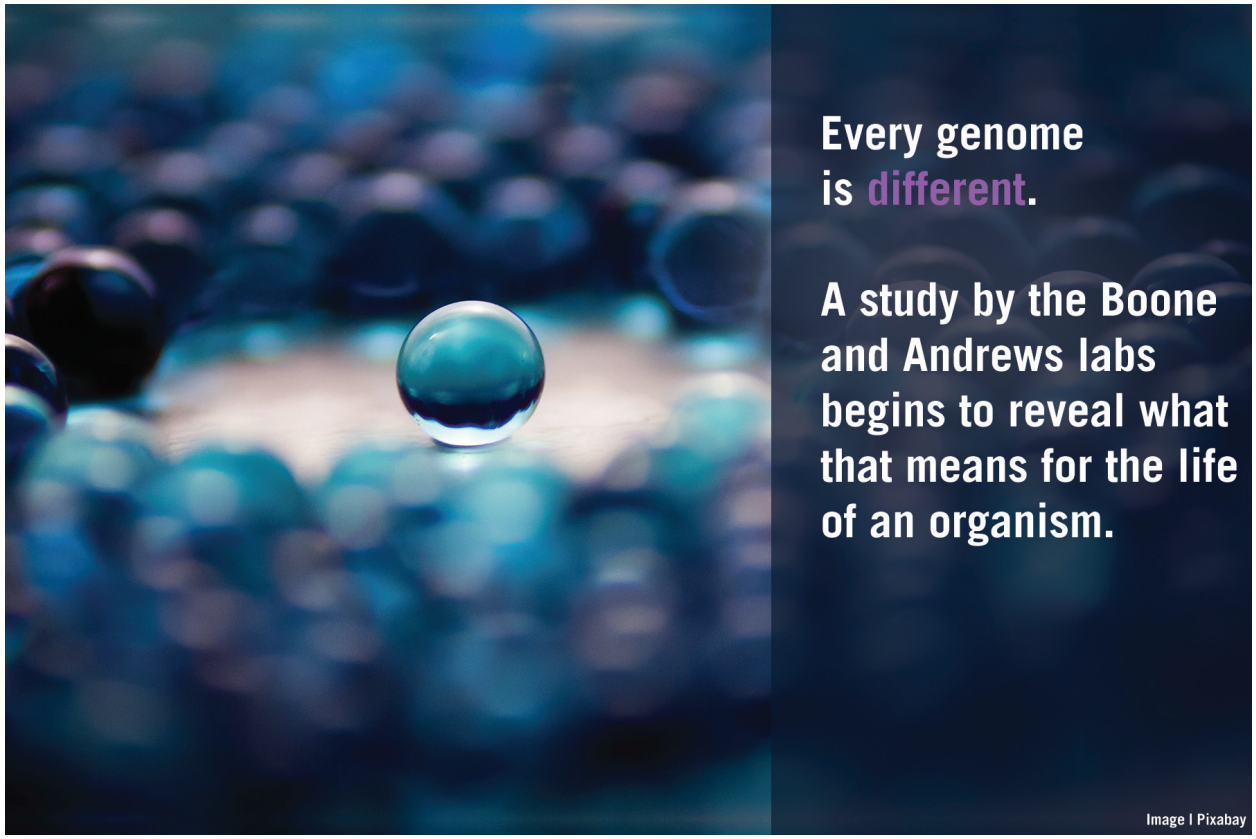


RESEARCH INSIGHTS



How Genetic Background Influences Trait Inheritance

By Jovana Drinjakovic
February 25, 2019.

Almost every family has a hard-drinking, bacon-loving, exercise-averse relative who despite all odds lived happily to a ripe old age while another perished before their time despite being mindful about their health. Looking at their genomes, it would be impossible to tell who's the lucky one.

This is because of genetic background—countless and mostly subtle differences in the genomes of any two people, which affect gene function in ways scientists don't yet understand.

A new study led by **Brenda Andrews** and **Charles Boone**, Director and Professor at the Donnelly Centre, respectively, begins to unpick how genetic background shapes the differences between members of the same species. The team also included **Gerry Fink**, professor of genetics at MIT and member of the Whitehead Institute.

Their findings are published in the journal *Proceedings of the National Academy of Science* of the U.S.

"Genetic background confounds our ability to interpret the information stored in an individual genome," says Andrews. It also makes it hard for physicians to predict disease severity in relatively straightforward cases where a disease-causing gene is well known. Two people carrying a same mutation that causes cystic fibrosis, an inherited lung disorder, can develop a mild and a severe form of disease due to the differences between their genetic

backgrounds.

With 3 million differences in the DNA code between any two people, the study of genetic background effects in humans is still a daunting prospect. But scientists are beginning to make headway by looking at simpler organisms such as yeast.

"Genetic background has the power to make the original phenotype (a physical outcome of gene function) less or more severe," says **Jing Hou**, a postdoctoral fellow in the lab who spearheaded the study. This is true for human diseases and it is also true in yeast which is a very good model to study this." This is because the yeast genome is smaller than human and therefore easier to study.

To begin to unpick the genetic background effects, Hou compared how gene mutations manifest themselves in two closely related yeast strains, S288c and ∑1278b, SC and Sigma from here, respectively. The two strains are 0.2 per cent different at the DNA level, which is about the same amount of genetic diversity between any two people. In an earlier work, the Boone and Andrews labs, in collaboration with Fink's group, established that mutations in 57 genes, about one percent of all yeast genes, have different outcomes between SC and Sigma, causing cell death in either one or the other strain, but not both. These genes are called "conditional lethals" and whether or not a cell needs them depends on other, so-called modifier genes. But which ones?

By mating the two strains, Hou was able to identify these modifier genes thanks to their ability to mask the damaging mutations and rescue survival of the hybrid progeny.

"Genetic background has the power to make the original phenotype (physical outcome of gene function) less or more severe. This is true for human diseases and it is also true in yeast

Hou found that while most conditional lethal genes have multiple modifiers, whose effects are more complex and harder to establish, some have only one modifier and are easier to study. This is the case with CYS3 and CYS4 genes, which help make cysteine, an essential amino acid. Both CYS3 and CYS4 are conditionally lethal in Sigma, but not in the SC strain, which means that Sigma cells die when either gene is missing. Hou discovered that this is thanks to a single modifier gene called OPT1, which works downstream from the CYS genes and can compensate for their loss in the SC strain. Sigma cells happen to carry a mutation in the OPT1 gene and this makes them fully reliant on the CYS genes to produce cysteine.

In another experiment, Hou looked across 20 different yeast strains, from about 1000 naturally found isolates whose genomes have been sequenced. She found a different modifier of the CYS genes in another strain used in the making of Japanese rice wine sake.

With all this information, Hou was able to scan the genomes of all 1000 yeast isolates and accurately guessed which other strains will act like Sigma or the Sake yeast and be completely reliant on the CYS genes to survive. This is similar to being able to single out, from 1000 patients with the same genetic disorder, those individuals who have a higher chance of developing a more severe form of disease.

Being able to predict a biological outcome from genome sequence alone is one of the goals of precision medicine and this early work in yeast raises hopes that similar studies will be possible for human cells.

"Just based on sequence and the knowledge of this pathway we could predict gene essentiality across the whole species," says Hou. "I think we will be able to predict human risk of disease if we have good enough knowledge of how genes work together in pathways."

For Hou, the yeast work continues and on a much bigger scale. With **Guihong Tan**, a research associate in the lab, she is working to identify all the genes across 200 isolates whose effects are modified by the genetic background. Tan thinks this number will be 800 genes, but Hou is more conservative in her estimate. "I think we'll find about 200," she says. It's an uncharted territory and the bets are on, with a bottle of champagne as prize that Hou hopes to pop once they collect all the data.

Study Finds Large Molecular Differences Between Stem Cells Grown on Different Biomaterials

By Jovana Drinjakovic
April 15, 2019.

The genes neccessary for the growth and survival of stem cells are influenced by the biomaterials on which they're cultured, Donnelly Centre investigators have found.

Different substrates, used to coat the surface of the lab dish for the cells to adhere to, can change the cells' molecular states—and potentially their behavior—and should be considered in future research.

"Cells are often maintained on different substrates under assumption that the nature of the substrate does not make that much of a difference," says **Jelena Tomic**, one of the lead authors on the paper and a research associate in the lab of **Jason Moffat**, a professor of molecular genetics at the Donnelly Centre.

While there had been reports that these biomaterials can influence certain molecular changes in cells, the extent of those changes had not been studied in detail – until now.

Writing in the journal *Cell Reports*, the researchers used the gene editing CRISPR technology to study which genes are essential for embryonic stem cell proliferation. They found that two commonly used substrates have a much more profound effect on the cells' molecular properties than previously appreciated.

The effect is thought to be caused by substrate molecules interacting with receptors on the cell surface to influence cellular behaviour.

In addition to Tomic, post-doctoral researcher **Barbara Mair** and graduate student **Sanna Masud** were also lead co-authors of the study. The study itself was done in collaboration with Senior Scientist **Gordon Keller**'s group at University Health Network, and was made possible thanks to the University of Toronto's Medicine by Design initiative that supports regenerative medicine research through collaboration among experts from diverse disciplines.

Stem cells, like those found in embryo, hold promise for regenerative medicine thanks to their unique properties. They can multiply to make more stem cells, and they are pluripotent, which means that under right conditions they can turn into any cell type in the body. This makes them an ideal source of cells for generating tissue in the lab to study and treat disease. Over the last couple of decades, researchers have developed a variety of methods to maintain stem cells in a pluripotent state or make them turn into specialized cell types such as neurons.

"Every lab uses a different way of growing cells, it's what fits your lab best," says Masud. "But, our data show that it clearly makes quite a significant difference what you are growing your cells on."

To investigate substrate effects, the team split the same batch of stem cells and multiplied them in dishes whose surface was coated with different substrates. One substrate consisted of a bed of immature mouse cells, known as mouse embryonic fibroblasts, or MEFs, which are thought to mimic the cells' natural environment in the embryo. The other was laminin, a component of the matrix the cells are embedded inside the body. In addition to MEFs and laminin, several other substrates are used for growing stem cells, but their effects remain unclear.

"Our study provides the stem cell field with data to assess how their substrate can inherently bias their cells' genetic makeup even before they start doing any experiments

The researchers were surprised to find the extent to which the stem cells were dissimilar at the molecular level depending on whether they were grown on MEFs or laminin. First, the scientists looked at differences in gene usage and found that as many as half of all genes that were turned on differed between the two cell populations.

Working with the Centre for Regeneration and Commercialization of Regenerative Medicine in Toronto, the researchers created embryonic stem cells that have an inducible CRISPR switch, allowing them to turn off, one at a time, all of ~20,000 human genes to find those required for pluripotent cell growth. These types of studies were technically too challenging before CRISPR was developed a few years ago. The data revealed that cell proliferation in the pluripotent state in the two cell populations was maintained by partially overlapping sets of genes.

"People have anecdotally observed that the growth substrate can affect the cells' behaviour, so that in itself is not too surprising but the large extent to which it does is very surprising," says Mair. "Our study provides the stem cell field with data to assess how their substrate can inherently bias their cells' genetic makeup even before they start doing any experiments."

The study also uncovered several novel genes essential for stem cell growth on both MEFs and laminin and which will be the focus of future research.

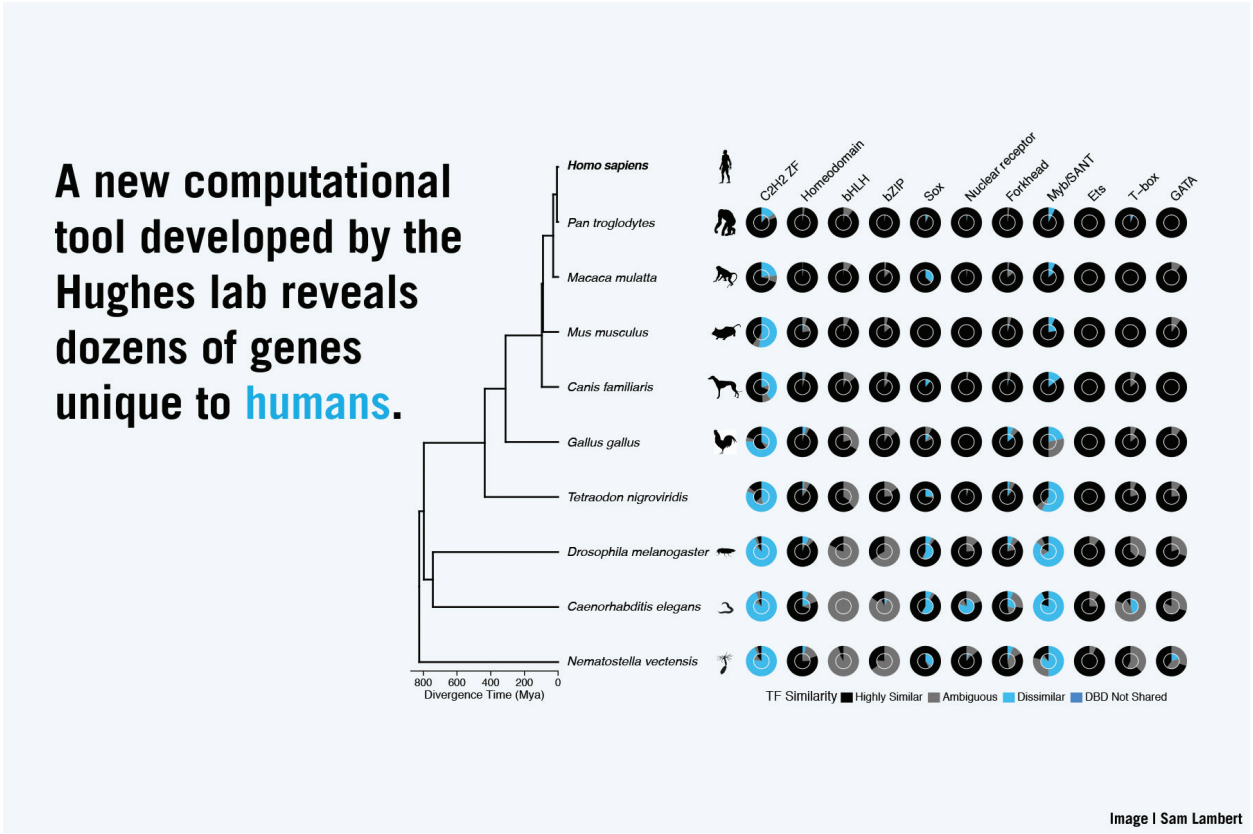


Image | Sam Lambert

Scientists Uncover Genes That Could Hold Key to How Humans Evolved

By Jovana Drinjakovic
May 27, 2019.

Donnelly Centre investigators have found that dozens of genes, previously thought to have similar roles across different organisms, are in fact unique to humans and could help explain how our species came to exist.

These genes code for a class of proteins known as transcription factors, or TFs, which control gene activity. TFs recognize specific snippets of the DNA code, known as motifs, and use them as landing sites to bind the DNA and turn genes on or off.

Previous research had suggested that TFs which look similar across different organisms also bind similar motifs, even in species as diverse as fruit flies and humans. But a new study from Professor **Timothy Hughes**' lab at the Donnelly Centre, shows that this is not always the case.

Writing in the journal *Nature Genetics*, the researchers describe a new computational method which allowed them to more accurately predict motif sequences each TF binds in many different species. The findings reveal that some sub-classes of TFs are much more functionally diverse than previously thought.

"Even between closely related species there's a non-negligible portion of TFs that are likely to bind new sequences," says **Sam Lambert**,

"Even between closely related species there's a non-negligible portion of TFs that are likely to bind new sequences.We think these molecular differences could be driving some of the differences between chimps and humans

former graduate student in Hughes' lab who did most of the work on the paper and has since moved to the University of Cambridge for a postdoctoral stint.

"This means they are likely to have novel functions by regulating different genes, which may be important for species differences," he says.

Even between chimps and humans, whose genomes are 99 per cent identical, there are dozens of TFs which recognize diverse motifs between the two species in a way that would affect expression of hundreds of different genes.

"We think these molecular differences could be driving some of the differences between chimps and humans," says Lambert, who won Jennifer Dorrington Graduate Research Award for outstanding doctoral research at U of T's Faculty of Medicine.

To reanalyze motif sequences, Lambert developed new software which looks for structural similarities between the TFs' DNA binding regions that relate to their ability to bind the same or different DNA motifs. If two TFs, from different species, have a similar composition of amino-acids, building blocks of proteins, they probably bind similar motifs. But unlike older methods, which compare these regions as a whole, Lambert's automatically assigns greater value to those amino-acids— a fraction of the entire region— which directly contact the DNA. In this case, two TFs may look similar overall, but if they differ in the position of these key amino-acids, they are more likely to bind different motifs.

When Lambert compared all TFs across different species and matched to all available motif sequence data, he found that many human TFs recognize different sequences—and therefore regulate different genes— than versions of the same proteins in other animals.

The finding contradicts earlier research stating that almost all of human and fruit fly TFs bind the same motif sequences, and is a call for caution to scientists hoping to draw insights about human TFs by only studying their counterparts in simpler organisms.

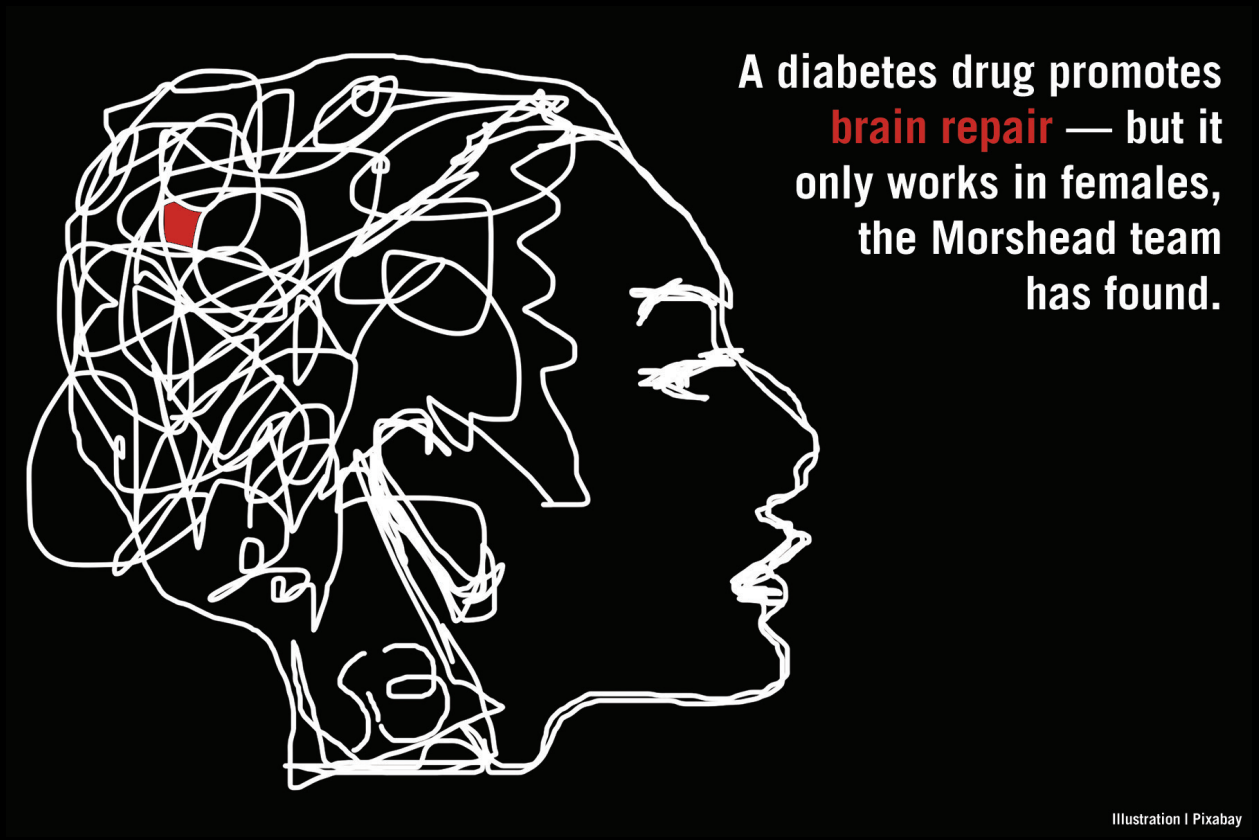
"There is this idea that has persevered, which is that the TFs bind almost identical motifs between humans and fruit flies," says Hughes. "And while there are many examples where these proteins are functionally conserved, this is by no means to the extent that has been accepted."

As for TFs that have unique human roles, these belong to the rapidly evolving class of so-called C2H2 zinc finger TFs, named for zinc ion-containing finger-like protrusions, with which they bind the DNA.

Their role remains an open question but it is known that organisms with more diverse TFs also have more cell types, which can come together in novel ways to build more complicated bodies.

Hughes is excited about a tantalizing possibility that some of these zinc finger TFs could be responsible for the unique features of human physiology and anatomy—our immune system and the brain, which are the most complex among animals. Another concerns sexual dimorphism: countless visible, and often less obvious, differences between sexes that guide mate selection—decisions that have an immediate impact on reproductive success, and can also have profound impact on physiology in the long term. The peacock's tail is a classic example of such a feature.

"Almost nobody in human genetics studies the molecular basis of sexual dimorphism, yet these are features that all human beings see in each other and that we are all fascinated with," says Hughes. "I'm tempted to spend the last half of my career working on this, if I can figure out how to do it!"



A diabetes drug promotes brain repair — but it only works in females, the Morshead team has found.

Illustration | Pixabay

Metformin Promotes Brain Repair in Sex Dependent Manner

By Jovana Drinjakovic
September 11, 2019.

Males are straightforward while females are complicated. This misguided view lies behind an overwhelming exclusion of female animals from drug research out of fear that their fluctuating hormone levels will muddle the data. But now a study by Donnelly Centre scientists shows that a female sex hormone plays a key role in promoting brain repair and opens the door to the development of more effective treatments.

A team of researchers led by **Cindi Morshead**, a professor in the Donnelly Centre and Chair, Division of Anatomy at the Department of Surgery, found that metformin, a widely prescribed drug to treat diabetes, promotes repair in adult female brains and is dependent on the sex hormone estradiol.

Their findings are described in a study published in the journal *Science Advances*.

The research builds on previous work, which was done in collaboration with **Freda Miller**'s group at the Hospital for Sick Children, that sought to find treatment for childhood brain injury. They found that the widely prescribed drug metformin can induce brain repair and improve motor function in newborn mice that had a stroke. Metformin works by activating stem cells in the brain, which can self-renew and give rise to different types of brain cells to

replace those killed by injury. Because brain injury in early life can lead to lifelong difficulties with learning and memory, the researchers now wanted to find out if metformin also promoted cognitive recovery.

"You can fix a hole in someone's brain but if they don't function better it's irrelevant to them," says Morshead, also a professor in U of T's Institutes of Medical Science and Biomaterials & Biomedical Engineering.

"To know that there are both age and sex dependent effects — it has such implications for treatment and therapeutics

Graduate student **Rebecca Ruddy** induced stroke in newborn mice, followed by daily metformin treatment before the animals were tested in a puzzle box test that measures learning and memory.

To the researchers' delight, metformin was able to activate neural stem cells in the brain and promote cognitive recovery as shown by mice who were able to learn new tasks and form short and long-term memories. But the data also revealed something unexpected. Metformin did not affect all the animals in equal manner. It only worked in adult females.

"When we first looked at the data, we did not see the benefit of the metformin treatment," says Morshead. "Then we noticed that adult females tended to do better than the males."

Professor Cindi Morshead, centre, with graduate students Rebeca Ruddy, left, and Kelsey Adams, right, who did the research.

A closer look revealed that metformin selectively activated the adult female neural stem cells while having no effect on the males. This turned out to be due to the female sex hormone estradiol, which somehow enhances the stem cells' ability to respond to metformin. When female mice had their ovaries removed and lacked the female sex hormone, the stem cells did not respond to metformin treatment. Conversely, the male hormone testosterone appears to inhibit this process.

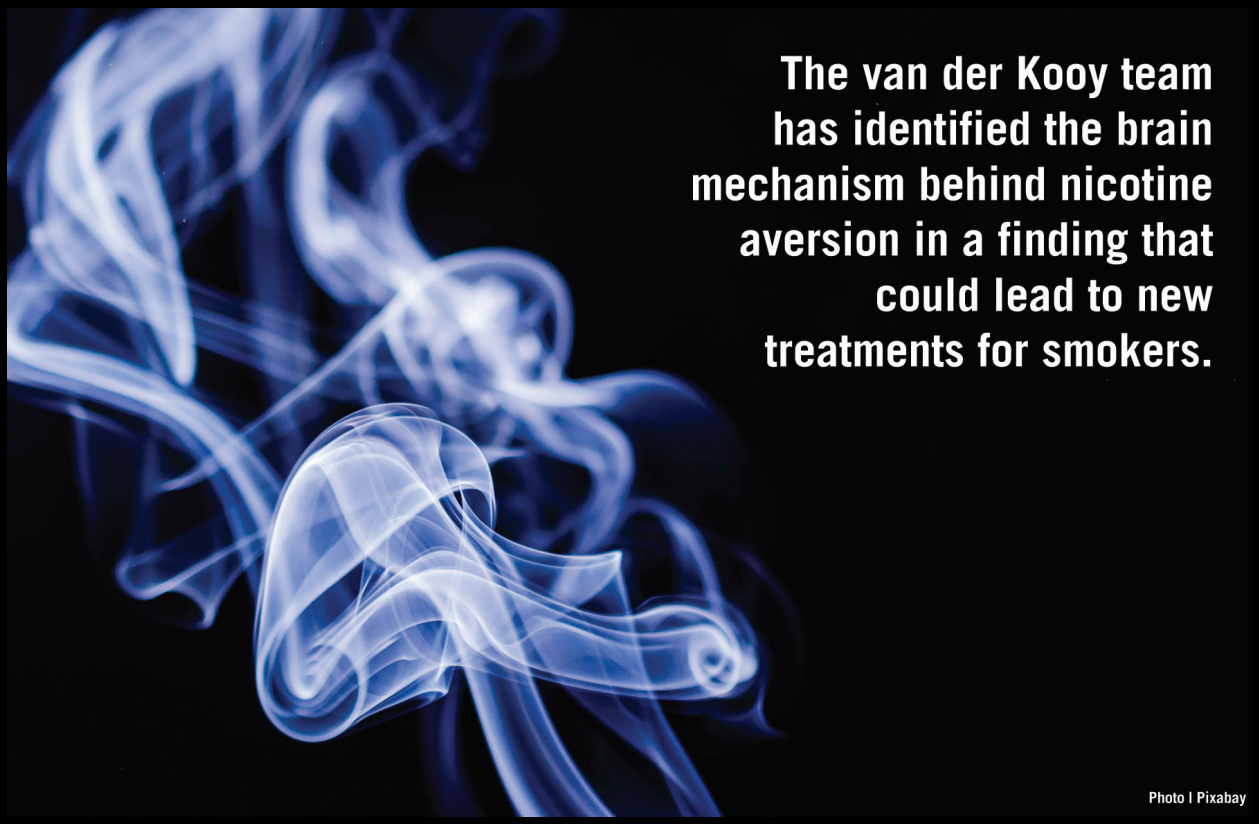
"To know that there are both age and sex dependent effects —it has such implications for treatment and therapeutics," says Morshead.

The findings come at a time when scientists are reckoning with the data bias that is skewed against women due to the predominant use of male animals in research.

"The thinking was that we're going to study males because everything you need to know is found in the male brain, and then the female brain just complicates things with hormones," says Morshead. "It's very misguided and troublesome for advancing neurological health."

As preclinical research informs human studies, the sex bias is believed to have led to failed clinical trials, misdiagnosis and inappropriate therapies for women, as highlighted in a recent article in *Science*.

Human trials of repurposing metformin as a brain repair drug are ongoing, with a pilot study testing it in children who suffered brain injury, led by Morsehead's collaborators Drs. **Donald Mabbott** and **Eric Bouffet**, Head of Neurosciences and Mental Health Program and Director of Brain Tumour Programs, respectively, at SickKids. Although the current patient cohort is too small to detect any sex effects, the plan is to increase the number of patients to see if sex also affects treatment outcome in people, said Morshead.



The van der Kooy team has identified the brain mechanism behind nicotine aversion in a finding that could lead to new treatments for smokers.

Photo | Pixabay

Why Nicotine Initially Feels Disgusting and how this Could Help Smokers Quit

By Jovana Drinjakovic
November 22, 2019.

If you have ever smoked, or know someone who has – they might tell you that smoking a cigarette probably felt disgusting at first.

Taryn Grieder has a personal interest in understanding why people continue to smoke despite the initial revulsion and countless health risks.

"In my family we have six people and five of us—everyone but me—smoke, or at least they did smoke," says Grieder, research associate and neuroscience lecturer at U of T, who lost her dad prematurely to smoking.

Grieder has been investigating nicotine addiction for more than a decade, first as a doctoral student and now as a staff scientist, in Professor **Derek van der Kooy**'s lab in the Donnelly Centre.

Her research has now identified the elusive brain cells responsible for nicotine aversion, raising hopes that they could be harnessed to develop new treatments to help smokers quit.

The findings are published in the journal *Proceedings of the National Academy of Sciences* of the U.S.

Scientists have long known that nicotine has a dual effect on the brain, where it stimulates both pleasure and aversion. It was thought that the opposing effects came from nicotine activating its

receptors in different parts of the brain.

But Grieder found that both reward and aversion are sensed by two different populations of brain cells, or neurons, residing in the same area, called the ventral tegmental area, or VTA, which is a key player in the brain's reward system.

"Now we know that nicotine hits different populations of neurons in the same area, from which neurons project to the different brain regions," says Grieder, who also teaches neuropsychology at U of T and other universities.

When someone smokes for the first time, the nicotine will target all its receptors in the VTA to stimulate both pleasure and aversion. But if the person continues to smoke, their brain will change.

"Aversion should be there all the time, but the more someone smokes, they're going to have changes in the amounts of the receptors and in the signaling processes in the brain reward system," says Grieder.
Smoking is complex and influenced by many factors. Some people find the first cigarette rewarding if they are under stress, for example, which Grieder's previous research suggests is thanks to nicotine's ability to reduce the negative effects of stress. Others may find smoking more pleasurable when they are under the influence of alcohol or other drugs because their reward signalling is already heightened so that nicotine aversion becomes less significant.

Although the two cell populations are intermingled in the VTA, the researchers were able to separate them with a genetic trick. They took advantage of a mouse strain with no nicotine receptors. These animals do not show either reward or aversion when exposed to nicotine.

"When someone decides to smoke, if we could give them something that only makes nicotine aversive, then I think we could help them quit much more easily

They infected the mice with viruses that were engineered to carry and reintroduce nicotine receptors into one of the two main types of neurons in the VTA— dopamine or GABA neurons, named after the neurotransmitter chemical that they release. The mice were next exposed to doses of nicotine comparable to heavy smoking in a standard behavioral test that measures the rewarding or aversive effects of drugs.

The data revealed that the dopamine neurons in the VTA are responsible for aversion, whereas the GABA neurons signal reward, in contrast to the accepted thinking in which dopamine is always the main reward signal.

The difference, Grieder says, is down to whether or not the animals are dependent on nicotine. While the dopamine neurons are responsible for aversion in non-dependent animals, they signal both reward and the aversiveness of withdrawal once dependence takes hold. What was once pleasurable becomes a necessity to keep supplying the brain with nicotine.

"When you make the switch to addiction there's a switch in the brain's motivational system," says Grieder. "It's not about getting the good feeling anymore—it's about relieving the bad feelings of not having enough drug in the system."

Grieder hopes that the discovery of the brain mechanism behind nicotine aversion, provided it is similar in the human brain, will open the doors to finding more effective treatment for smokers wanting to quit. Currently, there's only nicotine replacement therapy, in which smokers are gradually weaned off nicotine, with moderate success.

Grieder suggests that a new treatment based on her research would be similar to Antabuse, a drug that causes severe nausea when taken with alcohol to deter alcoholics from drinking.

"When someone decides to smoke, if we could give them something that only makes nicotine aversive, then I think we could help them quit much more easily," says Grieder.

FUNDING SPOTLIGHT

Donnelly Researchers Win $9 Million to Develop Cancer Therapeutics, Diagnostic Tools

By Jovana Drinjakovic
February 5, 2019.

Donnelly Centre investigators are developing new cancer treatments with fewer harmful side effects.

"We've come a long way detecting genetic changes that lead to cancer," says **Jason Moffat**, Professor of molecular genetics in the Donnelly Centre. "But our treatment abilities have not kept up and most patients still receive decades-old treatments that do not target the individual genetic nuances of each individual's tumour and are highly toxic as well."

Moffat and **Charlie Boone**, also a professor in the Donnelly Centre, have set up a drug discovery pipeline called Absyn to identify and target genetic changes unique to cancer cells—cancer's Achilles' heel—for which they won $2.7million in Genome Canada's Disruptive Innovation in Genomics competition.

Four Donnelly Centre teams have won almost $9 million in research funding to develop technologies for drug discovery and genome-based diagnostics. The funding comes from the total $56 million awarded to Canadian researchers by Genome Canada, provincial governments and industry partners, it was announced by Science Minister **Kirsty Duncan** earlier this week.

Most cancer treatments take 15 years and $1 billion to develop. But cancer moves much faster than that, morphing into new forms that resist treatment, sometimes in real time. Based on a technology that uses the gene editing tool CRISPR for finding cancer's weak points, previously developed by Moffat's lab, Absyn would shave many years off the time it takes to develop a drug ready to test on people.

Absyn combines antibody technology with the concept of "synthetic lethality", in which two genes that compensate for each other are targeted simultaneously by drugs to trigger cell death. The two-hit approach is a more selective way of eliminating cancer while leaving healthy tissue unharmed. And it's harder for cancer to evolve resistance to combination therapy than it is for individual drugs.

Boone also won close to $1 million in Genome Canada's Bioinformatics and Computational Biology competition to develop BridGE-SGA, a computational platform for uncovering genetic interactions relevant to disease, in collaboration with **Chad Myers**, of the University of Minnesota-Twin Cities.

Aaron Wheeler, a professor of chemistry in the Donnelly Centre, received $3million to develop a new tool for quick and safe prenatal diagnostics. Current approaches are invasive and can lead to miscarriage while data analysis can take weeks to complete. Wheeler's new method combines a safe way of isolating fetal cells, developed by collaborating physicians at the Sinai Health System, with the team's lab-on-a-chip technology for a fast and accurate detection of genetic abnormalities in the fetus.

Igor Stagljar, a professor of biochemistry in the Donnelly Centre, received a $2.2 million funding boost to commercialize SIMPL, a method for detecting protein interactions in cells and which stands for split intein-mediated protein ligation. SIMPL has the potential to identify protein interactions that go awry in cancer which can then be targeted with chemicals to find new therapeutics.

Gary Bader on International Team Receiving $4 million (U.S.) Award from Chan Zuckerberg Initiative

By Ann Perry
July 16, 2019.

A group of Toronto researchers that published the first single-cell map of the human liver last fall is part of an international team that has been awarded $4 million (U.S.) by the Chan Zuckerberg Initiative to advance understanding of the organ across diverse life stages and genetic backgrounds.

Gary Bader, a professor and computational biologist at the Donnelly Centre, **Sonya MacParland**, a scientist at the Toronto General Hospital Research Institute (TGHRI) at University Health Network (UHN) specializing in liver immunology, and **Ian McGilvray**, a senior scientist at TGHRI and a transplant surgeon at UHN, are among 19 investigators and collaborators from around the world who are sharing the award. Part of the Human Cell Atlas, an international effort to map all cells in the human body, the collaboration is bringing together liver mapping efforts from around the world to build a more complete picture of the human liver.

"We have been working on building a global team of researchers who are all interested in mapping the human liver in different ways," said Bader, who is a member of the organizing committee of the Human Cell Atlas. "This grant from the Chan Zuckerberg Initiative really speeds up the development of the human liver map and allows us to move in novel directions by combining

diverse research projects and data into one map."

The international collaboration is a "direct extension" of the liver mapping work he and his Toronto collaborators have already done with support from Medicine by Design, Bader added.

"We have a specific plan to collect a range of samples to cover a lot of diversity, allowing us to understand the variability in the human liver across the population

Their project — titled A Reference Cell Atlas of Human Liver Diversity Over a Lifespan — is one of 38 that are sharing $68 million (U.S.) in funding through the Chan Zuckerberg Initiative's Seed Networks for a Human Cell Atlas program. Co-founded by Facebook chief executive officer Mark Zuckerberg and his spouse, paediatrician Priscilla Chan, the Chan Zuckerberg Initiative seeks to harness technology to solve some of the world's greatest problems and is actively supporting the Human Cell Atlas.

The three-year award is significant because it supports international collaborations, which often are ineligible to receive money from country-specific research funders, Bader said. The liver project includes computational biologists, clinicians, engineers and life scientists from Canada, Singapore, Germany, Belgium, the U.K., the U.S. and Israel. The team will meet in Toronto to kick off the project in late July.

The international nature of the research team means it will have access to samples that better represent the full diversity of human livers, including age, sex and genetics.

"One of the goals of the Human Cell Atlas is to capture human diversity," Bader said. "We have a specific plan to collect a range of samples to cover a lot of diversity, allowing us to understand the variability in the human liver across the population."

For the Toronto-led part of the project, Bader, MacParland and McGilvray have joined forces with a new collaborator, **Mei Zhen**, a senior investigator at the Lunenfeld-Tanenbaum Research Institute at Sinai Health System. Zhen is an expert in volumetric electron microscopy, a technology that captures high-resolution, three-dimensional images by assembling individual images of extremely thin slices of tissue samples. Zhen has been developing this technology for studying neural systems in *C. elegans*, tiny worms that are part of the nematode family.

This is believed to be the first time the technology will be used to image the liver as part of a tissue map project. Bader said the organ is a good candidate because it is made up of tiny, repeating, hexagonal-shaped structures called lobules.

"Because of the biology of the liver, it is an interesting opportunity to understand the whole organ by studying its individual modules," Bader said.

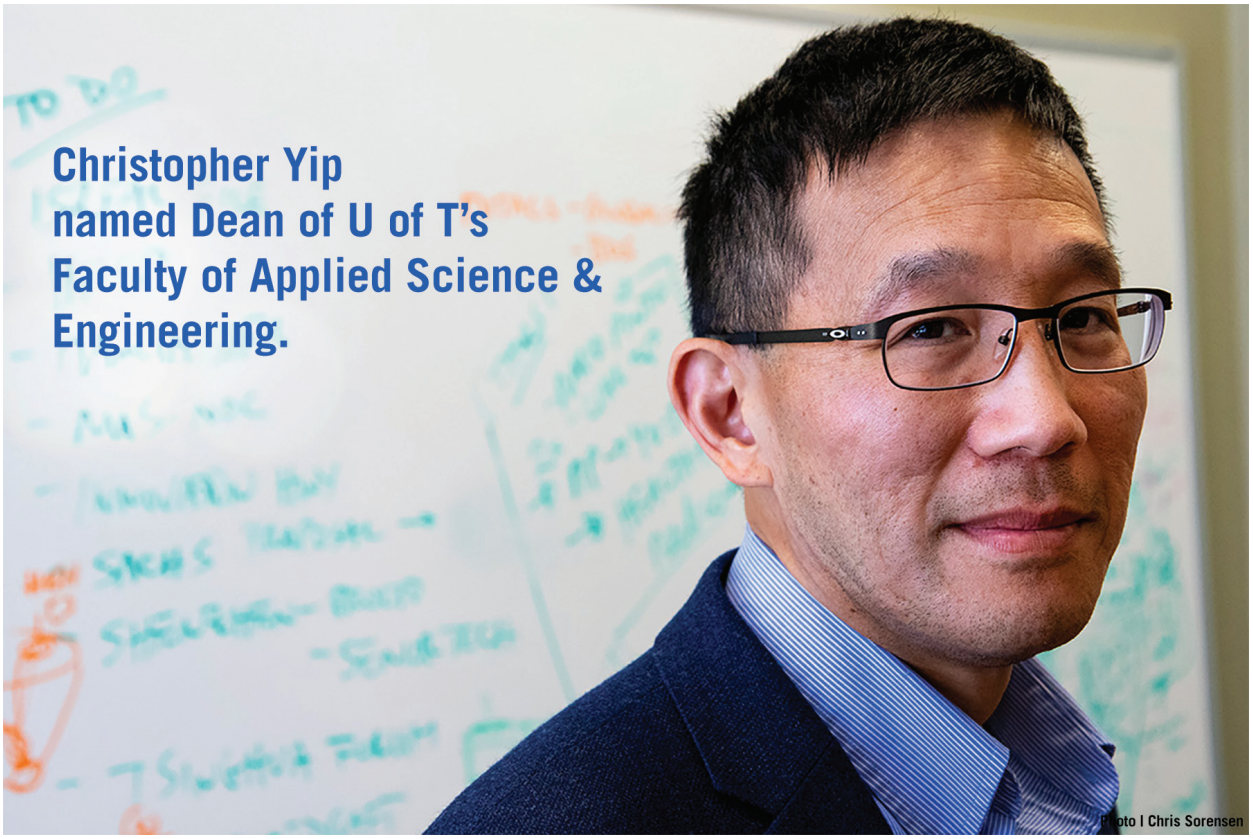
The Toronto team plans to link these images with genomics data by applying computational methods and deep learning to analyze the vast amounts of data the project will generate, ultimately creating a unified map.

"Medicine by Design helped catalyze this team, and we are delighted it is taking a leadership role in international efforts to create a next-generation map of the human liver," said **Michael Sefton**, Donnelly Centre investigator and executive director of Medicine by Design. Sefton is also a University Professor at the Institute of Biomaterials & Biomedical Engineering (IBBME) and the Michael E. Charles Professor in the Department of Chemical Engineering & Applied Chemistry. "This investment by the Chan Zuckerberg Initiative is an affirmation of the excellence and innovation of their research, and supports the collaborative, interdisciplinary approach that is at the core of Medicine by Design."

All data, tools and protocols generated from the Chan Zuckerberg Seed Networks for a Human Cell Atlas projects will be freely available to the research community.

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

APPOINTMENTS & AWARDS



Christopher Yip Named New Dean of U of T's Faculty of Applied Science & Engineering

By Chris Sorensen
March 28, 2019.

Christopher Yip plans to draw on his extensive experience supporting research and academic relationships – both at the University of Toronto and beyond – in his new role as dean of the university's Faculty of Applied Science & Engineering.

Yip, who currently serves as U of T's associate vice-president of international partnerships, will serve a five-year term that begins July 1.

"I'm really looking forward to the opportunity to lead the faculty," said Yip, who is a professor in the departments of chemical engineering and biomedical engineering with cross-appointments to biochemistry and the Donnelly Centre for Cellular and Biomolecular Research, where his lab is located.

"It's a tremendous, world-class unit that's so vibrant, energetic, flexible and adaptive – it's leading in so many different areas."

Yip previously served as director of the Institute of Biomaterials and Biomedical Engineering, or IBBME, an interdisciplinary hub that connects engineering, medicine and dentistry. There, he oversaw a number of initiatives, including the launch of a new biomedical engineering minor for undergraduates, a new biomedical

engineering master's degree, the creation of a new design studio and an expanded teaching lab.

Under Yip's watch, IBBME helped lead two major collaborative projects: the Ted Rogers Centre for Heart Research's Translational Biology and Engineering program and Medicine by Design.

"Professor Christopher Yip's service to U of T, both as director of IBBME and associate vice-president of international partnerships, has been exemplary," said **Cheryl Regehr**, the university's vice-president and provost.

"His leadership, vision and dedication to academic collaboration and innovation will be key to the Faculty of Applied Science & Engineering's future success."

Yip will replace **Cristina Amon**, who has been dean of the Faculty of Applied Science & Engineering since 2006. Amon was the faculty's longest serving dean in the past half century and the first-ever woman to hold the position. Under her leadership, the faculty became a global hub for interdisciplinary research and education and set a new standard when it comes to diversity, with women making up 40 per cent of undergraduate enrolment in 2017 for the second year in a row.

As for Yip, he received his bachelor's degree in applied science from U of T and his PhD in chemical engineering from the University of Minnesota. His research, in the field of molecular imaging, is focused on understanding how molecules and proteins assemble themselves to create functional structures.

He said his time at IBBME provided him with key insights into how researchers from different fields can work together.

"You learn how to drive interdisciplinary relationships," he said. "You learn how to make things work in different [research] cultures."

That education continued when he arrived at Simcoe Hall. But there was one important difference: Yip was now able to observe how all of the university's constituent parts fit together – not to mention how U of T connected with outside institutions.

As associate vice-president of international partnerships, Yip helped create new awards and funding opportunities for PhD students and partnered with MaRS Innovation and Toronto Global to facilitate international research partnerships, attract corporate investment and build entrepreneurial initiatives.

Yip also helped launch the Toronto-Tsinghua Entrepreneurship and Innovation Forum and helped strengthen links with key academic partners, including University College London, the University of Manchester, Zhejiang University, the Hong Kong University of Science and Technology, the National Centre for Scientific Research and the National University of Singapore.

Now, Yip said, his goal will be to apply everything he's learned to his new role at the Faculty of Applied Science & Engineering, where he hopes to increase international visibility and opportunities for faculty and students.

He added that, in some ways, the job of dean resembles what he's trying to accomplish in his research.

"The tools that I'm using at a molecular scale are very similar to what you need to get people to interact – and to get them to work together as functional units," he said. "I like to help build, facilitate and encourage people to do things.

"Other people's success is really what drives me."

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

Photo | Calvin Thomas

Ben Blencowe and Molly Shoichet Elected Fellows of U.K.'s Royal Society

By Perry King
April 30, 2019.

Two Donnelly Centre investigators are among 50 scientists who have been elected fellows of the Royal Society, the United Kingdom's national academy of sciences.

Molecular geneticist **Benjamin Blencowe** and biomedical engineer **Molly Shoichet** will join the centuries-old institution – composed of eminent scientists, engineers and technologists from the U.K. and the Commonwealth.

The third U of T researcher elected this year is earth scentist **Barbara Sherwood Lollar**. All three are also fellows of the Royal Society of Canada.

Admitting up to 52 fellows and 10 foreign members out of about 700 candidates each year, the fellowship recognizes scientists who have made substantial contributions to their fields.

"The fact that the Royal Society recognized outstanding researchers in three separate disciplines demonstrates the range of talent, creativity and leadership that U of T fosters and grows," said **Vivek Goel**, U of T's vice-president of research and innovation. "Election to the Royal Society is an important international recognition of their exceptional work. U of T congratulates them on this incredible achievement."

New fellows are considered and selected by Royal Society members from any sector of the scientific community.

Blencowe, a professor in the Donnelly Centre for Cellular and Biomolecular Research and the department of molecular genetics, is a pioneer in the development and application of high-throughput RNA profiling technologies. He recently led the discovery of a gene regulatory network linked to autism – work that could lead to new therapies.

Speaking about the Royal Society appointment prior to the announcement, Blencowe praised past and present departmental chairs for giving him the opportunity to do his research and for fostering a "collaborative spirit" with researchers of varying backgrounds.

"A wonderful thing about Toronto is this collaborative environment where researchers work really well together and come up with amazing discoveries," said Blencowe, a winner of the Natural Sciences and Engineering Research Council of Canada's Polanyi Award in 2011.

"It's a tremendous honour that could not have happened without the contributions of a remarkably talented team of researchers that I have the pleasure of working with every day."

Shoichet, University Professor and a world-leading expert on regenerative medicine and tissue engineering, is Ontario's former chief scientist and has published more than 500 papers, patents and abstracts, and given more than 350 lectures worldwide in regenerative medicine, tissue engineering and drug delivery. Her latest projects include AmacaThera, a U of T-based health startup that is developing alternatives to post-surgical painkillers – a key source of the current opioid crisis.

"It's a tremendous honour that could not have happened without the contributions of a remarkably talented team of researchers that I have the pleasure of working with every day

Shoichet is honoured to join this list of scholars "whose work has shaped and changed our understanding of our world, and what is possible."

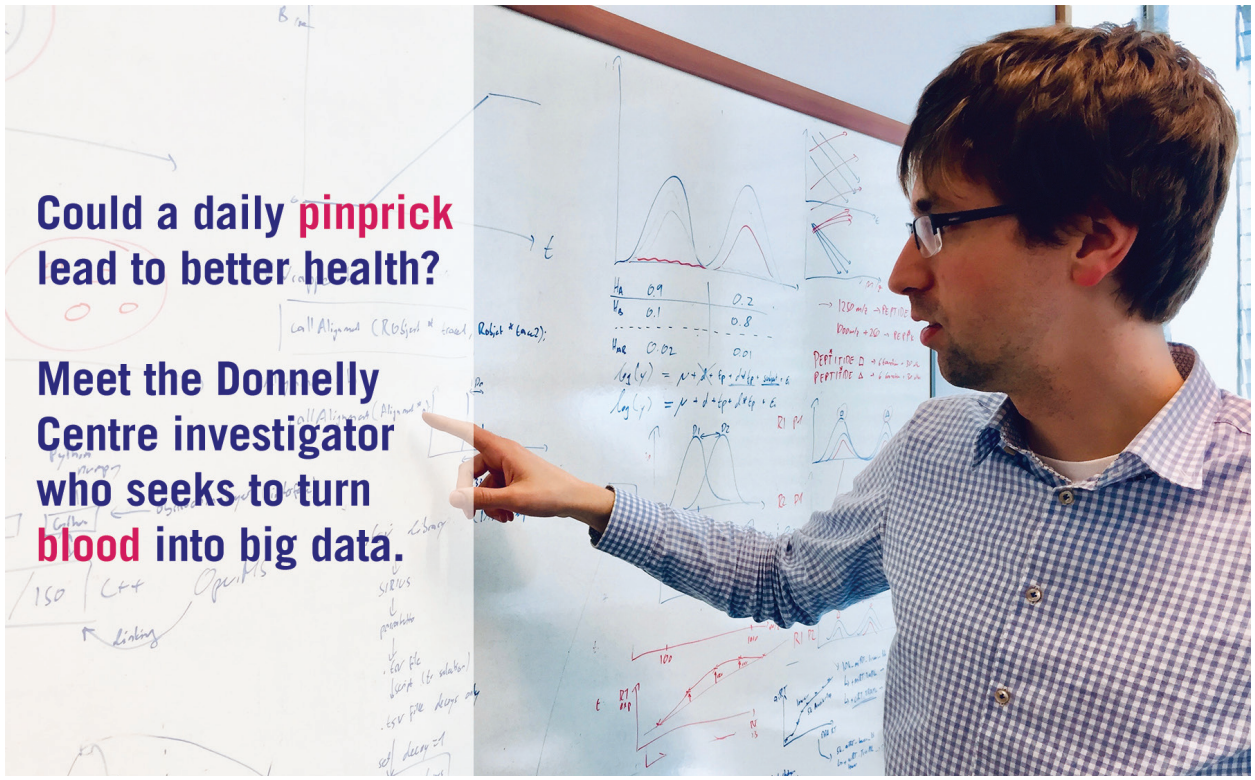
"I am thrilled to be named among more than 180 women engineers, scientists and researchers who blazed this trail before me," said Shoichet, who holds appointments in the department of chemical engineering and applied chemistry, the Institute of Biomaterials and Biomedical Engineering and the Donnelly Centre.

Shoichet, an Officer of the Order of Canada, is the only person to be elected a fellow of all three of Canada's national academies and is a foreign member of the U.S. National Academy of Engineering.

"It's wonderful to be sharing this recognition with two other brilliant scientists at the University of Toronto, Barbara Sherwood Lollar and Benjamin Blencowe," she added.

The new fellows will be formally admitted to the society at their Admissions Day ceremony in July.

The original version of this story appeared on *U of T News*.



Hannes Röst Named Canada Research Chair in Mass-Spectrometry-based Personalized Medicine

By Jovana Drinjakovic
June 14, 2019.

Instead of occasional blood tests measuring only a handful of parameters, more frequent molecular tracking could hold the key to long-lasting health.

This is how one U of T researcher envisions a path to personalized medicine in which disease diagnosis and treatment will be tailored to an individual's unique physiology. But that requires collecting a lot of data first.

"To make medicine truly personalized, we need to profile people at the molecular level as much as possible to understand molecular changes that occur over lifetime," says **Hannes Röst**, Assistant Professor at the Donnelly Centre, who is developing tools to make this happen.

As a newly appointed Canada Research Chair in Mass Spectrometry-based Personalized Medicine, Röst seeks to improve mass spectrometry methods for molecular profiling by increasing both their accuracy and throughput.

Röst is the thirteenth investigator in the Donnelly Centre to be named CRC, with more than a third of its faculty now holding the prestigious appointment. Created two decades ago, the CRC program seeks to attract and retain best researchers from diverse disciplines to make Canada a leader in research and innovation.

Mass spectrometry is used to identify diverse molecules present

in, say, blood or other complex clinical samples, based on their size and electric charge. Although widely used in research labs, its slow pace and reproducibility issues have marred its uptake in the clinic.

Solving these problems will enable measuring countless proteins and metabolites, products of enzyme reactions, which are made by the body and hold clues to health and disease. Scientists now think that each person has a unique 'molecular barcode', a baseline that could help define what normal health looks like at the molecular level in a way that is more informative for detecting disease onset than comparing individuals to the population-level data.

"If you know you were healthy 10 years ago and if you start to change in some way, then maybe this type of change relative to yourself is much more informative in terms of disease development than comparing you to the rest of the population," says Röst.

Such individual baselines are still a distant prospect and require collecting vast amounts of personal multi-omics data including gene, protein and metabolite levels, over long periods of time from healthy and patient populations. A technology that is fast and accurate is key to achieving this goal.

Fortunately, Röst is well-equipped to tackle the remaining challenges having trained with leading mass-spectrometry researchers, first as a PhD student with proteomics pioneer **Ruedi Aebersold**, at the Swiss Federal Institute of Technology (ETH) in Zurich, and then as a postdoctoral fellow working with **Michael Snyder**, Director of the Center for Genomics and Personalized Medicine at Stanford University.

"To make medicine truly personalized, we need to profile people at the molecular level as much as possible to understand molecular changes that occur over lifetime

At Stanford, Röst helped track sweeping molecular changes in 30 women over the course of their pregnancies. The largest of its kind, the study measured several thousand hormones and other molecules from about 1000 blood samples which had been collected from every woman for every week of pregnancy starting from the first trimester until the delivery date. The data revealed what that while pregnancy progressed through the same molecular states in all women, the timing and duration of hormone surges was different in each individual, indicating that each pregnancy is unique.

After joining the Donnelly Centre as faculty in 2017, Röst has been working to expand this type of personal omics research while at the same time improving the technology for it.

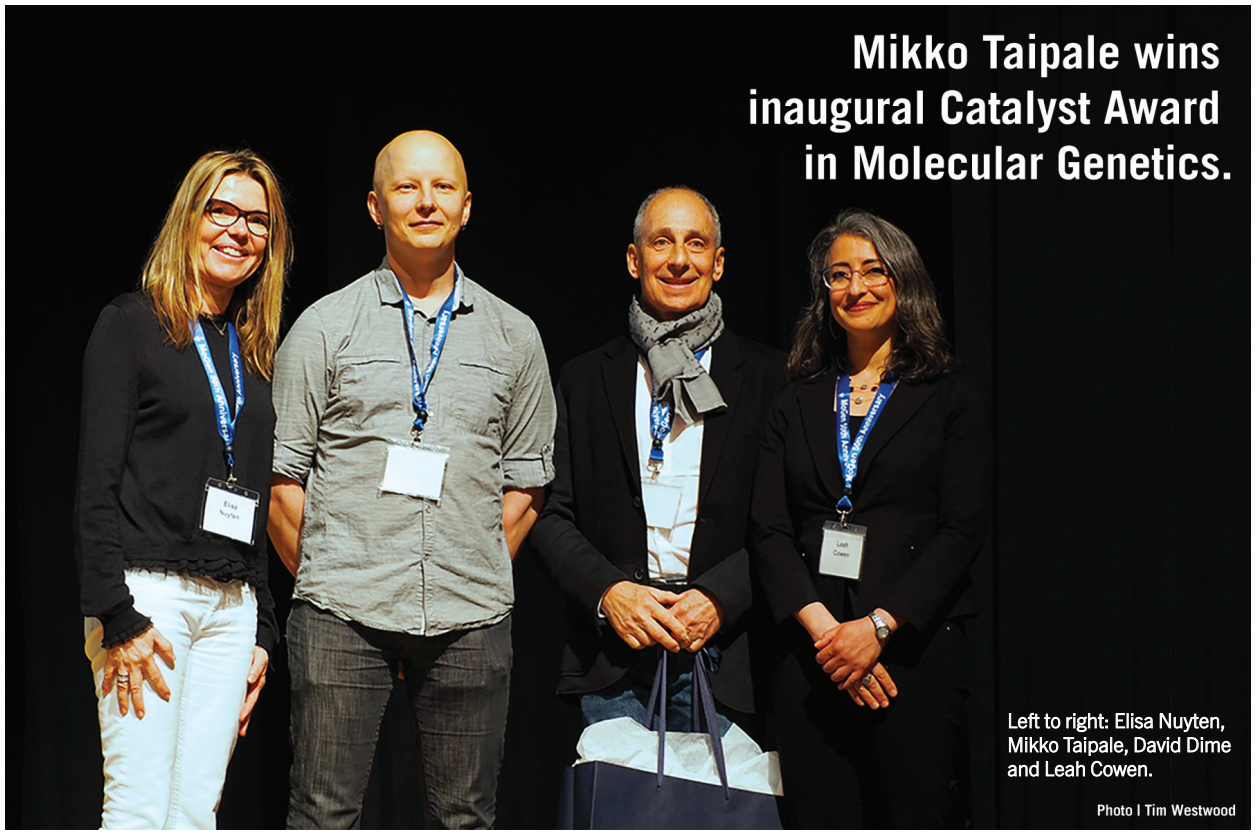
Earlier this year, the first research paper published by his lab described a computational method which can correct sampling errors introduced by mass spectrometry instruments for a more accurate reading of the levels of thousands of different proteins in one sample.

Röst recently won an inaugural $250,000 New Frontiers research grant, established by the federal government in support of early career researchers pursuing high-risk, high-reward research. The funding will support a project seeking to transform cancer diagnostics by analyzing blood samples donated by a large cohort of patients several months before they were diagnosed with one of many types of cancer. If successful, the project will reveal a diagnostic method that could detect cancer before any currently available test.

In another project, Röst and collaborators from Spain, Italy, Germany and Romania are looking to identify biomarkers associated with the recurrence of glioblastoma, an aggressive form of brain cancer, to better understand the molecular changes leading to relapse and target them for therapy.

It's early days but the data generated by Röst and researchers like him are making personalized medicine a more likely prospect.

"We still don't know what "healthy" or "normal" looks like at the molecular level," says Röst. "But we're working on it."



Left to right: Elisa Nuyten, Mikko Taipale, David Dime and Leah Cowen.

Photo I Tim Westwood

Mikko Taipale Wins Inaugural Catalyst Award in Molecular Genetics

By Jovana Drinjakovic
June 5, 2019.

High-risk research can bring high rewards, but for early career researchers seeking tenure and funding renewal it often makes more sense to stick with projects that are safe and guaranteed to yield data. Fortunately for **Mikko Taipale**, he can now do both.

Taipale, Assistant Professor in the Donnelly Centre and Department of Molecular Genetics (MoGen), is the inaugural recipient of the David Dime and Elisa Nuyten Catalyst Award in Molecular Genetics. The award was established by Dime, a U of T alum, to support exploratory research projects which are not obvious candidates for government funding.

"It's a huge honour to receive this award," says Taipale, who holds Canada Research Chair in Functional Proteomics and Proteostasis and is an Azrieli Global Scholar at the Canadian Institute for Advanced Research. "It is amazing that David decided to give this money away to MoGen—he could have spent it otherwise, but he decided to support research."

"It's truly humbling for my lab to be the recipient of his generous gift," he says.

Taipale received the award at the symposium celebrating the department's 50th anniversary. **Leah Cowen**, Professor and Chair of the department, thanked Dime

and his wife **Elisa Nuyten** for their gift calling it "incredibly important and of tremendous value to the department's effort to support innovation and discovery."

Since joining the Donnelly Centre as junior faculty in 2014, Taipale has established a research program that seeks to uncover how cells regulate abundance of gene-encoded protein molecules. Because having too much or too little of a given protein can lead to disease, researchers are increasingly looking for ways to manipulate protein levels for therapy.

The $50,000 award will allow Taipale's team to further develop a new technology called PROTACs, for Proteolysis Targeting Chimeras, to reveal therapeutic targets in cancer cells. Unlike widely used small molecule inhibitors that block protein function, PROTAC allows targeted degradation of unwanted proteins in a way that is permanent.

David Dime graduated and obtained his PhD in chemistry from U of T. While working, in the early 1980s, as a research associate at the Department of Medical Genetics, as MoGen was then known, he realized that his colleagues doing biomedical research lacked a dedicated supply of chemistry reagents for their experiments. With support from U of T, Dime launched his company,

"I think that science is really going to save this world and it gives me real pleasure to be able to support scientific research

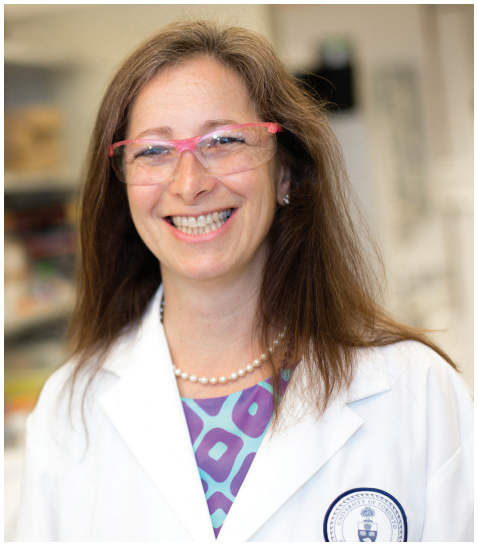
Toronto Research Chemicals, which has grown into a successful business employing 350 people, of whom 200 are scientists, and supplying the biomedical research community worldwide.

Dime's motivation to establish the Catalyst Fund was driven not only by a desire to give back to U of T but also by a true passion for science. "I love science," he said at the symposium. "I think that science is really going to save this world and it gives me real pleasure to be able to support scientific research."

U of T's Department of Molecular Genetics was founded in 1969 by University Professor Emeritus **Louis "Lou" Siminovitch** who recognized early on the potential of genetic and molecular biology research in modern medicine. Siminovitch, who is 99 years old, attended the symposium along with other former department chairs, including **James Friesen**, who co-founded the Donnelly Centre and served as its inaugural Director **Brenda Andrews**, who's been at the Centre's helm since 2004.

Molly Shoichet Named Distinguished Woman in Chemistry or Chemical Engineering

By Carolyn Farrell
February 15, 2019.



University Professor Molly Shoichet (Photo by Roberta Baker, U of T Engineering).

University Professor **Molly Shoichet** (ChemE, IBBME) has been named a 2019 Distinguished Woman in Chemistry or Chemical Engineering by the International Union of Pure and Applied Chemistry (IUPAC). The recipients were announced Feb. 11 to mark the International Day of Women and Girls in Science.

Shoichet is a renowned researcher working at the intersection of engineering, chemistry and biology. She is particularly well-known for the design of innovative materials to enhance tissue regeneration in the central nervous system.

Her work is tackling two key challenges in this area: cell survival and integration. She pioneered a new approach to deliver drugs locally to the injured spinal cord and brain, overcoming the blood-brain barrier through a minimally-invasive, injectable polymer that provides local and sustained release to the injured tissue. She has also designed new polymers for 3D cell culture and is now testing these for drug screening in cancer.

A passionate advocate for science and engineering, Shoichet has provided strategic advice to both the federal and provincial governments through her service on Canada's Science, Technology and Innovation Council and the Ontario Research Innovation Council.

In 2014, she was appointed by U of T to the newly created role of Senior Advisor to the President on Science & Engineering Engagement, a role she held for four years. A year later, she co-founded Research2Reality, a national social media initiative that engages the general public in research. She recently served as Ontario's first Chief Scientist, with a mandate to advance science and innovation in the province.

Shoichet is the only person to be elected a fellow of all three of Canada's National Academies and is also a foreign member of the U.S. National Academy of Engineering. In 2017, she was awarded the Killam Prize in Engineering. She is a member of the Order of Ontario and an Officer of the Order of Canada.

"I am delighted that Professor Molly Shoichet continues to be recognized internationally for her groundbreaking research and her leadership in promoting science and engineering," said Dean Emerita **Cristina Amon**. "On behalf of the Faculty, I congratulate her on this richly deserved honour and I thank IUPAC for celebrating the achievements of women scientists and engineers."

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

IDEA TO IMPACT

Photo | Pexels

U of T Startup Raises $3.25 Million to Eliminate Prescription Opioids After Surgery

By Chris Sorensen
January 18, 2019.

A University of Toronto startup has raised $3.25 million to develop a gel-based drug delivery system that could eliminate the need to give patients powerful painkillers following surgery – a key source of the current opioid crisis.

The startup, AmacaThera, is built on a gel technology developed in the Donnelly Centre lab of **Molly Shoichet**, Ontario's former chief scientist, that dramatically extends the duration of anesthetics injected at the site of a surgical incision.

That, in turn, means surgeons may no longer need to send patients home with prescriptions for powerful – and potentially addictive – painkillers like OxyContin.

"It's actually a pretty high percentage of addicts who start taking these opioids early on for surgical reasons," says Shoichet, a University Professor in U of T's department of chemical engineering and applied chemistry, and Institute of Biomaterials and Biomedical Engineering, whose lab is located in the Donnelly Centre for Cellular and Biomolecular Research.

"If this could obviate the need for people to take opioids in the first

place, it would have a real societal benefit."

More than half of all opioid-related deaths in Ontario in 2016 involved prescription drugs, according to a study last year led by **Tara Gomes**, an epidemiologist at St. Michael's Hospital and an assistant professor at U of T's Institute of Health Policy, Management and Evaluation, and the Leslie Dan Faculty of Pharmacy. The same study also found one third of deaths involved people being actively treated with a prescription opioid.

AmacaThera's key technology is a gel that can be easily stored and injected at room temperature, but firms up once it enters the body. It has been formulated to deliver commonly used anesthetic drugs to surgical sites and keep them there for two to three days.

By contrast, the same drugs delivered through conventional injections disperse quickly and lose their effectiveness in a matter of hours.

"Right now, drugs are given as a solution, which just won't stay at the incision," explains **Mike Cooke**, who has spent a decade working in Shoichet's lab and is AmacaThera's CEO.

"It gets into the blood and washes away into the body. But the gel keeps the pain medication at the site where you need it."

Founded in 2016, AmacaThera has received support from UTEST and the Creative Destruction Lab, two of U of T's nine entrepreneurship hubs. It has also received support from MaRS and the Ontario Bioscience Innovation Organization.

In its first, or "seed," round of financing, AmacaThera managed to raise $3.25 million from Sprout BioVentures, Viva Biotech and Grey Sky Venture Partners. The money will be used to test and manufacture the gel in a certified lab and complete a Phase 1 clinical trial, which Cooke expects to begin in about a year.

"If this could obviate the need for people to take opioids in the first place, it would have a real societal benefit

"There is a large unmet need for a non-opioid pain control following surgery," said **Todd McIntyre**, a partner at Seattle-based Grey Sky, in a statement, "and AmacaThera's technology provides a unique solution to the sustained release of acute pain medications."

Cooke and Shoichet first hatched the idea for AmacaThera while Cooke was working as a postdoctoral researcher in Shoichet's lab. At the time, he was using a version of the gel to transplant stem cells, with promising results. The gel had also been formulated into an anti-adhesive barrier to prevent scar tissue from fusing to organs after surgery.

In an effort to maximize the chance of success, Cooke and Shoichet canvassed more than 100 surgeons and anesthesiologists in search of a problem that needed solving, and ultimately settled on drug delivery. Next, they went back to the lab to see if their gel could be reformulated to fit the bill.

"We wanted to do the business-pull model versus the research-push model — and that's because we're starting a business, not starting a research project," says Shoichet, who has been involved in two previous startups based on research from her lab.

The end result was a product with a well-defined market. Another key factor in the decision: AmacaThera's drug delivery application faces a relatively straightforward regulatory approval process.

"People normally need the product to last a couple of days, not months or years," Shoichet says. "So the clinical trial is straightforward and the drugs are already in use. It's a de-risked strategy."

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

Machine Learning Could Eliminate Unnecessary Treatments for Children with Arthritis

By Jovana Drinjakovic
February 26, 2019.

Arthritis is not just an ailment of old age—it can affect children too, causing lifelong pain and disability in its most severe forms. Fortunately, some kids grow out of it. Knowing which patients will develop milder forms of disease could spare them unnecessary treatment and potential medication side effects but currently doctors have no way of predicting disease course or severity.

That could now change thanks to a machine learning tool developed by **Quaid Morris**, Professor of computer science at the Donnelly Centre, Dr. **Rae Yeung**, Professor of Paediatrics, Immunology and Medical Science at the University of Toronto, and their recently-graduated, co-supervised student **Simon Eng**.

Writing in the journal *Plos Medicine*, the researchers describe a computational approach based on machine learning, a form of artificial intelligence in which the computer learns to recognize recurrent patterns from a sea of data. The algorithm was able to classify patients into seven distinct groups according to the patterns of swollen or painful joints in the body. Moreover, it also accurately predicted which children will go into remission faster and which ones

will develop a more severe form of disease.

An estimated 24,000 Canadian children are suffering from arthritis. While its triggers still remain unclear, the disease occurs when the immune system mistakes the body's own cells for foreign invaders, attacking the lining of the joints to cause swelling, pain and possibly long-lasting damage. There is no cure and the treatment consists of progressively more aggressive and costly medications, starting with anti-inflammatory pain relief drugs, such as ibuprofen, to stronger drugs including methotrexate (a chemotherapy agent), steroids, and biological agents (such as anti-TNF and anti-IL-1) that switch off parts of the immune system.

"The final stage of treatment is very effective in some children, but also very expensive, and it's not clear what the long-term effects are," says Morris. "When you are inhibiting the function of the immune system, this type of treatment can be associated with potential side-effects including increased risk of infection and others."

"Knowing which children will benefit from which treatment at which time is really the cornerstone of personalized medicine and the question doctors and families want answered when children are first diagnosed," says Yeung who is also a Paediatric Rheumatologist and Senior Scientist at SickKids.

As a first step, the researchers set out to subtype the children who developed arthritis but had not been treated with medications yet. They analysed clinical data from 640 children, collected between 2005 and 2010 as part of the pan-Canadian study Research in Arthritis in Canadian Children, Emphasizing Outcomes (ReACCh-OUT). All children received detailed physical examinations as part of their care which included documenting the location of painful (also known as active) joints in the body.

"Now we understand the disease much better we can group children into these different categories to predict response to treatment

The data revealed seven major patterns of joint activity: joints in the pelvic area, fingers, wrists, toes, knees, ankles and an indistinct pattern. And while the majority of children fell into a single category, about one third of patients had active joints that belonged to more than one group. These patients with non-localized joint involvement generally had worse outcomes and took longer to go into remission than the patients whose active joints fall into a single pattern.

Although unique patterns of joint involvement are recognized at the bedside, the current patient classification for childhood arthritis only takes into account the overall number of affected joints. It is clear that better descriptions of joint involvement are needed that predict disease course and disease severity. It was striking from the data that children with non-localized joint involvement are different. Physicians had already observed this before as they were treating these children with strong medications but were still not able to control the disease.

"Identifying this group of children early will help us target the right treatments early and prevent unnecessary pain and disability from ongoing active disease," says Yeung.

Because of the complexity of the disease, with multiple joints affected and in a way that can change over time, as well as a relatively small number of patients available, the team had to look beyond standard statistical methods to detect patterns of joint pain.

"We had to use machine learning just to detect these seven patterns of disease in the first place," says Morris, whose team modified the technique known as multilayer non-negative matrix factorization. "And then we realized there are some children who do not fall into any of the patterns and they have a very bad version of the disease. Now we understand the disease much better we can group children into these different categories to predict response to treatment, how fast do they go into remission and whether or not we can tell they are in remission and remove therapy."

The Fraser team have developed a new method for finding drugs that kill parasites, a major global health threat.

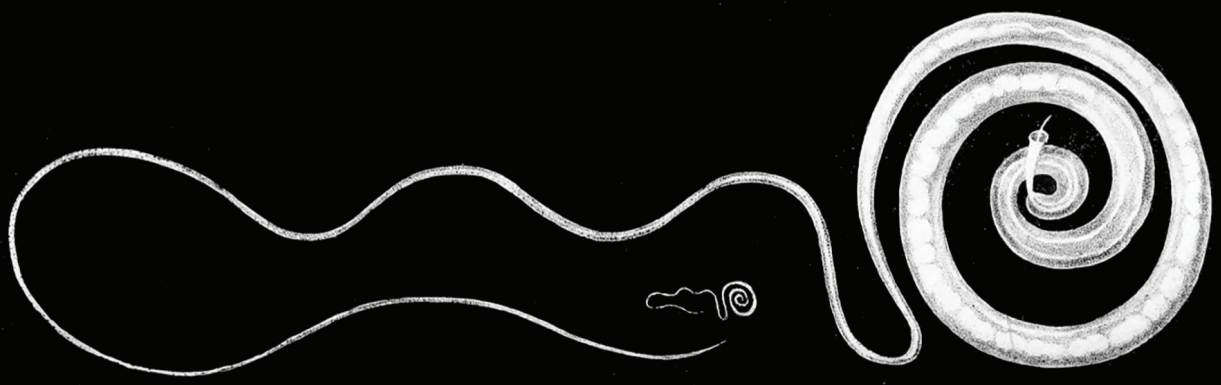


Illustration | WikiMedia

Airless Worms: New Hope Against Drug-Resistant Parasites

By Jovana Drinjakovic
June 29, 2019.

Andy Fraser did not set out to study parasites but when his team stumbled on an intriguing finding he could not look away.

Over one billion people, including 880 million children, are infected with intestinal nematode worms, such as roundworms, hookworms and whipworms, according to the World Health Organization. The infections are especially common in the developing world due to a lack of clean water and sanitation. If left untreated, they can leave a lasting mark on health and can also be lethal.

"We serendipitously discovered a new way to kill these parasites without harming the human host," says Fraser, a professor of molecular genetics in the Donnelly Centre.

"These parasites pose a major global health burden and as their resistance to the available drugs continues to grow, so does the need to develop new therapies," he says.

The work was led by three graduate students, **Samantha Del Borrello**, **Margot Lautens** and **Kathleen Dolan**, and in collaboration with **Amy Caudy**, also a professor in the Donnelly Centre. Their findings are described in a study published online in *eLife*.

Fraser's team were testing their new method for unpicking how drugs affect the movement

of a nonparasitic nematode, *Caenorhabditis elegans*, used as a stand-in for humans by researchers across the world. But a fluke finding prompted them to use this lab worm as a model for parasites instead.

The first drug they tried was cyanide because its effects are well known and they wanted to make sure the new system works. Cyanide blocks respiration and, as expected, when added to the lab dish containing the worms, it quickly paralyzed them. But to the researchers' surprise, the worms did not die. They resumed wriggling about as if nothing happened when the drug was washed out 24 hours later. "Our worms were clearly doing something very different to everything we knew about respiration in other animals," says Del Borrello.

It turned out that the cyanide made the worms switch to another, unusual form of metabolism that makes energy without needing oxygen. This type of anaerobic metabolism has been known to occur in parasitic worms, allowing them to survive for long periods of time in the airless confines of the gut. Instead of oxygen, these parasites rewire their metabolism to produce energy using a molecule called rhodoquinone, or RQ.

Crucially, humans do not make RQ. That makes it a perfect target for drug development because the drugs will selectively kill the parasites without touching their human host.

Having tricked the lab worm into making energy like a parasite, the team could now apply all the genetic and molecular tools that have been developed for C. elegans to begin to work out how RQ is made. This has remained an outstanding question in a field that has seen little progress since RQ was first discovered 50 years ago in parasitic worms, for which such tools still do not exist.

"These parasites pose a major global health burden, and as their resistance to the available drugs continues to grow, so does the need to develop new therapies

But first, they needed oysters. Oysters, and other coastal mollusks, are among the few organisms beside the nematodes that produce RQ, probably as an adaptation to changing oxygen levels brought about by tide turns. Because RQ is not commercially available, Dolan had to extract it from the oysters she bought at the store and use it to optimize the mass spectrometry instrument that was later used to detect RQ in worms.

Then began the hunt for the genes responsible. They tested about 80 different mutant worm strains before finding one unable to make the molecule—and thus unable to survive in cyanide— indicating that the mutated gene is required for RQ biosynthesis. The gene, called kynu-1 (pronounced as 'kai-noo 1') turned out to code for an enzyme that carries out an early step in RQ synthesis. This finding upended widely accepted ideas about how RQ is made. Most importantly, it also showed them clear ways to try to block RQ synthesis with drugs.

Del Borello is now testing thousands of compounds to find candidates that kill C.elegans when it's using RQ and which could be developed into new drugs against parasites.

"It's great that we figured out the science behind it, but what I am most excited about is finding drugs that target the RQ-dependent metabolism," she says. "We haven't reached the tipping point quite yet in terms of drug resistance, but we also don't have anything in the pipeline to help out when we do."

They already have several promising candidates, which will next be tested on animals, such as mice and sheep, before moving on to human trials. But even if a drug for livestock could be found, it would help save agricultural industry billions of dollars estimated to be lost from lower productivity that is caused by nematode infections in farm animals.

From testing new equipment to solving parasite metabolism, the research took everyone by surprise. "This was not at all what we expected when we started out," says Lautens who credits the whole team for their success. "That we've been able to contribute to a field that has not seen much progress in many years is a testament to how hard everyone's been working on it with a lot of different perspectives."

New Partnership to Tackle Treatment-Resistant Lung Cancer

By Jovana Drinjakovic
July 19, 2019.

Professor Igor Stagljar

Donnelly Centre investigator **Igor Stagljar** and Toronto-based biotechnology company Cyclica have launched a partnership to advance treatment of drug-resistant lung cancer.

Together they will identify small molecules that can inhibit the mutated epidermal growth factor receptor (EGFR), a protein whose normal function is frequently disrupted in non-small cell lung cancer (NSCLC), the most common and type of lung cancer.

NSCLC is found in approximately 85 per cent of all lung cancer patients. Evolved drug resistance has been a key challenge for treating NSCLC due to EGFR mutations, which are present in roughly 17 per cent of people with lung cancer in the United States. The prevalence of these mutations increases to being present in half the number of patients of Eastern Asian descent, and are more common in women than men. Additional research in treating NSCLC is critical to developing effective precision medicines that can target the evolving nature of this disease.

The partnership brings together Stagljar's proprietary MaMTH Drug Screening (MaMTH-DS) technology, developed in the Donnelly Centre and designed for the discovery of small molecule compounds capable of inactivating the triple mutant EGFR, with MatchMaker™, Cyclica's artificial intelligence platform, which will narrow down a shortlist of the most promising lead compounds identified by Stagljar's lab. Cyclica will also computationally optimize the molecular structures of the selected compounds for desired pharmacological properties, before they are synthesized by Stagljar's team, who will also test their efficacy in human cells.

"We are extremely pleased to be working with Cyclica since our collaboration represents a unique approach that unites two completely novel and complementary approaches, Cyclica's artificial intelligence MatchMaker™ and our MaMTH-DS live-cell drug discovery assay, for the rapid identification and validation of novel EGFR inhibitors in NSCLC," says Stagljar, also a professor in the University of Toronto's Departments of Biochemistry and Molecular Genetics.

"Our joint efforts will accelerate our ability to build novel EGFR inhibitors with these cutting-edge technologies and will thus speed up their implementation in the clinic."

All IP generated from this project related to the compounds will be shared equally by the University of Toronto and Cyclica.

"We are thrilled to be working with the world class Stagljar Lab to leverage our drug discovery platform to progress our shared interests in creating novel advanced lead compounds for non-small cell lung cancer," says **Naheed Kurji**, President & CEO, Cyclica.

"This project is an example of the growing integration between science and industry focused on commercialization, and a testament to the hyper innovative work being done in our own backyard at the University of Toronto."

The Sidhu lab have engineered antibodies that unlock the body's regenerative potential.

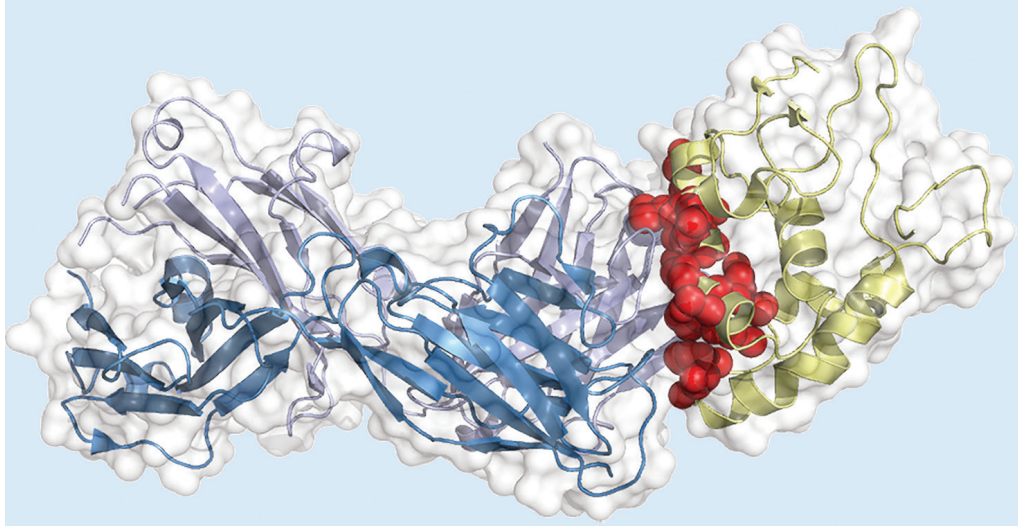


Image | Toronto Recombinant Antibody Centre

Synthetic Antibodies Hold Promise for Regenerative Medicine

By Jovana Drinjakovic
August 26, 2019.

Our bodies make antibodies to fight infections. But the synthetic versions of these molecules could hold the key to stimulating the body's ability to regenerate.

The findings come from a decade-long collaboration between the teams of **Sachdev Sidhu**, a professor in the Donnelly Centre, and **Stephane Angers**, Associate Dean of Research in the Leslie Dan Faculty of Pharmacy, that have been creating synthetic antibodies for diverse applications.

Antibodies are increasingly being developed into drugs thanks to their ability to bind and affect the function of other proteins in cells.

Now Sidhu and Angers' teams have created antibodies that could one day stimulate tissue in the body to repair itself, as described in a study published online in *eLIfe*, an open-access journal. A newly launched Toronto startup, AntlerA Therapeutics, will turn the antibodies into drug-like molecules for regenerative medicine.

The work was done in collaboration with the Toronto Recombinant Antibody Centre, co-founded by Sidhu in the Donnelly Centre, which has created a massive catalog of synthetic antibodies for research and drug discovery.

"We are developing new molecules that have never been seen before and whose potential for regenerative medicine is enormous," says Sidhu, also a professor in U of T's Department of Molecular Genetics and co-founder of AntlerA.

Engineering new molecules

The antibodies were engineered to mimic key growth factors, proteins called Wnt (pronounced as "wynt") that normally instruct stem cells—cells that can turn into any cell type in the body — to form tissue in the embryo. Wnt proteins also activate stem cells for tissue repair following injury in adults.

Scientists have long sought to co-opt Wnt as a tool for activating tissue regeneration. But these efforts were stymied by the molecules' complicated chemistry — Wnt proteins are attached to fat molecules, or lipids, which makes their isolation in active form difficult.

"People have been trying for decades to purify Wnt proteins and make drugs out of them," says Sidhu. "Drug development would require further engineering of Wnt proteins. But Wnt are difficult to purify, let alone engineer—therefore they unlikely become drugs."

The associated lipids also prevent Wnt proteins from dissolving in water, making them unsuitable as medicines because they cannot be injected.

That's why the researchers decided to design antibodies that behave like Wnts, by binding to and activating two classes of Wnt receptors, Frizzled and LRP5/6, on the surface of cells, but are also water soluble and therefore easier to work with.

Called FLAgs, for Frizzled and LRP5/6 Agonists, the antibodies can be designed to replicate any one of the hundreds possible Wnt-receptor combinations (humans have 19 different Wnt proteins that can activate 10 Frizzled and eight co-receptors including LRP5/6).

To generate FLAgs, **Yuyong Tao**, a postdoctoral fellow in Sidhu's lab, came up with a new molecular configuration that does not exist in nature. Whereas natural antibodies have two binding sites, allowing them to bind to two targets, FLAgs have four, which means that a single molecule can recognize multiple receptors at the same time and mimic how Wnt proteins act in the body.

Stimulating tissue self-repair

When added to cell culture, FLAgs were able to substitute for Wnt proteins— a hard-to-source but necessary ingredient in culture medium—and stimulate the formation of stem cell-derived intestinal organoids, three-dimensional balls of tissue that resemble the small intestine.

"These 3D organoids hold great potential for research and drug discovery but to grow them you need a source of Wnt proteins to activate stem cells," says Angers, whose team presented the findings earlier this month at an eminent Gordon conference in the U.S. "Now we have a defined protein, which we can easily obtain in large amounts and which can support the growth of organoids from various tissues."

"This is going to be really important and transformative for a lot people in the field," he says.

Strikingly, when injected into mice, the FLAgs activated the gut stem cells, showing that the antibodies are stable and functional inside the body. The finding raises hopes that FLAgs could be used as treatment for irritable bowel disease and other ailments to regenerate the intestinal lining when it is damaged. Other FLAg variants show promising results in lung, liver and bone regeneration as well as having the potential for treating eye disease.

AntlerA has already attracted investment to develop FLAgs into therapeutics for vision loss and bowel diseases. The startup's name was inspired by FLAgs' geometrical shape which resembles the antlers of deer and moose which are the fastest regenerating organs in animals.

"The type of discovery we report in our study was possible with a convergence of expertise," says Angers, co-founder of AntlerA. "Thanks to the close collaboration and proximity between our labs, we were able to apply protein engineering to activate a critical stem cell signaling pathway with the ultimate goal to develop regenerative medicine promoting the repair of diverse tissues in the body."

COLLABORATION SPOTLIGHT

Drugs Made in Nature: Donnelly Researchers Team up with Japanese Scientists to Mine Microbes for New Therapeutics

By Jovana Drinjakovic
December 17, 2019.

Charles Boone first set foot in Japan fresh out of undergrad in 1983 when he lived and worked with a local family on a rice farm in Chiba prefecture, just outside Tokyo. There he fell in love with many things Japanese, not least its cuisine which owes much of its flavours to fermenting microorganisms. Years later, the microbes would lure Boone back to Japan, albeit for a different reason.

Boone, a professor of molecular genetics at the Donnelly Centre, is best known for his research that has revealed how thousands of genes coordinate to sustain basic cellular processes. But he also wants to find new medicines, and thinks that little germ-like microbes can be the best place to look.

"So many of the drugs we use today have come from microorganisms," says Boone. "And there's still an enormous untapped potential out there."

Over the last decade, Boone has been working with **Minoru Yoshida** and **Hiroyuki Osada**, both professors at the RIKEN Centre for Sustainable Resource Science, to identify new compounds from microbes with the potential as research tools and pharmaceuticals.

Another Donnelly investigator and U of T professor, **Andrew Fraser**, is also collaborating with the RIKEN teams to find new drugs against parasites.

Surrounded by cherry trees on a research campus just outside Tokyo, the RIKEN Centre houses the world's largest collection of natural compounds—some 40,000 chemi-

cals and other derivatives produced mainly by soil microbes and plants, as well as some synthetic compounds.

"The RIKEN collection is exceptional because it contains so many pure natural products" says Boone. "This makes it easier to investigate how those molecules might be acting on living cells."

Collected by Osada's team over the last 15 years, the medical potential of the vast majority of compounds remains unexplored, however.

"We still don't know why the microbes are producing these compounds," says Yoshida.

It could be that microbes are using these chemicals as weapons against other microbes or as communications tools, as most of them seem to be non-toxic. Whatever the reason behind their making, the researchers hope to tap into this chemistry for new molecular tools and drugs.

It's not incidental that Japan has such a rich resource of natural compounds, for it hails from the country's long tradition of microbial exploits in the production of food and drink. Take the rice wine sake, for example, which involves the sophisticated use of a filamentous fungus to transform pure rice into a suitable carbon source for fermentation by yeast cells.

The microbial knowhow allowed Japanese scientists to discover, in the second half of the 20th century, more than 100 new antibiotics, as well as the anti-parasite block buster drug ivermectin, a finding that was recognized by a Nobel Prize in 2015. "Drug applications came naturally out of using microbes for food fermentation," says Yoshida, whose 1990 discovery of trichostatin A, a drug that interferes with how the DNA is packaged inside the cells, from a *Streptomyces* bacterium, transformed the study of epigenetics and led to similar compounds that are being trialed on patients as a treatment for cancer and inflammation.

According to a recent report, the majority of approved medications come from nature, or are synthetic molecules inspired by the natural products. Infection-fighting antibiotics and cyclosporine, an immunosuppressant that has made transplant medicine possible, are only some examples.

Natural products make good drugs because they were honed by evolution to act on living cells, said Yoshida. They tend to be large and structurally diverse molecules that engage with their cellular receptors more specifically than the purely synthetic drugs, meaning they can be used at low doses and elicit fewer unwanted side effects.

Despite their clear potential, the pharmaceutical industry has shifted its focus from the natural compounds, which are also difficult to purify and synthesize on an industrial scale, to searching for drug candidates among large pools of synthetic chemicals.

But Boone thinks this is may be a mistake. "It seems ridiculous to be shunning the natural products given that the majority of drugs we use today have come from nature," says Boone. "And our work suggests that there are a lot of compounds out there that could be useful for research and also medicine."

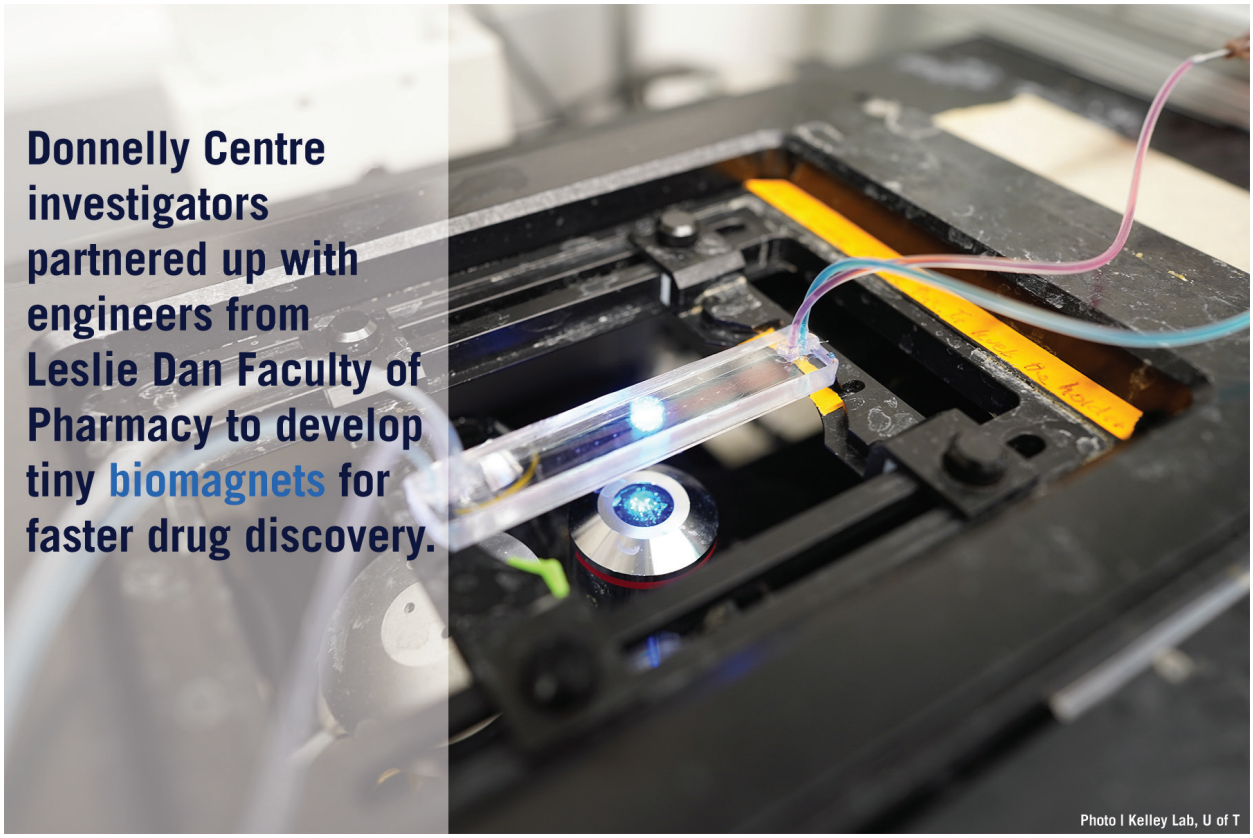
A 2017 study by Boone, Yoshida and Osada's teams found that the RIKEN collection holds more medically promising compounds than several stockpiles of synthetic chemicals widely used in research. They did this by identifying the molecular mechanism of action for thousands of compounds, using a large-scale application of the yeast cell-based chemical genomics platform, developed by Boone's lab in the Donnelly Centre. Many of these housekeeping processes in yeast cells are also found in human cells and have been implicated in a variety of diseases, from cancer to Alzheimer's.

But, there are many more compounds left to test.

More recently, **Sheena Li**, a postdoctoral fellow who worked in Boone's lab at RIKEN, where he holds a joint appointment, and has since moved to the Donnelly Centre, found that one compound from the RIKEN collection acts as a powerful antifungal by blocking an important enzyme in yeast cells. As such, the compound holds promise for the treatment of drug resistant fungal infections which are becoming a serious global health threat.

Altogether, the team have identified about 50 products with medical potential. The next step is to check if these chemicals act in the same way in human cells.

"We are now trying to see what these compounds are doing in human cells," says Li. "It's a great step forward to be able to take something that you invested so much time studying in yeast into the human system."



Researchers Enlist Tiny Biomagnets for Faster Drug Discovery

By Jovana Drinjakovic
August 26, 2019.

What started as a hallway conversation between colleagues is now an "engine for the discovery of new therapeutic targets in cells" thanks to Medicine by Design, says **Shana Kelley**, University Professor in the Leslie Dan Faculty of Pharmacy at the University of Toronto.

Kelley's lab was developing a portable, chip-like device that uses tiny magnets to sort large populations of mixed cell types as part of her Medicine by Design team project. She wondered if the device could be coupled with a CRISPR-based gene-editing technology, developed by another Medicine by Design team leader, **Jason Moffat**, a professor in the Donnelly Centre for Cellular and Biomolecular Research. They reasoned that the two methods together could speed up combing through the human genome for potential drug targets. "We casually agreed to combine our technologies — and it worked incredibly well," says Kelley.

"This is the advantage of being part of the dynamic research ecosystem of Toronto and Medicine by Design," says Kelley. "I would have never known how to position this technology and link it with CRISPR it if I did not have all these great people around to talk to."

The result of their joint effort, also

in collaboration with **Stephane Angers**, a professor at Pharmacy, and **Edward Sargent**, University Professor at the Department of Electrical and Computer Engineering, is called MICS, for microfluidic cell sorting, described in a study published today in the journal *Nature Biomedical Engineering*.

MICS will enable researchers to scour the human genome faster when searching for genes, and their protein products, that can be targeted by drugs.

In one hour, MICS can collect precious rare cells, in which CRISPR revealed promising drug targets, from a large and mixed cell population of The same experiment would take 20-30 hours using the gold standard method of fluorescence-based sorting.

Researchers use CRISPR to switch off in cells each of around 20,000 human genes and see how this affects levels of a disease-related protein which, say, helps cancer spread. This can reveal other gene candidates, and the proteins they encode, that work in the same pathway and which could be targeted with drugs to remove the target protein and halt cancer. The caveat is that genetic screens result in mixed cell populations, with a desired effect present in a vanishingly small proportion of cells which have to be scooped out for further study. Most cell-sorting instruments use laser beams to separate fluorescently labelled cells, but this takes time.

MICS works faster thanks to tiny magnets engineered to bind to the target protein, which leaves the cells sprinkled with magnetic particles. About half the size of a credit card, its surface is streaked with strips of magnetic material that ferry the cells from one end of the device to another. Once at the far end, the cells fall into distinct collection channels based on how many particles they carry as a proxy for the amount of the target protein.

"As many as one billion cells can travel down this highway of magnetic guides at once and we can process that in one hour," says Kelley." It's a huge gamechanger for CRISPR screens."

To test if MICS can reveal new drug targets, the researchers focused on cancer immunotherapy, in which the immune system is engineered to destroy tumour cells. They looked for a way to reduce the levels of the CD47 protein which sends a "don't eat me" signal to the immune system and is often hijacked by cancer cells as a way of escaping immune detection. Others have found that blocking CD47 directly has harmful side effects, prompting the Medicine by Design team to look for the genes that regulate CD47 protein levels.

A genome-wide CRISPR screen revealed a gene called QPCTL which codes for an enzyme that helps camouflage CD47 from the immune system and that could be blocked with an off-the-shelf drug.

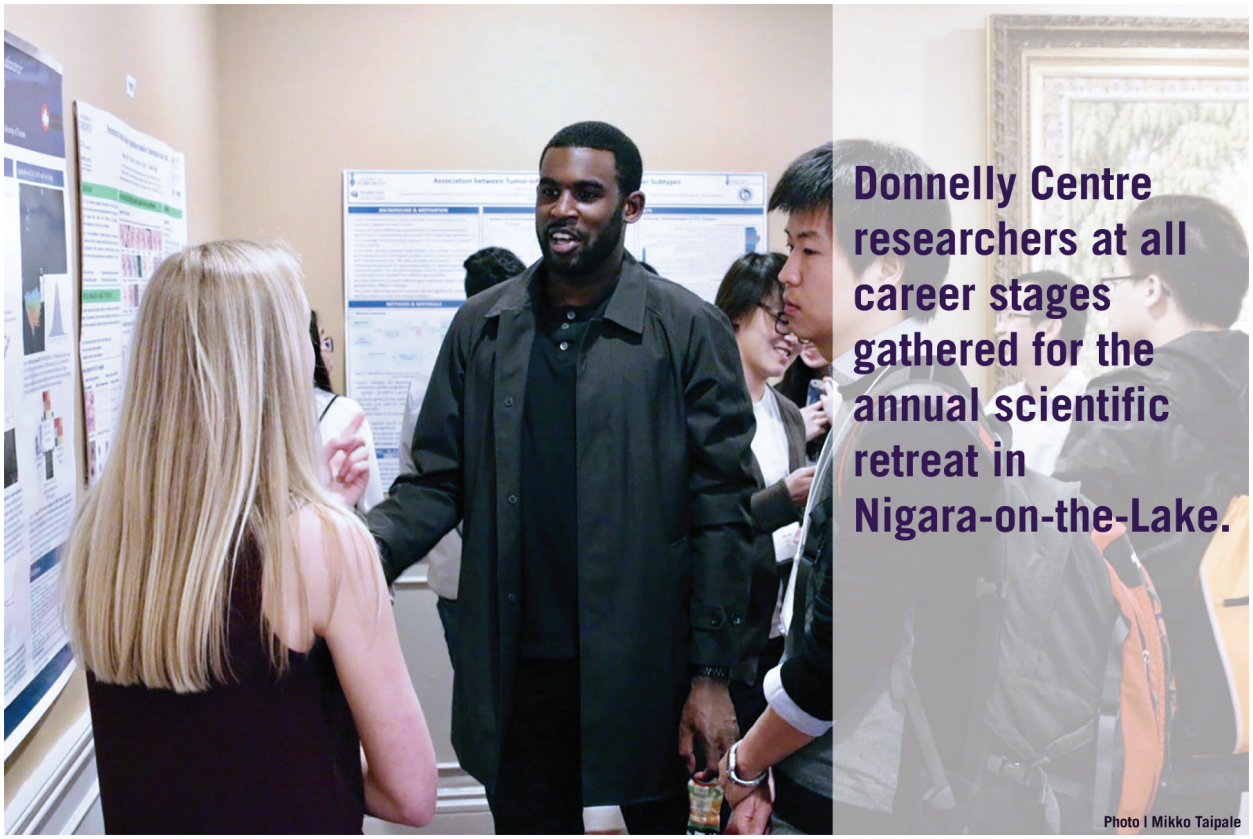
"If you can modulate CD47 levels by acting on QPCTL , that could be an interesting way to trick the immune system to clear cancer" says Moffat.

It's early days still, but Kelley and Moffat are hopeful about QPCTL's therapeutic potential in cancer, perhaps as a way to get macrophages to target tumor cells. They are also launching a multi-lab collaboration PEGASUS project, for Phenotypic Genomic Screening at Scale, which will scale up the technology to interrogate a broad range of therapeutic targets.

On the regenerative medicine front, MICS will help reveal the genes that activate stem cells to turn into specialized cell types, which will make easier harvesting of desired cell types for therapy.

Although Kelley's team initially developed magnetic cell sorting for isolating tumour cells from the blood, its repurposing for drug target discovery could have a wider impact, with MICS already attracting significant interest from the research community and industry.

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



Donnelly Centre 2019 Scientific Retreat Overview

By Jovana Drinjakovic
May 24, 2019.

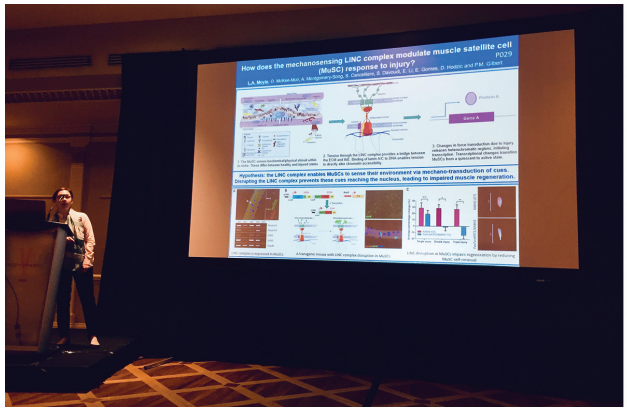
Almost two hundred Donnelly Centre trainees and faculty gathered for the third annual scientific symposium, on May 9, 2019, at the Queen's Landing conference center in Niagara-on-the-Lake. The symposium took place over two days and included two keynote lectures, delivered by **Edward Marcotte**, a professor at the University of Texas at Austin, and **Angela DePace**, an associate professor at Harvard University.

Donnelly Centre trainees also gave short talks in the fields of proteomics, bioinformatics, bioengineering and molecular biology, while some 80 trainees presented their research in two poster sessions and pitches.

A career panel composed of representatives from the biotechnology sector and research publishing groups were also present to offer their insight and advice on postgraduate careers outside academia.

Overview of scientific presentations

Marcotte presented a new method for single-molecule protein sequencing. Termed fluorosequencing, the imaging-based method involves anchoring fluorescently labeled protein molecules onto a glass slide followed by stepwise chemical degradation. Seven years in the making, the platform can process thousands to millions of molecules in parallel and has the potential to elevate proteomics to the level of throughput



PhD student Bella Xu presenting her research on muscle repair in Professor Penney Gilbert's lab, left, and researchers at banquet dinner, right.

and sensitivity akin to next generation DNA sequencing.

DePace, the second keynote speaker, discussed how natural sequence variants dispersed across regulatory regions in the genome impact molecular and organismal phenotypes. Using developing fruit fly embryos, DePace showed examples of how regulatory DNA, from single enhancers to entire developmental loci, can drive precise gene expression patterns, despite variants in the underlying sequence.

Donnelly Centre trainees—graduate students (GS), postdoctoral fellows (PDF) and research associates (RA)—delivered short 15-minute talks in four themed sessions: Proteomics, Bioinformatics, Bioengineering and Molecular Biology.

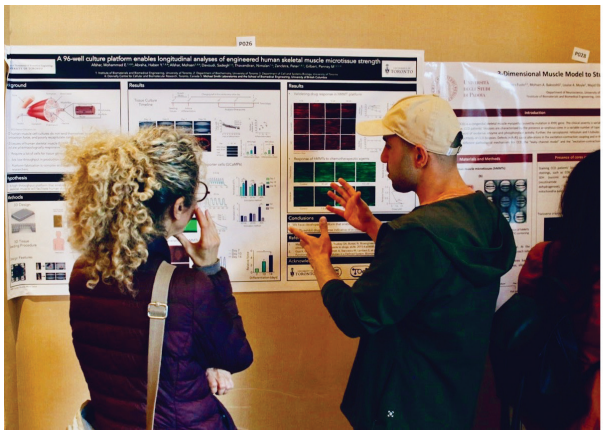
The Proteomics session covered a new live-cell platform (MaMTH-DS) for discovery of small molecules targeting the triple mutant EGFR that is frequently mutated in lung cancer (**Punit Saraon**, PDF, Stagljar lab); protein interaction map of Hsp70 chaperones, J domain proteins, and their clients (**Benjamin Piette**, GS, Taipale lab) and how environmental changes impact binary protein interactions in yeast (**Dayag Sheykhkarimli**, GS, Roth lab).

During the Bioinformatics session, new computational methods were presented for correcting errors introduced by mass spectrometry instruments measuring protein levels (**Shubham Gupta**, GS, Röst lab); a method for reconstructing tumour phylogeny from multiple tissue samples (**Jeff Wintersinger**, PDF, Morris lab); an artificial algorithm for designing antibody H3 loops for immunotherapy (**David Beccera**, PDF, Kim lab) and mathematical modeling of cell differentiation during development based on cell cycle length (**Maria Abou Chakra**, PDF, Bader lab).

The Bioengineering session covered a new tissue culture platform for the discovery of drugs capable of stimulating muscle repair (**Bella Xu**, GS, Gilbert lab); delivery of hydrogel-encapsulated ChABC enzyme to promote tissue healing following stroke injury (**Marian Hettiaratchi**, PDF, Shoichet lab) and a novel digital microfluidics platform for single cell analysis (**Erica Scott**, PDF, and **Julian Lamanna**, GS, both in Wheeler lab).

Research in Molecular Biology included talks on: the regulation of protein localization during replication stress *S. cerevisiae* (**Brandon Ho**, GS, Brown lab); immune T cell engineering for cancer immunotherapy (**Karim Shalaby**, PDF, Sidhu lab), how exosomes affect neuronal polarity and axon growth (**Samar Ahmad**, PDF, Attisano lab) and the role of C2H2-Zinc finger proteins in regulating RNA through direct binding (**Syed Nabeel-Shah**, PDF, Greenblat lab).

This year's symposium also had two Poster Pitch sessions during which selected trainees had two minutes and a single presentation slide to present their research. They also exhibited posters in the poster sessions. One presenter was **Kyle Turner** from the Donnelly Sequenc-



80 trainees presented their research and received feedback from colleagues across two poster sessions.

ing Centre who gave an overview of the ongoing collaborations within Donnelly Centre labs highlighted how new equipment and technology developments at the facility will further aid their research.

Career panel and awards

Members of the career panel were science graduates who went on to have diverse careers in the biotechnology sector and research publishing. The panelists were: **Myles Axton**, Editor-in-Chief of Genetics & Genomics Next at Wiley, **Si Lok**, Lead of Technology Development at The Centre for Applied Genomics at the Hospital for Sick Children, **Tyler Luyben**, of Edesa Biotech, business development expert **Ella Korets-Smith**, of Antibe Therapeutics Inc, TO Health and EKS Business Development, **Frederic Sweeney**, then Chief Business Officer of Northern Biologics and **Emily Titus**, Director of technology development at the Centre for Commercialization of Regenerative Medicine.

The panelist offered advice on skills needed to succeed in their respective fields, emphasizing the value of analytical thinking, as one of the most transferrable skill obtained during a PhD which graduates often take for granted.

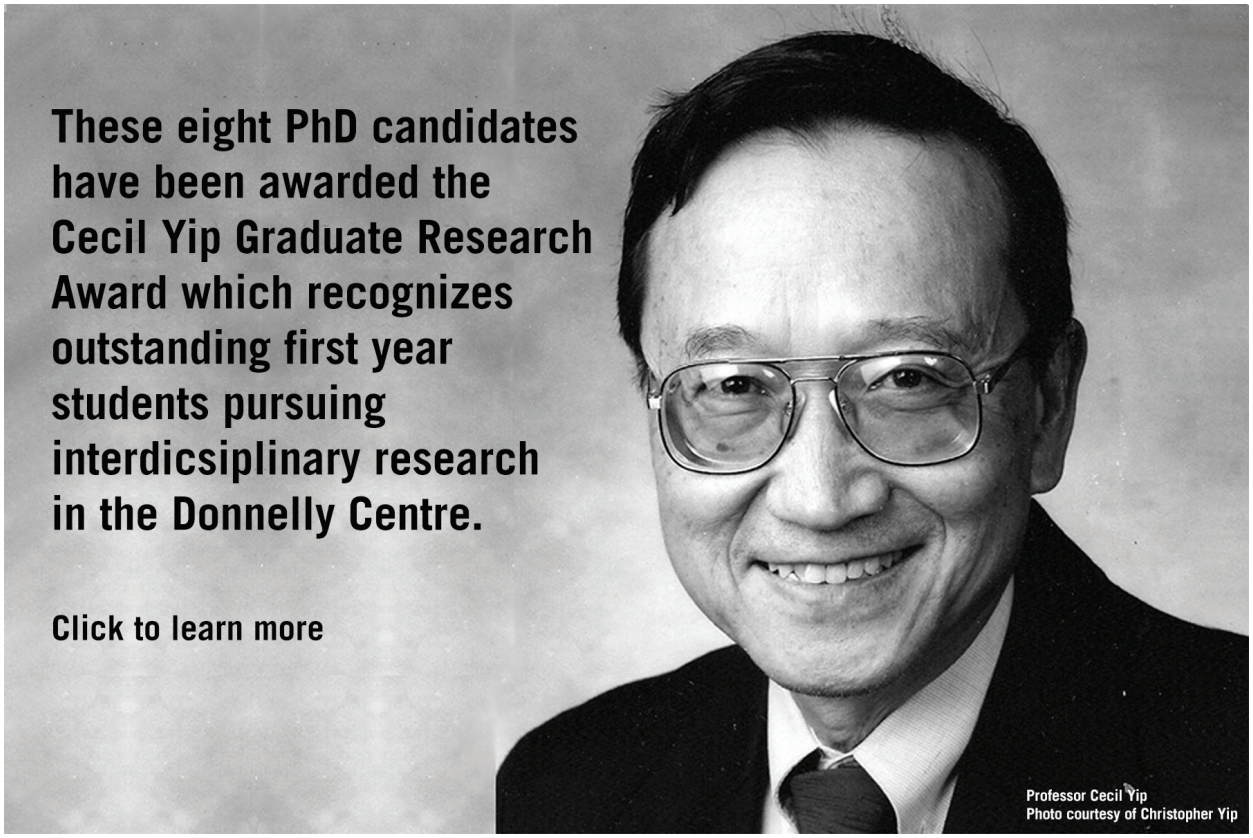
Career panelists of life science PhDs offered insight on diverse job paths outside academic environment.

At banquet dinner, Acting Director **Charlie Boone** congratulated trainees who won awards over the last year and presented them with award certificates for the Cecil Yip Doctoral Award, Jenifer Dorrington Graduate Research Award, Donnelly Centre Research Thesis Prize, Charles H. Best Postdoctoral Fellowship and the inaugural Research Excellence Awards.

The planning of the symposium was once again led by Donnelly Centre investigator Mikko Taipale who was helped by the graduate students, Samantha Del Borrello, Jessica Lacoste, Benjamin Piette, Aleksei Shkurin, Tajinder Ubhi, Kevin Wang and Owen Whitley and postdoctoral fellows Punit Saraon and Nick Stepankiw.

Finally, we would like to thank the sponsors: U of T's Department of Molecular Genetics, Deep Genomics, Phenomic AI, Illumina and ThermoFisher Scientific.

TRAINEE SPOTLIGHT



Meet Winners of Cecil Yip Graduate Research Award

By Jovana Drinjakovic
April 21, 2019.

Eight students in their first year of graduate studies pursuing research in artificial intelligence, nanotechnology and bioengineering have been awarded the 2019 Cecil Yip Graduate Research Award.

With bachelor degrees in life sciences, math, physics, and engineering, and enrolled in graduate programs at U of T Departments of Molecular Genetics (MoGen), Chemical Engineering and Applied Chemistry (ChemE), Computer Science (CS) and the Institute of Biomaterials and Biomedical Engineering (IBBME), the 2019 winning cohort embodies the mandate of the Donnelly Centre as an interdisciplinary research institute at the forefront of biomedicine.

Established as a tribute to **Cecil Yip**, former Vice-Dean of research in the Faculty of Medicine and a co-founder of the Donnelly Centre, the award recognizes students at the beginning of their graduate program whose collaborative research in one of the Centre's labs has the potential to lead to tangible advances in medicine.

"This year's applicants reflect how the world-class collaborative interdisciplinary research environment of the Donnelly Centre has become a magnet for top scholars and trainees," says **Christopher Yip**, Chair of the award committee, Dean of U of T's Faculty

of Applied Science and Engineering and Principal Investigator in the Donnelly Centre.

"While the review committee was impressed and excited by all of the applicants and their innovative and ambitious research projects, the awardees were selected based on the compelling translational aspects of their proposals and the catalytic role played by the Donnelly Centre."

Other committee members are: Professors **William Ryu**, **Quaid Morris** and **Igor Stagljar**, who are all Principal Investigators in the Donnelly Centre. Morris did not vote on applications from students under his tutelage.

Awarded projects

Leveraging advances in AI-based machine learning, genome biology and stem cells, the awardees' research has the potential to improve treatment of some of the most common ailments including cancer, heart disease, blindness and stroke.

Jarrett Barber (Morris lab, MoGen) is developing a machine learning tool for determining the evolutionary history of a tumour using mutations found in individual cells of the tumour. Several applications of this tool will be to identify cancer-driving mutations, develop better diagnosis and prognosis criteria, and aid in the development of personalized therapies. Barber, who has a degree in astrophysics, is in Mogen's Computational Biology in Molecular Genetics, established in 2014 for students who want to apply their background in quantitative subjects to data analysis in health research.

Jingping Qiao (Morris lab, MoGen), co-supervised by **Lincoln Stein**, a professor in the Ontario Institute for Cancer Research (OICR), is trying to establish a method for linking 3D medical images of breast cancer to the tumour's genetic makeup. If successful, the tool could help oncologists perform minimally invasive diagnosis, track disease progress and choose treatment.

Kimberly Skead (Morris lab, MoGen), co-supervised by **Philip Awadalla**, a professor at OICR, is researching how mutations accumulated over a person's lifespan affect health. Specifically, she is developing machine learning tools for identifying individuals at risk of cancer or heart disease based on patterns of mutations appearing in their blood cells to improve early detection of disease in European, Canadian and African contexts.

A promising strategy for treating cancer more precisely, to avoid damage to healthy tissue, is to deliver drug-filled nanoparticles directly into tumours. However, only a tiny fraction of these particles actually reach tumours for reasons that aren't clear. **Jamie (Liu Yi) Wu**, (Chan lab, IBBME) is researching how nanoparticles interact with proteins in the blood and with the tumour vasculature to find out how this affects their transport and improve targeting.

Tracking of diverse molecules in patient's blood and other tissues has the potential to reveal disease earlier than available methods. This requires better tools for analyzing data collected by mass spectrometry instruments that can identify diverse molecules from a tissue sample. Two students, co-supervised by Morris and **Hannes Röst**, are working on this using neural network-based approaches— **Leon Xu** (MoGen), is developing tools for better protein detection, while **Adamo Young** (CS), is working on improving detection of metabolites, which are products of enzymatic reactions.

Discoveries in stem cell biology have opened possibilities for treating disease by stimulating the body to repair itself as well as by transplanting healthy cells to replace those that are damaged. **Eric Ho** (Shoichet lab, ChemE), is researching strategies for a non-invasive, localized drug delivery into the brain after a stroke. He is developing biomaterials that would enable a controlled release of protein therapeutics that have the potential to stimulate local neural cells to orchestrate brain healing.

Margaret Ho (Shoichet lab, IBBME) is tackling blindness from retinal degeneration. While cell transplantation has shown promise for the restoration of vision, poor implant survival has stymied progress in this area. Ho is developing methods to increase production of donor photoreceptors, light-detecting nerve cells, and boost their survival through local delivery of neuroprotective factors.

2019 Dorrington Prizes Recognize Graduate Research in RNA Biology and Cancer

By Jovana Drinjakovic
March 19, 2019.

Kaitlin Laverty, **Mandeep Gill** and **Shrey Sindhwani** are this year's winners of the Jennifer Dorrington Graduate Research Award. Their doctoral research has the potential to transform our current understanding of molecular biology and cancer.

"This year's Dorrington winners have already made important discoveries in their respective fields which have opened new areas of research," says Professor **Gary Bader**, Chair of the Dorrington Award Committee with Professors **Liliana Attisano**, **Henry Krause** and **Cindi Morshead** as members. All are Principal Investigators in the Donnelly Centre. "They represent the future of science and are highly deserving of the Jennifer Dorrington Award," says Bader.

Established in 2007, the annual Dorrington Award recognizes outstanding graduate students in the University of Toronto's Faculty of Medicine who are doing research in Donnelly Centre labs. The award was founded by the Dorrington family as a tribute to **Jennifer Dorrington**, who was a professor in U of T's Banting and Best Department of Medical Research where she carried out pioneering work on ovarian physiology.

Biology meets artificial intelligence

The youngest of the winners, Laverty is in her third year of graduate studies in U of T's Department of Molecular Genetics and is doing research in computational biology co-supervised by Professors **Timothy Hughes** and **Quaid Morris**.

"Receiving the Dorrington award is recognition that I'm on the right track in my graduate career and motivation to continue on this path," says Laverty.

In her research, Laverty seeks to broaden our understanding of how RNA molecules work. These are short copies of the DNA scripts that serve as templates for building proteins and play other vital roles in the cell. RNAs are regulated by a class of proteins called RNA-binding proteins, or RBPs, and Laverty is working to find out how RBPs recognize the correct RNA molecules to bind. It is thought that the RBPs recognize specific parts of the copied genetic code within an RNA molecule as well as parts of its three-dimensional structure. She is developing machine-learning tools, a form of artificial intelligence in which computers learn to recognize recurrent patterns in the data, to predict from the sequence of an RNA molecule its shape and what proteins it will bind. It's a challenging task—humans have 1500 different RBPs but scientists know for only 200 of them which RNAs they bind.

"I am trying to not only identify the sequence the proteins are binding to but also what structure they are binding. On top of that we have to consider the fact that the RBPs can bind to two or more parts of the RNA molecule at variable spacing from one another, which makes the problem even more difficult," says Laverty.

Many RBPs have been linked to neurodegenerative diseases, including Alzheimer's. Knowing how RBPs work will lead to a better understanding of how disease occurs and could also offer clues for developing new therapies.

As a side project, Laverty recently completed a computational assembly of the cannabis genome, which details the arrangement of the biosynthetic genes on the

2019 Dorrington Award winners Kaitlin Laverty (left), Mandeep Gill (centre) and Shrey Sindhwani (right).

chromosomes. The long-awaited chromosome map came on the heels of cannabis legalization in Canada and will help further research into the plant's medical potential. Laverty's findings attracted media attention and were covered by the *Toronto Star*, *Vice*|*Motherboard* and other outlets.

"I am thankful for the mentorship of Tim and Quaid", she says. "Of course, their expertise in the fields of functional genomics and machine learning has been instrumental, but more importantly they treat their students as independent and capable scientists from the moment we join the lab. That level of respect for my opinions and abilities has helped me to achieve more than I thought possible."

Laverty previously won the Cecil Yip Doctoral Research Award, which recognizes excellence in first year students pursuing cross-disciplinary research in the Donnelly Centre.

New hope for bladder cancer

Dorrington winner Mandeep Gill is in the sixth and final year of PhD which she is conducting in Professor Attisano's lab. A student in U of T's Department of Biochemistry, Gill is investigating how mistakes in the so-called Hippo pathway, which regulates cell growth, can lead to cancer.

"I am very honoured to receive the Dorrington award because it will help me achieve my goal which is to make a significant contribution in cancer research to improve patients' lives," says Gill.

The Hippo pathway normally halts cell proliferation but these checks and balances are often switched off in cancer in ways that are not well understood. Gill discovered a protein called NUAK2 which is highly expressed in aggressive high grade bladder tumours where it inhibits the Hippo pathway, publishing her findings in the journal *Nature Communications*. Moreover, Gill and group showed that by blocking NUAK2, either by treating with drugs or by mutating the gene, reduces the growth of cancer cells and breast tumours in mice. The lab is currently working to develop anti-NUAK2 compounds that could be used on patients.

Gill first decided to dedicate her career to cancer research while working at the Lombardi Cancer Centre in Washington D.C. as a research assistant before starting graduate school. Researching breast tumour samples taken from patient biopsies helped her realize how different the disease can be from one person to another and that a more personalized approach to treatment is required. Ever since, helping patients has been at the forefront of her mind and Gill plans to continue her research of cancer as a postdoctoral researcher after graduating.

Gill credits her mentor and collaborators for her success. "I am grateful to Liliana for her support and for giving me the opportunity to work in a collaborative environment within and outside the Donnelly Centre," says Gill who worked closely with **Frank Sicheri** and **Jeff Wrana**'s labs at Sinai Health System's Lunenfeld-Tanenbaum Research Institute and also with **Michael Moran** at the Hospital for Sick Children. "Every morning I come to the lab with hope and passion that my research can contribute a little in the advancement of understanding complexity of the disease and ultimately save lives."

Clearing obstacles to nanomedicine

Shrey Sindhwani is also tackling cancer but he's taking a different approach to Gill. A graduate student in the U of T's Institute of Biomaterials and Biomedical Engineering, in Professor **Warren Chan**'s group, Sindhwani is developing nanotechnology for targeting tumours more precisely with drugs. Now in his seventh year of the MD/PhD program, Sindhwani is training to become a physician-scientist with a focus on improving cancer care.

"For cancer, one of the big challenges is that the kinds of drugs we use are very toxic and have their own side effects," he says of standard chemotherapy which indiscriminately destroys all proliferating cells including healthy cells behind tissue turnover.

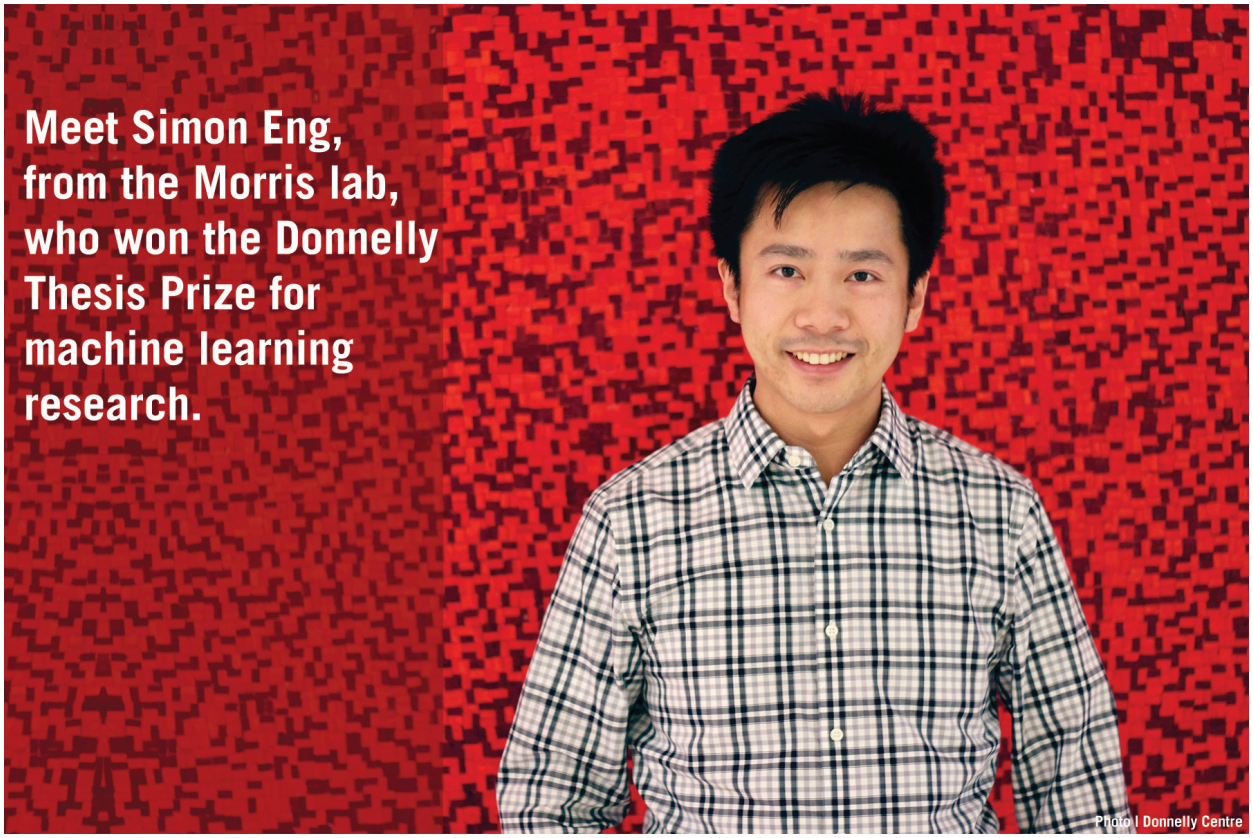
A potential solution to targeting cancer more precisely lies in nanoparticles which could be engineered to deliver medicines directly into the tumour. Although promising, nanoparticles come with a serious drawback—only one in 100 reach the tumour site after being injected into the bloodstream, as Chan's lab found a few years ago.

The focus of Sindhwani's research has been to reveal and overcome the obstacles preventing the particles from reaching tumours. One hurdle comes from proteins in the blood that wrap around the nanoparticle in a way that changes its final destination. By identifying these proteins and how they interact with the particles, Sindhwani is developing computational models that predict where the nanoparticles will end up to improve drug delivery. To understand what happens to the particles once they reach the tumour, he is also developing a technology that makes tumours transparent to light so that he can see get a complete view of drug distribution at the site of action.

"Tumours seem to have a very disorganized architecture with a lot of variation in space and time, so if you want to capture all the information about its biology and how drugs and nanoparticles work inside the tumour, you need to see it as a whole," he says, adding that the technique allows them to create a tumour map including blood vessels and other cell types around it. The result is a three-dimensional tissue map revealing the challenges the nanoparticles need to overcome to reach the tumour. "Going forward, I want to come up with ways to knock down these challenges so that more nanoparticles can reach the cancer cells and deliver more drug to it," he says.

"None of this work would have been possible without the input of my lab members Syed, James and Anthony and my supervisor Warren Chan," he says. "We started this work when there was very little known, and Warren has given us his full guidance and support for us to explore the unknown."

After finishing his PhD, Sindhwani will go back to medical school to complete his training as a physician-scientist, a position that will allow him to both see patients and pursue research. In this way, he'll be able to test observations from the clinic in the lab to get a better sense of disease and patients' needs.



Simon Eng Wins Donnelly Thesis Prize for Machine Learning Research on Childhood Arthritis

By Jovana Drinjakovic
May 23, 2019.

At a recent conference on childhood arthritis, **Simon Eng** met not only other researchers in the field but also patients who shared what it's like to live with aching joints and their hopes for the future.

"These kids are very passionate about finding appropriate treatment," says Eng, who during his PhD in the Donnelly Centre developed a computational tool for classifying patients into distinct disease groups to help doctors better tailor treatment that has fewer side effects. "It was amazing to see the excitement in their eyes about how our work could help them."

Childhood arthritis has no cure and treatment consists of pain medication and immune-suppressing drugs which do not work in everyone and may have side effects.

For his research, Eng won the 2019 Donnelly Thesis Prize, awarded annually for the best doctoral research completed at the Centre. He was co-supervised by computational scientist and Donnelly Centre investigator, **Quaid Morris**, and Dr. **Rae Yeung**, rheumatologist and Senior Scientist at the Hospital for Sick Children.

"On behalf of the award committee, I would like to congratulate Simon

on this deserving award," says **Jason Moffat**, Chair of the award committee with Donnelly Centre investigators **Cindi Morshead**, **William Ryu** and **Aaron Wheeler** as members.

"This was a competitive year with amazing candidates but Simon's work provides the basis for a new way of understanding and potentially treating childhood arthritis," says Moffat.

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

To Eng, the award is "a celebration of a fruitful collaboration" that saw immunologists, clinicians, and AI experts join forces to tackle a major problem in childhood health.

"I am very grateful to my supervisors Quaid and Rae who are leading researchers in their fields," he says. "With co-supervision you learn there are multiple ways of approaching the same problem and you get to choose the best of what both of them bring to the table."

One challenge in straddling the worlds as disparate as immunology and computer science is finding a common language. But Eng was up to the task having earned degrees in both as an undergraduate at the University of British Columbia in Vancouver. "It meant that I was able to both do the data analysis and interpretation and facilitate discussion between the two teams."

Childhood arthritis occurs when the body mistakes its own cells for foreign invaders and attacks joint tissue, causing swelling and throbbing pain. With about 24,000 Canadian children suffering from it, it is the most common childhood rheumatic disorder.

Furthermore, children can experience very different symptoms but so far there was no good way of classifying them into distinct subcategories to reflect the underlying biology of the disease. As a result, patients can end up receiving medication that is not suitable for them.

"The reason we are so concerned about patient classification is from the treatment perspective," says Eng. "If we can come up with a classification that encapsulate the biology of the disease, this could provide hints as to how we can treat these different patient groups to give them most specific treatment as possible to avoid side effects."

Eng came up with a computational approach based on unsupervised machine learning, a type of artificial intelligence, that can classify patients into seven distinct categories based on the pattern of inflamed joints. The algorithm can also predict which patients will go on to outgrow their arthritis and can be spared the more aggressive medications, as described in a landmark study published earlier this year in the journal Plos Medicine.

Collaborating with several Canadian consortia, Eng had access to a wealth of clinical, demographic, and biological patient data, including gene and protein expression. By applying machine learning to these diverse datasets, he was able to identify patterns which distinguish distinct disease subtypes. Eng remained at SickKids to combine all his findings into a single disease classification system. His hope is to develop an app to help doctors diagnose patients on the spot after initial examination.

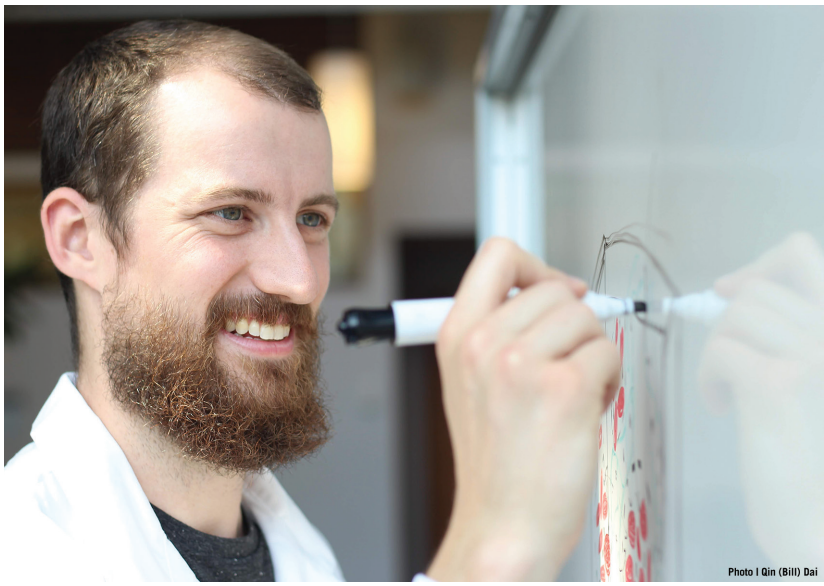
"One of the things we are working on is to build an app so that a clinician can examine a kid in the clinic, enter all the joints that have arthritis and ideally the system will spit out what the joint pattern is maybe even suggest a course of treatment."

His next career move? "We'll see what happens," he says, revealing only that a career in a health tech is on the table.

Benjamin Kingston Becomes 2019 Royal Bank of Canada Graduate Fellow

By Qin Dai
April 10, 2019.

Benjamin Kingston has won the 2019 Royal Bank of Canada (RBC) Graduate Fellowship. This award was a result of an academic-industry collaboration between Borealis AI, RBC, and Entrepreneurship Office at the University of Toronto. Valued at $50,000, this prize was awarded to fund Artificial Intelligence (AI) related research that has the potential to be translated into a commercial product.



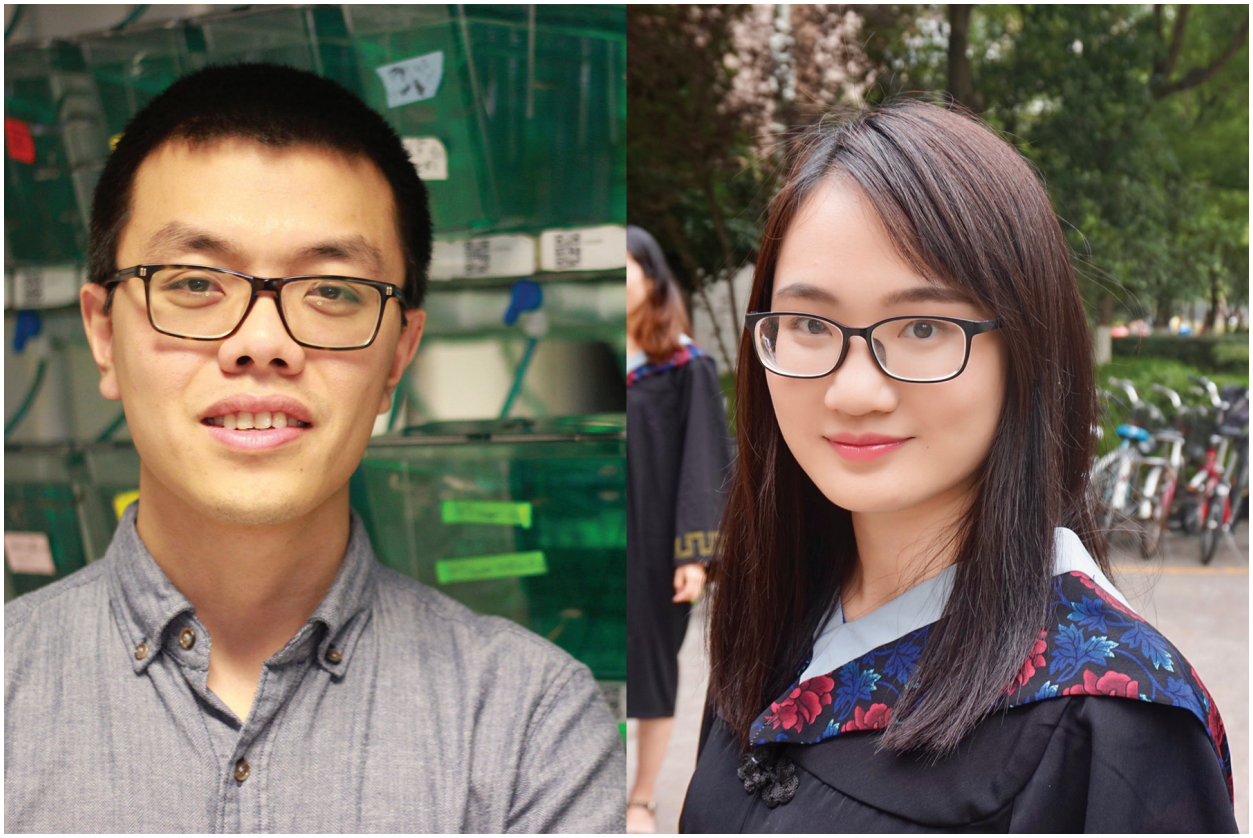
Benjamin Kingston, a graduate student in Professor Warren Chan's group, has won the RBC Graduate Fellowship to develop new AI-powered approaches to map individual patient tumours.

Benjamin Kingston is a 3rd year PhD candidate in Professor **Warren Chan**'s lab located at the Donnelly Centre. Benjamin's research is focused on using AI to interpret and quantify structural differences in human tumour biopsies. This structural interpretation can provide crucial information on how doctors diagnose and treat cancer in humans.

"We have developed a 3D imaging technology to visualize tumour biopsies from patient samples," Benjamin said, "I can then use AI algorithms to extract information from these images to create a personalized structural profile of the patient's tumour."

One defining feature of the tumour is its blood vessels, which provide nutrients and blood supply to the tumour and are used to deliver drugs. These blood vessels can be extremely chaotic, and therefore human interpretation of these tumours can be highly subjective, potentially leading to the wrongful diagnosis. "If we can use AI to analyze what kind of blood vessel allow therapeutics to reach the cancer cells easily, we can predict how the patient will react to chemotherapeutics before subjecting them to treatments that do not work. It's a personalized approach to medicine."

Benjamin's vision is to eventually create a personalized cancer prognosis algorithm by curating data from thousands of patient tumour samples. "We have access to large banks of tumour biopsy samples collected over the past 20 years. Since the results from these tumour samples are known, we can hopefully correlate patient outcome to specific features within the tumour." said Benjamin.



Donnelly Centre Trainees Win Inaugural PRiME Fellowships

By Jovana Drinjakovic
September 10, 2019.

Donnelly Centre trainees, **Jiabao Liu** and **Yu-Xi Xiao**, have won the inaugural PRiME Fellowship Awards for their research with implications for metabolic syndrome and cancer, respectively.

The fellowships are awarded by the University of Toronto's Precision Medicine Initiative, launched earlier this year to advance the development of targeted treatments through interdisciplinary collaboration. Led by **Shana Kelley**, University Professor at the Leslie Dan Faculty of Pharmacy, PRiME bridges research from Pharmacy, the Faculty of Medicine, the Faculty of Arts & Science and the Faculty of Applied Science & Engineering.

Liu and Xiao are among the 10 awardees who were selected by the Fellowship Committee based on the strength of their research proposals that seek to identify new disease targets, therapies and diagnostics for precision medicine.

As a postdoctoral research fellow in Professor **Henry Krause**'s lab in the Donnelly Centre, Liu studies nuclear receptor (NR) proteins which play a role in nutrient-sensing and have been implicated in the metabolic syndrome and other diseases. NRs turn genes on and off in response to hormones and other small molecules, some of

which are found in food. However, the extent of molecules capable of activating these receptors is not known and this has impeded their study. Collaborating with **Carolyn Cummin**'s group at Pharmacy, Liu has set out to to identify the small molecules that bind to diverse NRs to better understand their function and to find potential therapeutics. Liu currently also holds the Charles H. Best Fellowship, awarded annually to an outstanding postdoctoral fellow in the Donnelly Centre.

"Ligand identification for human nuclear receptors and characterizing their functions require a combination of analytical chemistry, biochemistry, molecular genetics,and pharmacology," says Liu. "PRiME provides an excellent platform for me to setup collaboration with scientists from diverse areas, and will boost my project and speedup the research translation."

Yu-Xi Xiao is a graduate student in Professor **Jason Moffat**'s lab in the Donnelly Centre where she is developing a new technology for studying how different genes contribute to cancer. Like other common diseases, cancer is caused by variants in multiple genes, but how these interact is still unclear. Genome editing tool CRISPR has allowed scientists to combine multiple genetic defects in cells and measure their outcome and the Moffat lab has made leading contributions in this area. Xiao's project brings the CRISPR system together with a microfluidics platform, which allows more efficient handling of the cells and was developed by the Kelley lab at Pharmacy, in a new high-throughput pipeline that will allow her to study how multiple genes affect cell proliferation and changes in cell-surface proteins that are important in cancer.

"Not only does this award fund the development of a powerful genome perturbation tools that allow alterations of more than one gene at a time, it also provides a great platform for collaborating with researchers that devote themselves to precision medicine, which can be valuable for the project and my personal development in academia," says Xiao.

"One of the initial focuses of PRiME is to build a strong program for our trainees, including resources and support for both internal and external funding opportunities," said Kelley. "Building a strong community of translational trainees will provide an excellent foundation for the initiative as we pursue a presence in the international research landscape."

Juline Poirson Wins Charles H. Best Fellowship

By Jovana Drinjakovic
January 28, 2019.

The Donnelly Centre is delighted to announce that **Juline Poirson** is our latest Best Fellow.

Established in 2001 in support of the next generation of biomedical research leaders, the annual Charles H. Best Postdoctoral Fellowship is awarded to an outstanding postdoctoral researcher in the Donnelly Centre. The decision to award Poirson was made by the award committee members: **Brenda Andrews**, Director of the Donnelly Centre, **Peter Roy**, **Andy Fraser** and **Zhaolei Zhang** as Acting Chair. All are faculty members in the Donnelly Centre and University of Toronto professors.

Poirson joined **Mikko Taipale**'s lab two years ago to study how protein stability contributes to cancer.

"I am really thankful for the fellowship," says Poirson. "It's a great support for me to encourage me to continue to do what I love the most, which is science."

Before joining Taipale's lab, Poirson completed her doctoral studies at the University of Strasbourg in France with Drs. Murielle Masson and Gilles Travé. There she studied how human papilloma virus, which causes cervical cancer, overcomes the host cell's defense mechanism. The virus does this by co-opting the cell's waste disposal system, also known as the ubiquitin proteasome system, which remains the focus of Poirson's current research.

"Juline did her PhD on high-throughput protein/protein interactions in the ubiquitin/proteasome field so she has the perfect background for the project," says Taipale. "She's also a great lab member and we are very lucky to have her expertise at hand. I'm convinced she will make major contributions to our understanding of the ubiquitin-proteasome system in cancer and other diseases."

Proteins that are no longer needed are targeted for destruction by the ubiquitin-proteasome system, or UPS. More than 600 enzymes known as ubiquitin ligases are involved in this process where each enzyme targets for degradation only a subset of proteins by sticking a ubiquitin protein label on them. But what proteins are targeted by which enzymes remains largely unknown.

Because the UPS is crucial for the normal functioning of the cell, linking the ubiquitin ligases to their protein targets holds potential for drug discovery. Perturbing these specific molecular interactions could yield more precise drugs with fewer side effects.

Poirson's goal is to identify proteins which are known to drive cancer and whose levels are controlled by the UPS. Since starting her postdoc, she has already found about 20 cancer proteins whose levels go up after the UPS has been blocked, suggesting that they are targeted for degradation. This already is a major finding as many of these proteins have not been previously linked to the UPS.

Dr. Julie Poirson is the 2019 Best Fellow

Using the CRISPR genome editing technology she is now working to identify enzymes responsible which will shed light on new molecular pathways in cancer and potential drug targets.

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

Research Excellence Awards Recognize Advances to Personalized Medicine

By Jovana Drinjakovic
July 23, 2019.

Could a patient's future health be computationally predicted? Can we target cancer more precisely to avoid harmful side effects of the treatment? These are the questions tackled by postdoctoral researchers **Shraddha Pai** and **Michael Aregger**, who are the 2019 winners of the Donnelly Centre Research Excellence Awards.

By developing and implementing advanced methods in computer science and functional genomics, Pai and Aregger's research is helping advance personalized medicine, also known as precision medicine, which seeks to tailor treatment to an individual patient.

Established last year, the annual awards recognize two postdoctoral researchers in the Donnelly Centre who have achieved excellence in interdisciplinary and collaborative research, as judged by their record of scientific publications and research presentations.

"Research is a long road filled with obstacles and negative results, and peer recognition such as this is rewarding and motivating in its own right," says Pai, a postdoctoral fellow in computational biology.

Working with **Gary Bader**, a professor of computer science and molecular genetics in the Donnelly Centre, Pai has developed a computational method called netDx, which integrates diverse patient information, such as clinical records, DNA

sequencing and gene expression data, brain scans and others, to distinguish between patients with different outcomes. The method uses machine learning, a form of artificial intelligence, and can be adapted for most clinical problems requiring patient classification. Pai and Bader have made netDx publicly available as a user-friendly software package to encourage other researchers to apply it to their questions of interest.

netDx is already helping researchers by revealing patterns in data that shed light on the underlying biology of disease. But Pai wants to see netDx helping patients too.

"We hope the eventual benefit will be to patients, by avoiding clinical treatment that is not useful to improving the patient's quality of life, " says Pai.

In collaboration with **Quaid Morris**, also a professor of computer science in the Donnelly Centre, Pai has improved the algorithm's processing speed so that it can handle datasets from 500 patients, the largest cohort so far. Furhter improvements will see netDx applied to even larger cohortsto build more robust clinical predictors.

Since joining Bader's team, Pai has established new projects in fields as diverse as depression research, autism genetics, and pulmonary research. As a member of the data analysis team for a cross-national project Canadian Biomarker Integration Network in Depression (CAN-BIND1), she is also working to predict anti-depressant treatment response in diverse individuals.

"It is extremely rewarding to bring my unique expertise in statistical data analysis and machine learning to a team with interdisciplinary clinical researchers, and work on a translational project with the potential to change clinical care in the near-term," she says.

As well as predicting health outcome, precision medicine seeks to develop treatments suited to an individual's ailment. This is particularly challenging in cancer, which comes in many forms and evolves over time to resist treatment.

Michael Aregger seeks to identify new therapeutic targets by identifying genes involved in cell metabolism, which undergoes extensive changes during cancer.

Aregger joined **Jason Moffat**'s lab in the Donnelly Centre, in 2014, attracted by the lab's expertise in identifying gene function a genome-wide scale.

In 2015, Aregger published a landmark study revealing which genes are essential for cell proliferation in different cancer cell lines, opening the door to the development of targeted therapies.

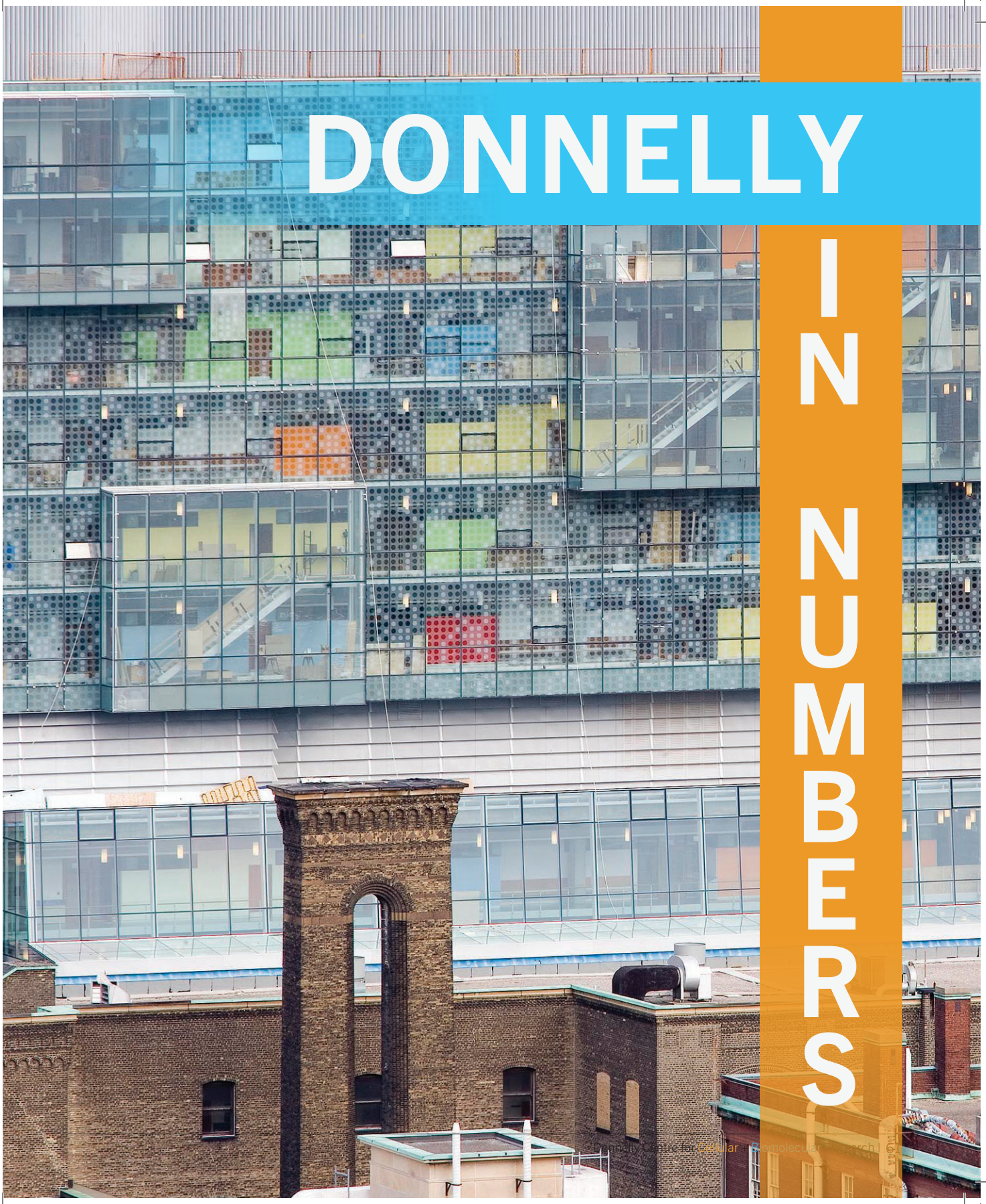
"The goal of my research is to understand how cells are able to rewire their metabolism in response to different environmental conditions such as nutrient availability or upon pharmacological perturbation of metabolic pathways," says Aregger. Aregger is using the gene editing tool CRISPR to systematically switch off metabolism genes to find out which ones are essential for cell proliferation in cancer.

These studies revealed an extensive cross-talk between metabolic pathways, and also uncovered genes responsible for adapting to changes in metabolism. The findings expand our understandiung of how cancer cells become treatment resistant and could help the rational design of drug combinations.

In a joint project with **Benjamin Blencowe**'s group at the Donnelly Centre, Aregger has also developed CHyMErA, an advanced CRISPR-based tool for switching off up to four genes in any combination to study their combined roles. It also allows researchers to reveal gene roles that are often masked by other genes in the genome that have related functions.

Aregger also collaborates with **Brenda Andrews** and **Charles Boone**, of the Donnelly Centre, and **Chad Myers**, a professor of computer science at the University of Minnesota Twin Cities, as well as **Anne-Claude Gingras** and **Jim Dennis**, both at the Lunenfeld-Tanenbaum Research Institute and **Thomas Kislinger** at Princess Margaret Cancer Centre.

Aregger says he is "pleased to receive the Research Excellence Award" and hopes this "will have a positive impact on his future career". "This award helps highlight the my research as well as how it benefits the wider research community."



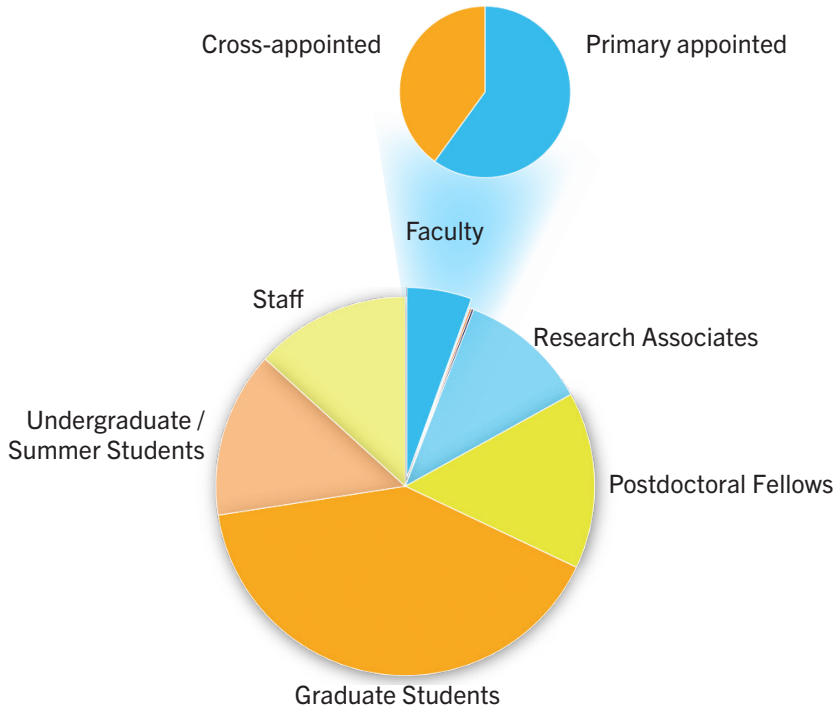
DONNELLY

IN NUMBERS

Personnel

The Donnelly Centre currently houses a total of 543 occupants, representing scientists at all stages of their careers as well as members of staff, as follows:

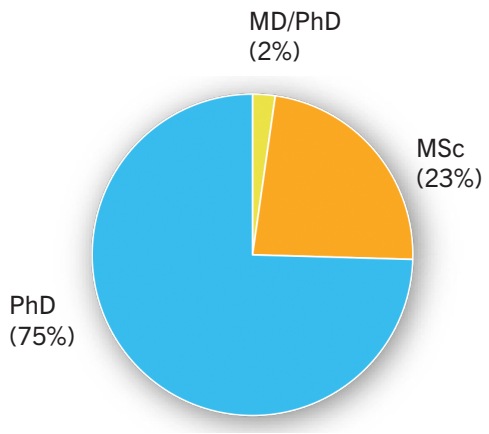
29 Faculty members, 17 of whom are primary appointees
1 Professor Emeritus
1 Visiting Professor
60 Research Associates
82 Postdoctoral Fellows
220 Graduate Students
77 Undergraduate students, 62 of whom are summer students
72 Research and admin staff



Graduate Students

Our 220 graduate students come from diverse U of T departments, as shown by the numbers in brackets below:

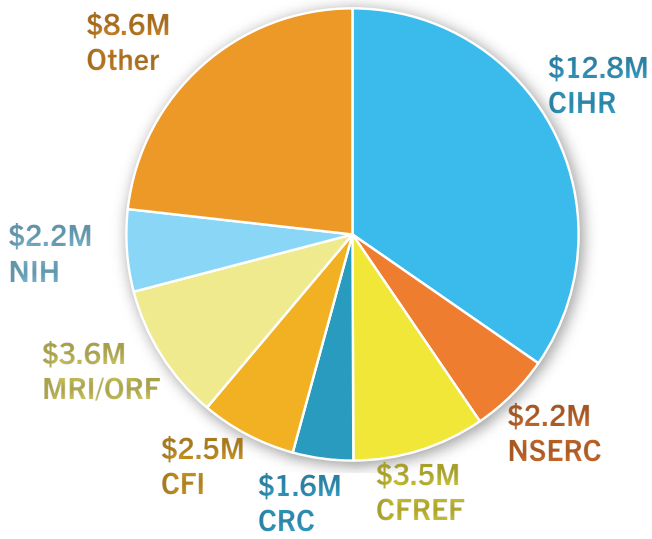
Surgery (1)
Electrical and Computer Engineering (1)
Immunology (1)
Laboratory Medicine and Pathobiology (2)
Chemical Engineering (9)
Chemistry (11)
Computer Science (12)
Institute of Medical Science (13)
Biochemistry (13)
Institute of Biomaterials and Biomedical Engineering (40)
Molecular Genetics (105)



164 students (75%) are PhD candidates, 51(23%) are pursuing a Masters degree and 5 (2%) are in the MD/PhD program.

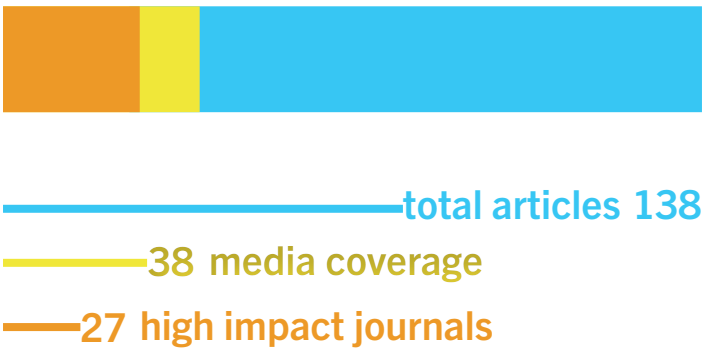
Annual Funding Breakdown

The majority of the funding for infrastructure, research and personnel is supported by the grants from the Canadian federal government. The graph on the right shows a breakdown of total research grants raised by both primary and cross appointed faculy. “Other” sources of funding represent other federal and provincial grants as well as support from foundations.
The data presented are for the period from July 2018 to June 2019.



Abbreviations: CIHR (Canadian Institutes of Health Research), NSERC (National Science and Engineering Council), CFREF (Canada First Research Excellence Fund), CRC (Canada Research Chair program), CFI (Canada Foundation for Innovation), MRI/ORF (Ministry of Research and Innovation/ Ontario Research Fund), NIH (U.S. National Institutes of Health).

Publication Output

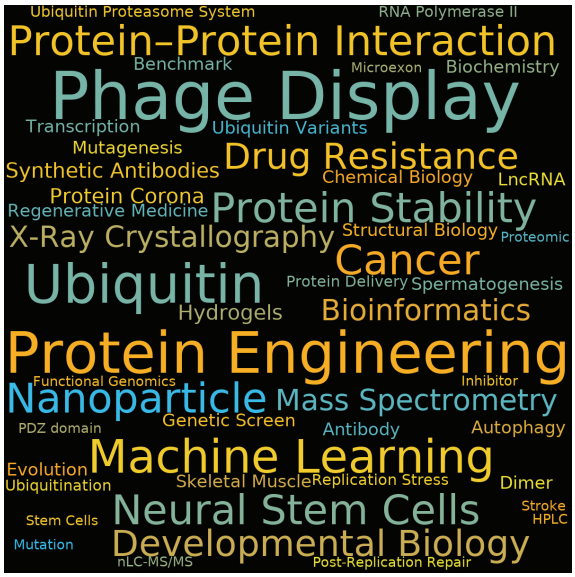


In 2019, Donnelly Centre investigators have published 138 articles in peer-reviewed academic journals, of which 27 articles were published in high impact journals*, while 38 received notable media coverage with an Altmetric score greater than 20.

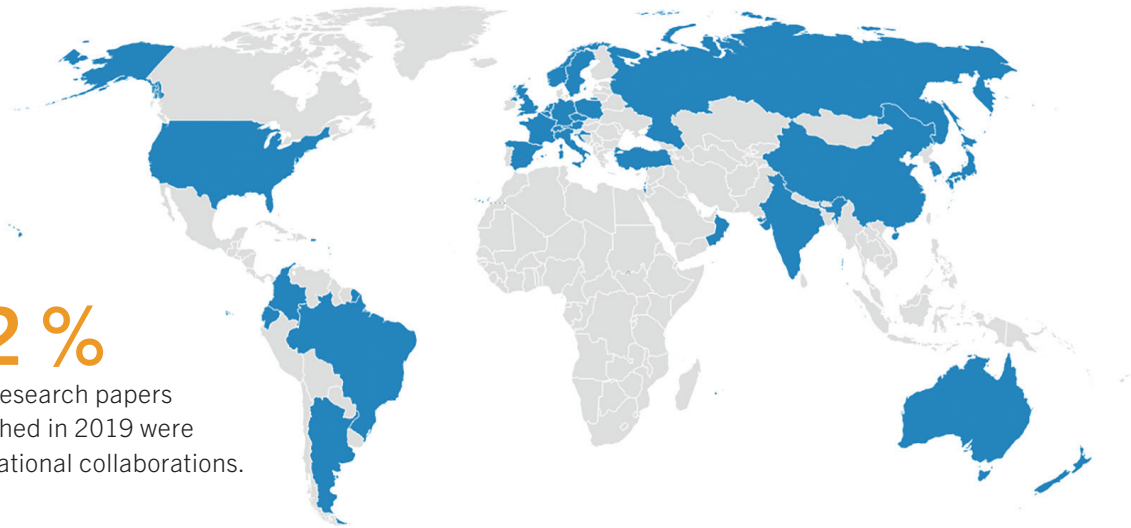
*The following journals were considered as high impact: *Biomaterials, Blood, Cancer Cell, Cell, Cell Reports, Cell Stem Cell, Cell Systems, Developmental Cell, Molecular Cell, Nature, Nature Biotechnology, Nature Cell Biology, Nature Chemical Biology, Nature Communications, Nature Genetics, Nature Medicine, Nature Methods, Nature Protocols, Proceedings of the National Academy of Sciences of the United States of America* and *Science*.

Research Topics

Researchers in the Donnelly Centre work on diverse life sciences topics, with many teams collaborating across scientific disciplines. The map on the right representes the frequency of top 49 keyword identifiers from a total of 138 publications produced by Donnelly Centre faculty in 2019 and was generated using WordCloud for Python. The font size represents the relative frequency with which a given keyword or phrase appears.



International Collaboration

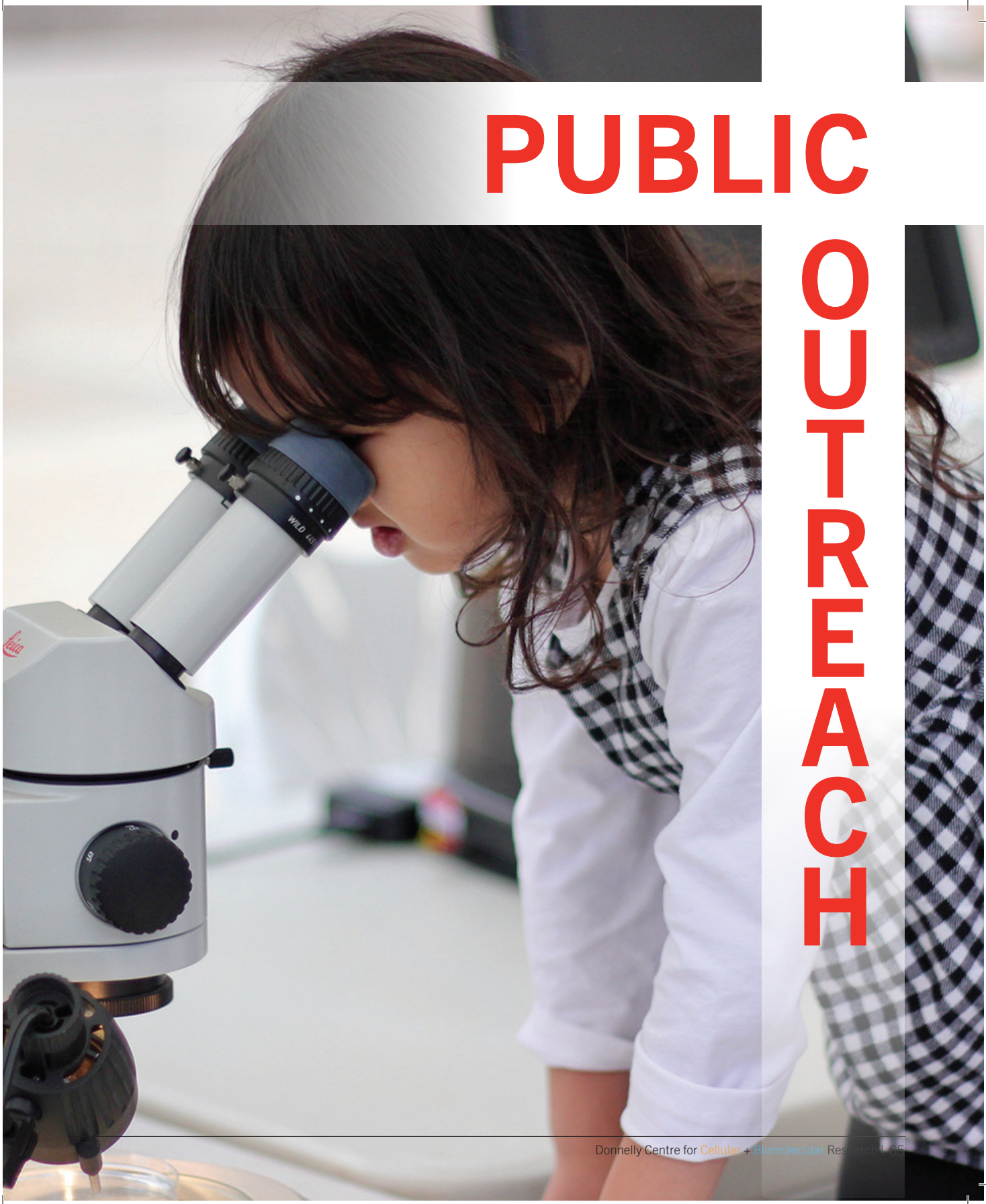


62 %

of all research papers published in 2019 were international collaborations.

In blue are the countries from which co-authors of research articles published by Donnelly Centre investigators in 2019 come from. Generated by Datawrapper.

PUBLIC OUTREACH



Sixth graders from Norway Public School doing DNA extraction experiments in Donnelly Centre lab.

2019 Public Science Outreach Highlights

By Jovana Drinjakovic
December 8, 2019.

2019 was a busy year for the Donnelly Centre Science Outreach!

In March, we welcomed 30 students, in grades 10-12, through Step Into STEM, an organization that seeks to provide STEM learning opportunities for youth from underrepresented groups. The students visited the Andrews, Morris and Roy labs where they learned about yeast genetics, artificial intelligence and drug discovery.

Also in March, **Samantha Yammine** from the van der Kooy team teamed up with the Visions of Science Network Learning, another organization that champions STEM among the underrepresented and underprivileged youths, to give 20 students a tour of her lab and tell them about their stem cell research.

On May 2, the Donnelly Centre participated in Bring Our Children to Work Day, which gathered 25 of our employees' kids, in grades 4-12. Organized by **Christine Misquitta**, formerly of the Sidhu lab, the event was an opportunity for the students to learn about DNA biology through hands on experiments and other activities. I

In May, we also took our science

Step Into STEM participants and coordinators during their visit to the Centre.

outdoors for Science Rendezvous, a national all-day celebration of science, which at U of T takes place along St George street. Among the many science and educational props, for this year's theme of Science and Art, we had the masterpieces of Leonardo da Vinci and Banksy rendered in yeast by **Matej Usaj** and **Bryan-Joseph San Luis** from the Boone and Andrews labs. The visitors to our booth also had a chance to paint with lab tools such as liquid droppers on a blank canvas that resembled a Jackson Pollock piece by the end of the day.

While our outreach program primarily focuses on Canadian youth, we also hosted 40 government officials, as well as Canadian and international enterpreneurs and other stake holders in the life sciences sector who toured the Centre during the Innovate Canada conference, which took place in Toronto from May 21-24, 2019. **Patricia Mero** from the Moffat lab gave the visitors an oveview of research in the Donnelly Centre, after which they were shown the automated cell genetics and imaging plthe atforms in the Andrews and Boone labs and the three dimensional muscle tissue culturing system developed by the Gilbert lab.

On June 12, 45 students in grade 6 from Norway Public School visited the Centre for a day to learn about biology, through hands on activities, including isolating DNA from cells, yeast mating and guessing the function of mutated genes in *C. elegans* worms based on their behavior.

We look forward to future opportunities to help instill curiosity and excitement about science among our youngest citizens!

If you are interested in science-learning opportunities in the Donnelly Centre, we would love to hear from you. Or you can visit the Donnelly Centre Youth Science Outreach page on our website.

The Donnelly Centre Science Rendezvous exhibit featured a "lab" photo booth (left), painting with research equipment (centre) and Leonardo da Vinci's Mona Lisa depicted by patterned growth of yeast cell colonies (right).

Summer Program Gives Undergraduates Crucial Research Experience

By Jovana Drinjakovic
August 28, 2019.

"I never knew what you did in a PhD," says **Justine Lau**, whose previous summer jobs were working as a camp instructor or in a restaurant. "It was really interesting to see the life of grad students, learning basic lab skills that I 'm going to take on in future years."

Lau, who is going into the second year of medical sciences studies at Western University, spent her summer working in **Mikko Taipale**'s lab in the University of Toronto's Donnelly Centre for Cellular and Biomolecular Research, where she studied the molecular basis of congenital diseases. Her first brush with research is unlikely to be the last.

"I always thought of researchers as working on their own and I was surprised by the amount of collaboration that happens in the lab," she says. "I am a very social person so I really liked that."

For **Allysia Chin**, who researched biomarkers in brain cancer in Molly Shoichet's lab, learning how to explain her research to the public was as important as learning new lab skills. "Communicating science to a lay audience is often overlooked, but it is so important because at the end of the day the research we do is for them," says Chin, heading into the final year of her chemical biology degree at McMaster University in Hamilton. Communicating science effectively will stand her in good stead when she fulfills her dream of becoming a clinician scientist which

she hopes to train for at U of T's MD-PhD program. "I love the dynamics of the school and inclusion and diversity it represents," says Chin.

Lau and Chin are among almost 60 undergraduates from U of T and other universities who participated in the Donnelly Centre Summer Undergraduate Research Program. The goal of the program is to immerse students in a real research environment, cultivate their curiosity about science and give them research experience required to enter competitive graduate schools.

During their summer break, the students learned how to plan and conduct research projects in diverse medical research fields, draw insights from their data and present their research in seminars.

The program concluded with a research symposium during which 20 select students presented their projects as two-minute poster pitches to peers and lab members. The speakers were selected on the strength of their written research summaries.

"The students clearly put a lot of work into both their projects and their 2 minute presentations", says **Peter Roy**, a professor in the Donnelly Centre who was on the judging panel that awarded prizes for the best presentation and research summary. "The projects were so exciting, highlighting the cutting-edge research that the Donnelly is engaged in."

Other members of the panel were:

Undergraduate student Deiriai Myers presenting her summer research project she completed in Professor Charlie Boone's lab.

Shoichet, postdoctoral fellow **Tae-Hyung (Simon) Kim**, Senior Research Associate, **Helena Friesen**, and graduate students **Clarence Yeung** and **Ziyang (Jason) Wang**.

"This undergraduate symposium was designed to model what a future career in science would look like—how to compile data in a concise way, scientifically explain findings in a formal research summary, and to present work in a limited amount of time at conferences in a way that would allow your peers, who are not familiar with your research, to understand what it is about" says **Sara Sharifpoor**, Research Program Manager for the Donnelly Centre and co-ordinator of the undergraduate research program.

"As a bonus, we also wanted to formally recognize the gifted students with high potential, in order to encourage them to pursue a future career in science and innovation," she says.

The two $250 prizes for the best e-poster pitch and research summary went to U of T students, **Jack Castelli** and **Jack Li**, respectively, both in the department of molecular genetics. Castelli was in **Fritz Roth**'s lab, where he studied how gene mutations affect the function of the encoded protein, while Li was in the Roy lab where he searched for new chemical compounds that can kill parasites.

"The symposium was put together really well and was fun to attend," said Castelli, adding that he enjoyed his time in the Donnelly with "loads of cool science going on, from all sorts of different fields of research."

Will he be back in the lab?

"I'd be devastated if this were my last summer in the lab," he says. "I am looking forward to attending graduate school and pursuing a Ph.D"

Select Media Coverage

Over the year, our researchers and their discoveries were featured in diverse national and international print and online media, some of which are highlighted below:

Peeking inside the mind of the worm for clues on how memories form, *Technology Networks*

Nella mente di un verme per capire i blocchi di memoria, *Le Scienze* (Italian)

Study reveals how genetic background influences trait inheritance, *The Telegraph*

How genetic background shapes individual differences within a species, *Science World Report*

Machine learning used to improve outcome for arthritic kids, *New Atlas*

New machine learning technique can boost treatment for arthritis in kids, *Business Standard*

Machine learning tool could prevent unnecessary treatments for kids with arthritis, *News Medical*

Not all stem cells are created equal, study reveals, *Long Room*

Understanding gene interactions holds key to personalized medicine, *Noticias de la Ciencia y la Technologia*

Gene interactions hold the key to unlocking personalized medicine, *Technology Networks*

Study reveals large molecular differences between stem cells grown on different biomaterials, *Medical Express*

Genes that may hold key to human evolution identified, *The Times of India*

Humans' DNA-binding motifs surprisingly distinctive, *GEN News*

Un malloppo di geni che potrebbe spiegare l'unicità dei sapiens, *Focus.It* (Italian)

Scientists discover new method to kill drug-resistant parasites, *The Times of India*

Unusual parasite metabolism, a ray of hope against drug-resistant parasites, *Business Standard*

Microrobots move cells, *Chemical & Engeneering News*

Microrobots to change the way we work with cellular material, *Tech Xplore*

Scientists develop antibodies that could stimulate the body to repair itself, *Interesting Engineering*

AntlerA leverages precision-engineered protein therapeutic platform to harness body's regenerative potential, *Wallstreet Online*

A promising brain-regenerating drug may only work for women and babies, a mouse study suggests, *Gizmodo*

A brain repair drug that only works in female, *BBC World Service Newshour*

Tiny biomagnets speed up drug discovery, *Technology Networks*

How scientists could help people quit smoking by targeting 'disgust' receptors, *CTV News*

How your brain seduces you into thinking cigarettes aren't gross, *Inverse*

Research on why nicotine initially feels disgusting could help smokers quit, *The Telegraph*

Tabac : comment l'aversion naturelle se transforme en addiction, *Futura-Sciences* (French)

Unangenehmer Nikotin-Effekt mit Potenzial, *Focus Online* (German)

Onderzoek verklaart waarom de eerste sigaret zo walgelijk vies is, *Scientias.nl* (Dutch)

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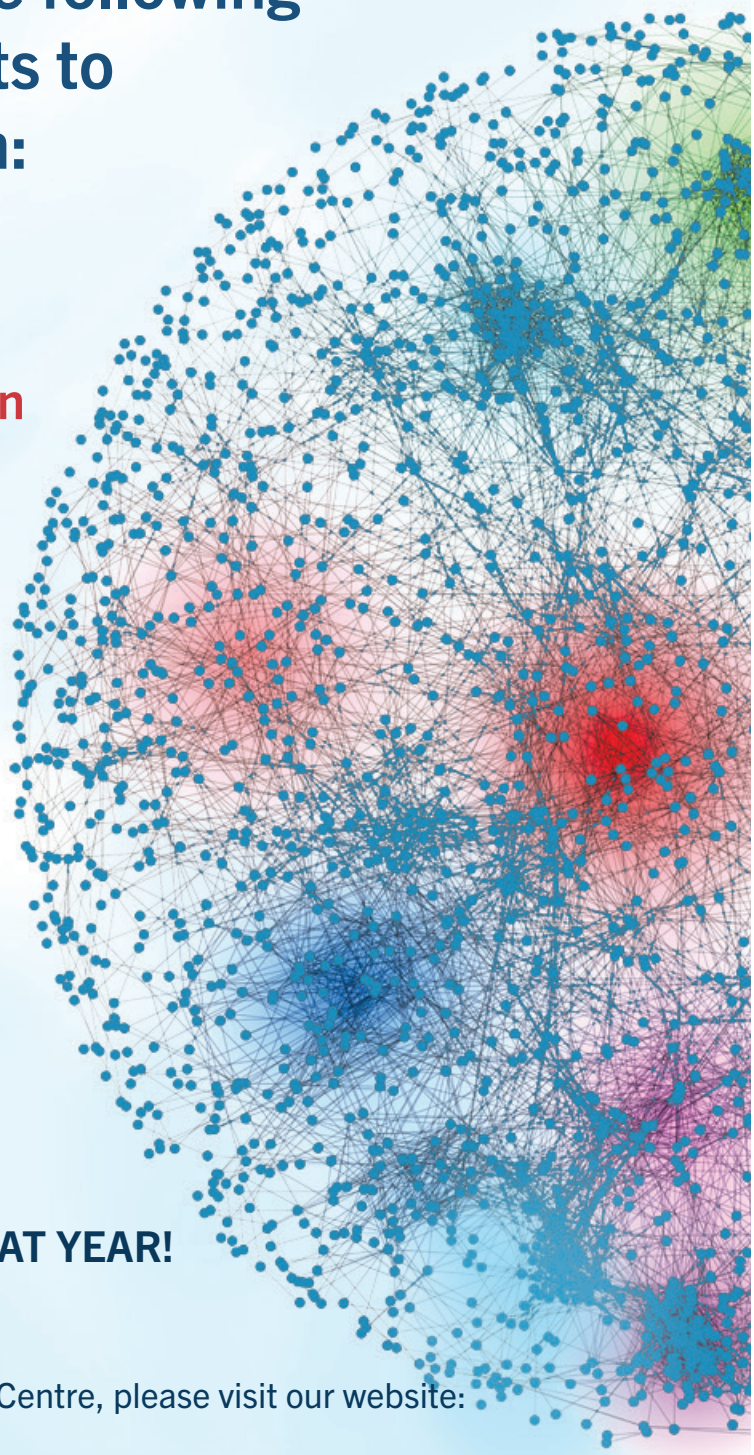

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For more information about the Donnelly Centre, please visit our website:

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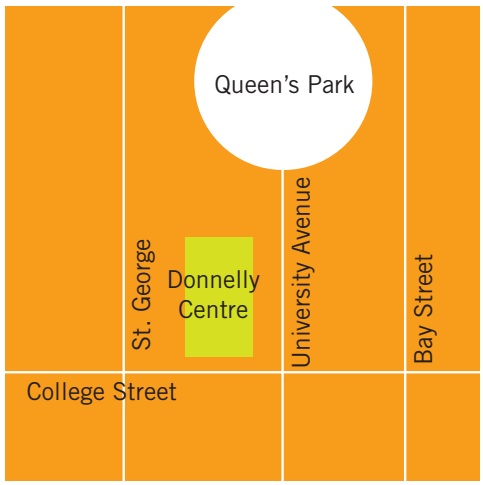

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