



Donnelly Centre
for Cellular + Biomolecular Research



TEMERTY FACULTY OF MEDICINE
UNIVERSITY OF TORONTO

DONNELLY CENTRE 2020

Annual Report

Founded in 2004 at the University of Toronto, Donnelly Centre for Cellular and Biomolecular Research is an interdisciplinary research institute where scientists make discoveries to improve health and medicine.

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.

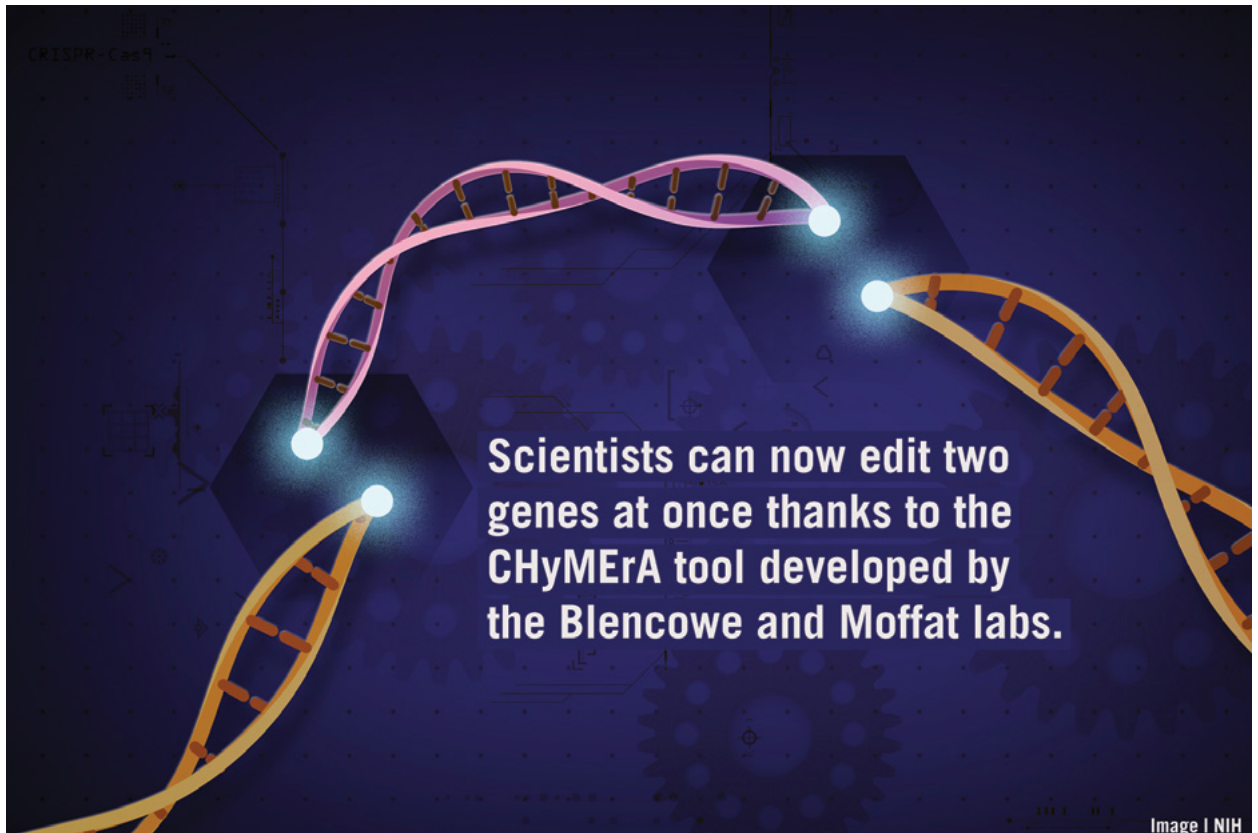
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RESEARCH

HIGHLIGHTS





Genome Editing Just Got More Versatile Thanks to New Technology Developed by Donnelly Centre Investigators

By Jovana Drinjakovic
March 16, 2020.

CRISPR-based DNA editing has revolutionized the study of the human genome by allowing precise deletion of any human gene to glean insights into its function. But one feature remained challenging—the ability to simultaneously remove multiple genes or gene fragments in the same cell. Yet this type of genome surgery is key for

scientists to understand how different parts of the genome work together in the contexts of both normal physiology and disease.

Now such a tool exists thanks to the teams of **Benjamin Blencowe** and **Jason Moffat**, both professors of molecular genetics at the Donnelly

Centre.

Dubbed ‘CHyMErA’, for Cas Hybrid for Multiplexed Editing and Screening Applications, the method can be applied to any type of mammalian cell to systematically target the DNA at multiple positions at the same time, as described in a study published in the

journal *Nature Biotechnology*.

Often described as genome scissors, CRISPR works by sending a DNA-cutting enzyme to desired sites in the genome via guide RNA molecules, engineered to adhere to the target site. The most widely used DNA-cutting enzyme is Cas9.

Since Cas9 first came to light, other Cas enzymes with distinct properties have been identified by scientists seeking to improve and expand the applications of the technology. Unlike the CRISPR-Cas9 technology, CHyMERa combines two different DNA-cutting enzymes, Cas9 and Cas12a, to allow more versatile applications. Cas12a is an enzyme that can be used to generate multiple guide RNA molecules in the same cell, which is key for simultaneous DNA editing.

Thomas Gonatopoulos-Pournatzis, research associate in Blencowe's group, had spent several years trying to develop combinatorial gene editing by testing Cas9 and Cas12a enzymes on their own. He then had the idea to combine these enzymes to generate the CHyMERa system.

"We had been trying a number of approaches to induce genetic fragment deletions and nothing worked as well as CHyMERa," he says. "I was thrilled when together with **Shaghayegh Farhangmehr**, PhD student in the Blencowe lab, we saw the first evidence that CHyMERa was successful in deleting gene segments. We obtained these results on Boxing Day and it was the best Christmas present I could have wished for."

The next step was to harness CHyMERa in large-scale screens to systematically analyze how genes act together, as well the functions of individual parts of genes. Blencowe's team, which studies the regulation and function of gene segments known as exons, approached Moffat, whose group had developed extensive experience with CRISPR technology.

"We obtained these results on Boxing Day and it was the best Christmas present I could have wished for"

"With CHyMERa, you can use the best of the two enzymes," says **Michael Aregger**, research associate in the Moffat lab, who played a key role in developing the screen-based applications of CHyMERa. "Cas9 has been improved by the community to have a very high editing efficiency, whereas Cas12a allows multiplexing of guide RNAs and therefore provides a lot more flexibility in finding sites in the genome that we can cut."

In one application of CHyMERa, the researchers targeted pairs of genes known as paralogs, which have a similar DNA code but remain poorly studied because they were difficult to research. Because paralogs arose by duplication of an ancestral gene, it had been assumed they would largely have similar roles. But their function could not be revealed by the existing single-gene targeting methods typically employed in genetic screens, mostly because the other paralog would

compensate for the one that's missing.

"With CHyMERa, we can take out both paralogs in pairs to see if that ancestral function is important for the cell to survive," says **Kevin Brown**, senior research associate in Moffat's lab and co-lead author on the study along with Aregger and Gonatopoulos-Pournatzis. "We are able to now interrogate a class of genes that was previously missed." After knocking out ~700 paralog pairs, almost all that exist in the human genome, the analysis confirmed that many of these gene pairs do indeed perform similar roles in cell survival, whereas others have distinct functions.

Another feature of CHyMERa is that both Cas9 and Cas12a can be deployed to nearby genome sites to cut out gene fragments such as exons. This allowed the team to individually delete thousands of exons that have been linked to cancer and brain function but were not amenable to targeting with Cas9 alone. Exons are variably included into genes' transcripts and can modify the function of the encoded proteins, although how individual exons contribute to cellular processes remains largely unknown. Out of 2,000 exons analyzed by CHyMERa, over 100 were found to be critical for cell survival, enabling future research to now focus on shining light on their potential roles in disease.

"Once we identify exons that have a critical role in disease, we can use this information to develop new therapies," says Gonatopoulos-Pournatzis.

The Chan team provided a fresh view about how encapsulated nanomedicines reach their destinations in the body.



Nanoparticles inside blood vessel cells | Chan lab

Most Engineered Nanoparticles Enter Tumours Through Cells And Not Between Them

By Qin Dai and Jim Oldfield
January 14, 2020.

Donnelly Centre researchers have discovered that an active rather than passive process dictates which nanoparticles enter solid tumours, upending decades of thinking in the field of cancer nanomedicine and pointing toward more effective nanotherapies.

The prevailing theory in cancer nanomedicine — an approach that enables more targeted therapies than standard chemotherapy — has been that nanoparticles mainly diffuse passively into tumours through tiny gaps between cells in the endothelium, which lines

the inner wall of blood vessels that support tumour growth.

The researchers previously showed that less than one per cent of nanoparticle-based drugs typically reach their tumour targets. In the current study, they found that

among nanoparticles that do penetrate tumours, more than 95 per cent pass through endothelial cells — not between gaps among those cells.

“Our work challenges long-held dogma in the field and suggests a completely new theory,” says **Abdullah Syed**, a co-lead author on the study and postdoctoral fellow in the lab of **Warren Chan**, a professor at the Institute of Biomaterials and Biomedical Engineering and the Donnelly Centre for Cellular and Biomolecular Research.

“We saw many nanoparticles enter the endothelial cells from blood vessels and exit into the tumour in various conditions. Endothelial cells appear to be crucial gatekeepers in the nanoparticle transport process.”

The journal *Nature Materials* published the findings today.

Syed compares nanoparticles to people trying to get into popular restaurants on a busy night. “Some restaurants don’t require a reservation, while others have bouncers who check if patrons made reservations,” he says. “The bouncers are a lot more common than researchers thought, and most places only accept patrons with a reservation.”

The researchers established that passive diffusion was not the mechanism of entry with multiple lines of evidence. They took over 400 images of tissue samples from animal models, and saw few endothelial gaps relative to

nanoparticles. They observed the same trend using 3D fluorescent imaging and live-animal imaging.

Similarly, they found few gaps between endothelial cells in samples from human cancer patients.

The group then devised an animal model that completely stopped the transportation of nanoparticles through endothelial cells. This allowed them to isolate the contribution of passive transport via gaps between endothelial cells, which proved to be miniscule.

“A better understanding of the nanoparticle transport phenomenon will help researchers design more effective therapies”

The researchers posit several active mechanisms by which endothelial cells might transport nanoparticles into tumours, including binding mechanisms, intra-endothelial channels and as-yet undiscovered processes, all of which they are investigating.

Meanwhile, the results have major implications for nanoparticle-based therapeutics. “These findings will change the way we think about delivering drugs to tumours using nanoparticles,” says **Shrey Sindhwani**, also a co-lead author on the paper and an MD/PhD student in the Chan lab. “A better understanding of the nanoparticle

transport phenomenon will help researchers design more effective therapies.”

The research included collaborators from the Department of Physics (University of Toronto), Cold Spring Harbor Laboratory (New York, USA) and the University of Ottawa.

**When two are better than one —
the Boone and Andrews labs
shed light on why some gene
pairs are retained while
other perish.**



Photo | Wikimedia Commons

When Two are Better Than One: Why Some Gene Duplicates are Retained While Others Perish

By Jovana Drinjakovic
June 25, 2020.

Whole genome duplication followed by massive gene loss has shaped many genomes, including the human genome. Why some gene duplicates are retained while most perish has puzzled scientists for decades.

A Donnelly Centre study, published in *Science*, has found that gene retention depends on the degree of “functional and structural

entanglement”, which measures interdependency between gene structure and function. In other words, while most duplicates either become obsolete or they evolve new roles, some are retained forever because, evolutionarily speaking, they’re simply stuck.

“Why are some duplicates retained while most are eliminated? We tried to find some of the reasons for this

retention to help us understand evolutionary forces that shape genomes,” says **Elena Kuzmin**, a co-lead author of the study and former PhD student of **Charles Boone**, a professor of molecular genetics in the Donnelly Centre, who co-led the study.

The study was also led by **Brenda Andrews**, University Professor and Director of the Donnelly Centre,

and **Chad Myers**, Professor of computer science at the University of Minnesota-Twin Cities.

Whole genome duplication is seen as a major source of raw genetic material for evolution to act on. Duplicated gene copies, also known as paralogs, can be found across eukaryotes, organisms that include single-celled yeasts and all multicellular forms of life. Over evolutionary time, through random mutation, the DNA code of one gene copy diverges from the other until they are no longer recognized as duplicates. They either evolve new roles or waste into oblivion as noncoding DNA.

But some duplicates are retained, suggesting there may be an evolutionary advantage to the organism in keeping both. There is little agreement among scientists about why this might be the case, however. Genome evolution is not easy to study. “None of us were there to see what really happened with these genes,” says Boone. But he believes clues can be gained from studying functional relationships between paralogs and other genes in the genome.

The researchers turned to *Saccharomyces cerevisiae*, or baker’s yeast, whose relatively small genome makes such studies feasible. Most of its 6,000 genes exist as single copies, but 551 paralog pairs have remained from a duplication event some 100 million years ago.

Because paralogs started as

identical gene copies, their roles should to some extent be overlapping, or redundant. This indeed is the case for some yeast paralogs. In their 2016 *Science* paper, the team showed that 331 paralog pairs are redundant so that deleting either gene had no effect on the cells, whereas deleting both reduced their survival. This suggested that some paralogs are retained as essential backup in case either gene copy is lost.

But 240 paralog pairs are non-essential, that is, both can be deleted with no effect on cell survival. To unpick their functional requirement, the researchers looked for a context in which removing both genes is detrimental to cell fitness. They found it in triple mutant yeast lacking three genes—a paralog pair plus another gene. Fitness analysis of 550,000 double and 260,000 triple mutant strains revealed that the non-essential paralogs fall into two basic classes—those that continue to play overlapping roles, and those that have largely diverged in their functions.

A closer look at the genes’ DNA code revealed that the ability of non-essential paralogs to diversify their roles is determined by the molecular structure of the proteins they encode. The authors coined the term “functional and structural entanglement” to describe how much a gene’s cellular function is constrained by physical forces acting within its protein product. Membrane proteins, such as ion channels and receptors, provide examples. These proteins typically

contain multiple hydrophobic, or water-repelling, segments, which allow them to mix with hydrophobic lipid molecules that make up the cell membrane. Mutations to the underlying genes are likely to alter the proteins’ hydrophobic nature, impairing their ability to nestle within the lipid rich membrane which renders them nonfunctional as a result.

Computational modelling performed by **Benjamin VanderSluis**, a former postdoctoral fellow with Myers, aligned with experimental findings.

The greater the structural entanglement, the modelling showed, the greater the chance that a random mutation will harm the protein’s function. Under evolutionary pressure, the sequence of one paralog is maintained while the other one drifts into oblivion. At the other end of the spectrum, paralogs that are least structurally entangled have more freedom to evolve new roles. The middle level is occupied by paralogs with overlapping functions that coexist in a steady state. The entanglement model predicts that some paralog pairs will be maintained indefinitely with overlapping roles. It challenges the widely accepted view that all paralog pairs will eventually revert to a single gene state.

“We show that functional redundancy between paralogs is evolutionarily stable and can exist at steady state”, says Kuzmin, who is now a postdoctoral fellow at McGill University.

The Fraser lab has identified a molecular switch that allows parasites to survive inside hosts without oxygen raising hopes of new treatments.



Structure of the COQ2 enzyme | Fraser lab

No Air, No Problem: Scientists Find Molecular Switch Allowing Parasites to Survive Inside Hosts Without Oxygen

By Jovana Drinjakovic
September 11, 2019.

Around one billion people on the planet are infected with parasitic helminths, round worms that live in soil and colonize human guts through dirty water. The worms owe their ability to survive in the low oxygen environment of the human gut to a unique enzyme variant, Donnelly Centre researchers have found.

The findings raise hopes of new

treatments to quell growing resistance of parasites to available medications. Infections are common in less developed countries where they can leave long-lasting consequences on child development.

“When parasites are outside the body, which they are for a part of their lifecycle, they breathe oxygen just like we do,” says **Andrew Fraser**,

a senior author and a professor of molecular genetics in the Donnelly Centre for Cellular and Biomolecular Research.

“We were trying to understand how these parasites survive inside the human gut where there’s almost no available oxygen.”

The study was also co-led by **Gustavo Salinas**, a professor at

Universidad de la República in Uruguay, and Jennifer Shepherd, a professor at Gonzaga University in the U.S.

The findings have been published in *e-Life*, an online journal for life-sciences.

Most animals, including humans, rely on a molecule called ubiquinone (UQ) to transfer electrons to oxygen in the process of making energy. But when parasitic helminths inhabit their hosts, they switch to an unusual type of anaerobic metabolism that uses another electron carrier, rholoquinone (RQ).

In their previous study, Fraser's team uncovered that UQ and RQ are made from different precursor molecules by the same enzyme called COQ2. But how does COQ2 know to use the UQ precursor when there's oxygen around but use the RQ precursor when there's no oxygen?

"Somehow there has to be a switch," says Fraser. "If we could understand how that switch works and if we could take a small compound and interfere with that switch, prevent it from making RQ, that might be a way to kill a parasite in humans."

First clues emerged when **Michael Schertzberg**, a research technician in the lab, noticed that helminths produce two protein variants of COQ2. The variants are made by alternative splicing, a process through which gene coding segments, or exons, are variably included into templates

for protein synthesis, allowing for diverse proteins to be encoded by the same gene. The two COQ2 variants are identical but for a small part encoded by two mutually exclusive exons, dubbed A and E. These are exactly the same size — flipping from the A variant to the E variant is like switching a block in a complicated Lego structure.

The researchers next engineered *C. elegans* worm strains producing either enzyme variant alone to test their ability to make UQ and RQ. Although not a parasite, *C. elegans* is a highly related helminth that also uses rholoquinone. They found that the worms lacking the E variant lost their ability to make RQ and could no longer survive without oxygen.

Genome scanning across diverse animal lineages further strengthened the idea that the E variant is required for life without oxygen. The E variant is not even encoded in the COQ2 gene of most animals, including humans, who need air to live. It is only found in helminths and a few other species known to make RQ, such as oysters and other marine organisms, where it is likely an adaptation to changing oxygen levels in tidal environments.

Importantly, when they looked at the parasitic helminths *Ascaris* and *Strongyloides stercoralis*, they found that they also make and switch to the E variant when they are inside the host.

June Tan, a lead co-author and an expert in alternative splicing, has rarely seen in helminths two

alternatively spliced variants with such distinct functions, like flipping a switch.

"For me the most surprising finding was how restricted the E variant was to just those species that make RQ," says Tan, who is a postdoctoral fellow the lab.

"We think alternative splicing switches the enzyme core around the catalytic site so that it allows them to use a different precursor molecule to make RQ versus UQ."

When **Margot Lautens**, a PhD student in the lab, computationally laid each variant over the reference molecular structure of the enzyme, she indeed found that the A and E exons encode a core segment which is crucial for the catalytic activity. The researchers think that when oxygen levels dip, the enzyme flips its inner core from the prevalent A form to the less common E form which can make RQ and sustain a parasite's life.

The finding opens a therapeutic opportunity to specifically target the enzyme in the parasite without touching its counterpart in the host.

"If you look at the A form of COQ2, it looks the same in every animal. An inhibitor would act on human too," says Fraser.

"But the E variant has key differences and you could target just that form. This gives us a beautiful way to help us find inhibitors that will hit specifically the E form and that's what we're doing now."



A credit-sized tool developed by the Wheeler team will give new insights into cancer metastasis.

Photo | Michael Dryden

Credit-Card Sized Tool Provides New Insights into how Cancer Cells Invade Host Tissues

By Qin Dai
July 15, 2020.

A group of engineers from the Donnelly Centre have developed a credit-card sized tool for growing cancer cells outside the human body, which they believe will enhance their understanding of breast cancer metastasis.

The device, described in a paper published today in *Science*

Advances, reproduces various environments within the human body where breast cancer cells live. Studying the cells as they go through the process of invasion and metastasis could point the way towards new biomarkers and drugs to diagnose and treat cancer.

“Metastasis is what makes cancer

so deadly,” says **Aaron Wheeler**, a professor of chemistry and the corresponding author of this publication.

“If cancer cells would simply stay in one spot, it would be ‘easy’ to excise them and cure the disease.”

“But when cancer metastasizes,

cancer cells move through the body, making the disease difficult to treat. We decided to apply our expertise in microfluidics to develop a new tool to aid in studying how cancer cells begin to invade into surrounding tissues in the first steps in metastasis.”

Normally metastasis is studied in a petri dish cell culture or in whole animals. However, these model systems present problems in terms of cost, efficiency, or lack of representation.

“An oversimplified system like cells in petri dishes doesn’t mimic what happens in the body, while in an animal model, it’s difficult to isolate and study parameters that govern the invasiveness of a cell.” says **Betty Li**, a senior PhD student and leading author of the paper.

“Our system gives us control over all the specific parameters that we want to look at, while allowing us to make structures that better resemble what happens to the body.”

The device consists of patterned metal electrodes which can move extremely small droplets around through the use of electric fields. By selectively changing the water-repelling properties of the surface at various points, researchers can ‘pinch’ off the water droplets and form precise shapes.

In the paper, the researchers describe how they used a collagen matrix coated with a layer of basal membrane extract to mimic the

structure of the breast tissue seen by breast cancer cells during the first step of metastasis.

By placing cancer cells outside of these tissue mimics, researchers could observe the invasion process in detail, including measurements of speed and location.

“Using the tool we developed, researchers in the future can develop therapeutics that target some of these genes to halt the cancer metastasis

“One interesting thing we observed is that not all cancer cells within the same population have the same invasiveness,” says Li, “Some invaded into the tissue mimics while others did not, which prompted us to look at what gives the invaded cells such an advantage.”

Li and her team extracted cancer cells at various distances from the invasion point and subjected these cells to genetic sequencing.

“We identified 244 different genes that are differentially expressed between the cancer cells that invaded versus the ones that didn’t invade. This means that using the tool we developed, researchers in the future can develop therapeutics that target some of these genes to halt the cancer metastasis.” says Li.

“We think this type of tool will be

quite useful to the community, as cell invasion is important in cancer and also a host of other (non-pathological) processes, like tissue growth, differentiation, and repair.” says Wheeler.

Re-engineered Enzyme Could Help Reverse Damage From Spinal Cord Injury and Stroke

By Tyler Irving
August 24, 2020.

A team of researchers led by University Professor and Donnelly Centre investigator **Molly Shoichet** and from the University of Michigan has redesigned and enhanced a natural enzyme that shows promise in promoting the regrowth of nerve tissue following injury.

Their new version is more stable than the protein that occurs in nature, and could lead to new treatments for reversing nerve damage caused by traumatic injury or stroke.

“Stroke is the leading cause of disability in Canada and the third leading cause of death,” says Shoichet, a professor of chemical engineering and biomedical engineering at U of T’s Faculty of Engineering and senior author on a new study published in the journal *Science Advances*.

“One of the major challenges to healing after this kind of nerve injury is the formation of a glial scar.”

A glial scar is formed by cells and biochemicals that knit together tightly around the damaged nerve. While protective in the short term, a

glial scar can inhibit nerve repair in the long term.

About two decades ago, scientists discovered that a natural enzyme known as chondroitinase ABC — produced by a bacterium called *Proteus vulgaris* — can selectively degrade some of the biomolecules that make up the glial scar.

By changing the environment around the damaged nerve, chondroitinase ABC has been shown to promote regrowth of nerve cells. In animal models, it can even lead to regaining some lost function.

But progress has been limited by the fact that chondroitinase ABC is not very stable in the places where researchers want to use it.

In their latest paper, Shoichet and her collaborators tried a new approach to overcome this instability: they altered the biochemical structure of the enzyme in order to create a more stable version.

“Like any protein, chondroitinase ABC is made up of building blocks called amino acids,” says Shoichet.

“We used computational chemistry to predict the effect of swapping out some building blocks for others, with a goal of increasing the overall stability while maintaining or improving the enzyme’s activity.”

In the end, the team ended up with three new candidate forms of the enzyme that were then produced and tested in the lab. All three were more stable than the wild type, but only one, which had 37 amino acid substitutions out of more than 1,000 links in the chain, was both more stable and more active.

The next step will be to deploy the enzyme in the same kinds of experiments where the wild type was previously used.

Shoichet points to the multidisciplinary nature of the project as a key to its success.

“We were able to take advantage of the complementary expertise of the authors to bring this project to fruition, and we were shocked and overjoyed to be so successful,” she says. “It went well beyond our expectations.”



FACULTY APPOINTMENTS & AWARDS



University Professor
Brenda Andrews completes
third and final term as
Director of Donnelly Centre.

Photo by Mike Schertzberg

Brenda Andrews Completes Term as Director of Donnelly Centre

By Jovana Drinjakovic
August 18, 2020.

University Professor **Brenda Andrews** has much to be proud of as she steps down after 15 years as founding director of the Donnelly Centre for Cellular & Biomolecular Research.

Under Andrews' direction, the Centre has become a fertile training ground for future scientific leaders,

housed in a flagship 21st century science research facility. Public outreach has blossomed, and she's had a powerful impact as a role model and champion for young scientists. Andrews stepped down last month after three successive terms as director.

"The decision to begin my PhD

studies in Brenda's lab almost 30 years ago remains one of the most important and positive decisions I have ever made," says **Vivien Measday**, now an associate professor at the University of British Columbia.

"Brenda inspired me with her outstanding work ethic, unbelievable

efficiency, energy and focus as well as her ability to promote a collaborative research atmosphere with other labs. She has always been and will remain my number one role model for what a female scientist can achieve in Canada.”

Under Andrews’ leadership, the Centre has become a global hub for multidisciplinary research, education and innovation in biomedical science. Andrews also helped establish competitive internal fellowships and awards to attract and honour the best graduate students and postdocs, many of whom have gone on to have successful careers in industry and as independent investigators in world-leading research institutions.

“The Donnelly Centre today is recognized as a shining beacon of excellence for Canadian health research and Brenda as founding director could not be more widely admired and respected,” said former U of T President and Dean of Medicine **David Naylor** during a recent online event that celebrated Andrews’ legacy amid the coronavirus pandemic.

“Her qualities of leadership and good judgment have been widely recognized as well as her scientific rigour and ingenuity. It’s an extraordinary legacy,” said Naylor, who was Dean of Medicine when the Centre was founded and appointed Andrews as its founding director.

Globally recognized for her pioneering research in large scale genetics and cell biology,

Andrews has authored more than 200 scientific articles and reviews and received numerous national and international awards. She was named Companion of the Order of Canada, the highest national honor that can be bestowed on any citizen. Andrews is a fellow of the Royal Society of Canada, an international member of the U.S. National Academy of Sciences and holds the highest academic rank of University Professor, among other honors and appointments.

“The Donnelly Centre today is recognized as a shining beacon of excellence for Canadian health research and Brenda as founding director could not be more widely admired and respected

Bridging the split between basic and applied sciences, Andrews has long supported efforts for the discoveries in the Centre to be turned into medical advances. She spearheaded the launch of the Accelerator for Donnelly Collaboration, a biotechnology incubator for start-ups and companies to partner with the Centre’s investigators. The accelerator was made possible thanks to a generous gift from Terrence Donnelly, whose initial gift also helped found the Centre.

“The past 15 years have been a remarkable journey,” says Andrews.

“These are exciting times for biomedicine, in no small part thanks to the insights and the technological advances made by the Centre’s investigators.”

“Together we have built a vibrant research community and I am tremendously proud of all we have accomplished.”

Andrews has recruited and fostered a community of top researchers from diverse fields of science at all stages in their careers, who are asking some of the biggest questions in biology and inventing technologies to answer them. During her tenure, the Centre’s investigators have transformed our understanding of the core cellular machinery and how it is linked to disease.

Concurrently, the Donnelly Centre has increased female representation among trainees to 40 per cent, while more than half of the global speakers invited to give seminars at the Centre have been women. Science public outreach has also thrived, with the Centre hosting educational events aimed at instilling curiosity and love of science among young Canadians, especially girls.

Andrews has been instrumental from the outset in creating the environment for Donnelly Centre researchers to flourish.

Housed in a stunning building fit for 21st century science, with open concept labs that foster collaboration, the Centre was

envisioned as a modern-day successor to the Banting and Best Department of Medical Research (BBDMR). The iconic BBDMR institute was founded in 1930 by Nobel laureate Frederick Banting and Charles Best on the heels of their insulin discovery; it was the first U of T department dedicated solely to research.

At the turn of last century, late U of T Professor **Cecil Yip** and Professor Emeritus **James Friesen** recognized the need to draw expertise from different fields of science to fully harness the potential of rapidly evolving genomic technologies in health research.

“Together we have built a vibrant research community and I am tremendously proud of all we have accomplished

Andrews, who previously served as Chair of BBDMR and Chair of the Department of Molecular Genetics, oversaw the integration of the BBDMR labs with research teams from the Faculties of Medicine, Engineering and Arts and Science into the newly founded Donnelly Centre in 2005. She also led the recruitment of top research talent, which has continued apace in spite of the COVID-19 pandemic.

Andrews completed her doctoral and postdoctoral training at U of T and the University of California San Francisco, respectively, returning to

U of T as an assistant professor in the Department of Medical Genetics (now Molecular Genetics), which she also chaired from 1999-2004.

A scientific community builder, Andrews contributes her time and expertise to various organizations at home and abroad. She is the founding editor-in-chief of the journal *Genes|Genomes|Genetics*, an open access journal of the Genetics Society of America. She is also as a member on the Governing Council of the Canadian Institutes for Health Research, the primary federal funding agency for medical research, and she served as the inaugural director of the Genetic Networks program at the Canadian Institute for Advanced Research.

Andrews' final term as director ended on June 30, 2020. Her long-time collaborator, Prof. **Charles Boone**, will serve as Interim Director until the appointment of new Director by the Faculty of Medicine.



Molly Shoichet Receives Gerhard Herzberg Canada Gold Medal, Canada's Highest Honour for Science and Engineering Research

By Liz Do
November 10, 2020.

University Professor **Molly Shoichet** (ChemE, BME, Donnelly Centre), a world-leading researcher in tissue engineering, has received the Gerhard Herzberg Canada Gold Medal for Science and Engineering — Canada's most prestigious

award for science and engineering research.

The Herzberg Gold Medal is awarded by the Natural Sciences and Engineering Research Council (NSERC) in recognition

of research contributions characterized by both excellence and influence.

"I was completely overwhelmed when I was told the good news," says Shoichet. "There are so many

exceptional people who've won this award and I admire them. To think of my peers putting me in that same category is really incredible."

A pioneer in regenerative medicine, tissue engineering and drug delivery, Shoichet and her team are internationally known for their discovery and innovative use of 3D hydrogels.

"One of the challenges facing drug screening is that many of the drugs discovered work well in the lab, but not in people, and a possible explanation for this discrepancy is that these drugs are discovered in environments that do not reflect that of the body," explains Shoichet.

Shoichet's team has invented a series of biomaterials that provide a soft, three-dimensional environment in which to grow cells. These hydrogels — water-swollen materials — better mimic human tissue than hard two-dimensional plastic dishes that are typically used. "Now we can do more predictive drug screening," says Shoichet.

Her lab is using these biomaterials to discover drugs for breast and brain cancer and a rare lung disease. Shoichet's lab has been equally innovative in regenerative medicine strategies to promote repair of the brain after stroke and overcome blindness.

"Everything that we do is motivated by answering a question in biology, using our engineering and chemistry tools to answer those questions," says Shoichet.

"The hope is that our contributions will ultimately make a positive impact in the cancer community and in treating diseases for which we can only slow the progression rather than stop and reverse, such as with blindness."

"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 also an advocate for and advisor on the fields of science and engineering. She has advised both federal and provincial governments through her service on Canada's Science, Technology and Innovation Council and the Ontario Research Innovation Council. From 2014 to 2018, she was the Senior Advisor to the President on Science & Engineering Engagement at the University of Toronto. She is the co-founder of Research2Reality, which uses social media to promote innovative research across the country. She also 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 a foreign member of the U.S.

National Academy of Engineering, and fellow of the Royal Society (UK) — the oldest and most prestigious academic society.

In 2014, Shoichet was appointed University Professor, a distinction held by less than two percent of the faculty at the University of Toronto. 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.

"What's really wonderful for me in getting this Herzberg Gold Medal is the recognition of the importance of interdisciplinary research, and the recognition of the team — of the brilliant graduate and undergraduate students, post-doctoral fellows, technicians and collaborators with whom I have the privilege to work," says Shoichet.

"I'm so grateful to work with amazing people who bring their creative ideas and challenge me to think more innovatively."

"Professor Shoichet is a trailblazer and an inspiration to the engineering and science community, here at U of T, across the country and around the world. Her research continues to advance knowledge towards practical, and incredibly vital, applications in human health," says U of T Engineering Dean Chris Yip. "On behalf of the Faculty, my enthusiastic congratulations to Molly on receiving this tremendous honour."

Michael Sefton Elected to the U.S. National Academy of Engineering

By Carolyn Farrell
February 7, 2020.

University Professor and Donnelly Centre investigator **Michael Sefton** has been elected as an international member of the United States National Academy of Engineering (NAE) “for advances in biomaterials and tissue engineering through cell microencapsulation and leadership of large-scale research initiatives.”

The NAE provides engineering leadership in service to the United States and globally; its members rank among the world’s most accomplished engineers.

Sefton, a University Professor at the Institute of Biomaterials & Biomedical Engineering (IBBME), the Michael E. Charles Professor in the Department of Chemical Engineering & Applied Chemistry and Executive Director of Medicine by Design, is a world leader in biomaterials, biomedical engineering and regenerative medicine. He was one of the first to combine living cells with polymers with the aim of creating artificial tissues, effectively launching the field now known as tissue engineering.

Sefton’s lab, has created

biomaterials that actively promote the growth of blood vessels, accelerating wound healing and supporting the development of lab-grown tissues. These novel materials are the first of a new class of biomaterials with drug-like activity, but without any drugs (or cells) included within the material. This opens up a world of possibilities for creating drug delivery systems and regenerating tissues without cells.

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

serves as executive director of Medicine by Design, a U of T initiative accelerating discoveries in regenerative medicine to improve treatments for conditions such as heart failure, diabetes and stroke.

Sefton has received several of the most distinguished awards in engineering and biomedicine, including the U.S. Society for Biomaterials Founders Award, the Killam Prize in Engineering, the Engineers Canada Gold Medal, the Lifetime Achievement Award from the Tissue Engineering and Regenerative Medicine International Society and the Terumo Global Science Prize. He is a fellow of the Royal Society of Canada, an international member of the U.S. National Academy of Medicine, and an Officer of the Order of Canada.





Professor Charlie Boone named inaugural Banting & Best Distinguished Scholar.

Photo | Calvin Thomas

Charlie Boone Named Inaugural Banting & Best Distinguished Scholar

By Jovana Drinjakovic
October 26, 2020.

Professor and interim Director of the Donnelly Centre **Charlie Boone** is the recipient of the first Banting & Best Distinguished Scholar award which recognizes top researchers at the Temerty Faculty of Medicine who are having life-changing impact through their discoveries.

The award was established to support outstanding researchers who have completed terms as Tier 1 Canada Research Chair, a prestigious appointment by the federal government reserved for scientists and scholars who are world-leading in their fields.

Professor Boone's title as the inaugural Banting & Best Distinguished Scholar marks the centenary of insulin discovery by Frederick Banting and Charles H. Best (who was incidentally a classmate of Boone's grandfather at medical school). The groundbreaking discovery launched

the Banting & Best Department of Medical Research, which gave way to the Donnelly Centre — with Boone at its helm since July this year.

View this interactive timeline to learn more about the history of the Donnelly Centre.

The Banting & Best Distinguished Scholar Program was made possible by the transformational gift from the Temerty Foundation to U of T's Faculty of Medicine.

Boone was named Canada Research Chair in Proteomics, Bioinformatics and Functional Genomics in 2007 and held the appointment for the maximum two seven-year terms. He previously held the same title at the Tier 2 level, which recognizes top researchers at early stages of their careers.

Globally renowned for his research in large scale genetics, Boone has made pioneering contributions to understanding the genotype to phenotype relationship, which seeks to explain how genes encode the traits of an organism. With his long-term collaborator **Brenda Andrews**, University Professor and inaugural director of the Donnelly Centre, Boone has established an automated high-throughput platform for measuring how different genetic mutations and drug compounds affect cellular fitness.

This research has opened the door to a new way of understanding how genes contribute to disease, with a potential for developing finely-

tuned therapies. He has authored numerous research articles, many in top scientific journals, and his research was also featured in mainstream media, including *The Globe and Mail* and *Quanta Magazine*.

For his research excellence Boone has received awards and appointments, at home and abroad. These include the Premier's Research Excellence Award, the Edward Novitski Prize for creativity in genetics from the Genetics Society of America, the Emil Christian Hansen Award for Microbiology from the Carlsburg Foundation in Copenhagen (jointly won with Andrews), as well as the Ira Herskowitz Award in yeast genetics. He was twice the International Research Scholar of the Howard Hughes Medical Institute in the U.S. and holds the Anne and Max Tanenbaum Chair in Molecular Medicine at the Temerty Faculty of Medicine.

Boone is Fellow of the Royal Society of Canada and Fellow of the Canadian Institute for Advanced Research (CIFAR) in the Fungal Kingdom: Threats and Opportunities program, and he was previously Fellow and co-Director of CIFAR's Genetics Networks Program. He is also Fellow of the American Academy of Microbiology and of the American Association for the Advancement of Science.

A leader in his field, Boone also contributes to the research community by helping organize flagship meetings and conferences

in yeast genetics as well as serving on editorial boards of various scientific journals.

Boone completed his undergraduate training in chemistry and mathematics at Queens University and obtained a PhD in biology from McGill University. After launching his independent research career as Assistant Professor at Simon Fraser University, he moved to his alma mater before joining U of T, first as Associate Professor and then Professor of molecular genetics in the Banting and Best Department of Medical Research. He's been with the Donnelly Centre since 2004 as one of its founding faculty members, following the integration of the BBDMR into the newly minted institute. When Andrews completed her leadership terms earlier this year, Boone took over the reins as the Centre's interim director.

A builder of collaborative science, Boone has forged partnerships with international institutions including the Chemical Genomics Research Group at the RIKEN Center for Sustainable Resource Science in Tokyo and the Zhejiang University School of Medicine in China where he holds adjunct positions.



Genome Scientist Tim Hughes Awarded Canada Research Chair

By Jovana Drinjakovic
December 16, 2020.

“We need something cheerful in our lives right now,” says **Tim Hughes** as he beams from the screen, alluding to the dazzling backdrop aimed at brightening the pandemic gloom.

Hughes, a professor of molecular genetics in the Donnelly Centre for Cellular and Biomolecular Research

at the Temerty Faculty of Medicine, hasn't left his house much since the start of the coronavirus crisis. He spends his days on video calls, overseeing research and boosting the morale of his team of computational biologists who, like him, are fortunate to be able to work safely from home.

As the world continues to grapple with coronavirus, they are looking for answers to the fundamental question of how cells interpret the information in their genomes. Knowing this would allow scientists to not only predict how genetic mutations cause disease, but also how pathogens hijack our genes to

their own benefit to potentially help us fight future outbreaks.

The globally renowned genome scientist, and one of the world's most cited researchers, according to data company Clarivate that specializes in academic publishing, Hughes has now been named Tier 1 Canada Research Chair in Decoding Gene Regulation, a prestigious appointment by the federal government reserved for scientists and scholars who are world-leading in their fields.

The appointment will enable him to remain at the forefront of the exploration of the human genome, which remains no less mysterious than when it was first sequenced almost two decades ago.

“Our overarching goal is to find out how cells look at their DNA and figure out what to do about it,” says Hughes, who is also John W. Billes Chair of Medical Research. “One problem is that we don't even have a good handle on how the cells know where the genes are.”

The 20,000 or so protein-coding genes make up a mere two percent of the total human DNA. But Hughes' attention is focused on the remaining 98 per cent of the genome which holds the clues to how the genes are regulated.

How should a cell be?

Whether a cell resides in the brain or in the kidney, its genome is the same as in all other cells in the body. A cell's identity and function stem

from the genes that are switched on, or expressed, in it at any given time, in a process orchestrated by thousands of DNA-binding proteins.

Scattered across the genome, mostly in the non-coding part, are “regulatory regions”, stretches of the DNA code, or sequence, on average 150 basepairs long, which contain landing sites for various DNA binding proteins. Among them are the transcription factors which directly switch genes on or off by binding to sequence “motifs” often only 5-10 basepairs in length.

Humans have 1500 transcription factors, each binding to one or a few motifs, which can be repeated in the genome between tens and hundreds of thousands of times. It's thought that there are two million regulatory regions, each containing a distinct set and arrangement of motifs and thus recognized by numerous transcription factors, that control gene expression in some way.

The goal of matching transcription factors to their motifs—and ultimately the genes they regulate—has turned out career-defining for Hughes.

“I did not know that it would turn out to be much more difficult than anything else and that I would be basically working on the same problem for my entire life,” says Hughes.

A part of the problem is that for any gene there can be dozens of distinct regulatory regions. And since each regulatory region is unique, this

makes it difficult to draw general conclusions from studying individual genes and transcription factors that regulate them, which is how most research in the field is done.

“This seems like it would be an almost impossible starting point but it's really important because these regulatory sequences are where most of the functional DNA in human is located and in many other species,” he says, referring to genome sequencing studies that have identified numerous associations between regulatory regions and various diseases.

Which is why Hughes' approach has been to meticulously go through each and every human transcription factor and identify their landing sites.

The work involves fishing out DNA motif sequences bound by different transcription factors and using computational modelling to predict which genes they regulate. They have so far identified motifs for thousands of transcription factors in diverse species, including hundreds in human, which are stored in one of the largest open-access databases of its kind, Cis-BP.

Genome interpreter

Hughes did not set out to become a biologist. He first studied physics, at the University of Iowa, but switched halfway to music, which had always been a big part of his life. After graduating and realizing that being a professional musician “was too much work for the money and that

I'd be better off having a day job and playing music at night", he obtained another degree, in electrical engineering.

An interest in molecular biology came through friends. Thanks to good grades and a lab job, he earned a PhD place at the renowned Baylor College of Medicine in Houston, TX, where he studied telomeres, the chromosomal ends involved in cellular aging.

Next came a postdoctoral stint with Rosetta InPharmatics, a Seattle startup co-founded by four academics, including a Nobel laureate. The company was using the then cutting-edge DNA microarray technology to measure expression levels of thousands of genes at once.

He published a landmark paper showing that hundreds of genetic mutations and drug molecules induce distinct gene expression patterns in otherwise identical cells and that these patterns can offer insights into how genes cooperate under different scenarios. The experience propelled Hughes to the forefront of genomic revolution that saw biology transform into a data science—and one he had an edge in thanks to his unconventional training.

Hughes joined U of T as faculty in 2001, starting his own lab at the Banting and Best Department of Medical Research before moving in 2004 to the newly founded Donnelly Centre.

Beyond motif mapping, the lab's varied research includes the 2018 publication of the first complete chromosome map of the cannabis genome to aid the investigation of the plant's potential in medicine and industry.

In other projects, they revealed clues to how genomes evolve. They found evidence suggesting that the largest family of human transcription factors, comprising 700 members, evolved to silence DNA elements inserted by ancient viruses and that over time these sequences became coopted into regulatory motifs for the human genes.

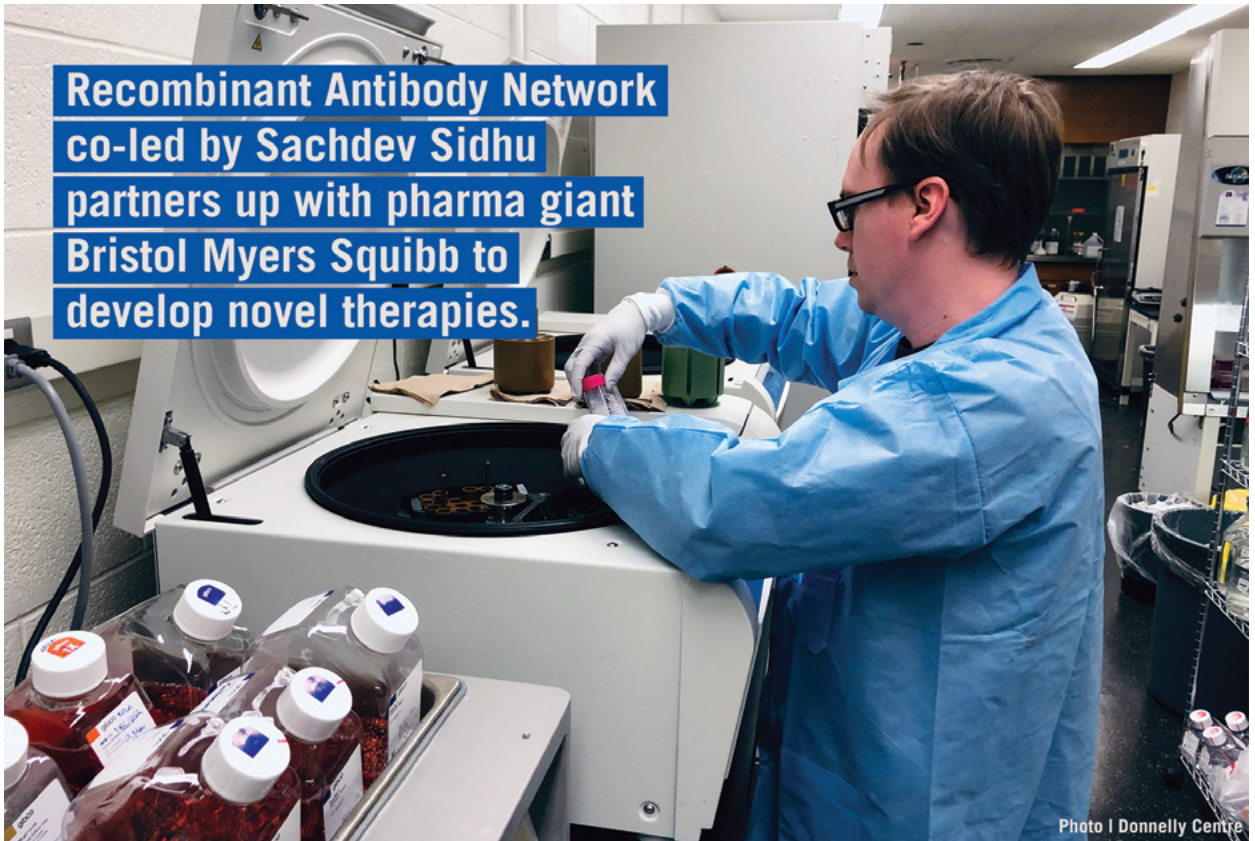
More recently, they found that several large transcription factor families that are found across species bind different motif sequences much more often than previously thought, which could help explain how species evolve at the molecular level.

Initially mislabeled as "junk DNA", the vast swaths of the noncoding genome have proven to be anything but. But with so much still unknown, Hughes might have to spend the rest of his career figuring it out.

A scanning electron micrograph (SEM) of a biological structure, possibly a cell or a small organism. The central part is a dense, rounded mass composed of many small, rounded units. From this mass, numerous long, thin, radiating filaments or processes extend outwards, creating a star-like or fan-like appearance. The background is a solid blue color.

RESEARCH

TRANSLATION



Recombinant Antibody Network Partners with Bristol Myers Squibb to Develop Novel Therapies

By Jovana Drinjakovic
May 13, 2020.

The Recombinant Antibody Network (RAN), a consortium comprising research groups from the University of Toronto, UC San Francisco (UCSF) and the University of Chicago have announced that they have entered into a second research

collaboration with Bristol Myers Squibb, aimed to create and develop high-performance recombinant antibodies against diverse targets in human cells. The first collaboration was launched in 2015 with Celgene, later acquired by Bristol Myers

Squibb in 2019.

Under the new agreement pioneered by **James Wells** of UCSF with Bristol Myers Squibb, Bristol Myers Squibb will further invest in the RAN's state-of-the-art antibody

engineering program to expand target discovery to oncology, immunology, and neurology. “Our partnership with Bristol Myers Squibb is a testament to the RAN’s ability to produce antibody molecules with a strong therapeutic potential,” says **Sachdev Sidhu**, one of the founding members of the RAN and a co-founder of the Toronto Recombinant Antibody Centre (TRAC) at U of T’s Donnelly Centre where he is also a professor of molecular genetics.

As one of the largest academic-industry partnerships, the collaboration also offers unique opportunities for trainees to be involved in cutting-edge research with clinical application. Additionally, the collaboration provides an opportunity for potential sharing of research performed by both RAN scientists and Bristol Myers Squibb scientists. RAN has published dozens of publications resulting from their new innovative science and discovery at all four institutions.

“This is a spectacular example of how industry and academics can work hand-in-hand to discover new medicines,” says Wells, a co-founder of RAN and a professor of pharmaceutical chemistry in the UCSF School of Pharmacy. “RAN project teams include scientists, students, post-docs and staff at university collaborating with Bristol Myers Squibb scientists to consult on projects and discuss progress on a monthly basis.”

Antibodies as therapeutics

Antibodies are naturally produced by the body to fight infections. Thanks to advances in protein engineering, scientists can now create tailored synthetic antibodies to inhibit disease processes or mark cancer cells for destruction by the immune system.

“This is a spectacular example of how industry and academics can work hand-in-hand to discover new medicines

Over the past two decades, antibodies have emerged as the fastest-growing class of therapeutic molecules with more than 50 approved so far. Unfortunately, antibody development remains an imprecise science, conducted on a case-by-case basis.

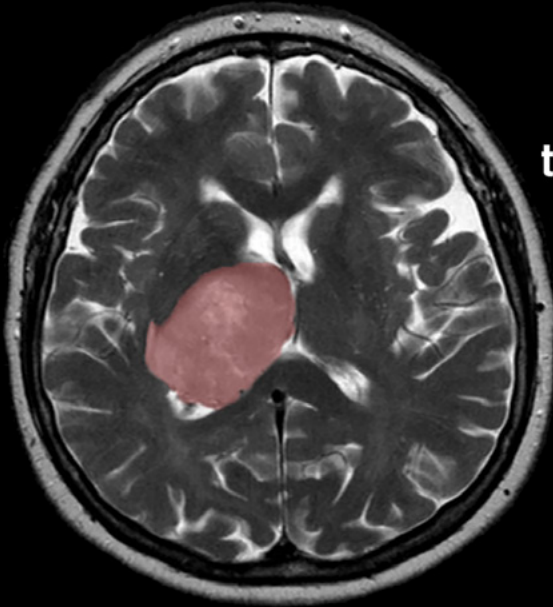
As veterans of the former Protein Engineering Department at Genentech Inc., Sidhu, Wells and **Anthony Kossiakoff**, a professor of biochemistry and molecular biology at the University of Chicago, founded RAN in 2012 to make antibody design and production more efficient.

The consortium has developed a fully automated, high-throughput antibody engineering platform and has generated thousands of antibodies against hundreds of cell surface proteins. The RAN

generates recombinant antibodies from cloned synthetic genes using phage display technology that are selected for high performance. The ongoing partnership with Bristol Myers Squibb will enable the RAN to continue to develop and apply cutting-edge technologies for the discovery of new cell surface targets and selection of clinically promising antibodies, as well as to expand research collaboration with the disease biology communities at the three universities.

“We created the RAN to address a large, unmet need in both research tools and therapeutic antibody development,” said Kossiakoff, from UChicago. “The RAN will continue to solve the problems that are inherent in traditional antibody approaches, and help to expand treatments for a variety of diseases, including cancer.”

**Donnelly spin-off
Empirica Therapeutics
acquired by U.S. firm
to develop immunotherapy
for brain cancer.**



Brain scan with a tumour highlighted in red | Wikimedia Commons

Donnelly Spin-off Empirica Therapeutics Acquired by U.S. Firm to Develop Immunotherapy for Glioblastoma

By Jovana Drinjakovic
June 30, 2020.

Empirica Therapeutics, a startup co-founded by Donnelly Centre investigator **Jason Moffat** was acquired by Century Therapeutics, a U.S. based company developing off-the-shelf cell therapy products for cancer. Century will develop Empirica's proof-of-principle treatment for glioblastoma, an aggressive form of brain cancer,

into therapy that can be tested on patients.

Moffat co-founded Empirica in 2018 with Dr. **Sheila Singh**, professor in the Department of Surgery at McMaster University, to leverage their combined expertise in cell engineering, functional genomics and brain tumour modelling. The

teams recently demonstrated the potential of CAR-T cell therapy, in which immune cells are instructed to kill tumour cells, for the treatment of glioblastoma in preclinical models, as published in a May 2020 *Cell Stem Cell* paper.

“Recent advances in immunotherapy have offered

hope to patients with previously untreatable cancers,” says Moffat, a professor of molecular genetics at U of T and the Canada Research Chair in Functional Genomics of Cancer who served as Empirica’s Chief Scientific Officer. “We hope that our approach of specifically targeting glioblastoma cells with CAR-T therapy will give the patients a better quality of life and increase their chances of survival.”

Philadelphia-based Century Therapeutics will further develop this type of treatment for patients. Backed by Bayer, Fujifilm, and Versant Ventures, the company specializes in developing cell therapies from induced pluripotent stem cells (iPSCs) that have been genetically engineered to avoid immune rejection. Century is working to harness the power of stem cells to develop curative cell therapy products for cancer that overcome the limitations of first-generation cell therapies.

Chimeric antigen receptor T cell (CAR-T) therapy involves genetically engineering a patient’s immune T cells to target and bind to a specific protein present on cancer cells directly and eliminate them. Century’s technology skirts the need to collect patient’s own immune cells thanks to its ability to manufacture allogeneic, or “off-the-shelf”, T cells that can be implanted without rejection.

“Our team is excited to become part of Century Therapeutics, whose iPSC-derived allogeneic cell therapy platform is creating promising

treatments for patients who need them most,” says Singh, who is also a Canada Research Chair in Human Cancer Stem Cell Biology and served as Empirica’s Chief Executive Officer.

Now known as Century Therapeutics Canada, the new subsidiary will be based at McMaster Innovation Park.

Empirica’s first CAR-T program was focused on a protein called CD133, which was the first brain tumor initiating cell marker discovered by Singh while she was a PhD student at the University of Toronto. Subsequent work by both the Singh and Moffat groups led to a deeper functional understanding of CD133 and the development of an antibody that binds CD133 and marks cells for therapy.

When used in mice with human glioblastoma, CD133-targeting CAR-T therapy was considered a success due to reduced tumor burden and improved survival. These pre-clinical results were partly supported by the Terry Fox Research Institute New Frontiers Program Project Grant awarded to a multidisciplinary team of scientists including Singh and Moffat.

Glioblastoma is the most common and aggressive form of brain cancer owing to tumour heterogeneity at the molecular level and its ability to evolve into new forms that resist therapy. Standard treatment involves surgery, radiation and chemotherapy but most patients relapse within seven to nine months, while median survival between


diagnosis and death has not extended beyond 16-20 months over the past decade.

CAR-T will be delivered in recurrent glioblastoma patients after Moffat and Singh’s teams found that a population of CD133 positive glioblastoma cells remain following initial treatment.

“If we can hit those cells at minimal disease, we should buy the patient more time”, says Moffat. “And hopefully we’ll find a way to figure out how to combine multiple CAR-Ts, for example, by combining CD133 and other targets to potentially even cure the disease.”

Empirica Therapeutics was supported by investments from U of T’s strategic partners, the Centre for Commercialization of Antibodies and Biologics and the Centre for Commercialization of Regenerative Medicine. “We are proud to have been involved with the launch and growth of Empirica,” said Rob Verhagen, former CEO of CCAB.

“The outcome with Century marks another stride in building a productive life science industry at U of T and McMaster and we look forward to seeing this valuable research benefiting patients in the future,” he said. The startup was also supported by the McMaster Industry Liaison Office and the Ontario Bioscience Innovation Organization through important connections to relevant business networks and partners.



A drug stimulation of neural stem cell repair developed by the Morshead team shows promise for childhood brain injury.

Illustration | Pixabay

Drug Stimulation of Neural Stem Cell Repair Leads to Promising Impact on Treatment of Childhood Brain Injury

By Julie Crijen
July 27, 2020.

Through a cross-species study of metformin, a common drug used to treat Type 2 diabetes, a team of researchers and clinicians from the Donnelly Centre and The Hospital for Sick Children (SickKids) has shown that it could one day be possible to repair brain injury using

resident cells in the brain.

“No one’s actually shown before that you can take a drug where there’s a known mechanism on endogenous stem cells and demonstrate that it’s even possible to induce brain growth and positive recovery,” says **Donald**

Mabbott, Program Head and Senior Scientist in the Neurosciences & Mental Health program at SickKids, and co-author of a study published in *Nature Medicine* on July 27.

Mabbott says metformin is a potential game-changer in terms

of how childhood brain injury is treated.

“We’re really moving from a model that says ‘let’s help children manage and compensate for their injury,’ to ‘let’s actually treat the injury itself in an active way by harnessing the brain’s own capacity for repair,’” says Mabbott, who is also a professor of psychology at U of T.

The published research showed that metformin has positive sex-dependent effects on neurogenesis, which is the process of growing neurons in the brain, and cognition in animals, while also demonstrating that it is safe to continue into a Phase III clinical trial on humans. The human participants in this study were paediatric brain tumour survivors who had received cranial radiation.

“This study is so novel compared to most studies because it looked at both animal models and human participants. And we found these really consistent and interesting effects in terms of memory and brain recovery,” says Medicine by Design-funded researcher and study co-author **Cindi Morshead**, a professor at the Donnelly Centre for Cellular and Biomolecular Research and chair of the Division of Anatomy in the Department of Surgery at U of T.

“This pre-clinical work in animal models will inform the design of the new study, currently in place, to help the brain recover from injury,” says Morshead.

Morshead says that she is excited by not only the promising results of the study, but also the way its novel design encouraged clinical translation.

“There’s a lot of history of pre-clinical models not working – drug therapies that go to the clinic and then don’t make it to the next phase. That can be devastating, for a lot of reasons. But I think, in us combining human and animal work, it really promoted the translation of this work into human testing,” Morshead says.

Medicine by Design funding was instrumental to enabling this study. In a past multi-disciplinary project led by **Gary Bader**, a professor at the Donnelly Centre and the Department of Molecular Genetics, U of T – and also involving **Freda Miller**, Senior Scientist, Neurosciences & Mental Health program, SickKids, and Morshead, both co-authors on the *Nature Medicine* publication – the team mapped brain development over time using single cell genomics. Insights into the circuits that control brain tissue growth led to the identification of compounds that can stimulate resident stem cells to promote brain tissue repair, including metformin.

“I am so excited by this paper since it describes a potential endogenous stem cell-based therapy for brain disorders that are currently untreatable,” says Miller. “And, just as importantly, the metformin story provides a classic example of why we need to support basic research, and why working

in collaborative teams is essential. The original finding that metformin recruits endogenous brain stem cells came from fundamental studies on how stem cells build the brain developmentally, and then it was moved forward to animal models and humans by highly interdisciplinary scientists and clinicians like Dr. Morshead and Dr. Mabbott.”

Miller is continuing her work to develop endogenous repair strategies for both brain and muscle in another Medicine by Design-funded team project.

At the core of Medicine by Design’s team projects is convergence — bringing together experts from a range of disciplines including stem cell biology, computational science, biomedical engineering and clinical medicine. The *Nature Medicine* study exemplifies the translational impact that a multi-disciplinary team-based approach can have, particularly when pre-clinical and clinical studies are run in parallel.

This study presents important evidence that stimulating resident stem cells is a feasible approach for tissue repair in settings where regeneration does not readily occur. And, since metformin is an approved drug, the time line for further clinical testing and regulatory approval could be accelerated.

The results from both the rodent and human trials have informed a Phase III clinical trial on paediatric brain tumour survivors treated with cranial radiation currently starting at 14

hospitals in Canada and Australia.

In the lab, investigators found that metformin enhanced the recovery of endogenous neural precursor cells (NPCs) in the dentate gyrus (DG), a part of the brain that plays a critical role in learning and memory. But the results were sex-dependent: Metformin was sufficient to rescue neurogenesis and behaviour in females, but not males.

In addition to the results to the lab study, a concurrent study with 24 children found that metformin is safe to use, with no significant adverse events reported, and is well tolerated by this population.

Both Mabbott and Morshead say their work is motivated not just by the novel science of activating cells that are already resident in the brain to repair injury, but also by their desire to offer hope to a vulnerable population.

“Working as a clinical psychologist with families for 20 years, it was really the families that motivated me – in fact, they challenged me,” says Mabbott. “My job was to tell parents that while their child was successfully treated for brain cancer there was a cost – as their child will have learning problems, cognitive disabilities, and some will never live independently. It was a parent who said to me, ‘That’s not good enough, you have to figure out a way to help our kids recover better.’ That’s what motivated me to start to look at how to harness brain plasticity for repair.”

“Until recently, our after-care

programs were offering very little to children suffering the consequences of radiation treatment to their brain,” says **Eric Bouffet**, an investigator on the study and Director of the Brain Tumour program, Haematology/Oncology, and Senior Associate Scientist, SickKids. “This study suggests that we can repair some of the damage associated with radiation to the brain, and children with brain tumours worldwide may potentially benefit from this discovery.” Dr. Bouffet is also a professor of paediatrics at U of T.

For Medicine by Design, accelerating the translation of new regenerative medicine therapies into patient impact is a strategic priority. And the implications of this work go beyond childhood brain tumour survivors, says Morshead. Toronto researchers are also looking at metformin and cerebral palsy, and metformin as a preventative treatment for cranial radiation.

Northern Biologics Inc., a Donnelly Centre and UHN spin-off and developer of antibody-based therapeutics, acquired by Boehringer Ingelheim

Northern Biologics Inc., a Donnelly Centre and Univesity Health Network spin-off and developer of antibody-based therapeutics, was acquired today by Boehringer Ingelheim (BI), the world's largest private pharmaceutical company.

Northern Biologics was the first modern UHN spin-off backed by venture capital. Its acquisition follows in the footsteps of a string of similar successes for UHN spin-offs created by UHN's Technology Development and Commercialization office, including AVROBIO (link is external) and BlueRock Therapeutics (link is external).

Northern Biologics was founded in 2014 through the biggest biotech deal in Canada at the time. It was created based on licenses for intellectual property developed by Donnelly Centre investigators Drs. **Sachdev Sidhu** and **Jason Moffat**, Princess Margaret Cancer Centre Senior Scientists Drs. **Benjamin Neel** (currently at the Perlmutter Cancer Center), **Brad Wouters** and **Robert Rottapel**.

Northern Biologics has pursued the development of new drugs and a

platform for antibody generation. These efforts are advancing antibody-based treatments for cancer and fibrosis, with a focus on the emerging field of the tumor microenvironment.

As with Bluerock Therapeutics, Northern Biologics operations have been located at the Princess Margaret Cancer Research Tower in the MaRS Discovery District since its founding. This enables close collaboration between the company and UHN's research community. Through this work, Northern Biologics has discovered and developed two programs acquired by Boehringer Ingelheim, and these assets are now progressing toward human clinical trials at UHN hospital sites, which will benefit local patients first.



The Sefton team improves transplantation success rate of artificial islets for treatment of diabetes.

Artificially grown islets | Sefton Lab

Researchers Develop Method to Improve Artificial Islet Transplantation Success Rate

By Qin Dai
January 17, 2020.

Researchers from the Donnelly Centre, Institute of Biomaterials Biomedical Engineering (IBBME), and Chemical Engineering have developed a method to fine-tune the cellular composition of artificial islets – the organ responsible for

regulating blood glucose in the body. This advance could improve the success of implantable islets to treat people living with diabetes. The study was led by senior graduate student **Alexander Vlahos** in University Professor **Michael**

Sefton's lab, and the findings were recently published in the journal *Biomaterials*.

In a healthy individual, pancreatic islets are responsible for secreting insulin – a vital molecule that

regulates glucose level in the human body. This function is severely dampened in those living with diabetes, where significantly lower insulin production can lead to blindness or kidney failure.

Recent advances have enabled researchers to implant artificial islets (called pseudo-islets) directly under the skin to regenerate normal glucose modulation in animals. This provides a longer lasting and hands-off method for diabetes management as opposed to repeated insulin injection.

“The success rate of transplantation is dependent on the health of the pseudo-islet,” says Vlahos, the lead author of the publication. “Most of the islet cells die soon after transplantation. In our study, we developed a method to fine-tune the size and composition of the pseudo-islet to improve the success of implantation.”

The researchers first harvested donor islets and isolated the cells responsible for insulin production. The key was to next recombine them in a 3D environment to resemble an islet. These artificial islets were then reintroduced into a diabetic animal to restore glucose level. The authors also observed proper blood vessel formation, a hallmark of healthy regeneration of an organ.

“The next step is to evaluate the therapeutic impact of human artificial islets,” says **Sean Kinney**, a co-author on the study. “The ultimate goal is to implant these islets into humans and have them

last a decade. But there’s still quite a few barriers we have yet to overcome.”

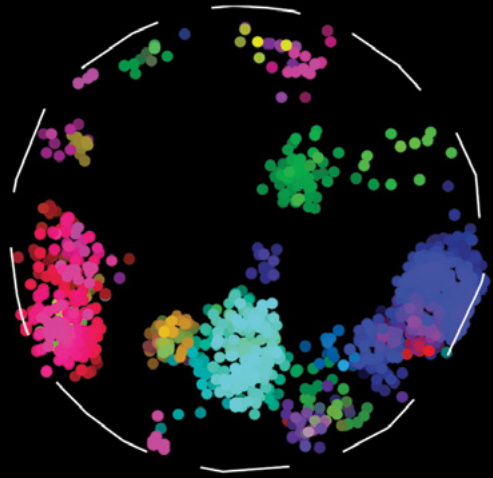
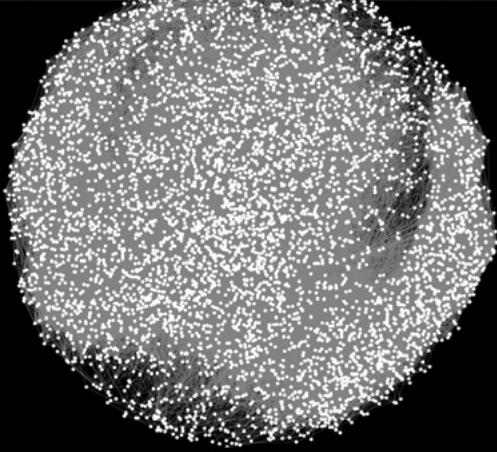
Improvement to transplantation success is crucial for its translation into the clinic. Due to the scarcity of islet donors, this is not yet a widely adaptable method. Normally one islet transplantation would require three donors, but if the engraftment rate is better, three donors could be reduced to one. This can effectively increase the number of patients this method can serve.

“Creating artificial islets gives us the opportunity to create an organ that is better than what nature has provided,” says Sefton, the corresponding author on this research. “Islets have evolved to control our blood sugar and we have learned to transplant them. We can now engineer them to be better than nature when transplanted – to reduce their oxygen consumption per unit of insulin produced or to better withstand the host response.”



COLLABORATION HIGHLIGHTS

The Roth lab and colleagues at Harvard University created the world's largest map of protein contacts.



Human protein interaction diagrams | Roth lab

World's Largest Map of Protein Connections Holds Clues to Health and Disease

By Jovana Drinjakovic
April 8, 2020.

The human body is composed of billions of cells, each of which is made and maintained through countless interactions among its molecular parts. But which interactions sustain health and which ones can cause disease when they go awry? The human genome project has provided us with a

“parts list” for the cell, but only if we can understand how these parts go together, or interact, can we really begin to understand how the cell works and what goes wrong in disease.

To answer these questions, scientists needed a reference map

of interactions—an interactome—between gene-encoded proteins, which make up cells and do most of the work in them.

Almost a decade in the making, the human protein map is now available thanks to a joint effort, involving over 80 researchers in the United States,

Canada, Spain, Belgium, France and Israel, led by **Marc Vidal**, **David Hill** and **Michael Calderwood**, at the Center for Cancer Systems Biology (CCSB) at Dana-Farber Cancer Institute, and **Frederick Roth**, a professor of molecular genetics and computer science at the Donnelly Centre.

The largest of its kind, the **human reference interactome** (HuRI) map charts 52,569 interactions between 8,275 human proteins, as described in a study published in *Nature*.

Humans have about 20,000 protein-coding genes but scientists still know remarkably little about most of the proteins they encode. Fortunately, this information can be gleaned from interaction data thanks to the “guilt by association” principle, according to which two proteins that have similar interacting partners are likely involved in similar biological processes.

“We can use our human interactome map to predict protein function,” says Roth, who’s also Senior Scientist at the Sinai Health System’s Lunenfeld-Tanenbaum Research Institute in Toronto.

“People can look up their favourite protein and get clues about its function from the proteins it interacts with.”

The data are already revealing new cellular roles for human proteins involved in programmed cell death, release of cellular cargo and other essential processes, for example.

And, by integrating protein interaction data with tissue-specific gene expression, the teams have been able to identify protein networks behind the development and maintenance of various tissues, revealing new therapeutic targets for diverse diseases.

Furthermore, using HuRI as a reference, they were also able to determine how disease-causing protein variants bring about network rewiring to reveal the molecular mechanisms behind those particular disorders.

“Changes in the interactions of a protein is one possible mechanism of disease, and this map provides a starting point to study the impact of disease associated variants on protein-protein interactions,” says Calderwood.

The Toronto and Boston teams previously did two smaller studies mapping a total of ~14,000 protein interactions. Now HuRI has interrogated proteins encoded by nearly all human protein-coding genes and expanded the map four-fold.

To create HuRI, the researchers co-expressed in pairs almost all human proteins in yeast cells. When the two proteins interact, or bind to one another, they form a molecular switch which boosts yeast cell growth—a sign that an interaction has occurred.

The team tested all possible pairwise combinations among 17,500 proteins for their ability to interact with each other in three

separate versions of a yeast-based assay, each done in triplicate, amounting to a staggering three billion separate tests. The results yielded ~53,000 high-confidence binary interactions between more than 8,000 proteins, which were verified by other methods. The majority of interactions had never been detected before.

Although the largest of its kind to date, the HuRI map remains incomplete, representing between 2-11 per cent of all human protein interactions. Roth said that one reason why many interactions were missed is probably because yeast cells lack certain human-specific molecular factors that are needed for proper protein function.

Despite these limitations, HuRI has more than tripled the number of known interactions between human proteins and will serve as an important resource for the research community. Already 15,000 people have visited the data web portal, which was built by **Miles Mee**, **Mohamed Helmy**, and **Gary Bader**, also a professor in the Donnelly Centre, since HuRI was made available on bioRxiv, an open-source online publisher, in April 2019.

“We already had lots of people download the whole dataset and so I imagine we’ll see the iteration of our previous paper, which has already been cited over 800 times and it is less than a third of the size of HuRI,” says Roth.

Dozens of genes enabling cancer's evasion of the immune system identified by the Moffat lab and US company Agios Pharmaceuticals.



A cancer cell surrounded by killer T cells | NIH

Donnelly Investigators Identify Dozens of Genes Enabling Cancer's Evasion of Immune System

By Jovana Drinjakovic
August 26, 2019.

Donnelly Centre investigators have mapped the genes allowing cancer cells to avoid eradication by the immune system in a finding that paves the way for the development of immunotherapies that would be effective for larger patient populations and across different tumour types.

“Over the last decade, different forms of immunotherapy have emerged as really potent cancer treatments but the reality is that they only generate durable responses in a fraction of patients and not for all tumour types,” says **Jason Moffat**, a professor of molecular genetics in the Donnelly

Centre who led the work.

The study, published in *Nature*, also revealed the need for new therapy to take into account the genetic composition of tumours because of mutations in the cancer cells that can potentially make the disease worse in response to treatment,

often referred to as cancer resistance mutations.

“It’s very important to understand at the molecular level how cancer develops resistance to immunotherapies in order to make them more broadly available. Advances in systematic genetic approaches have let us key in on genes and molecular pathways that are commonly involved in resistance to therapy,” says Moffat, who holds Canada Research Chair in Functional Genomics of Cancer.

In immunotherapy, a patient’s own immune cells, known as T killer cells, are engineered to find and destroy cancer cells. But treatment resistance has precluded its use in most patients, especially those with solid tumours.

“It’s an ongoing battle between the immune system and cancer, where the immune system is trying to find and kill the cancer whereas the cancer’s job is to evade that killing,” says **Keith Lawson**, a co-lead author completing a PhD in Moffat’s lab as part of his medical training in the Surgeon-Scientist Program at U of T’s Faculty of Medicine.

Tumour heterogeneity—genetic variation in tumour cells within and across individuals that can impact therapy response—further complicates matters.

“It’s important to not just find genes that can regulate immune evasion in one model of cancer, but what you really want are to find those genes that you can manipulate in cancer

cells across many models because those are going to make the best therapeutic targets,” says Lawson.

The team, including collaborators from Agios Pharmaceuticals in Cambridge, Massachusetts, looked for genes that regulate immune evasion across six genetically diverse tumor models derived from breast, colon, kidney and skin cancer. The cancer cells were placed in a dish alongside the T cells engineered to kill them, where the ensuing onslaught served as a baseline for the immune response. The researchers next deployed the gene editing tool CRISPR to switch off one-by-one every gene in the cancer cells and measured the resulting deviations from the killing baseline response.

They identified 182 “core cancer intrinsic immune evasion genes” whose deletion makes the cells either more sensitive or more resistant to T cell attack. Among the resisters were all the genes known to develop mutations in patients who stopped responding to immunotherapy, giving the researchers confidence that their approach worked.

Many of the found genes had no previous links to immune evasion.

“That was really exciting to see, because it means that our dataset was very rich in new biological information,” says Lawson.

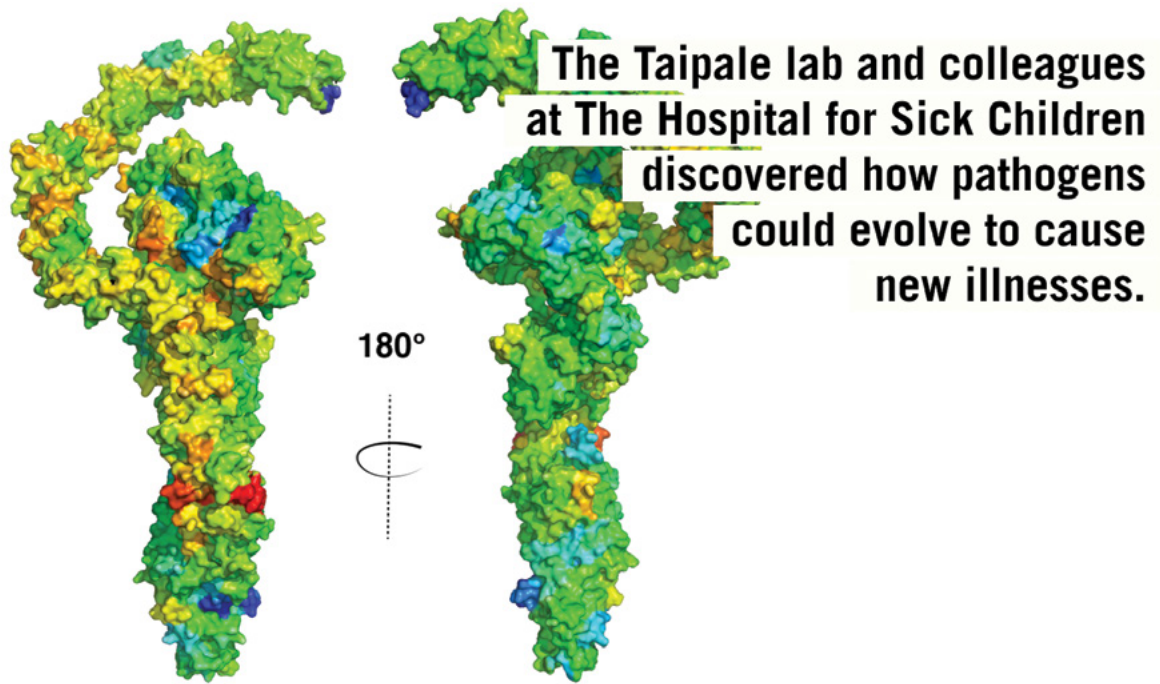
Genes involved in autophagy, a process when cells increase recycling their components to

mitigate damage following stress, came up as key for immune evasion. This raises a possibility that cancer’s susceptibility to immunotherapy could be boosted by targeting its autophagy genes.

But as the researchers delved deeper, they found that deleting certain autophagy genes in pairs rendered the cells resistant to T cell killing. It means that if a tumour already harbors a mutation in one autophagy gene, a treatment that combines immunotherapy with a drug targeting another autophagy gene could make the disease worse in that patient.

“We found this complete inversion of gene dependency,” says Moffat. “We did not anticipate this at all. What it shows us is that genetic context, what mutations are present, very much dictates whether the introduction of the second mutations will cause no effect, resistance or sensitivity to therapy”.

As more research explores combinatorial effects of mutations across different types of cancer cells, it should become possible to predict from a tumour’s DNA what type of therapy will be most effective.



Clostridial toxin structure overlay | Taipale lab

“Fascinating Machines of Death”: How Bacterial Toxins Might Evolve to Cause New Illnesses

By Jovana Drinjakovic
June 25, 2020.

Similar bacterial toxins have evolved to bind different receptors on human cells leading to different diseases. Donnelly Centre investigators have found.

Two almost identical bacterial toxins cause distinct illnesses—diarrhea and fatal toxic shock syndrome—by binding to unrelated human recep-

tors. The study also highlights a mechanism by which pathogens have evolved distinct receptor preferences to infect different organs.

“I always think of bacterial toxins as fascinating machines of death in how they find new ways to enter host tissue,” says **Mikko Taipale**, a co-leader of the study and an associate

professor of molecular genetics in the Donnelly Centre.

The work was also co-led by **Roman Melnyk** and **Jean-Philippe Julien**, both senior scientists at the Hospital for Sick Children in Toronto and associate professors of biochemistry at U of T.

The findings are published in the journal *Cell*.

Many are familiar with *Clostridium difficile*, a gut-dwelling bacterium that can cause diarrhea. Lesser known is its close relative, *Paenibacillus sordellii*, which also lives in the gut and in the female reproductive tract. Infections are rare but fatal and can occur when the bacterial toxin escapes into the bloodstream, during birth for example, and spreads into the lungs and other organs.

Both species are thought to be part of the microbiome, the body's resident bacteria, but it's not clear why they harm some people and not others.

The toxin released by *C. difficile* acts through Frizzled, a cell surface receptor with a role in tissue regeneration. Although *P. sordellii* produces a similar toxin, it does not bind Frizzled. The nature of its receptor remained unknown and the U of T team decided to find it.

The researchers took an unbiased approach by systematically switching off every gene in human cells and exposing them to the *P. sordellii* toxin. Cells that survived turned out to lack genes encoding cell surface proteins called semaphorins, and other experiments confirmed that two members of this class, Semaphorin6A and Semaphorin6B, are indeed the receptors for the toxin. Both receptors are present in the lungs as expected, although their role there remains unclear.

Identifying the receptor opens the door to finding treatment. The researchers were able to halt infection in mice by co-injecting the toxin with purified semaphorin fragments, which bound and neutralized the toxin before it could reach the real receptors.

But the finding was unexpected and led to more surprises.

Like Frizzled, semaphorins play important roles in the body, most notably in the developing nervous system where they help guide projecting nerve fibers. That a bacterial toxin impairs lungs through a protein receptor usually found on nerve endings was surprising enough.

But even more surprising was that it binds a receptor with no structural resemblance to Frizzled.

"Here we have two toxins that are so similar to each other, but they use completely different receptors," says Taipale. "We did not expect to find that."

The difference is explained by a tiny part of the toxins that differs considerably between *C. difficile* and *P. sordellii*. Found in the middle of the toxin, it forms a surface by which both toxins contact their receptors, as revealed by cryo electron microscopy, which allows a detailed three-dimensional view of molecular structure.

Each toxin protein is composed of about 2500 amino-acids and the researchers were able to pinpoint those that directly engage with the

receptor. Swapping a mere 15 of these amino acids between the two toxins was sufficient to switch receptor preference. In other words, they created a *P. sordellii* toxin that targeted Frizzled and vice versa.

"We were floored when we saw that the toxins shared a surface each evolved to uniquely interact with distinct cells," says Julien, who along with Taipale plays for The Flying Puckheads, the hockey team of U of T's Faculty of Medicine.

It appears that while the rest of the toxin is under strong evolutionary pressure to remain unchanged, the receptor-binding surface is free from such constraints. This can allow toxins to evolve into variants that can bind new receptors to invade other tissues and hosts.

Receptor switching is not unique to bacteria, however. SARS-CoV-2 and coronavirus strains that cause the common cold use the same part of the now famous spike protein to bind diverse receptors, which might explain differences in disease severity.

"This is a nice example of how viruses and bacteria – from completely different domains of life -- have found similar molecular tactics to change their receptor targets in human cells," says Taipale. "And it also reminds us how much cool biology one can find in the microbial world!"

Blood Test Could Predict Diabetes Years Before it Strikes

By Jovana Drinjakovic
May 21, 2020.

Scientists have identified metabolites in blood that accurately predict whether a woman will develop type 2 diabetes after experiencing a transient form of illness during pregnancy. The discovery could lead to a test that would help doctors identify patients at greatest risk and help them potentially avert the disease through interventions such as diet and exercise.

The research was part of a collaborative effort co-led by **Hannes Röst**, an assistant professor of molecular genetics and computer science at the Donnelly Centre, and **Michael Wheeler**, a professor of physiology at U of T's Faculty of Medicine, **Feihan Dai**, a research scientist of physiology and **Erica Gunderson**, a research scientist at the Kaiser Permanente Division of Research in Northern California.

"This is the holy grail of personalized medicine to find molecular differences in seemingly healthy people and predict which ones will develop a disease," says Röst.

The identified metabolic signature

can predict with over 85 per cent accuracy if a woman will develop type 2 diabetes (T2D), as described in a study published in the journal *Plos Medicine*.

About one in 10 women will develop gestational diabetes (GD) during pregnancy which puts them at higher risk of T2D, with 30 to 50 per cent of these women developing the disease within 10 years after delivery.

Wheeler and Gunderson first uncovered metabolic signatures predictive of T2D in their 2016 pilot study of 1033 women with GD. Gunderson recruited for the Study of Women, Infant Feeding and Type 2 Diabetes After GDM Pregnancy (SWIFT), one of the largest and most diverse studies of its kind.

The new study builds on prior research, following the same cohort of women over a longer time period during which more women developed T2D. By profiling the blood samples on a deeper level and tracking them over time, the researchers were able to identify new compounds associated with the

disease.

Baseline blood samples were collected between six and nine weeks after birth and then twice over two years. The women's health was followed through their electronic medical records for up to 8 years. During this time, 173 women developed T2D and their blood samples were compared to 485 women enrolled in the study, matched for weight, age, race and ethnicity, who had not developed the disease.

"This study is unique as we are not simply comparing healthy people to people with advanced disease," says Röst. "Instead, we are comparing women who are clinically the same—they all had GD but are back to being non-diabetic post-partum."

The researchers hope to turn their discovery into a simple blood test that women could take soon after delivery, perhaps during an early visit to the doctor with their baby.



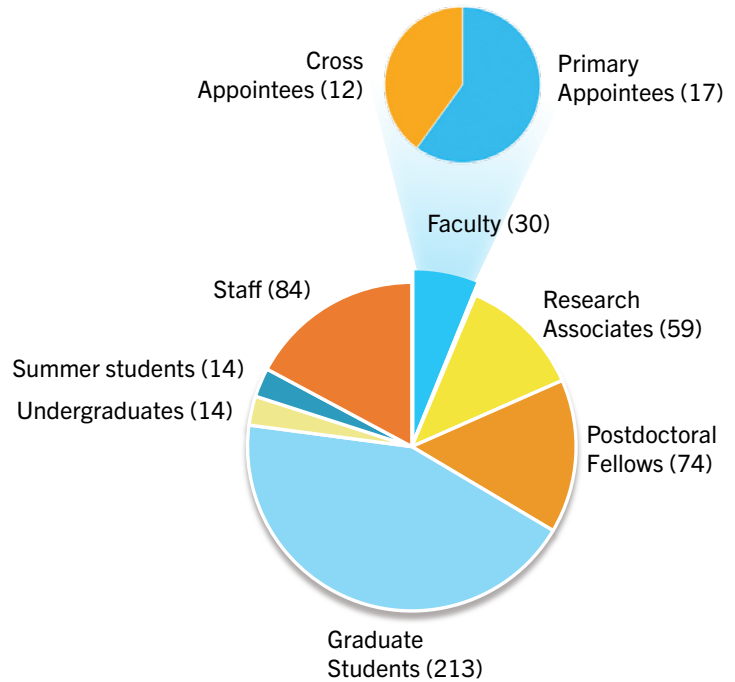
DONNELLY

IN NUMBERS

Personnel

The Donnelly Centre currently houses a total of 489 occupants, representing scientists at all stages of their careers as well as members of staff, as follows:

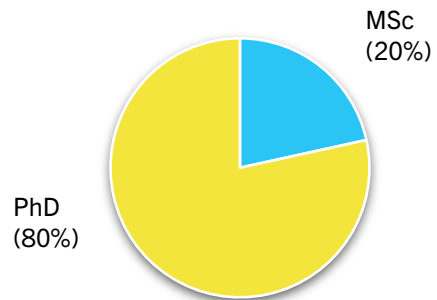
- 30 Faculty members, 17 of whom are primary appointees
- 1 Professor Emeritus
- 59 Research Associates
- 74 Postdoctoral Fellows
- 213 Graduate Students
- 28 Undergraduate students, 14 of whom are summer students
- 84 Research and admin staff



Graduate Students

Our 213 graduate students come from diverse U of T departments, as shown by the numbers in brackets below:

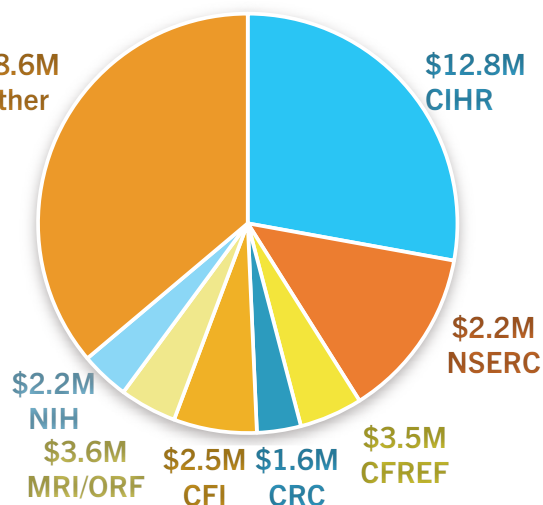
- Surgery (1)
- Physics (1)
- Pharmacology & Toxicology (2)
- Chemical Engineering (11)
- Chemistry (7)
- Computer Science (18)
- Institute of Medical Science (15)
- Biochemistry (15)
- Institute of Biomaterials and Biomedical Engineering (54)
- Molecular Genetics (89)



171 students (80%) are PhD candidates whereas 42 students (20%) are pursuing a Masters degree.

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 faculty. “Other” sources of funding represent other federal and provincial grants as well as support from foundations. The data presented are for the period from June 2019 to June 2020.



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



total articles 129

media coverage 55

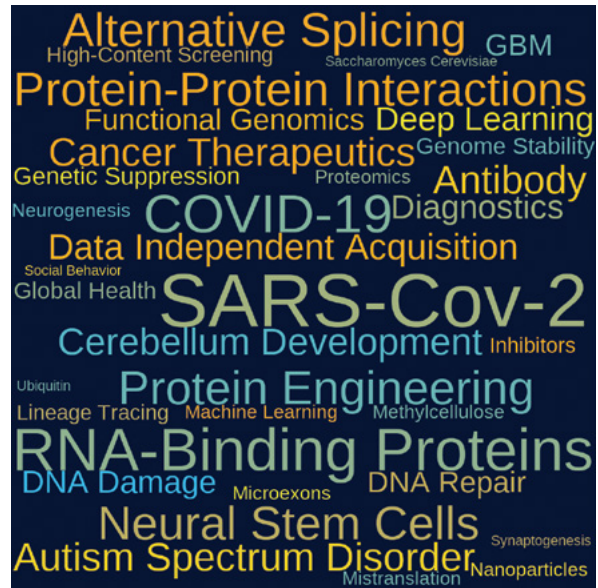
high impact journals 43

In 2020, Donnelly Centre investigators have published 129 articles in peer-reviewed academic journals, of which 43 articles were published in high impact journals*, while 55 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*.

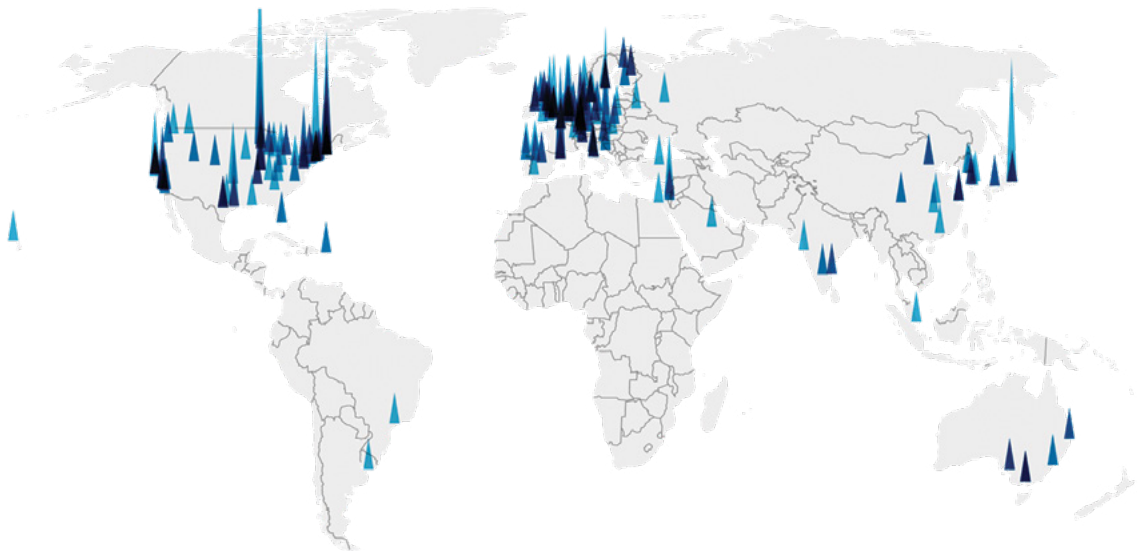
Research Themes

Researchers in the Donnelly Centre work on diverse life sciences topics, with many teams collaborating across scientific disciplines. The map on the right represents the frequency of top 49 keyword identifiers from a total of 129 publications produced by Donnelly Centre faculty in 2020 and was generated using WordCloud for Python. The font size represents the relative frequency with which a given keyword or phrase appears.



International Collaboration

Donnelly Centre investigators collaborate with researchers from all over the world.



Spikes mark home institutions of the researchers who have co-published scientific articles with Donnelly Centre investigators in 2020. Spike size corresponds to the number of published papers while darker shade denotes overlapping location.

TRAINEE

AWARDS





▲ Top L-R: Ronald Xie, Daniela Isaacs-Bernal, Zahra Sepahi, Kenny Rebelo and Elana Sefton. Bottom L-R: Amber Xue, Delaram Pouyabahr, Kai Slaughter, Zoe Clarke and Erik Jacques.

2020 Yip Awards Recognize Early Graduate Research in Cross-Disciplinary Biomedicine

By Jovana Drinjakovic
September 11, 2020.

How can the molecular makeup of liver cells point to better treatments? Can we deliver drugs directly into tumours? What is the role of a long-mysterious protein particle in cells?

These are some of the questions

being asked by the recipients of the 2020 Cecil Yip Graduate Research Award, which recognizes first year students conducting cross-disciplinary research in the Donnelly Centre with the aim of revealing biological insights about health and

disease.

The annual award was established in honour of late U of T Professor **Cecil Yip**, former vice-dean of research at the Faculty of Medicine and co-founder of the Donnelly Centre,

which has become a global hub for scientists from diverse fields working to improve human health.

Enrolled in graduate programs at U of T's Departments of Molecular Genetics (Mogen) and Chemical Engineering & Applied Chemistry (ChemE) and the Institute of Biomedical Engineering (BME), this year's winners are working at the intersection of genomics, bioengineering and computer science on projects that could reveal new ways to tackle liver disease, cancer and other ailments.

"On behalf of everyone on the award committee I would like to congratulate the recipients of the 2020 Yip Doctoral Research Award," says **Christopher Yip**, Dean of the Faculty of Applied Science & Engineering and Principal Investigator in the Donnelly Centre where he also serves as Chair of the award committee. "The awarded projects are at the cutting edge of biomedicine and provide fantastic opportunities for our students to hone a diverse set of skills as we train them to become inventors of tomorrow," he says.

Donnelly Centre investigators **Will Ryu**, **Igor Stagljär** and **Jason Moffat** served as committee members to elect recipients.

Three Yip awardees, **Ronald Xie**, **Delaram Pouyabहार** and **Zoe Clarke**, from Professor **Gary Bader**'s group, are focusing on the liver, a key metabolic organ for which there are limited treatment options. The lab previously helped create the

world's first map of liver cells at the molecular level and they are now using it to find clues that could lead to new therapies.

"The awarded projects are at the cutting edge of biomedicine and provide fantastic opportunities for our students to hone a diverse set of skills as we train them to become inventors of tomorrow"

Xie (Mogen) is combining volumetric electron microscopy with gene expression data from liver cells to map the organ down to nano-meter resolution. This will help produce a detailed molecular map at the level of single cells, but it requires a complex integration of cell imaging and genomics data. Xie is also developing neural network algorithms, a form of artificial intelligence, that automatically track cells in 3D to help him with analysis.

Pouyabहार (Mogen) is developing computational models to enable a comparison of the molecular makeup of healthy and sick liver cells across different species. The goal is to be able to better predict how the human liver will respond to medications, or if a transplant will be rejected, by studying it in other animals.

And Clarke (Mogen) is tracking the development of viral-induced

hepatocellular carcinoma, the most common type of liver cancer, to shed light on how the disease starts and develops. She is tracking the chronic viral infection in individual woodchuck liver cells at different stages of disease to capture how tumours change over time. She plans to model these data with applied evolutionary principles to search for an explanation of how chronic viral infections cause cancer.

The liver is also the focus, albeit from a different angle, of Yip awardees **Elana Sefton** and **Zahra Sepahi** in Professor **Warren Chan**'s lab. The lab seeks to engineer nanoparticles filled with cytotoxic drugs which, once injected into the bloodstream, would deliver the treatment directly into tumours. But, a few years ago, they discovered that the majority of injected nanoparticles end up in the liver. They are now working to better understand why this happens and how the particles could be better diverted to tumours.

To this end, Sefton (BME) is investigating the so-called Kupffer's cells, which are resident immune cells in the liver and thought to be chiefly responsible for sopping up nanoparticles. The receptors on the cells' surface could be binding the proteins from the bloodstream that coat the particles as they travel through the body, not the particle itself. Sefton will first identify these receptors and then determine the blood proteins on the particle that are binding to the receptor(s). These results will guide the design and synthesis of nanoparticles to

improve their delivery to tumours.

Meanwhile, Sepahi (BME) is investigating how nanoparticle size and dose affect their delivery efficiency. Recent work from the lab found that more particles reach tumours when they are injected at a higher dose. At the same time, smaller nanoparticles seem to be more efficiently delivered at lower doses. By identifying a relationship between nanoparticle size and dose, Sepahi will establish a robust approach for future research and clinical applications of cancer nanomedicines.

Yip awardee **Kai Slaughter** (BME) in University Professor **Molly Shoichet**'s lab is also developing new methods to deliver drugs into cells but his approach employs a modified bacterial toxin. His goal is to use a weakened toxin which does not cause disease but whose natural ability to efficiently enter human cells could be exploited for the delivery of therapeutics.

Two more Yip winners in the Shoichet lab are working on regenerative medicine projects concerning lung disease and blindness. **Chang (Amber) Xue** (BME) is studying lymphangioliomyomatosis, or LAM, a rare fatal disease that stems from abnormal growth of smooth muscle cells, mostly in the lungs. By investigating human LAM cells in culture, Xue hopes to learn how the disease develops and find drugs that might be able to halt it.

Daniela Isaacs-Bernal (ChemE)

is investigating the possibility of awakening stem cells in the eye to repair tissue damage in patients who lost vision from it. In collaboration with **Derek van der Kooy**'s lab, also in the Donnelly Centre, which recently identified cellular factors that prohibit retinal regeneration, Isaacs-Bernal is developing a controlled release strategy for the delivery of inhibitors of these factors into the mouse retina to activate its repair

Just as retinal stem cells hold promise for vision repair, so could the stem cells that reside in the muscles be harnessed to repair injury and wasting from old age. **Erik Jacques** (BME) in Associate Professor **Penney Gilbert**'s lab is searching for cellular factors in the developing muscle and its environment that could be harnessed to activate regeneration. He is setting up an automated platform that will allow him to perform genome wide screens in search of these factors using skeletal muscle tissue grown in a dish, previously developed in the lab.

Last but not least, **Kenny Rebelo** (Mogen) in Professor **Benjamin Blencowe**'s group is combining cryo-electron microscopy, molecular biology and computational approaches, in collaboration with the groups of Fred Allain, at ETH in Zürich, and Oliver Mühlmann, at the University of Berne, to reveal the composition and function of the 40S ribonucleosome, a relatively large cellular particle composed of RNA and protein molecules. Although known to science for decades,

the particle's role has remained a mystery, but Rebelo's research already points to its involvement in the transport of molecules in and out of the cell's nucleus where the DNA is stored.

2020 Dorrington Awards Celebrate Graduate Research in Rare Diseases, Computer Vision and 3D Cancer Modelling

By Jovana Drinjakovic
February 18, 2020.

Sky is the limit, literally, for graduate student **Sanna Masud**, who plans to become an astronaut.

Here on earth, Masud, a fourth year PhD student in the Donnelly Centre for Cellular and Biomolecular Research, studies gene interactions in Barth syndrome, a rare genetic disorder that weakens the heart muscle and can be lethal. Her know-how of rapidly evolving genomic technologies will come in handy when she eventually applies to the Canadian Space Agency, which is increasingly seeking life scientists to shed light on how space environment affects the genome before humans can be sent on longer missions.

Along with **Nil Sahin** and **Benjamin Kingston**, Masud is a winner of the 2020 Jennifer Dorrington Graduate Research Award, awarded annually to three outstanding PhD candidates in U of T's Faculty of Medicine who are doing research in the Donnelly Centre.

The award was established in honor of **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 “

The 2020 Dorrington awardees reflect the wide scope of cutting-edge research projects in the Centre,” says **Gary Bader**, a professor of molecular genetics and computer science and Chair of the award committee, whose members are U of T Professors and Centre's investigators: **Liliana Attisano**, **Henry Krause** and **Fritz Roth**.

“Our 2020 winners are doing some of the most innovative research in biology that has already revealed important new insights and has the potential to improve patient lives,” says Bader.

Mapping Genetic Networks behind Barth Syndrome

Masud is co-supervised by **Charlie Boone** and **Jason Moffat**, both professors of molecular genetics at the Centre.

“Both Charlie and Jason are so passionate about the science,” says

Masud.” “For a graduate student, it's great having supervisors who can talk for hours about a million ideas around the project and be just as excited about it as they were on day one.

With their guidance, Masud is developing a complete genetic interaction map for Barth syndrome to find other genes that might be involved. The disorder, for which there is no treatment, is caused by the loss of a single gene that encodes a protein called tafazzin. It affects each person differently with a large range in symptoms and their severity. Disease variability is probably due to genetic modifiers, other genes in the genome that affect how the body deals with the loss of tafazzin. Masud hopes to identify these modifiers to shed light on the role of tafazzin in the cell and provide clues to developing new treatments.

“It's nice to know that a project like this is recognized and that it could make a meaningful contribution,” says Masud of receiving the award. “As a rare disease, Barth syndrome does not get much attention and so



▲ 2012 Dorrington Award winners, L-R: Sanna Masud, Nil Sahin, and Benjamin Kingston.

it is nice to hopefully develop a bit more traction for it and get more resources.”

In her previous project, published in *Cell Reports*, Masud helped identify large differences at the molecular level between stem cells grown on different materials which could affect their use in therapy.

When she’s not helping run U of T’s sailing club, Masud enjoys running, swimming and fencing as a way of keeping fit for future space travel.

Cell Sorting Algorithms

Advances in AI-powered computer vision are changing modern life, from smartphone banking to medical diagnoses. But when it comes to cell biology, computers still have a lot to learn—and Dorrington awardee **Nil Sahin** is teaching them.

Sahin, in her fifth year of PhD in

molecular genetics, is developing algorithms for sorting cells from microscopy images into distinct classes based on their appearance.

“It’s known as outlier detection, a classical problem in computer science,” says Sahin. “These algorithms learn what normal things look like and they recognize abnormalities.”

Abnormalities might be caused by genetic mutations, revealing clues about gene function at the cellular level. Data analysis remains a bottleneck, however, with many labs still sorting images by eye.

Sahin has an undergraduate background in both computer science and biology, and continued to develop these skills under the mentorship of **Brenda Andrews**, Director of the Donnelly Centre and a pioneer of large-scale cell

biology studies, and **Quaid Morris**, a professor of molecular genetics and machine learning expert.

“It was a great partnership that I had the opportunity to create because they are both world-renowned in their fields,” says Sahin. “And they are always available with their constant support and motivation when I need it the most.”

Working with the images of yeast cells, which have the same basic structure like human cells but are easier to study thanks to their smaller genome, Sahin has been developing computational tools that can sort individual cells based on the shape of their 18 internal compartments. Scoring how each of the 6,000 yeast genes affects compartment shape means analyzing billions of cells. She quickly realized there is no one-size-fits-all algorithm that can

handle the task, applying instead distinct algorithms across the compartments.

In a study published in the journal *Molecular Systems Biology*, Sahin helped identify all the genes involved in endocytosis, a process by which cells take up nutrients and other molecules from their environment. The gene list might reveal drug targets for many diseases, like cancer, in which this process is flawed.

The Dorrington award is a “wonderful recognition”, Sahin said. “It is a great career boost and proved to me that I am doing well in my research.”

Going forward, Sahin wants to apply her computational skills to help patients.

“By applying outlier detection principles, I want to develop tools that would help physicians make more accurate predictions from medical images about patient’s health.”

She previously won a 2016 Cecil Yip Doctoral Research Award, which recognizes excellence among the first-year students pursuing cross-disciplinary research in the Donnelly Centre.

3D Tumour Mapping

Like most people, Dorrington awardee **Benjamin Kingston** was personally affected by cancer through friends and family, which shaped his research interest.

“Cancer is such a complicated disease and so different from person to person,” says Kingston. “Even within one person the tumour structure and cell make-up is diverse.”

All this—and the fact that tumours are made from a patient’s own cells— has made it difficult to make treatments that specifically kill cancer without harming healthy tissue.

Four years ago, Kingston joined the group of **Warren Chan**, Director of the Institute for Biomaterials and Biomedical Engineering and investigator at the Donnelly Centre, to explore tiny nano-scale particles as a means to deliver drugs directly into tumours.

“Warren is a great mentor, always willing to stand up for his students,” says Kingston, who is in the graduate program at IBBME. “He’s really good about pushing me to do better science and to be a better-rounded scientist.”

Nanoparticles can be engineered to deposit drugs into tumours after being injected into the bloodstream, but the outcomes of human trials have been disappointing. Now, thanks to Kingston and others in the Chan lab, we know why.

Their research, published in *Nature Materials*, has cast doubt on the accepted view about how nanoparticles reach tumours. Instead of passively leaking from blood vessels, the particles are

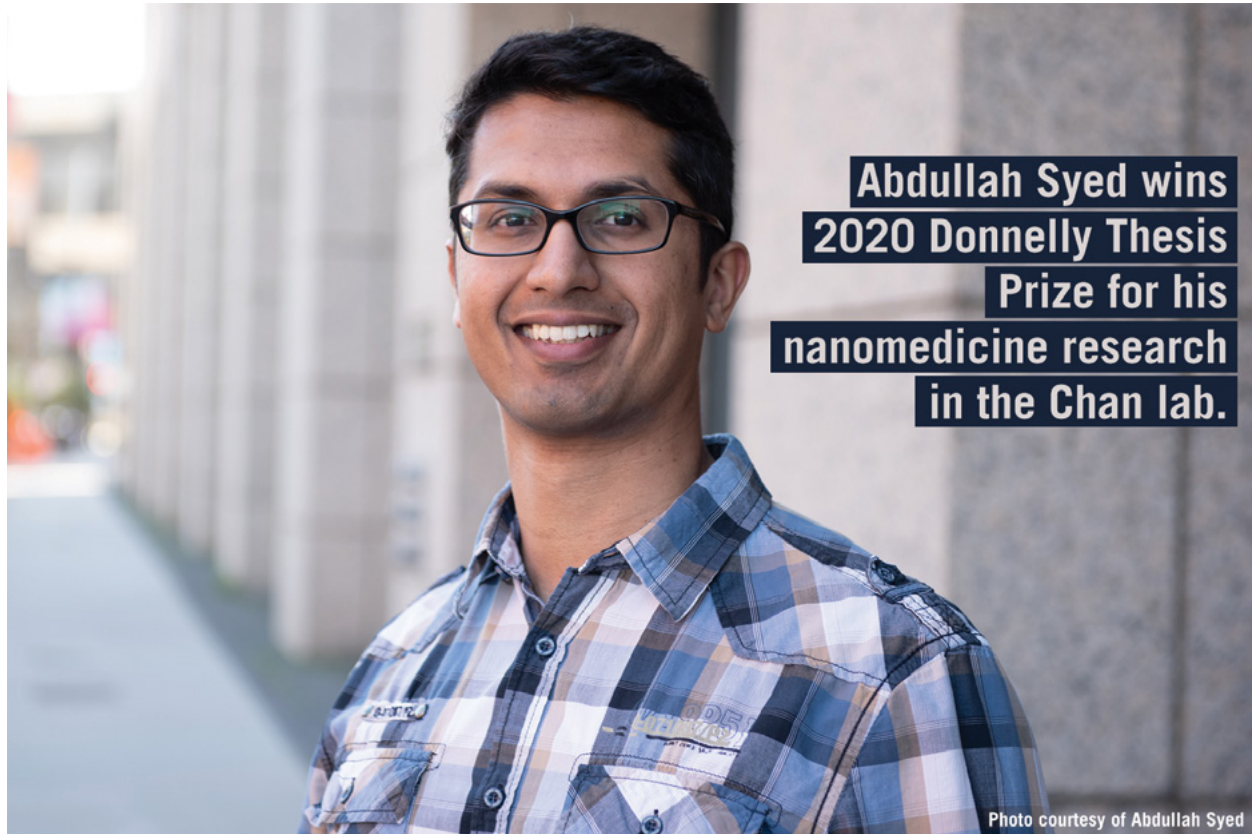
actively transported through the walls of blood vessels, although the exact mechanism remains unclear. Kingston is now developing imaging tools to map tumours in three dimensions, along with intertwined blood vessels and immune cells, all of which can impact drug delivery.

“Some structures of tumours might be more conducive to certain therapies than others, which would be important for the development of personalized cancer medicine,” he says.

The Dorrington award is a great boost for Kingston who hopes to become a professor one day. “Winning this award is a prestigious achievement because a lot of graduate students I looked up to had won this award when I first came to the Donnelly Centre.”

“I am very appreciative of the people that support research,” he says. “All these discoveries form the foundation that allows us develop better therapies for patients.”

Kingston also previously won a Cecil Yip Graduate Research Award in 2017, and was named Royal Bank of Canada Graduate Fellow in 2019.



**Abdullah Syed wins
2020 Donnelly Thesis
Prize for his
nanomedicine research
in the Chan lab.**

Photo courtesy of Abdullah Syed

Abdullah Syed Wins 2020 Donnelly Thesis Prize

By Jovana Drinjakovic
May 13, 2020.

When **Abdullah Syed** moved to San Francisco in January for his dream research job, he did not expect to end up confined to his apartment due to the COVID-19 lockdown.

With his research on hold, Syed is dividing time between helping set up a SARS-CoV-2 testing lab and learning new computer programs for future data analysis. Such advance

preparation allowed him to make fast progress during his PhD, for which he won a prize.

Syed is the winner of the 2020 Donnelly Centre Research Thesis Prize, awarded annually for the best doctoral research completed at the Centre. An engineer by training, he studied how tiny nano-scale particles travel through the body

to deliver drugs directly to tumours under the supervision of **Warren Chan**, a principal investigator at the Centre and the director of U of T's Institute for Biomaterials and Biomedical Engineering.

"The committee was very impressed with Syed's work," says **Jason Moffat**, Chair of the award committee with Donnelly Centre

investigators **Molly Shoichet**, **William Ryu** and **Aaron Wheeler** as members.

“In a short time, Syed developed new tools that allowed him to challenge a central dogma in cancer nanomedicine and open new research avenues that could ultimately improve therapy for patients,” says Moffat.

Nanoparticles are engineered molecules that tend to accumulate inside tumours after being injected into the bloodstream. Scientists across the world seek to harness these particles for cancer diagnostics and to deliver medications to cancer cells.

“A lot of medications we use to treat cancer don’t reach cancer cells very well and also cause a lot of damage to healthy cells,” says Syed. “If we could improve drug delivery to cancer cells, a lot of treatments would have a better chance of working.”

Despite their potential, nanoparticles have had mixed success in clinical trials, prompting Syed and his colleagues to investigate in more detail their transport in the body.

“We wanted to explore how nanoparticles get past blood vessels to be able to make this process more efficient,” says Syed.

With fellow graduate student **Shrey Sindhwani**, Syed adapted a method called CLARITY, which renders tissues see-through and

allows imaging of whole tumours by microscope. Having a clear view of the entire three-dimensional structure of the tumour and associated blood vessels allowed them to better observe the particles’ journey between them.

“In a short time, Syed developed new tools that allowed him to challenge a central dogma in cancer nanomedicine and open new research avenues that could ultimately improve therapy for patients”

To their surprise, the particles did not passively leak from the blood vessels to be taken up by cancer cells, as had been widely accepted in the field. Instead, active transport appears to be involved, meaning that cells expend energy to move particles and their cargo across the cell barriers.

“The fact that nanoparticle transport is an active process opens new doors now,” says Syed. “It’s really hard to change a passive process. But when you have an active process, that means there are components driving it, and if we can find the components that drive or inhibit the transport, then it should be possible to make it more efficient.”

The findings, published in the current issue of the prestigious journal *Nature Materials*, could

change how nanoparticles are used for cancer diagnosis and treatment.

It was not all smooth sailing for Syed however, who switched to cancer drug delivery from another project half way in his PhD.

“It was a rough ride in the beginning, but it was really great having Warren as a mentor to help me through,” says Syed. “He taught me to think about coherent long-term goals and that you should not just do experiments for the sake of experiments but to focus on solving a major problem.”

Syed is quick to point out that his success also comes from teamwork and bouncing ideas off others in the lab. He especially enjoyed working alongside Sindhwani, whom he’s been friends with since they were both engineering students at the University of Waterloo.

After graduating last year, Syed moved to California for a postdoctoral stint with Jennifer Doudna, who is world-renowned for her co-discovery of the gene editing system CRISPR-Cas9, at the University of California, Berkeley. His focus there is on developing methods for delivering CRISPR components into tissues and organs for future gene therapies.

Syed hopes to return to Canada to start his own research group one day. But for now, he’s just waiting for the coronavirus crisis to pass so he can be back in the lab doing what he loves best—science.



Photo | Donnelly Centre

Zheng Luo Wins 2020 Best Fellowship for Research that Aims to Improve Splicing Code

By Jovana Drinjakovic
February 7, 2020.

Zheng Luo was half way through his PhD in China, when he read, in 2016, a scientific article published by the team led by Donnelly Centre investigator and U of T professor **Benjamin Blencowe**, that would prompt his move to Toronto three years later.

“After I was introduced to Ben’s awesome work, I started learning more about it and thought this is what I want to do for my postdoc,” says Luo, who joined the lab last April to study alternative splicing, a process allowing cells to generate vastly more protein variants from a

limited number of protein-coding genes.

And now, Luo has been named the 2020 Charles H. Best Fellow—a prestigious appointment awarded annually to an outstanding postdoctoral trainee in the Donnelly

Centre. Established in 2001, and named after **Charles H. Best**, who co-discovered insulin in 1921 as a young graduate at the University of Toronto, the fellowship provides support for postdoctoral researchers who have the potential to become leaders in their fields.

“It’s great privilege to be recognized by the Best fellowship committee,” says Luo. “The award will help me fulfill my research goals and it’s a great boost at this stage of my career.”

The focus of Luo’s research is how protein diversification by alternative splicing is regulated by the cell. When a gene is switched on, its entire message is copied into a transcript, from which some coding fragments, or exons, are spliced out and therefore not included into the translated protein. Whether or not an exon is included can modify protein function and impact health. This is especially the case in the brain, where altered splicing regulation has been linked to autism, schizophrenia and other brain disorders.

The clues to which gene fragments are spliced in or out in different tissues are written in the surrounding gene sequences, known as the “splicing code”. While a lot of the splicing code has been worked out, including in a landmark work from Blencowe and colleagues published in *Nature* in 2010, recent research has revealed unconventional splicing events, whose rules Luo is working to decipher. “While we and others have worked

on the splicing code for many years, the rules governing the fidelity of this process remain poorly understood,” says Blencowe. “Luo is applying a new approach to this problem that I believe holds tremendous promise.”

“His work should enable more accurate predictions of the consequences of different types of sequence variation on splicing.”

Luo brings to the project an extensive experience in computational biology gained during his PhD in a leading laboratory headed by Professor Li Yang, at the Shanghai Institutes for Biological Sciences, CAS.

“My goal is to improve the splicing code by learning from different features in the DNA sequence how splicing maintains its high fidelity,” Luo says. “If we have a better understanding of splicing mechanisms directed by the code, that may allow us to develop new therapies.”

It’s an ambitious project, but Luo has all the support he needs.

“I feel very fortunate to have Ben as a mentor,” says Luo. “He is not only a leader in the field but is also a very supportive.”

“He always encourages scientific discussion and the sharing of ideas which really helps my research.”

Luo was selected as the best candidate by the fellowship committee co-chaired by Donnelly Centre investigator **Charlie Boone**

and Research Program Manager **Sara Sharifpoor**, with Centre’s investigators **Peter Roy**, **Andy Fraser**, **Tim Hughes** and **Hannes Röst** as members.

We thank The Charles H. Best Foundation for their continued support for this award.



2020 Research Excellence Awards Recognize Efforts to Harness Artificial Intelligence for Cell Biology, Regenerative Medicine

By Jovana Drinjakovic
October 13, 2020.

Two Donnelly Centre researchers are being recognized for their work on developing new technologies that merge cell microscopy with machine learning, a form of AI, to advance research in biology and regenerative medicine.

Research associate **Mojca Mattiazzi**

Ušaj and postdoctoral fellow **Shuailong Zhang** are the winners of the 2020 Research Excellence Awards, awarded annually to outstanding postgraduate researchers in the Donnelly Centre whose projects cross the boundaries between scientific fields.

Working with geneticists, cell biologists and computational scientists, Mattiazzi Ušaj has created an automated pipeline for extracting from individual cells the information about their inner compartments, or organelles, from microscopy images each containing hundreds of cells.

Zhang, who has an engineering background, has teamed up with stem cell scientists and bioengineers to develop AI-powered microrobots that can find and collect the stem cells from brain tissue for applications in regenerative medicine.

“The caliber of this year’s applicants was as outstanding as ever, which speaks to the research productivity of our institute even during the pandemic,” says **Charles Boone**, a professor of molecular genetics and the interim director of the Donnelly Centre. “The winners, Shuailong and Mojca, presented amazing projects, in very different fields, and they both highlight the collaborative and interdisciplinary nature of the Centre.”

Analysing single cells with AI

Large-scale approaches in genetics and microscopy have enabled collection of vast amount of images containing clues to how disease unfolds at the cellular level. But extracting this information has proved a bottleneck with researchers in many labs still processing cell images by eye.

To overcome this obstacle, Mattiazzi Ušaj combined the automated high-throughput genetic and imaging platform, established by her mentors, Boone and **Brenda Andrews**, in the Donnelly Centre, with AI-powered image recognition for data analysis, in collaboration with machine learning expert **Quaid Morris**.

The result is a pipeline for extracting from single cells hundreds of quantitative measurements that describe internal organelles which have distinct cellular roles such as nutrient uptake or waste disposal. With benchmark measurements collected from millions of individual healthy cells, these can then be used to better assess how genetic mutations or drug compounds affect health and fitness at the subcellular level.

Mattiazzi Ušaj has mainly been working with yeast cells, which are structurally similar to human cells but have smaller genomes and are easier to manipulate in the lab. In one project, she looked at how the deletion of each of the yeast 6,000 genes impacts endocytosis, a process by which cells take up nutrients and signals from their surrounding and transport them inside tiny vesicles into other organelles in the cell’s interior. The study revealed the genes involved in endocytosis and will aid further research into how it goes awry in disease. But it also led to an unexpected finding, which was that most gene deletions did not have the same effect in all the cells.

If a genetic error does not manifest in all the cells that have it, this is known as incomplete penetrance. Individual cells can also differ in the severity of a particular trait, but the molecular mechanisms for either phenomenon are not known. Mattiazzi Ušaj can now begin to uncover them in a systematic manner using the automated

pipeline she developed. This will be one of the first projects in her own lab at Ryerson University where she will start as Assistant Professor in January.

“We want to understand for a particular genetic background and environment, what are the different sources of variability that contribute the most,” she says. The research could bring a better understanding of disease and how to treat it.

The award is a great motivation for future work, she said.

“In research you have more downs than ups. So this recognition is very motivating,” she says. “I’m very fortunate to have had great colleagues and collaborators contributing to my research, and amazing support from Charlie and Brenda.”

AI-controlled microrobots for brain dissection

Shuailong Zhang’s research is combining AI with regenerative medicine to develop a robotic microsurgery method for capturing stem cells from brain tissue. The highly collaborative projects brings together engineering expertise from the laboratory of Zhang’s postdoctoral adviser **Aaron Wheeler** with stem cell biology, in collaboration with **Cindi Morshead** in the Centre and **Peter Zandstra**, a former investigator at the Centre and now Director of Michael Smith Laboratories at the University of British Columbia.

Stem cells are special because of their ability to self-renew and turn into other cell types, raising hopes that they could be used to grow transplant tissue in the lab as well as spur regeneration in the body. Researchers around the world seek to harness the scarce resident stem cells in the brain for the treatment of stroke injury, Alzheimer's and other forms of brain damage. A method that plucks intact stem cells directly from brain tissue would enable the discovery of the molecular signals these cells receive from their microenvironment to activate regeneration.

Zhang has already developed light-controlled microrobots that can handle individual cells in a crowded environment. Known as optoelectronic tweezers, the method uses light beams to trigger an electric field which propels the robot in a desired direction. The tiny robots, whose diameter equals twice that of a human hair, can move the cells around and selectively pick up individual cells from a group of cells for molecular profiling.

At present, the stem cells have to be fluorescently labeled so that Zhang can see them under the microscope to be able to point the laser at the cells using a joystick. But the stem cells are rare and often mixed with cellular debris, which makes their isolation difficult. The ultimate goal is to automate the entire collection process so it can be executed by a computer algorithm.

Working with **Mike Shaw**, a machine learning expert at the

University College London, UK, he is developing an algorithm of what the brain stem cells look like under the microscope, in hope that one day, we will be able to guide the microrobots straight to them inside the brain slice.

Earlier this year, the international team won an inaugural grant of more than \$1million from the new Canada-UK Artificial Intelligence Initiative for the project.

AI-powered microrobots offer many advantages—the cells could be harvested in their natural form without having to label them first and the harvesting would be more accurate and efficient.

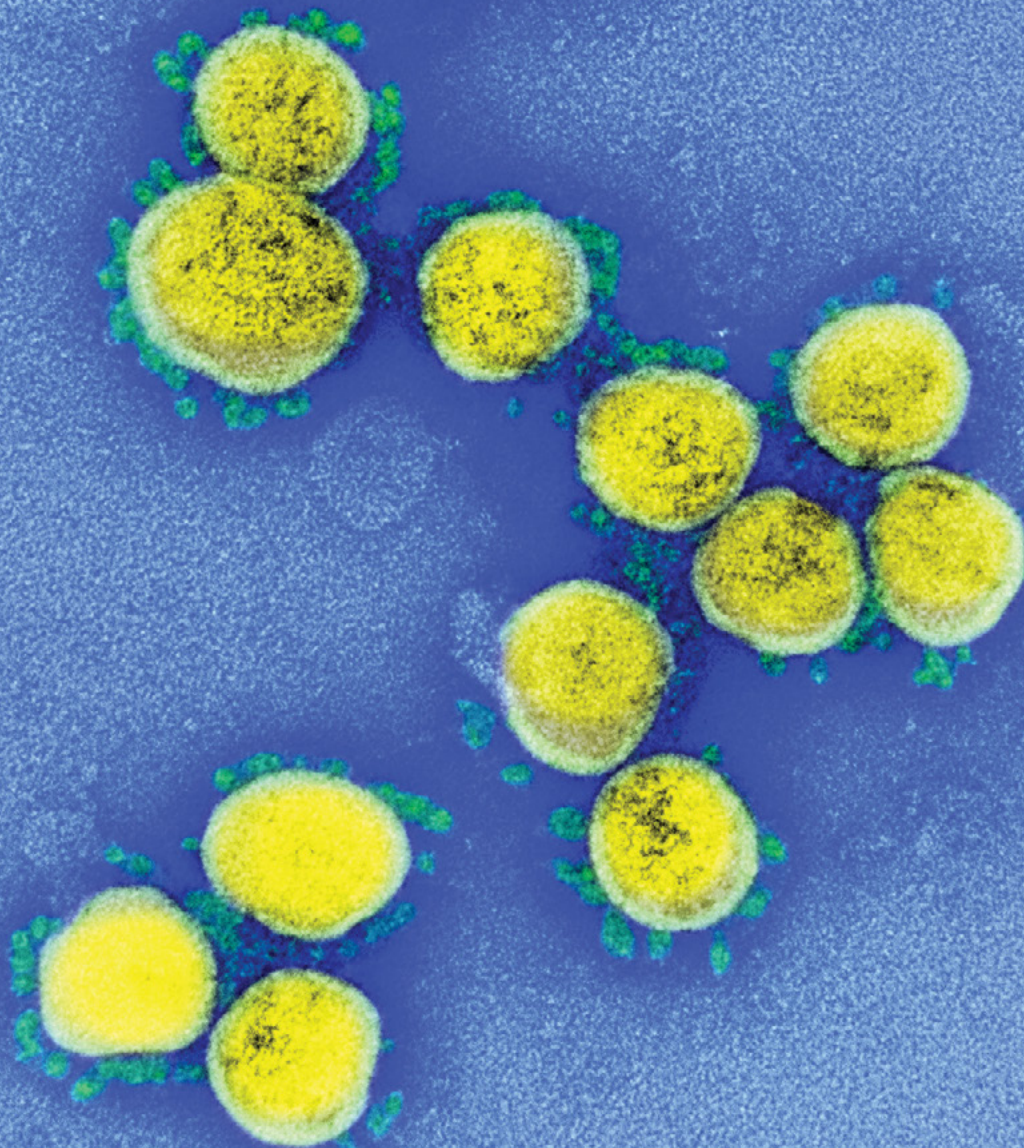
“You can train the network to find the cells more accurately,” says Zhang. “And if we can make the whole thing automated, it would also increase efficiency and reproducibility of the system and make it more widely usable, not only for stem cells, but also for many other cell species.”

The award is an important recognition to Zhang, who hopes to build a career as an independent researcher in Canada or in China where he is from.

“This award is important to me because it recognizes my contribution in developing this technology,” he says. “But the award is not just for me—it is also for everyone else on our team working on this project.”

COVID-19

RESEARCH



Donnelly Centre Investigators are Developing Therapeutic Antibodies for Covid-19

By Jovana Drinjakovic
March 23, 2020.

Donnelly Centre investigator **Sachdev Sidhu** is on a team receiving \$535,318 from the federal government to engineer antibody molecules that can neutralize coronavirus in the body.

Sidhu already leads another team that received \$886,090 in the first round of federal funding. The goal of that project is to design antiviral medicines that block viral replication.

“With our two funded projects, we are working to develop molecules that can target the virus both inside human cells and on the outside to prevent it from getting in,” says Sidhu.

The latest funded project, headed by U of T professor **James Rini**, of the Departments of Molecular Genetics and Biochemistry, aims to produce antibodies that can neutralize the virus before it invades cells. Such antibodies are naturally produced by the body in response to infection, but researchers hope to reduce the duration and severity of the disease by boosting the immune system with injected antibodies. Neutralizing antibodies are used to treat rabies, which is also caused by a virus, for example.

Also on the team is U of T professor

Alan Cochrane, of the Department of Molecular Genetics, an HIV virologist with expertise in viral RNA processing.

Other teams in Canada, as well as in the UK and US, are looking to infuse Covid-19 survivors’ blood plasma containing antibodies into patients to aid their recovery. Plasma transfusion, however, is fraught with challenges, such as variability in efficacy between different donors and risk of disease transmission. In contrast, synthetic antibodies are a defined drug in terms of molecular content, efficacy and dosing regimen.

The antibodies will be engineered to block the so-called S-protein that forms spikes on the virus surface. The spikes lock on to a protein called ACE2 on the surface of human cells to gain entry. Coating viral particles with synthetic antibodies should prevent the spikes from binding to ACE2.

In another approach, Sidhu and Rini will also engineer antibodies that bind ACE2 to make it inaccessible to the virus. This type of engineered immunity surpasses what is available to the natural immune system, since antibodies that react against self-proteins have been filtered out. If successful, the

approach may obviate worries about viral mutations that can render drugs ineffective to new emerging viral strains, as the host protein ACE2 does not change over time.

Sidhu’s team has advanced a technology called phage display to rapidly create and select human antibodies with desired biological properties, such as blocking the virus’ spike protein. Over the last decade, his team has created hundreds of antibodies with therapeutic potential, some of which are in clinical development through spin off and large pharmaceutical companies.

“Our advances in antibody engineering technologies, and access to the complete genomes of the Covid-19 virus and its relatives, provides us with an opportunity to create tailored therapeutic antibodies at a scale and speed that was not possible even a few years ago,” says Sidhu.

“Ultimately, we aim to optimize methods to the point where the evolution of new drugs will keep pace with the evolution of the virus itself, providing new and effective drugs in response to new outbreaks.”

Rapid On-the-go Test for COVID-19

By Jovana Drinjakovic
April 22, 2020.

Donnelly Centre researchers led by **Warren Chan** are developing an automated, more sensitive and rapid test for COVID-19.

Widespread testing is needed to detect and quickly isolate infected people with mild or no symptoms to halt the virus' rapid spread.

The project is funded through the \$8.4-million Toronto COVID-19 Action Fund launched last month by U of T in support of high-impact research in the global fight against the novel coronavirus.

Powered by tiny light-emitting nanocrystals known as quantum dots, the test can simultaneously detect multiple components of the SARS-CoV-2 genetic material, making it more sensitive than most available methods which measure only one viral gene at a time. Single tests have a level of uncertainty and can give false negative results in people who are infected.

"A lot of available tests out there are faulty but people are using whatever is available and works best at this point," says Chan, Director of U of T's Institute of Biomaterials and Biomedical Engineering and Principal Investigator at the Donnelly Centre.

"Some of the tests were developed without even being tested on patient samples," he added, meaning that the tests have not been optimized for variable amounts of the virus across patients.

Chan is collaborating with infectious disease specialists, Drs. **Samira Mubareka**, of Sunnybrook Health Sciences Centre, and **Jonathan Gubbay**, of Public Health Ontario, who are providing patient swab samples from the frontline so that the test can be calibrated for clinical use. They first joined forces in 2016 to develop a test for the Zika virus, but switched their focus to COVID-19 as it began spreading out of China.

They are also working with **Gary Bader**, a professor of molecular genetics and computer science in the Donnelly Centre, who is tracking how the virus is evolving so that the test can be adjusted to capture new strains as they appear.

The test is based on quantum dots, nano-scale particles that glow in bright colours when struck by light. These particles can be fitted into umpteen microscopic machineries, each looking for signs of the virus while emitting a unique spectrum of light that can be harnessed for test readout. Such collective chemistry

produces more data points and serves to increase result confidence.

The test is also rapid, revealing results in under an hour, and it can be carried out outside hospitals or specialized labs. On-the-go testing like this employs a relatively recently developed chemistry in which DNA is amplified at constant temperature unlike the standard method that requires frequent temperature changes obtainable only with specialized instruments.

The device prototype stems from a career marked by deadly outbreaks. SARS was wreaking havoc in Toronto in 2003 soon after Chan joined U of T as a young faculty. He set out developing diagnostics with quantum dots, whose application in life sciences researchers were just beginning to explore.

"We have been putting this in place for 18 years," says Chan. "We took the time to develop all the science behind it and now we have a plug-and-play system that can be applied for various applications," he says.

The team together made the decision to continue working on their COVID-19 project during lockdown, for which it had to obtain special permission from the university.

Donnelly Centre Investigators and Colleagues to Identify Host Factors Essential for SARS-CoV-2

By Jovana Drinjakovic
May 9, 2020.

Supported by the Toronto COVID-19 Action Fund, Donnelly Centre investigators have joined forces with colleagues from across the university and affiliated hospitals, as well as McMaster University, to identify all components of the human cellular machinery involved in the life cycle of SARS-CoV-2.

Led by **Jason Moffat**, a professor of molecular genetics in the Donnelly Centre, the team will apply the CRISPR genome editing tool to pinpoint all gene-encoded protein factors in human cells exploited by the virus to get inside and multiply. The hope is that there are already clinically approved drugs that target some of these factors which could be quickly repurposed for COVID-19.

“We want to understand the host factors required for the life cycle of the virus on a very deep molecular level,” says Moffat. “Our goal is to see if we can repurpose any drugs in a rational way after we understand more what the host factors are doing.”

But he added that it is important also to understand the biology of the virus.

“Funding basic science is critical for understanding how to manage new biological threats like COVID-19”, says Moffat, “Had there been more opportunities for researchers to break down what the SARS virus was doing following the outbreak in 2003, we probably would have been in a much better position to manage the current pandemic.”

Like all viruses, SARS-CoV-2 hijacks host molecular machinery for its own ends. The virus gains entry by binding the ACE2 receptor. But there are certainly many more factors involved at various stages of its life cycle.

“We often think of viruses as simple – they introduce their genome into the host cell and replicate themselves to release more virus,” says Moffat’s co-investigator **Scott Gray-Owen**, a professor of molecular genetics at U of T who studies infection and how the body responds to it.

“But for any pathogen to cause infection in a host, it has to overcome many different aspects of the immune response. Our aim is therefore to find creative ways to intervene in how the virus replicates or evades immunity so as to stop its

spread and halt the progression of disease,” Gray-Owen says.

The researchers will deploy CRISPR, to switch off every gene in human cells infected with SARS-CoV-2 to find the genes that are essential for the virus’ replication.

Also on the team are Dr. **Samira Mubareka**, of the SunnyBrook Health Centre, and **Karen Mossman**, a professor of pathology and molecular medicine at McMaster University, who were among the first in Canada to isolate SARS-CoV-2 from patient samples and are providing the live virus for the experiments.

Furthermore, Professors **Jack Greenblatt** and **Benjamin Blencowe**, both in the Donnelly Centre, will study how gene expression changes in response to infection for more clues about how COVID-19 develops at the cellular level.

And **Mikko Taipale**, an associate professor of molecular genetics in the Donnelly Centre, and **Shana Kelley**, University Professor at the Leslie Dan Faculty of Pharmacy, will identify the factors required for the production and maintenance of the ACE2 receptor on the cell surface.

Donnelly Investigators are Developing Rapid, Sensitive Antibody Test for COVID-19

By Jovana Drinjakovic
May 15, 2020.

Donnelly Centre investigators are developing a blood test that can detect in under an hour if a person has been infected with SARS-CoV-2 and developed antibodies to it. Such serological tests are seen as crucial for measuring population immunity for better pandemic management.

“Until we have a valid drug treatment strategy or vaccine against COVID-19, we will have to perform mass blood testing in our corresponding countries,” says **Igor Stagljär**, a professor of biochemistry and molecular genetics in the Donnelly Centre, who leads the effort with support from Toronto COVID-19 Action Fund.

“These serological tests will be the only way we can reliably determine the extent of viral spread and identify those individuals who are able to safely return to work,” says Stagljär.

Serological tests look for antibodies in blood that are produced by the body to fight infection. Antibodies are protein molecules that bind and neutralize foreign proteins, known as antigens, that come from viruses and other pathogens.

Earlier this week, Health Canada

announced it approved the first serological test for COVID-19. However, concerns have been raised over some methods regarding their ability to detect potentially low antibody levels in people who were recently infected or suffered mild or no symptoms.

“Ideally we want to have a test that is very fast, low cost and accurate,” says Stagljär, whose team is working to achieve just that.

The test involves dousing a blood sample with purified SARS-CoV-2 proteins so that antibodies can bind to them. The viral proteins are engineered to carry pieces of a fluorescent protein that can only be reconstituted if antibodies are present in a chemical reaction that produces a flash of light—a positive result—which is detected by a plate reader instrument.

The test also employs a new technology called SIMPL, for split intein mediated protein ligation developed by Stagljär’s team and described this week in a study published in the journal *Nature Communications*. SIMPL helps strengthen the contact between antibodies and viral proteins to increase test sensitivity.

“We originally devised SIMPL to study interactions between proteins in living cells, however, we quickly realized that the technology could be adapted to dramatically improve the sensitivity of a COVID-19 serological assay” says **Zhong Yao**, a senior research associate in Stagljär’s lab responsible for both the COVID-19 and SIMPL projects.

The prototype lab test can detect different types of antibodies such as immunoglobulinM and immunoglobulinG that can help distinguish how long ago an infection occurred. IgM antibodies are produced first and are relatively short-lived, while IgG antibodies come later and linger in the bloodstream to confer longer-lasting immunity. While is still unclear how long the immunity to COVID-19 lasts, serological tests will help answer this.

Stagljär is collaborating with Drs. **Samira Mubareka** and **Mario Ostrowski**, of the Sunnybrook Health Sciences Centre and St. Michael’s Hospital, respectively, and **James Rini**, a professor of molecular genetics at U of T’s Faculty of Medicine.

Select Media Coverage

Donnelly Centre media mentions are shown in the chronological order in which they were published:

Gene Fragment Could Link Autism and Cognitive Impairment, [Technology Networks](#)

CRISPR development enables simultaneous gene editing, [Drug Target Review](#)

Mapping the Human Body, One Cell at a Time, [University of Toronto Magazine](#)

Most engineered nanoparticles enter tumours through cells, not between them, [NanoWerk](#)

CRISPR Tool Harnesses Two Cas Enzymes to Simultaneously Edit Multiple Genes, [Genetic Engineering & Biotechnology News](#)

Multiple Genome Fragments Can Now Be Edited at a Time, [Med India](#)

CRISPR development enables simultaneous gene editing, [Drug Target Review](#)

U of T scientists working on coronavirus treatment among recipients of Canadian emergency grants, [Toronto Star](#)

The vaccine hunters racing to save the world from the coronavirus pandemic, [The Telegraph](#) (UK)

Les chercheurs s'activent pour trouver une riposte, [La Presse](#) (Italy)

Tens of Thousands of Protein-Protein Interactions Reported in Human Reference Interactome Map, [GenomeWeb](#)

Das soziale Netzwerk unserer Proteine, [Spektrum.de](#) (German)

Fontos térkép készült az emberi testről, a vírusok és a rák elleni küzdelemben is segítget, [hvg.hu](#) (Hungary)

Publicado el "facebook" de las proteínas humanas, [Catalunyavanguardista](#) (Spain)

Startup targets glioblastoma tumors with CAR-T therapy, [Fierce Biotech](#)

CAR-T Cell Therapy Shows Promise against Glioblastoma in Mice, [Genetic Engineering & Biotechnology News](#)

Un nouveau traitement prometteur contre le cancer du cerveau, [Futura Sante](#) (France)

La investigación del cáncer nunca para (tampoco en la pandemia), [The Conversation](#) (Spanish)

Unique Metabolic Signature Predicts Transition to T2D After Gestational Diabetes, [Clinical Advisor](#)

DIABÈTE : Le test sanguin qui prédit le risque des années avant, [Sante log](#) (France)

Unique molecular mechanics can pave way for potential treatments for infections, [News Medical](#)

Boost in battle against drug-resistant parasites, as roundworms' ability to survive without oxygen revealed, [Russia Today Network](#)

No. 3: Because our best and brightest are leading the fight against Covid, [Toronto Life](#)

Over a Hundred Genes Found to Aid Cancer Evade the Immune System, [Genetic Engineering & Biotechnology News](#)

CRISPR Screen Uncovers Genes That Help Cancer Cells Evade Immune System, [Genomeweb](#)

Study calls out the genes that make cancer cells so hard to kill, [Big Think](#)

Engineer who designs gels to mimic human tissues wins Canada's top science prize, [CBC News](#)

University of Toronto researcher awarded Canada's top science prize, [The Globe and Mail](#)

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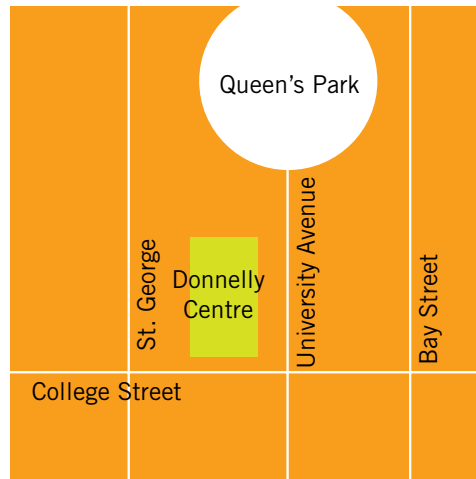
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THANKS EVERYONE FOR A GREAT YEAR!

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Donnelly Centre, University of Toronto

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

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