Donnelly Centre

for Cellular + Biomolecular Research

Annual Report | 2022

TEMERTY FACULTY OF MEDICINE
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The Donnelly Centre for Cellular and Biomolecular Research is a research institute at the University of Toronto where scientists from diverse fields make discoveries to advance science, medicine and health.

Founded in 2005, the Donnelly Centre has become globally recognized as a leading hub for research in systems biology, regenerative medicine and disease modeling.

The Centre was established thanks to an investment from the Government of Canada, the province of Ontario, private sector companies and the visionary philanthropist Dr. Terrence J. Donnelly. The Centre is grateful to Mr. Donnelly on his continued support.

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Director's Message

It is my great pleasure to introduce the 2022 Donnelly Centre Annual Report. It is not an exaggeration to say we have much to be proud of as we look back on the past 12 months. We continued to navigate the recovery from the pandemic and saw the return to in-person research activities as well as some normalcy in our every-day lives. At the same time, our faculty continued to be recognized for their research leadership with some of the most distinguished awards and appointments at home and internationally.

But it is more than that. The Centre has expanded its faculty community with two new appointments. I am thrilled that Professor **Milica Radisic** from U of T's Institute of Biomedical Engineering has joined the Centre, bringing her world-leading expertise in organ-on-a-chip engineering, disease modeling and treatment discovery. We are also fortunate to have Assistant Professor **Artem Babaian** joining our ranks whose innovative use of cloud computing for big data analysis holds immense potential for the discovery of new viruses.

On the discovery front, Donnelly Centre investigators continue to work tirelessly to advance the frontiers of knowledge. Their recent insights have shed light on some long-standing questions in cellular function with far reaching implications for our understanding and treatment of disease. These inroads are only possible with sustained support and funding for discovery science. Despite increasing global and national economic challenges, the Centre's investigators raised $36M in competitive research funding in last year alone—an extraordinary achievement and more than any other department at U of T's Temerty Faculty of Medicine.

Our community comprises over 400 members, including 32 faculty and over 300 graduate students and postdoctoral trainees working at the intersection of functional genomics, computational biology, regenerative medicine and, engineering. Their dedication and hard work are truly inspiring, and I am grateful to be part of such a talented and passionate community.

With this report, we bring you a selection of stories about 2022's research breakthroughs from Donnelly Centre scientists. I hope you will enjoy reading about our progress and more information can be found at:
http://thedonnellycentre.utoronto.ca/news

Stephane Angers, Director and Professor
Donnelly Centre for Cellular and Biomolecular Research

New Hope for Childhood Brain Cancer

> *Every time we look at cancer cells and profile them, we see substantial metabolic differences.*
>
> **Rafael Montenegro Burke,** Principal Investigator, Donnelly Centre

By Jovana Drinjakovic

Researchers from the Donnelly Centre at U of T and McMaster University have reported a potential breakthrough in medulloblastoma, a form of brain cancer that predominantly affects children and infants. The finding opens the door to the development of new targeted treatments that would be less harmful to the developing brain.

Available treatment has been around for decades and consists of non-selective chemotherapy and radiation that destroy not only the cancer cells but also the healthy stem cells that are essential for brain development, said **Rafael Montenegro-Burke**, a senior co-author of the research and an assistant professor of molecular genetics in the Donnelly Centre.

"The damage that you do to the stem cells will have a huge impact on the brain development of these kids and cognitive function later in life. The goal is to find a way to exclusively kill medulloblastoma and not harm the stem cells," he said.

Working with Dr. Sheila Singh, pediatric neurosurgeon and director of the Centre for Discovery in Cancer Research at McMaster University, the team was able to identify a molecule that is essential for the survival of medulloblastoma cells, and target it with drugs to destroy cancer without touching the stem cells.

The journal *Cancer Cell* publishing the findings.

The researchers took a relatively new approach of unbiased metabolomics to look for unique molecular signatures in the medulloblastoma cells that could be exploited for therapy. The field of metabolomics concerns the study of small molecules, or metabolites, which are produced by metabolic reactions in cells, or are taken up as nutrients from their surroundings. These include amino-acids, sugars, lipids and other small molecules.

Montenegro-Burke joined the Donnelly Centre in 2020 to establish one of the first metabolomics labs at the university. His group seeks to map metabolite diversity in healthy, and diseased cells and find out how metabolites contribute to disease, including cancer.

Compared to genes and proteins, metabolite diversity and function remain largely unexplored, said Montenegro-Burke. Yet metabolic rewiring is a key mechanism that allows cancer cells to rapidly adapt to a changing environment. It was first reported a century ago by German scientist Otto Heinrich Warburg, for which he won the Nobel Prize in 1931.

"We've known for a long time that cancer affects metabolism," said Montenegro-Burke. "The cancer needs all those nutrients not only to be able to grow, but also to

adapt to survive treatment and the immune system."

"Every time we look at cancer cells and profile them, we see substantial metabolic differences," he said.

The researchers focused on group 3 medulloblastoma, caused by an overabundance of the MYC protein that spurs cell proliferation. These tumours are "a particularly sinister subtype" as they often spread prior to diagnosis and recur, said **William Gwynne**, former postdoctoral fellow in the Singh lab and first author on the paper.

"Once the disease recurs, it is almost ostensibly incurable," said Gwynne, who is now a postdoctoral fellow in Montenegro-Burke's lab.

The team compared metabolite diversity between the cell lines derived from patient tumours and healthy stem cells. Using untargeted mass spectrometry, a method for detecting molecules based on their mass, they were able to detect tens of thousands of metabolites, the vast majority of which were unknown. They then applied computational biology approaches that allowed them to identify about one thousand metabolites, reaching the limit of available technology.

What immediately struck them was that high MYC levels correlated with availability of pyrimidine, a small molecule which is used to create a coating around the MYC protein that shields it from degradation.

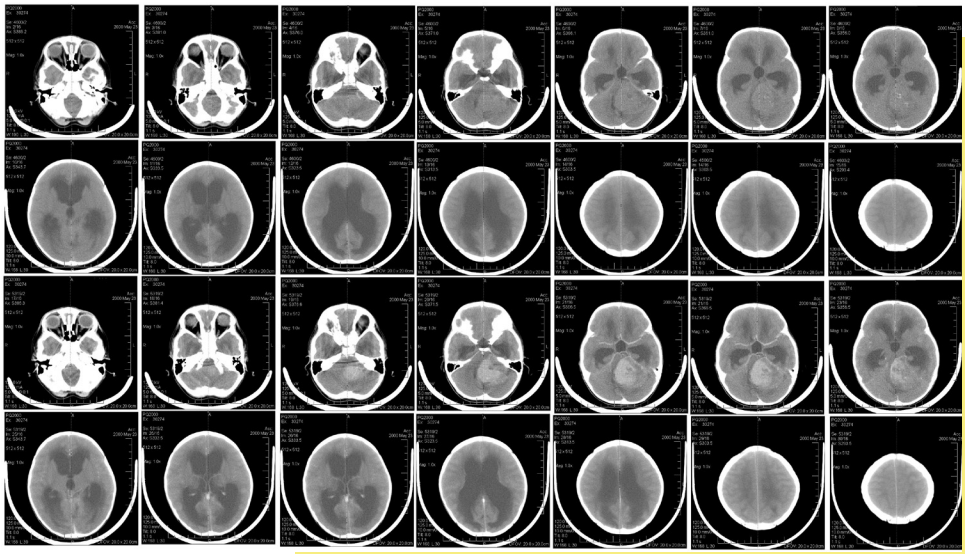
They reasoned that removing pyrimidine from medulloblastoma cells would lead to MYC destruction and halt cell proliferation. This is exactly what happened. Depleting pyrimidine either by removing the enzyme responsible for its biosynthesis, or by inhibiting its function with drugs, triggered MYC degradation in cancer cells, leading them to undergo apoptosis, also known as "cellular suicide".

"This metabolite is absolutely necessary for MYC to be functional and to drive tumours," said Montenegro-Burke.

"We don't yet fully understand its role, but we can start thinking about how to treat medulloblastoma." Gwynne added that the inhibitors of pyrimidine biosynthesis have a real potential as drug candidates, due to their ability to kill cancer at low doses while sparing the healthy stem cells.

Similar compounds are already making their way through clinical trials for the treatment of several other cancers. Here the drugs are used to kill cancer cells by blocking DNA synthesis that also requires pyrimidine. The researchers are pinning hopes that the ongoing clinical studies—should the drugs prove safe for use in patients—would pave the way for a medulloblastoma trial soon.

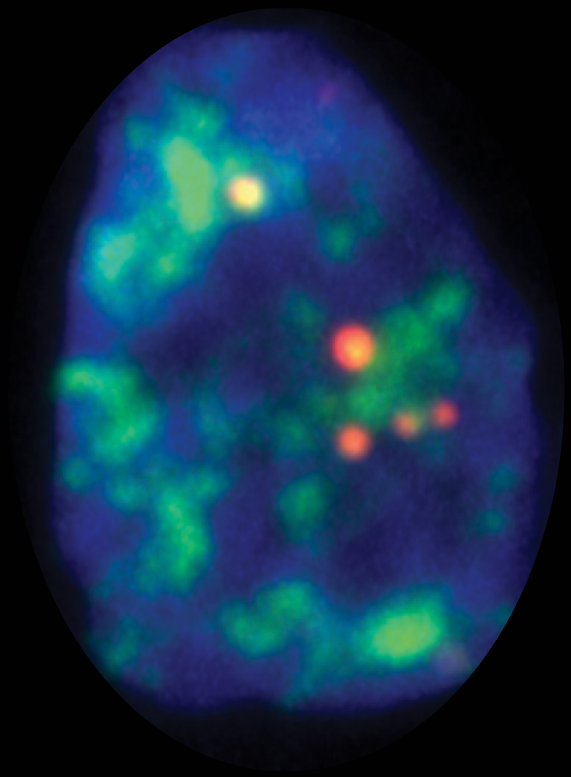
If effective, other patient populations could also benefit, as MYC is a known driver of different types of leukemia and breast and lung cancer, said Gwynne.



A sequence of brain scans of child with medulloblastoma tumour. Standard treatment involves chemotherapy and radiation that destroy both the cancer cells and the healthy brain stem cells that are essential for brain development. By targeting the cancer cells in a specific manner the researchers hope to develop new therapy that would be less harmful for youths whose brains are still developing. (WikiMedia Commons)

RNA Map of Cell Nucleus Holds Clues to Gene Regulation

By Jovana Drinjakovic



Donnelly Centre researchers have reported the first large-scale survey of RNA transcripts, or genes' messages, that are associated with different nuclear bodies in human cells. Their work suggests these structures act as hubs to coordinate gene regulation and cell division, opening new avenues for researching cellular function and how it breaks down in disease.

"It was known that some nuclear domains contain RNA, but the composition of that RNA was not systematically probed in previous studies," said **Benjamin Blencowe**, senior author on the study and a professor of molecular genetics in the Donnelly Centre for Cellular and Biomolecular Research, at the Temerity Faculty of Medicine.

"Our data has shed light not only on the RNA composition of different nuclear domains, but also provides clues as to the functions of some of these domains," he said.

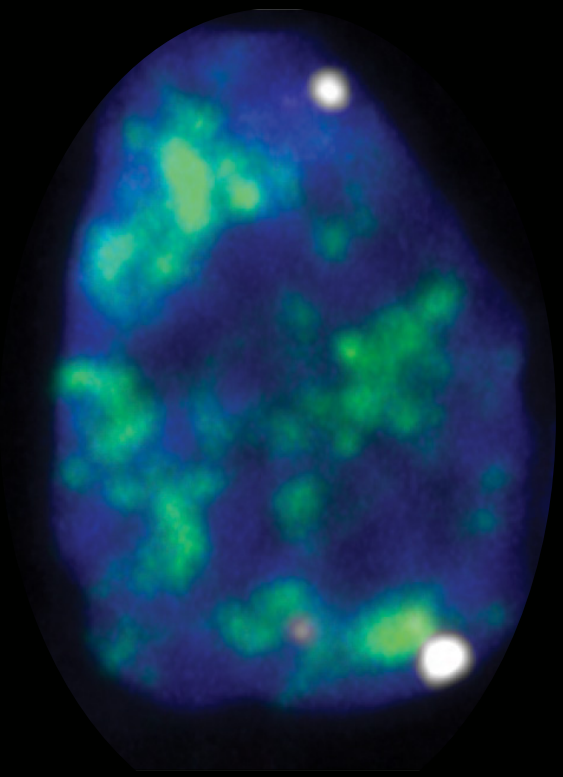
The leading journal *Molecular Cell* published the findings.

Most people are familiar with the cell nucleus from grade school biology as a storage compartment for DNA. But the nucleus also contains several distinct structures, called nuclear bodies or domains, whose roles scientists are just beginning to understand.

Until now, the information on nuclear body composition has

trickled in piecemeal because there were no methods enabling a systematic survey of RNA localized to these structures. But postdoctoral fellow Rasim Barutcu and graduate student Mingkun Wu realized they could apply a method called APEX-Seq, which had been developed by Stanford and Berkeley scientists.

APEX is an enzyme that can be fused to any protein of interest and allows labeling of RNAs, and other biomolecules, in its proximity. The labeled RNAs can then be isolated and identified by sequencing. By fusing APEX to various marker proteins residing in the different nuclear bodies, Barutcu and Wu were able to create RNA maps for each compartment in the nucleus. In this effort, they collaborated with Ulrich Braunschweig, a senior research associate in the Blencowe lab, and with the groups of **Anne-Claude Gingras**, at the Lunenfeld-Tanenbaum Research Institute, at Sinai Health System, **Philipp Maass**, at The Hospital for Sick Children, and Robert Weatheritt, at the Garvan Institute of Medical Research, Australia.



Microscopy images of cell nuclei with fluorescently labeled RNA transcripts which contain retained introns. On the left are shown transcripts associated with nuclear speckles, while on the right are shown transcripts associated with another nuclear body called the lamina. Image provided by Rasim Barutcu and Mingkun Wu (Blencowe lab).

The team discovered swaths of novel RNAs, from several hundred to thousands, across the nuclear bodies. Previously, only a handful of transcripts were known to be associated with some of these structures, said Barutcu, whose research was supported by the Banting Postdoctoral Fellowship and a fellowship from the Canadian Institutes of Health Research (CIHR).

One piece of data immediately struck the researchers. The nuclear bodies known as the speckles were associated with surprisingly high numbers of RNA transcripts with retained introns, segments which do not code for proteins.

When a gene is transcribed into RNA, introns must be spliced out in the nucleus before the transcript can be released out of the nucleus to serve as a template for making proteins.

The finding indicated that speckles are associated with a class of introns with delayed splicing. Further analysis revealed these transcripts hailed from the genes that control other genes and the cell division cycle. A timely control of genes involved in cell cycle progression is key to ensure their protein products are made only when they are needed as errors in this process often drive cancer.

The researchers think that the role of the speckles might be to coordinate intron removal from transcripts with their release from the nucleus. This mechanism would help ensure a rapid response to cellular signals to make the right kinds of proteins at the right time. Disrupting the speckles altered splicing patterns of the retained introns, supporting the idea that the speckles are linked to cell cycle progression.

This model opens up new ways of thinking about cell cycle regulation with implications for cancer research, said Blencowe, who holds the Canada Research Chair in RNA Biology and Genomics and the Banbury Chair in Medical Research.

“We’ve uncovered a mechanism involving differential intron retention linked to speckle integrity that could play an important role in not just normal cell division but also how it goes wrong in cancers,” he said.

New Biomaterial Opens Pathways to More Targeted Cancer Treatments

By Safa Jinje

A team of researchers, led by Donnelly Centre investigator and U of T Engineering Professor **Molly Shoichet** has designed a new way to grow cells in a laboratory that enables them to better emulate cancerous tumours. The platform — based on a type of material known as a hydrogel, a soft jelly-like substance — opens new ways to advance treatment options for cancer.

By investigating the natural molecules found in breast cancer tissue, **Alexander Baker**, a postdoctoral fellow, and **Laura Bahlmann**, a PhD candidate, were able to design a more compositionally defined and reliable alternative to the standard material typically used by cell biologists called Matrigel®. They shared their findings in a paper published in *Materials Today*.

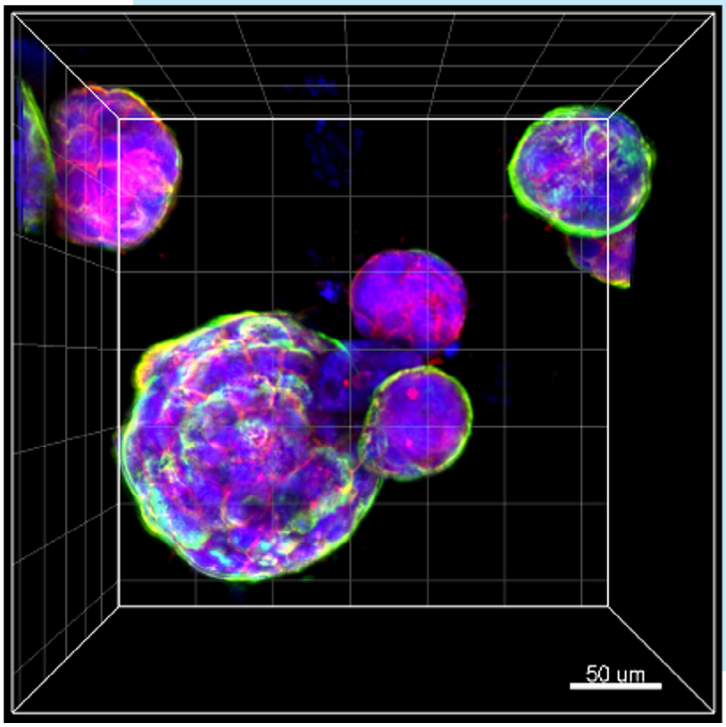
The new biomimetic hydrogel is composed of hyaluronan, which is found in healthy tissue and increases during the progression of many cancers, including breast, lung, brain, prostate, ovarian and pancreatic but notably absent from Matrigel®. These materials also contain laminin, a protein that is abundant in breast tissue.

Together, these two ingredients resulted in a hydrogel that closely mimics native tissue. It has all the beneficial properties of Matrigel®, but it goes further by facilitating communication between cells and the surrounding tissue.

When comparing lab-grown patient biopsy cells in the presence of their new hydrogel versus Matrigel®, the team observed different cancer cell growth rates and responses to drugs. When they took the same hydrogel and injected the patient cells to produce an animal model of the disease, they observed differences in the immune response, where Matrigel® seemed to bias the results, thereby confounding researchers' understanding. However, the new hydrogel provided an unbiased canvas to study how tumour growth impacts the host immune cellular response.

"With our increasing understanding of the immune system in cancer, the importance of unbiased results cannot be overstated," said Shoichet.

These results suggest that the new hydrogel can produce results that are more like those typically observed in human cancer tumours. One example is the ability of breast cells to self-assemble into 3D structures with key components oriented in a certain direction, a process known as



Patient-derived breast cancer organoids from a HER2- human biopsy directly cultured in hyaluronan/laminin-based hydrogels crosslinked with enzyme-degradable peptides via oxime chemistry. Cells were grown from single cells and grew into organoids over 14 days. Blue indicates the nuclei, which grow larger in cancer cells; green indicates CD44 (hyaluronan receptor), a cell surface adhesion receptor; and pink indicates F-actin, which regulates cell shape.

polarization.

Before a new cancer therapeutic can be approved for human use in Canada and the United States, Health Canada and the FDA require it passes in vivo animal studies. This includes patient-derived xenograft studies, which are models of cancer where the tissue or cells from a human tumour are implanted into immunodeficient mice. These models allow researchers to better emulate human cancer growth and can be used to study the effects of treatments on clinically relevant patient cancer cells.

But in some instances, the time required to produce these animal models for cancer research is too long. A lab-based approach to grow these valuable patient cells in a more defined material can accelerate the screening process.

The new hydrogel was designed to emulate the cancer cell microenvironment creating a highly reliable system for cancer studies. The researchers were able to control the inputs, resulting in controlled mechanical and biochemical properties relevant to the tissues they were emulating.
"The long-term goal for cancer research is to move away from animal studies," says Bahlmann. "If we could eventually say that our platform is predictive of the in vivo response, there would be a lot of advantages, including reducing the amount of time it takes to get results from a study."

The team collaborated with Dr. **David Cescon**, an oncologist at University Health Network, to obtain the patient breast cancer cells used in the study. And while much of the study was focused on breast cancer, they also used the platform to grow eight other cancer types — brain, colon, leukemia, lung, lymphoma, ovarian, pancreas and prostate — and expanded their research to study cell invasion.

The researchers hope to show that by growing other cancer cells in their hydrogel, they can discover new targets and new drugs for the treatment of breast and other cancers.

"I think we are moving towards the era of precision medicine, and if we can screen a patient's cells quickly and effectively, then we should be able to identify the best therapies for that individual. Our new hydrogel starts us down this journey of drug discovery," says Shoichet.

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

Protein's New Role Upends View About Its Impact on Cancer

By Jovana Drinjakovic

Donnelly Centre researchers have uncovered an unexpected role for a well-established gene regulator, Specificity Protein 1 (SP1) four decades after its initial discovery. As well as controlling gene activity, SP1 exerts another layer of control by influencing the stability of genes' RNA messages, Donnelly Centre researchers have revealed.

The finding is especially significant for cancer research, as it upends the established thinking about how Sp1 contributes to the disease and opens new avenues for treatment development.

"Sp1 has been known to be involved in cancer for a long time, but it was thought to be because of its ability to bind DNA and act as a transcription factor, because everybody knew about that," said **Jack Greenblatt**, senior author on the paper and a professor of molecular genetics in the Donnelly Centre.

"We think that's not the answer. We think it affects cancer through its ability to bind RNA and regulate transcript stability," said Greenblatt, who is also a University Professor, the highest academic rank at U of T.

The journal *Molecular Cell* published the findings.

Sp1 controls activation of around 6,000 genes— roughly a third of the human genome—which are mostly required for cellular sustenance.

And now there's also the RNA-binding Sp1, which holds sway over another, and mostly non-overlapping, group of 2,000 genes by impacting abundance of their mRNA copies, according to the study.

When a gene is switched on, its code gets copied into a messenger RNA, or a transcript, which serves as a template for building the encoded protein molecule. At its tail end, mRNA harbors the untranslated region, or UTR, which does not get translated into protein, but which has a regulatory role and is important for transcript stability. Research has shown that transcripts with long UTR tails are often less stable and get degraded more rapidly by cellular enzymes, while short-tailed UTRs are more protected from degradation.

"It is here, in the UTR, that Sp1 binds its target mRNAs," said **Syed Nabeel-Shah**, a PhD student in the lab and the research's co-first author, along with former post-doctoral fellow, **Jingwen Song**. When they depleted Sp1 from cells, they found that this led to an increase in certain transcripts' UTR length, indicating that Sp1 acts to yield shorter UTR tails. They further showed that UTR trimming is

accomplished by the RNA cleavage machinery, which snips the RNA near where Sp1 is bound.

Control of UTR length has emerged as an important layer of gene regulation. This is especially true in cancer cells, which abound in short-tailed transcripts. The shorter the UTR tail, the more stable the transcript, resulting in more protein templates — and ultimately more protein molecules that can be produced.

"Fast-growing cells need certain genes expressed at higher levels", said Greenblatt. "The effect of having shorter UTRs is often a higher concentration of mRNA, and consequently higher protein concentration."

It remained unclear how balance is skewed towards shorter UTRs in cancer cells, but the new research indicates that Sp1 holds part of the key.

Sp1 has long been known to be abundant across many types of cancer, including breast cancer, which the team focused their analysis on. They obtained RNA sequencing data from the Cancer Genome Atlas on one thousand breast cancer patients. They found that Sp1 levels correlate with its target transcript tail length and abundance. The more Sp1 in a patient sample, the shorter the tails in the same sample and the higher the mRNA levels when those tails are bound by Sp1. "All this goes to suggest that Sp1 promotes cancer through its RNA-binding role," said Nabeel-Shah.

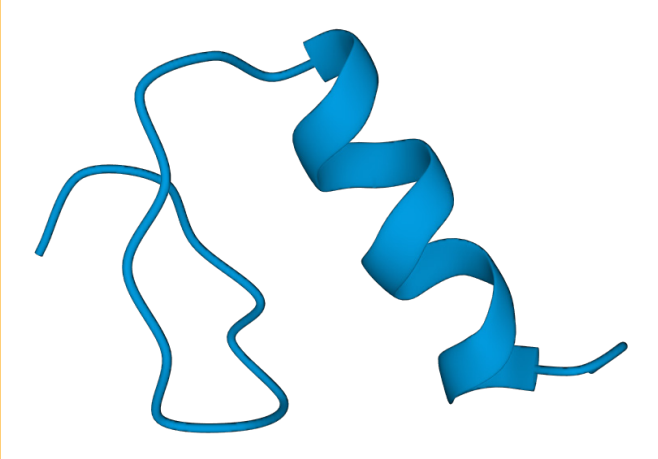
The finding is in contrast with the established view where Sp1 contributes to cancer by turbocharging the expression of its target genes as a DNA-binding protein. The researchers found no support in the data for this concept. They said there was no correlation between Sp1 levels in breast cancer cells and the amount of mRNA transcribed from the genes it targets on DNA.

Although they only looked at breast cancer, the researchers think that Sp1 plays a similar role in other types of cancer, given the large number of mRNAs it regulates.

The study opens up a new way of thinking not only about Sp1 and its role in cancer, but also about other similar proteins. Sp1 belongs to a family of C2H2 zinc finger transcription factors, which form the largest group of transcription factors in humans. The majority of its more than 700 members remain poorly explored, however.

Nabeel-Shah is now working to determine if other C2H2 proteins also bind RNA. So far, he has tested 150 of these proteins and found that 145 bind both DNA and RNA, suggesting that there might be many others with dual roles in gene regulation.

Sp1 could again turn out to be the first among many, just like four decades ago.



Molecular structure of the zinc-finger DNA binding domain of SP1. SP1 was the first human transcriptional regulator that was discovered, nearly 40 years ago. A staple in all molecular biology texbooks, it has solely been cast as a DNA-binding gene activator. The new research upends this thinking to show that SP1 also binds and regulates the genes' RNA messages. The parts of SP1 that engage with DNA and RNA, as well as their targets, are largely non-overlapping.

Startup To Develop Precision Cancer Therapeutics

By Jovana Drinjakovic

University of Toronto and the AI drug discovery company Cyclica have launched a biotech startup that will develop targeted therapies for difficult-to-treat cancers.

Perturba Therapeutics was founded by Donnelly Centre investigator **Igor Stagljar** in partnership with Cyclica.

"I am very excited about our collaboration with Cyclica, thanks to their powerful AI platform that has transformed research in my laboratory over the past few years," said Stagljar, who was named U of T's Inventor of the Year in 2015. "Our combined approach allows us to go after some of the most intractable cancers by selecting in silico drug molecules that specifically target oncogenic proteins."

"It will also accelerate drug development by cutting the time to preclinical testing from several years to months," he said.

The company builds on an earlier collaboration between Stagljar's lab and Cyclica, which produced two inhibitors of the osimertinib resistant triple mutant EGF receptor for the treatment of non-small cell lung cancer, the most common type of lung cancer, which Perturba will initially focus on advancing. Osimertinib is currently the drug of last resort for this type of cancer.

Perturba will also launch four programs targeting small GTPases, enzymes that are mutated in many cancers, but which have been difficult to target with conventional methods.

> *"Our combined approach allows us to go after some of the most intractable cancers by selecting in silico drug molecules that specifically target oncogenic proteins*
>
> **Igor Stagljar**,
> Principal Investigator &
> U of T Professor,
> Donnelly Centre

"What others view as 'undruggable,' we see as potential," said Naheed Kurji, co-founder, CEO and President of Cyclica.

The partnership brings together Cyclica's AI drug design technology with two first-in-class live cell-based assays from the Stagljar lab, called MaMTH and SIMPL, for validation of selected compounds.

The Stagljar lab is world renowned for its study of protein-protein interactions (PPIs), and MaMTH and SIMPL were initially developed for mapping human protein networks on a global scale. Understanding how proteins talk to each other is important, because when those interactions go awry, it can lead to disease.

Stagljar's team previously mapped interactions between disease-causing proteins and their partners, revealing potential "weak spots" that can be targeted by small molecule drugs for potential treatments of diseases ranging from cancer to cystic fibrosis.

Perturba's compounds work by specifically perturbing oncogenic PPIs in cancer cells, therefore sparing the surrounding healthy tissue from their harmful effects. But the hunt for such drugs has been slow using traditional approaches, often resulting in compounds with off-target effects, meaning they act on unintended proteins as well as their targets, which can have wide side-effects in the body.

Advances in AI have transformed drug discovery thanks to machine learning algorithms that can pick the best candidates from vast chemical libraries containing billions of molecules, which selectively inhibit disease-causing PPIs. That has opened the door to targeting previously undruggable proteins, which make up the majority of the human proteome.

"Lots of proteins have smooth surfaces with no pockets for drugs to bind to. But using Cyclica's approach we can screen protein surfaces for wild type and oncogenic versions, and we can then test our molecules very quickly in our live cell-based assays," said Stagljar.

"Cyclica's AI-augmented polypharmacology based drug design platform technology, complemented with Professor Stagljar's empirical live cell assays, allows us to approach targets we could not before," said Kurji. "We're so excited to partner with the world-class Stagljar lab in driving forward our shared vision."

Cyclica will provide initial funding for Perturba and will seek external funding as required.

Seeing Smaller Than Light To Help In Fight Against Disease

By Tyler Irving

Microscopes are some of the most powerful tools in cell biology — but what if the cell component that needs to be imaged is smaller than the wavelengths of visible light? A new study from Professor **Chris Yip** proposes a solution, one that could help advance research into cancer and other diseases.

"There are a couple of existing techniques to image things that are smaller than light, but they have drawbacks," says Yip, Principal Investigator in the Donnelly Centre and Dean of Faculty of Applied Science & Engineering. "One is electron microscopy, which relies on firing electrons at a sample. Another is atomic force microscopy, which involves dragging a tiny needle tip across a surface. But if the feature you're trying to image doesn't have a distinct shape or a unique electron density, it's hard to identify what you're looking at. And in our case, the thing keeps moving around."

The challenge facing Yip and his collaborators — including Professor of molecular genetics **Scott Gray-Owen** and PhD candidate in biomedical engineering, **Amine Driouchi**, — was to study how a particular protein known as CEACAM1 distributes itself over the surface of a living cell in real time.

Cell surface proteins are key to many different biological processes, influencing how cells take in nutrients and how they send signals to one another. Viruses also use cell surface proteins to get inside cells and hijack their biochemical machinery in order to replicate.

CEACAM1 is a cell surface protein found on certain types of cancer cells, and is suspected of playing a role in cell adhesion within tumours. How exactly it does this is not well understood, but the team believes that it may have something to do with the way it is arranged.

"On the surface of the cell, CEACAM1 can exist as a monomer — that is, by itself — or as a dimer, meaning two of them stuck together," said Yip. "It can also form aggregates or clusters. What we wanted to see was whether these different arrangements had any impact on its function in terms of helping cancer cells adhere to each other."

In research published in the *Journal of Biological Chemistry*, the team applied a variation of a technique known as Förster resonance energy transfer (FRET) to see whether CEACAM1 was arranged in clusters, dimers or individual molecules.

Conventional FRET is used to tell whether two different proteins are interacting with each other. Both proteins are tagged with unique fluorescent marker molecule, each of which absorbs light at one wavelength and emits it at

another. Crucially, the emission wavelength of marker A is the same as the excitation wavelength of marker B.

If the proteins are close together — which suggests they are interacting — exciting marker A will cause energy to jump across and light up marker B. If only marker A lights up, it means the proteins are too far apart to make this jump.

But in this case, the team was dealing with a single protein interacting with copies of itself, so it could not be tagged with two different markers. To overcome this challenge, the team made use of a different feature of light: its polarization.

After all the CEACAM1 molecules were tagged with the same fluorescent marker, the team hit the sample with polarized light at the right wavelength to excite this marker. When the fluorescent marker got excited and released a photon in response, the team tracked the polarization of the light produced.

"If the emission polarization is the same as the excitation one, that means that the photon was given off by the same molecule," says Yip. "But if it was different, that meant that energy was transferred from one CEACAM1 molecule to another one next door, which means they were close together."

So far so good, but the team had another challenge: the light signal produced was still not specific enough to establish where exactly the CEACAM1 molecules were.

"Blue light has a wavelength of about 450 nanometres, while red light is more like 650 nanometres," says Yip. "You can only resolve down to within half the wavelength of the light you're using, so even if the pixels in the resulting image are right on top of each other, the actual proteins could still be hundreds of nanometres apart, which is pretty far in molecular terms."

To overcome this, they used another technique, known as stochastic optical reconstruction microscopy, or STORM. In this technique, the fluorescent markers do not shine constantly, but instead blink on and off at random intervals. Microscopists can then analyze the photons given off, using statistical analysis to localize their source to within a few nanometres. The team combined the two techniques by creating a STORM fluorescent marker that attached itself to the fluorescent marker used for FRET. While neither technique is entirely new, the paper is the first to describe putting them together in this way.

Yip says that now that proof-of-concept has been demonstrated, it could be applied to many other contexts.

"Cell surface proteins are relevant to infectious diseases, genetic conditions, cancer, you name it," says Yip. "This technique will help us answer the basic questions, such as: how do they get themselves to the surface? What state are they in? Why are they distributed the way they are? And if we disrupt them, could we help treat some of these challenging medical conditions?"

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

Researchers Crack 30 Year Old Mystery of Odor Switching in Worms

By Jovana Drinjakovic

To smell or not to smell can be a matter of life and death, especially for soil-dwelling nematodes that chiefly rely on olfaction for survival. But how these worms discriminate between more than a thousand different scents has puzzled scientists for decades.

Now, Donnelly Centre researchers have uncovered a mechanism behind this process and show that it involves a conserved protein that helps equilibrate vision in humans. The implications of their finding stretch beyond nematode olfaction and could also help explain how our brains work.

The research was led by **Derek van der Kooy**, a professor of molecular genetics in the Donnelly Centre. The van der Kooy lab is renowned for its neuroscience research that uses a variety of model organisms, including the nematode *Caenorhabditis elegans*.

The journal *Proceedings of the National Academy of Science* published their work.

"The worms have an incredible sense of smell — it's absolutely amazing," said **Daniel Merritt**, first co-author on the paper and former graduate student.

"They can detect a wide variety of compounds, such as molecules released from soil, fruit, flowers, bacteria. They can even smell explosives and cancer biomarkers in the urine of patients," he said.

C. elegans are champion sniffers thanks to possessing around 1300 odorant receptors. Like in humans, who have about 400 receptors, each receptor is dedicated to sensing one type of smell, but this is where similarities end.

Our noses are lined with hundreds of sensory neurons, each expressing only one receptor type. When an odorant activates a given neuron, the signal travels deeper into the brain along its long process, or axon, where it is perceived as smell. Smell discrimination is enabled by a physical separation of axonal cables carrying different smell signals.

The worms, however, have only 32 olfactory neurons, which hold all of their 1300 receptors.

"Clearly, the one neuron-one smell strategy is not going to work here," Merritt said.

Yet, the worms can discriminate between different smells sensed by the same neuron. Pioneering research from the

early 1990s showed that when exposed to two attractive odors, where one is uniformly present and the other is localized, the worms crawl towards the latter. But how this behaviour is regulated at the molecular level remained unclear.

"It seems that all the information that is sensed by this neuron gets compressed into one signal, and yet the worm can somehow tell the difference between the upstream components. That's where we came to it," said Merritt.

Merritt and former master's student Isabel **MacKay-Clackett**, also a co-first author on the paper, reasoned that perhaps the worms are sensing how strong the smells are.

According to their hypothesis, the smells that are everywhere are not the most informative cues and would become desensitized, meaning the worms would ignore them. This would leave the weakly present smells, which might be more useful in guiding behaviour, able to activate their receptors and cause signal transduction.

The head of an adult C. elegans worm. An olfactory neuron expressing a particular type of odorrant receptor is shown in green.

They also had a hunch for how this could work at the molecular level. A protein called arrestin is a known desensitizer of G protein coupled receptors (GPCRs), a large family of proteins that perceive external stimuli, which odorant receptors belong to. Arrestins for example allow us to adjust vision in bright light by damping down signalling through the photon-sensing receptors in the retina.

The team wondered if arrestin might also act in worms to desensitize receptors perceiving a stronger smell in favour of those that sense a weaker one, when both are sensed by the same neuron. To test this, they exposed the worms lacking the arrestin gene to two different attractive smells in a Petri dish, where one was mixed into the medium to make it uniform, and the other was placed at one spot some distance from the worms.

Without arrestin, the worms were no longer able to find the source of the weaker smell. Like in the human eye squinting in bright sunshine, arrestin helps remove an overpowering sensation—ambient smell in this case—so that the worms can sense a localized smell and move towards it.

Arrestin is not required, however, when the smells are sensed with different neurons, suggesting that worms employ the same discrimination strategy as vertebrates when the smell signals travel down different axons.

The team looked at different sets of smells and neurons and found they all obeyed the same logic, said Merritt. They also used drugs to block arrestin and found that this too abolished smell discrimination.

The finding is significant because it is the first evidence showing that arrestin can fine tune multiple sensations.
"There is no case known in biology before this where arrestin is being used to allow for discrimination of signals external to the cell," said Merritt.

He added that the same mechanism could be playing out in other animals when multiple GPCRs are expressed on the same cell, especially in the brain. Our brains are bathed in neurochemicals that signal through hundreds of different GPCRs, raising a possibility that arrestin, of which there are four types in humans, could be key for information processing.

"Our work provides one piece of the puzzle how the worms' amazing sense of smell works. But it also informs our understanding of how GPCR signalling works more broadly within animals," said Merritt.

Research Advances Under-Skin Cell Therapy For Type 1 Diabetes

By Julie Crljen

New Medicine by Design-funded research out of the lab of Donnelly Centre investigator **Michael Sefton** continues to advance one of his lab's goals: developing a cell-based treatment for type 1 diabetes that can be implanted under the skin and would eliminate the need for insulin injections.

"Type 1 diabetes is an autoimmune disease. The immune system mistakenly attacks pancreatic cells that secrete insulin, a hormone that's needed to control blood sugar," says Sefton, a University Professor at the U of T's Faculty of Engineering & Applied Science and Medicine by Design's executive director. "To give the person with type 1 diabetes the cells back somehow is a logical treatment – but there are many hurdles to overcome before we can do so. This research is another step forward to this promising regenerative medicine therapy."

Medicine by Design is a U of T initiative that seeks to accelerate research in regenerative medicine and its applications.

The finding, published in the February issue of *Biomaterials*, showed that cells implanted under the skin of host animals

with diabetes allowed connections to the blood vessels and were able to regulate blood sugar. The researchers confirmed that the treatment allowed insulin-secreting cells to survive in the animals.

“This research showed us again that our method of transplanting pancreatic cells under the skin has a lot of promise as a future diabetes therapy,” says Sefton, “And that continuing to refine our methods is the key to this becoming a viable treatment for people living with type 1 diabetes.”

The Sefton lab has long investigated the possibility of using biomaterials under the skin as the delivery method for the pancreatic cells. This is because the skin is less hostile than other organs, which tend to launch a stronger immune attack against transplants. Also, Sefton’s lab has established in previous research that the addition of a component called methacrylic acid (MAA) aids with creating blood vessels that are needed for cells to survive and integrate into the host’s body.

Sean Kinney, a PhD Candidate in the Sefton lab and lead author on the paper, says this work builds on previous publications out of the Sefton lab, which have shown that MAA biomaterials are effective. This study refined the materials used in the transplantation by testing different types of injectable hydrogels and controls and focused more closely on the ability of the transplants to reverse diabetes.

“This study established an easily modified platform that makes under-skin cell transplantation simple in hosts who are immunocompromised,” says Kinney. “Now, in our ongoing projects, we can focus on how to ensure that transplants survive rejection even in hosts who are not immunocompromised.”

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

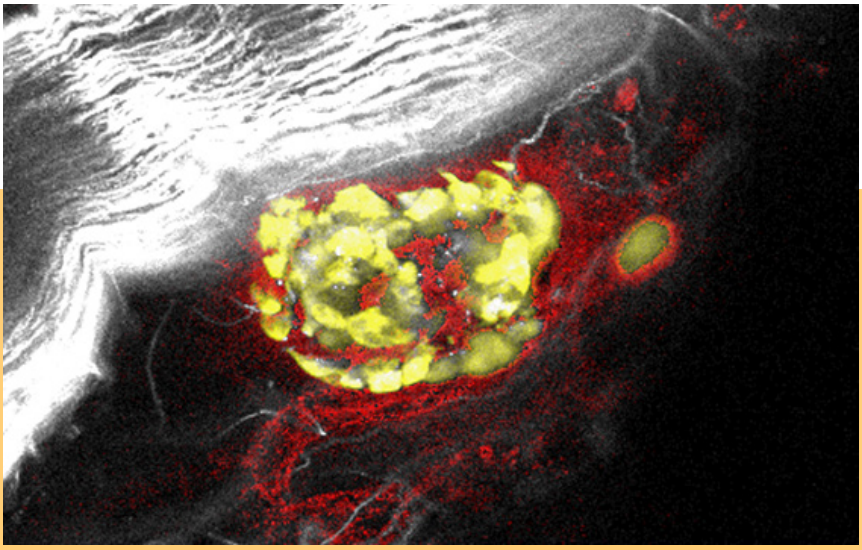
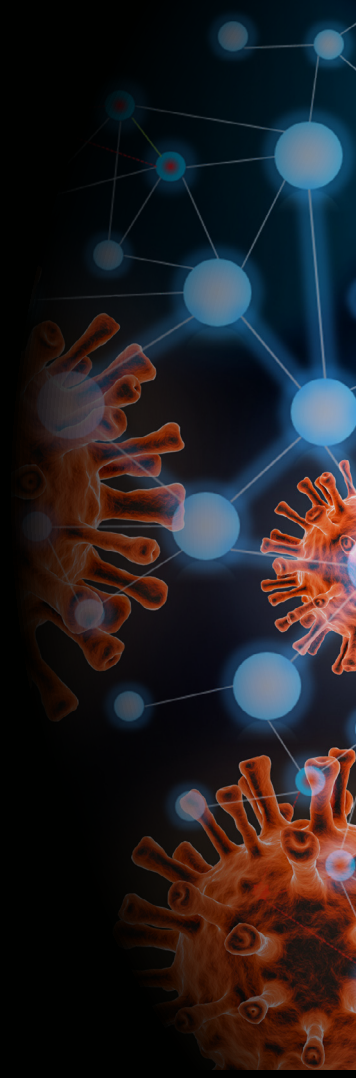


Image showing the transplanted pancreatic cells (yellow) with blood vessels (red) and nerves (white). (Image provided by Sean Kinney).

Researchers Reveal How SARS-CoV-2 Communicates With Human Cells



By Jovana Drinjakovic

What exactly are the molecular interactions between the virus causing COVID-19 and its human host? How might our genetic differences cause different disease courses? And how do still-emerging virus variants differ in their host-virus interactions? To answer these critical questions, an international consortium co-led by Donnelly Centre investigator **Frederick Roth** has generated a systematic map of molecular contacts between the SARS-CoV-2 virus and its human host.

"To really understand the mechanistic connections between virus and host, we need to know how the parts fit together," said Roth.

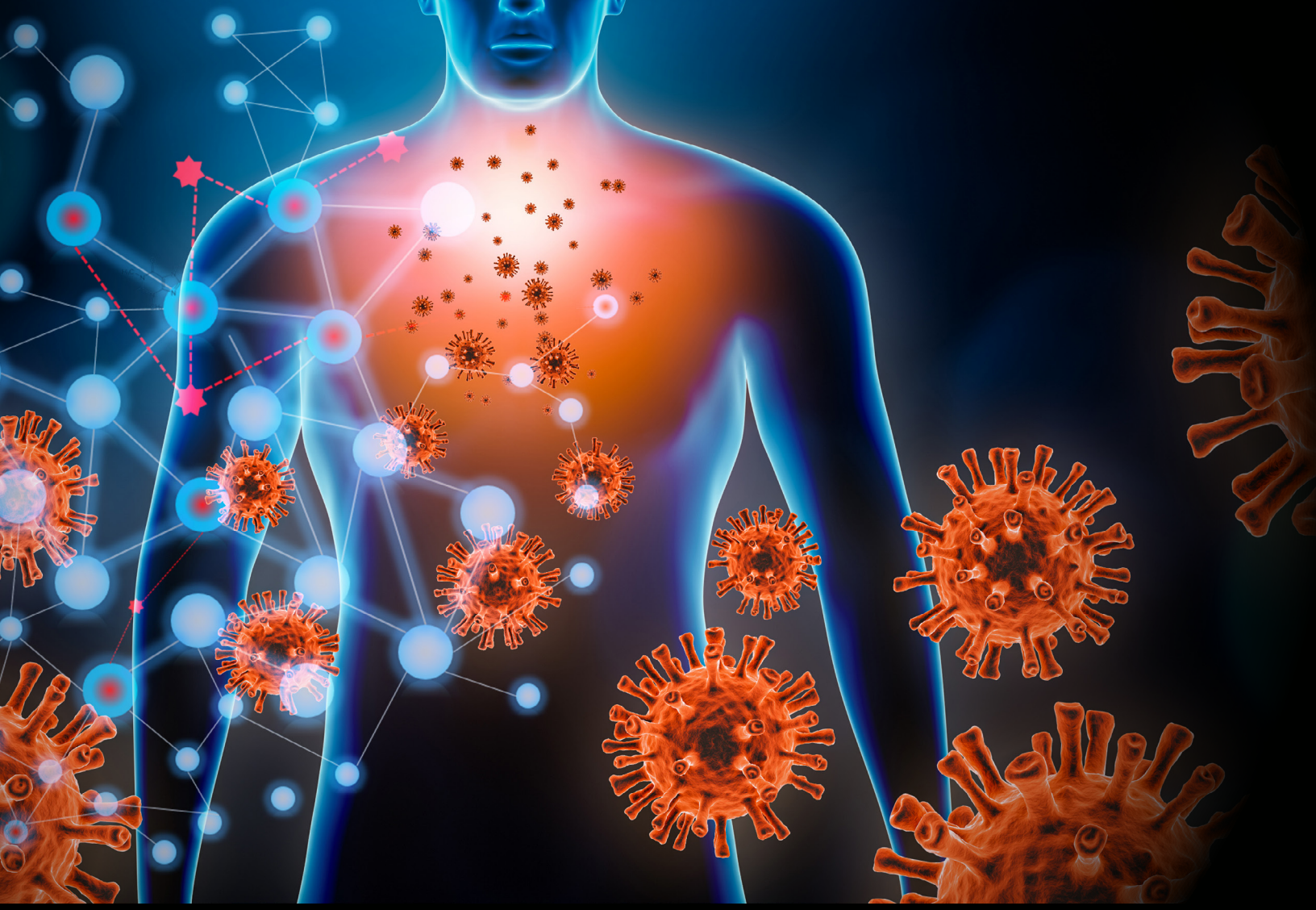
Roth and scientists like him believe that a greater understanding of how the virus interacts with human cells at the molecular level has the potential to reveal genetic differences between individuals that could be used to predict patients at higher risk of severe disease and tailor treatment accordingly, as well as point to new treatments.

The contact map, published in the journal *Nature Biotechnology*, reveals more than 200 direct protein-protein contacts, or protein interactions, between the viral and human proteins. These include novel chains of connections between SARS-CoV-2 and human proteins encoded by the genes that have been linked to an increased likelihood of severe COVID-19 in other studies. They also found connections between the viral proteins and genes involved in metabolic disorders like obesity and diabetes that are known to worsen disease severity and outcomes.

Although several previous large-scale studies had reported protein-protein associations, these studies only revealed pairs of proteins that were near one another, and could not precisely identify direct contacts.

Owing to the large scope of the project, the research was carried out at six sites in Europe and North America. In addition to Roth, the study was also co-led by Pascal Falter-Braun, of Helmholtz Munich, Germany, Caroline Demeret, of the Institut Pasteur in Paris, France, and Michael Calderwood and Marc Vidal, of the Center for Cancer Systems Biology at Harvard University in Boston, U.S.

Among the insights of the study is that the viral proteins



directly activate molecular pathways involved in inflammation and immune signalling. These contacts may help explain the exaggerated inflammatory reaction, that plays a major role in severe cases of COVID-19.

The identified protein contacts also include those that affect the function of SARS-CoV-2 by impacting the rate at which the virus replicates in cells. The researchers were for example able to confirm, that the human protein USP25 is recruited to help certain viral process and that its inhibition significantly reduces the multiplication of the virus.

“Many of the technologies and collaborations in this study were developed for other purposes, then quickly ‘pivoted’ to the COVID-19 pandemic, highlighting the value of fundamental research investments” says Dr. Dae-Kyum Kim, a lead author who began this work in the Donnelly Centre and continued it as an assistant professor at the Roswell Park Comprehensive Cancer Center in Buffalo, U.S.

Charting the contact map was at times like solving a huge puzzle and called for the latest technologies, including robotics for handling plates containing the cells and artificial intelligence for data analysis. The mammoth task involved systematically examining all possible pairwise interactions between around 30 viral proteins and 17,500 human proteins that were expressed in yeast cells for a faster throughput. In total, the team analyzed 450,000 protein pairs to identify the roughly 200 interactions that occur upon infection.

The effort was worth it, the researchers said The contactome map will serve as a platform for the scientific community to study individual interactions in more detail and to understand their impact on molecular mechanisms and clinical progression, and thus uncover starting points for new therapeutic interventions.

“Importantly, the methods and workflow used here, could be applied to future emerging pathogens, highlighting the value of putting a research surveillance network in place to more rapidly characterize new biological threats and explore therapies to address them,” said Roth.

New Faculty Appointments

The Donnelly Centre continued swelling its ranks of leading and emerging experts in the fields of functional genomics and regenerative medicine with the appointments of Drs. Jesse Gillis, Artem Babaian and Milica Radisic.

Jesse Gillis joined the Donnelly Centre as Associate Professor in an appointment shared with U of T's department of physiology. He holds the inaugural James B. Bassingthwaighte Chair in Integrative Physiology, a new endowed appointment in support of multidisciplinary research that employs quantitative approaches to help understand health and disease at the level of cells and organisms.

Gillis previously held a faculty position at the renowned Cold Spring Harbor Laboratory on Long Island, NY, where he first established his computational biology lab 10 years ago. There he developed a portfolio of computational biology projects seeking to decipher how the information stored in the genome is used to build organisms.

Using gene co-expression data from single cells, taken from various organs and species, the Gillis lab is building maps of gene function using AI to shed light on fundamental questions, such as how the different cell types arise during development. Through his involvement with the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, a multi-million initiative funded by the National Institutes of Health in the U.S., Gillis is working to identify all the cell types in the human brain. The goal of BRAIN is to produce a dynamic picture of the brain showing how individual cells and neural circuits interact in space and time. Through building up cell atlases across healthy brains to serve as a reference, Gillis expects to be able to apply this knowledge to try to understand brain disorders.

"The methodological overlap between my lab and the Centre is fantastic. The combination of computational biology and using high-throughput data is unrivalled in the Donnelly.

"I am excited to join the group of outstanding scientists in the Donnelly Centre and expand possibilities for deployment of our organ-on-chip systems in disease modelling, building on the Centre's expertise in genomic sciences.

Bioengineer **Milica Radisic** is Professor at U of T's Institute of Biomedical Engineering where she first established her now renowned lab for human tissue engineering. She joined the Donnelly Centre as faculty in Fall 2022 in a move that will bolster the Centre's efforts to advance knowledge and applications in regenerative medicine.

Radisic brings a wealth of expertise in bioengineering and organ-on-a-chip technology for growing human tissue in the lab. Her team was among the first in the world to use electrical impulses and specially designed bioreactors to guide heart cells to assemble into a self-beating structure. The team also designed an injectable tissue patch that could be used to repair hearts, livers or other organs damaged by disease or injury. More recently, in response to the coronavirus pandemic, they identified a treatment that could help combat complications from COVID-19 by restoring normal function to blood vessels and the heart.

A research translation leader, Radisic is a founding director of the Ontario-Quebec Center for Organ-on-a-Chip Engineering, and a co-lead of the Centre for Research and Applications in Fluidic Technologies, which seek to accelerate applications of microfluidic technologies in biomedicine. She also co-founded two companies, TARA Biosystems and Quthero, which are advancing technologies developed in her lab for the treatment of heart disease and wound healing, respectively.

Computational virologist **Artem Babaian** joined the Centre in Fall 2022 as Assistant Professor of molecular genetics to establish a research progam that uses big data to hunt for new viruses.

As an independent researcher, Babaian developed state-of-the-art computing systems and began innovating how cloud computing can be applied to the discovery of new RNA viruses. These viruses include SARS-CoV-2, influenza, and Ebola virus and use RNA instead of DNA as their genetic material.

Inspired to help fight against the COVID-19 pandemic, Babaian undertook a computational tour de the force that has transformed our understanding of the viral world. He recruited a team of world's leading bioinformaticians who developed a new way to analyze all publicly available genomic data, searching for the signatures of RNA viruses. The mammoth task saw them crunch 20 petabytes (20 million gigabytes) of data, that have been deposited over the last 14 years since large-scale sequencing became possible. In one 11-day analysis, Babaian and his team identified 130,000 new viruses, an almost ten-fold increase from the 15,000 species known previously. And this is only a sliver of existing species according to some estimates. Aided with exponential data growth and computational tools his team is building, Babaian aims to describe 100 million viruses by 2030. Discovering the full biodiversity of RNA viruses will not only prepare us better for combating future pandemics, but it can also give us clues to the origin of life on Earth, Babaian said.

"I am excited to be joining the Donnelly Centre that has positioned itself as a hub for not only computational biology but also for experimental molecular biology.

Funding Highlights

In 2022, Donnelly Centre investigators have raised more than $36 million in research funding from government agencies, non-profits and industry partners.

Engineering local drug delivery for the spinal cord and the retina

University Professor **Molly Shoichet** has received funding from several sources to advance her research in regenerative medicine and drug delivery. Shoichet is a co-principal investigator with Mend the Gap, an international collaboration of more than 30 researchers, engineers, scientists, surgeons and social scientists from Canada, the United States, Europe and Australia. Their initiative aims to find a way to promote repair and regeneration in the injured spinal cord, supported by $24 million from Canada's New Frontiers in Research Fund. The team takes its name from the fact that only a small gap, just a few centimetres long, is responsible for blocking the nerve impulses that normally flow through the spinal cord. Bridging that gap requires collaboration across a wide range of fields. Shoichet and her team bring their expertise in hydrogels — biocompatible materials that can help facilitate tissue repair.

The Shoichet lab also received almost $600,000 from the Canadian Institutes of Health Research (CIHR) to harness hydrogels for local drug delivery to the eye in a bid to develop treatments for blindness. Combined with a new method invented in the lab for a sustained release of protein therapeutics, the team aims to rescue vision loss in animal models of blindness by delivering drugs locally to the retina. Shoichet is collaborating with the vision researcher **Valerie Wallace** from the Krembil Research Institute, UHN, with the ultimate goal to advance knowledge towards clinical application. This project was also awarded $250,000 from Medicine by Design, a U of T initiative for regenerative medicine.

Mapping genetic variants behind heart disease

A consortium co-led by Professor **Frederick Roth** has received a US $8.2-million grant, or 10.8 million in Canadian dollars, to map genetic variants behind heart disease to improve diagnosis, prognosis and treatment. One in 100 people have genetic variations that can cause potentially life-threatening heart conditions. Yet genetic testing often returns ambiguous results where an identified variant has no known function and no prognostic value. Large scale studies of encoded protein variants in the lab have the potential to identify genetic changes that damage protein function and contribute to disease. Roth joined forces with leading experts from Vanderbilt University Medical Center, Stanford Medicine and Women's Hospital in Boston to "map" the specific variations in more than 25 key cardiac disease genes that affect heart function.

Funded by a four-year grant from the National Heart, Lung and Blood Institute of the National Institutes of Health (NIH), their newly formed CardioVar Consortium will generate a comprehensive atlas of "variant effect maps" to distinguish disease-causing variants from those that are harmless. Known worldwide for his work in experimental and computational genomics, Roth and his colleagues have published variant effect maps for nine human proteins already, including one for the calcium-sensing protein calmodulin, enabling rapid diagnosis of life-threatening arrhythmias in young children and genetic testing of their family members.

Building maps of cellular function

University Professor **Brenda Andrews** received $2.5 million from CIHR for projects seeking to establish how variation in the genome influences cellular function and trait manifestation in an organism. A pioneer of functional genomics, Andrews is using Baker's yeast, *Saccharomyces cerevisiae*, to address these questions fundamental questions that hold clues to the realization of personalized medicine, where disease risk and treatment can be predicted and tailored, respectively, from genome sequence. Andrews is leading the development of novel approaches which, combined with powerful microscopy and automated image analysis, will enable her team to zoom into and collect data from millions of individual yeast cells to get a population-level view of variation effects on cellular function.

As part of a long-term collaboration with Donnelly colleague **Charlie Boone**, Andrews has mapped networks of interactions between genes, showing that genes rarely act independently to determine phenotype. The new funding will support the development of unique datasets and tools that will reveal how groups of genes interact with each other and how networks of genetic interactions are rewired in response to different genetic backgrounds.

Mapping splicing diversity in single cells

Professor **Ben Blencowe**, has received $1.5 million from CIHR to develop novel approaches for the investigation of how alternative splicing (AS), a process by which cells regulate and diversify their protein content, impacts cell biology. AS is most pronounced in the nervous system where it plays a major role in establishing the complexity of cell types required for the development and functioning of the mammalian brain.
Research so far has focused on taking bulk measurements of AS events from many cells, calling for new approaches to be developed to be able to discover and understand how AS impacts biology at the level of single cells. The research has the potential to shed light on the molecular mechanisms underlying of neurological disorders such as autism and schizophrenia, which are associated with misregulated splicing.

Mapping liver cancer at the level of single cells

Professor **Gary Bader** received more than $1 million to investigate onset and progression of liver cancer by studying the molecular make-up of individual liver cells during this process. Bader is a world expert on single-cell transcriptomics that allows scientists to study gene expression in individual cells within a tissue. He is on the Organizing Committee of the Human Cell Atlas, a global consortium that is creating reference maps of human organs at the level of single cells. In 2018, him and his collaborators generated the world's first map of the human liver. Now they are taking the next step to learn how the various types of liver cells change and interact during cancer induced by Hepatitis B virus. By comparing healthy and diseased livers at the level of individual cells, they will learn how the disease develops from start to finish with the goal to identify genes that could be targeted for treatments. He is collaborating with liver transplant surgeon **Ian McGilvray** and liver immunologist **Sonya MacParland**, at the Toronto General Hospital, and liver physician and virologist Thomas Michalak at the Memorial University in St. John's, Newfoundland.

Promoting brain repair

Professor **Cindi Morshead** was awarded $750,000 from CIHR for the development of deep brain stimulation approaches in a bid to harness resident stem cells in the brain for tissue repair following a stroke injury. The lab recently showed that electrical stimulation promotes activation of stem cell-derived neural precursor cells leading to their expansion, migration and generation of new neural cells. The new funding will enable the design of novel electrodes and protocol optimization to also promote brain plasticity through the delivery of regenerative factors in a local and controlled fashion. Morshead also received a Connaught Innovation Award for her team's development of a novel gene therapy to promote the brain repair.

Protein-protein interaction mapping

Professor **Igor Stagljar** received more than $600,000 from CIHR to apply their recently developed technology for identifying protein interactions to a clinically relevant group of human proteins known as ABC transporters. ABC transporters are located in the membranes of cells where they pump out toxins in a process that has been co-opted by cancer cells to gain resistance to chemotherapeutic drugs. Previously the team applied their technology to the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), an ABC transporter whose mutation causes cystic fibrosis, to reveal hundreds of novel CFTR-interacting proteins that could influence disease severity. By identifying interacting partners of the remaining ABC transporters in human cells the team expects to reveal proteins that could be targeted for therapeutic applications.

Reading metabolites with DNA barcodes

Professor **Andy Fraser** received more than $600,000 from CIHR for research that has the potential to transform detection of small molecules produced by the body, also known as metabolites. These include sugars, amino acids, lipids and other compounds, whose composition differs between health and disease, and as such they hold great promise for personal health monitoring. However, gold standard methods for metabolite detection require expensive mass spectrometry instruments that are housed in centralized facilities with consequently long turnaround times. Furthermore, unlike DNA, metabolites cannot be amplified, making their detection difficult in small samples such as tears or sweat that are easy to collect for daily health checks. The Fraser lab developed a new method that uses DNA barcoding to identify small molecules in complex fluids making their detection both fast and amenable for point of care diagnostics.

Targeting cancer

Associate Professor **Mikko Taipale** received a $300,000 USD grant to develop new approaches to target cancer. The finding will support a search for protein molecules that could be harnessed to boost known tumour-suppressing factors in cells to inhibit tumour growth. Taipale has been awarded a competitive grant from The Mark Foundation for Cancer Research in the U.S. that seeks to accelerate research with the potential to transform the prevention, diagnosis and treatment of cancer. His team was one of eight international teams that have been awarded 2022 ASPIRE Awards in support of high-risk, high-reward research projects. The project will be carried out in collaboration with the groups of **Daniel Durocher** and **Frank Sicheri** at the Lunenfeld-Tanenbaum Research Institute, at the Sinai Health System in Toronto.

Faculty Appointments & Awards

As globally recognized leaders in their fields, Donnelly Centre investigators are bestowed upon some of the most prestigious honours reserved for top scholars. Highlighted are distinguished appointments won by our faculty in 2022.

Igor Stagljar
Fellow of the Royal Society of Canada and Member of the European Molecular Biology Organization

Donnelly Centre investigator and U of T Professor of biochemistry **Igor Stagljar** was elected a Fellow of the Royal Society of Canada (RSC) and an international member of the European Molecular Biology Organization (EMBO).

The RSC's mission is to recognize excellence and to provide counsel to governments and organizations for the betterment of Canadian society. Founded in 1882, the Royal Society of Canada recognizes Canada's leading intellectuals, scholars, researchers and artists. Fellowship in the RSC is one of the highest honours a Canadian scholar can achieve.

EMBO members are recognized for research excellence and outstanding achievement in life sciences. They too are called upon to advise policymakers and as such can influence the direction of the life sciences in Europe and beyond.

The appointments recognize Stagljar's research contributions to functional proteomics and drug discovery. He is renowned for his study of protein interaction networks in human cells and for harnessing insights gained for the development of new treatments for treatment-resistant lung cancer.

Molly Shoichet
Fellow of the U.S. National Academy of Inventors

A renowned researcher in the study of materials for drug delivery and tissue regeneration, Shoichet was recognized by the NAI for creating outstanding inventions that have made a positive impact on the quality of life and welfare of society. Shoichet and her team of researchers use a cross-disciplinary approach that applies engineering, chemistry and biology to design innovative solutions to medical challenges.

Her team has invented new ways to control therapeutic delivery based on novel affinity interactions and smart materials for use in oncology and pain. Another critical invention concerns ocular biomaterial solutions that aim to overcome eye diseases such as retinal detachment, glaucoma and age-related macular degeneration. Shoichet has also co-founded several biotechnology companies, inlcuding AmacaThera and Synakis, that are working to bring these inventions to patients.

Shoichet's research achievements have been recognized through numerous awards and honours. She has been elected a fellow of all three of Canada's National Academies. She is a member of the Order of Ontario and an Officer of the Order of Canada. She is also a fellow of the Royal Society, U.K.'s national academy of sciences, and is a foreign member of the U.S. National Academy of Engineering. She also received the Chemical Institute of Canada Medal and was awarded the Gerhard Herzberg Canada Gold Medal for Science, Canada's highest honour for science and engineering research.

Charles Boone
Member of the U.S. American Academy of Arts and Sciences

A pioneer in large scale genetics, Boone was recognized for his contributions to functional genomics that have transformed our understanding of how cellular processes are coordinated.

Together with **Brenda Andrews**, inaugural director of the Donnelly Centre, Boone led the effort to produce the first map of genetic interactions for any cell that shows how the complete set of genes within a genome work together to sustain cellular function. The map also revealed how these genetic interactions influence trait inheritance, a key consideration for predicting disease risk from an individual's genome and a fundamental goal of precision medicine.

For his research excellence, Boone has received numerous awards and appointments. Most recently, he was named inaugural Banting & Best Distinguished Scholar at the Temerty Faculty of Medicine in celebration of the centenary of the 1921 insulin discovery. His other awards include 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, as well as the Ira Herskowitz Award in yeast genetics.

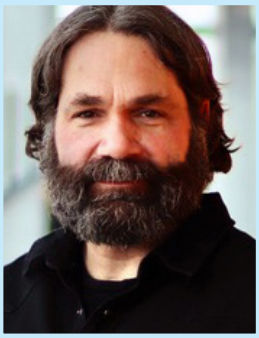
In addition to U of T, Boone is a Team Leader at the Chemical Genomics Research Group at the RIKEN Center for Sustainable Resource Science in Tokyo, and is a Fellow of the Canadian Institute for the Advancement of Research.

New and Renewed Canada Research Chairs

Established in 2000 by the federal government, the Canada Research Chair program seeks to recruit and retain top scientists and scholars in Canada. Tier 1 chairs are reserved for established researchers and bring $400,000 in research funding over seven years while early career faculty are supported by tier 2 chairs with $100,000 annually over five years. Both appointments can be renewed once.

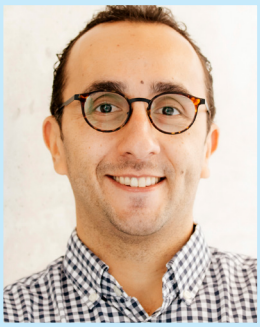
Benjamin Blencowe, Canada Research Chair in RNA Biology and Genomics (Tier 1, new)

Blencowe is a professor of molecular genetics and a world-renowned for his research on RNA biology. His work helped establish RNA splicing, a process by which cells diversify their protein content, as a key mechanism in the control of embryonic stem cells' ability to give rise to all different cell types. The team also showed that splicing of tiny gene segments called microexons is disrupted in neurological disorders such as autism with implications for diagnosis and treatment.



Peter Roy, Canada Research Chair in Chemical Genetics (Tier 2, renewal)

A professor of molecular genetics, Roy is internationally recognized for using the nematode *Caenorhabditis elegans* to understand how drug molecules interact with their cellular targets. The research has wide-ranging implications, from the discovery of new treatments for human diseases, to the development of novel pesticides to safeguard global food security. The lab recently established a multiplexed screening platform for small molecules with therapeutic potential that could vastly speed up drug discovery.



Rafael Montenegro-Burke, Canada Research Chair in Functional Metabolomics and Lipidomics (Tier 2, new)

Assistant professor Montenegro-Burke joined the Donnelly Centre in 2020 to establish one of the first metabolomics labs at the university. Using unbiased mass spectrometry methods, his goal is to map diversity and function of metabolites, small molecules produced by metabolic reactions in cells, which remains largely unexplored but is thought to play a critical role in disease. Recently, his team used this approach to reveal a specific vulnerability in childhood brain cancer and identify a treatment for it.

Penney Gilbert, Canada Research Chair in Endogenous Repair (Tier 2, renewal)

Gilbert is an associate professor of biomedical engineering in the Donnelly Centre where she studies the molecular processes that underpin muscle aging in a bid to slow down or even reverse the process to preserve muscle health. Her team recently developed a miniaturized human skeletal muscle model to study aging and screen for molecules that can spur muscle regeneration.

Mikko Taipale, Canada Research Chair in Functional Proteomics and Proteostasis (Tier 2, renewal)

Taipale is an associate professor of molecular genetics in the Donnelly Centre. His research seeks to uncover various aspects of protein biology and function using large-scale systems biology approaches. This includes identification of novel cell surface receptors for secreted proteins to help reveal how cells communicate with each other in health and disease.

1 *Gerhard Herzberg Gold medal*

3 *Order of Canada medals*

13 *Canada Research Chairs*

8 *Royal Society of Canada Fellows*

4 *University Professors*

Although the Donnelly Centre faculty make up a tiny proportion of professional academics nationally, they amass an outsized share of the most prestigious honours in Canada. Currently, the Centre is home to the recipients of three Order of Canada medals, eight RSC fellows, one Gerhard Herzberg Gold Medal, 13 CRCs and four University Professors, the highest academic rank at the university.

Research Excellence Awards

Established in 2018, the Donnelly Centre Research Excellence Awards recognize outstanding researchers at the postdoctoral level who are pursuing collaborative interdisciplinary projects in the Centre.

The 2022 award winners are **Louise Moyle** and **Shamini Ayyadhury** who were recognized for their efforts in advancing tissue engineering and computer vision, respectively.

Louise Moyle conducted her postdoctoral research in Associate Professor **Penney Gilbert**'s lab where she investigated how adult muscle stem cells repair skeletal muscle. Her aim was to glean insights that could be used to develop treatments for muscular disorders and muscle wasting in old age. Specifically, Moyle investigated how extracellular physical cues, applying force for example, affect the resident muscle stem cells that are responsible for tissue repair. While much is known about the role of growth factors in stem cell biology, mechanosensation has remained poorly explored. Moyle initiated an innovative and collaborative project with Professor **Aaron Wheeler**'s lab in the Donnelly Centre to measure gene expression changes in individual muscle stem cells lacking the protein machinery required for mechanosensation. This research has the potential to reveal key players involved in stem cell self-renewal and differentiation and to inspire new strategies for treatment development.

To increase collaboration across U of T, Moyle established the Myogenesis Scientific Discussion Group, a trainee-led seminar series featuring trainees working in muscle research labs from across U of T and its affiliated hospitals as well as international speakers.

Outside the lab, Moyle is an avid science communicator and a participant in public events such as Soapbox

Science, a platform for female researchers to promote their science and challenge the idea of a stereotypical scientist. She also participates in outreach efforts aimed at getting more Canadian youth excited about science and pursuing careers in STEM. In her free time, Moyle has also contributed to the Toronto Science Policy network that promotes communication between scientists and policy makers.

"I am so thrilled to be a recipient of a Donnelly Centre Research Excellence Award, and proud to be amongst a remarkable list of previous and current winners," said Moyle who has left to a position as Lead Scientist at the Centre for Commercialization in Regenerative Medicine (CCRM) in Toronto where she helps translate stem cell research into cell and gene therapies.

"It means a great deal to me as the project involved a lot of hard work and risk, which couldn't have been done without the support, guidance and enthusiasm of everyone in the Gilbert and Wheeler teams."

Shamini Ayyadhury is a computational biologist in Professor **Gary Bader**'s lab where she is developing computer vision approaches for the analysis of brain tumours, with a specific focus on glioblastoma (GBM), the most aggressive brain cancer sub-type. Ayyadhury is creating AI-centric pipelines, integrating computer vision with several single-cell techniques that can improve the analysis, stratification and treatment of patient-derived tissue samples. Her background as a wet-lab scientist guides her creativity in applying AI and other computational methods that will open the door for novel drug screening platforms and in understanding tumor evolution. Her efforts will further advance the long-standing collaboration between the Bader lab and the groups of the neurosurgeon Dr. **Peter Dirks** at The Hospital for Sick Children, Dr. **Trevor Pugh** at the Princess Margaret Cancer Centre and Dr. Samuel Weiss at the University of Alberta. They are striving to predict treatment from unique features of patient-derived glioblastoma stem cells, which are believed to drive tumour formation. She is also working with Dr. **Cheryl Arrowsmith** at the Structural Genomics Consortium, Dr. **David Andrews** from Sunnybrook Institute, as well as other international collaborators, on developing computer vision algorithms that will integrate high-throughput microscopy and single cell spatial molecular platforms to understand brain cancer architecture and 3D evolution.

Furthermore, Ayyadhury is an ambassador and Chair of the Education & Research Subcommittee with Brain Cancer Canada (BCC), where she actively engages with patients and caregivers, advocating the importance of interdisciplinary scientific research as well as non-traditional research involving the social, psychological and economic aspects of GBM treatment. She is also the President of the Pitchmasters Club, as part of the International Toastmasters organization, where she helps others with self-confidence and public speaking.

"When I received news of winning this award, I sighed – in relief," said Ayyadhury. "I felt an overwhelming sense of gratitude at being acknowledged for my work and also for my ideas and thoughts. Receiving this award will certainly motivate me to improve and advance myself and to remember to pay forward the support that I have received from my supervisors and colleagues."

Ayyadhury plans to pursue a career in interdisciplinary research, working to design AI-integrated imaging, robotics and wet-lab tools for early tumor detection, improving diagnosis and prognosis and the development of targeted treatments.

Charles H. Best Postdoctoral Fellowship

By Jovana Drinjakovic

The clues to how the mind works could be hiding in individual brain cells. And the 2022 Charles H. Best Fellow **Guillermo Parada Gonzalez** is on the hunt for them.

Parada Gonzalez is a postdoctoral fellow in **Ben Blencowe**'s lab where he is investigating how alternative splicing, a process by which cells diversify their protein content, impacts brain development. His project seeks to establish how alternative splicing contributes to the generation of different cell types in the brain and their ability to communicate with each other. The research could deepen our understanding of brain disorders, such as autism and schizophrenia, with implications for treatments.

"Winning the Best fellowship early in my postdoctoral training means a lot beyond the financial support it provides," said Parada Gonzalez. "Knowing that my work is appreciated by others motivates me to keep pushing forward with my research."

The prestigious annual award recognizes an outstanding postdoctoral scientist in the Donnelly Centre whose foundational research holds potential for medical breakthroughs. Established in 2001 by The Charles H. Best Foundation, the fellowship celebrates the memory of **Charles H. Best** who discovered insulin with Dr. **Frederick Banting** at the University of Toronto in 1921.

While the road from discovery to medical application may be a long one, Parada Gonzales knows he's on the right path. "History proves that understanding basic biology is key to the development of novel therapeutic approaches and advances in medicine in general," Parada-Gonzales.

During alternative splicing, the genes' protein-coding segments, or exons, are variably stitched together into RNA messages, which serve as templates for building proteins. This allows for multiple protein isoforms to be encoded by the same gene, generating a greater molecular diversity within and across cells. One consequence of a bountiful molecular toolkit is that cells can specialize for various roles as they build tissues and organs.

Blencowe's team previously showed that alternative splicing in the human body is most pronounced in the brain, and that this helps explain how it became the most complex organ on earth. They also discovered a highly conserved

and dynamic network of neuronal splicing events involving very short exons, known as microexons.

Although microexons encode tiny portions of protein material, they influence how proteins interact with each other, which is a critical feature of all cellular processes. Errors in microexon splicing result in disrupted protein interactions, which can interfere with brain wiring and cognition. The team also reported microexon splicing errors in the brains of autistic individuals, further underscoring their link to brain disorders.

Research so far has mainly focused on taking bulk molecular measurements of the brain. But advances in single-cell technology, which allow researchers to measure RNA messages from individual cells within a tissue, have opened new possibilities for investigating how splicing affects biology on a much finer scale.

“With bulk methods, it’s like you’re putting a whole brain in the blender and taking average gene expression measurements,” said Parada Gonzalez.

“But the brain, and especially the cortex, which is important for higher order functions, is among the most heterogeneous tissues in the body. Therefore, understanding alternative splicing events at cell type resolution is particularly important for gaining a deeper understanding of how the brain works,” he said.

Parada Gonzalez is not new to the field. During his PhD, at the Wellcome Trust Sanger Institute in Cambridge, UK, he developed MicroExonator, a computational tool for the detection and quantification of microexon splicing in bulk and single-cell profiling experiments. He is now collaborating with other members of the Blencowe lab and **Quaid Morris**, computational biology expert and former investigator at the Donnelly Centre, now at the Memorial Sloan Kettering Cancer Center, in New York City, to implement a machine learning approach to crack the genome code that governs microexon splicing.

For Parada Gonzalez, joining the Blencowe lab has been a dream come true. “Ben is a world leader in the field, and I’ve been following his work since I was an undergraduate student in Chile. It’s a great privilege for me to be in his lab and I look forward to ongoing fruitful collaborations,” he said.

Jennifer Dorrington Graduate Research Awards

The Jennifer Dorrington Graduate Research Award is awarded annually to three outstanding PhD candidates in graduate programs at the Temerty Faculty of Medicine who are conducting research in the Donnelly Centre.

The 2022 Dorrington award winners are Zoe Clarke, Matthew Osborne and Kai Slaughter who are advancing research in liver cancer, infectious disease diagnostics and drug delivery.

"The award committee was impressed with the scope of their projects and the progress they have made in making discoveries that hold real potential for improving medicine and health

Gary Bader, Chair of Dorrington Award Committee and Professor of molecular genetics

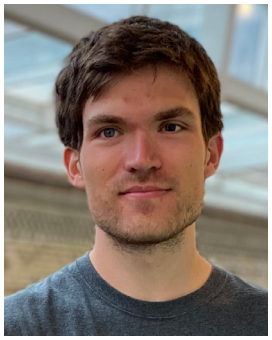
Established in 2006 by the Dorrington family, the award celebrates the memory of Professor Jennifer Dorrington who carried out pioneering research on ovarian cancer at the Banting and Best Department of Medical Research.

Zoe Clarke (Mogen) is in Dr. **Gary Bader**'s lab where she is investigating how an infection with the hepatitis B virus causes inflammation of the liver and ultimately cancer. She is applying computational biology to compare the molecular makeup of individual cells taken from healthy and diseased woodchuck livers. Like humans, woodchucks naturally succumb to hepB infection and this makes them a better animal model in which to study the link between inflammation and cancer than mice or rats, which do not naturally develop virus-induced tumours. Clarke's goal is to understand the molecular changes occurring in diseased liver cells and how they interact with other cells around them. This includes immune cells in the liver, which could one day be enlisted to fight off tumours, including those not caused by viral infection.

> ***"I am grateful to the Dorrington family for their support of science, and specifically my project. Receiving this kind of support really inspires me to work to the best of my ability, and reminds me how much of an impact my research can have on the community***

Matthew Osborne (BME) is developing rapid point of care diagnostics for Sars-CoV-2 and other viruses in the group of Dr. **Warren Chan**. The method is similar to PCR and therefore highly sensitive, but it also allows point-of care use, similar to rapid tests. Osborne envisages its use one day in remote communities which have had to wait several days for the results of their PCR tests processed in specialized labs. Most of his focus has been on miniaturizing the workflow into a disposable fist-sized cartridge into which reagents are added and the reactions occur. The method is powered by tiny light-emitting nanocrystals known as quantum dots, allowing for multiplexing, where multiple test reactions are run simultaneously. Having developed the method in a lab setting, Osborne has embarked on a collaboration with researchers at Public Health Ontario who are testing his device on patient samples.

> ***"I had read through the list of previous winners and some of them were from my lab, and they were pretty incredible researchers. I am thrilled to be in such company***



Kai Slaughter (BME) is in Dr. **Molly Shoichet**'s lab where he is trying to develop methods that would allow delivery of high doses of cancer drugs in nanoparticles. This is difficult to achieve with conventional means where large amounts of potentially toxic helper compounds are needed for the delivery of therapeutics. The team realized that they could engineer drug-rich formulations by exploiting the natural tendency of some small molecule drugs to form aggregates. This results in a nanoparticle that is comprised almost entirely of the active drug, therefore reducing the need for helper compounds. This approach holds potential for enhanced cancer therapies. Slaughter is working to solve a problem where the drugs are becoming trapped inside cellular compartments called endosomes by looking for a way to release the compounds into the cells' interior where they can exert their therapeutic effects.

> ***"It's great to be part of an interdisciplinary team. Prof Shoichet is always supportive and we're able to connect with collaborators in different places and have all the expertise and resources we need***

Cecil Yip Doctoral Research Awards

"The 2022 awardees are tackling some of the most challenging questions in human biology and disease through the development of new methods that will benefit researchers all around the world. I am excited to follow their progress and learn about the discoveries they will make.

Christopher Yip, Dean of Applied Science & Engineering, Chair of Yip Award committee and son of Prof Cecil Yip.

The 2022 Cecil Yip Doctoral Research Awards celebrate early graduate research in systems biology and nanomedicine. The annual award recognizes outstanding students in their first year of graduate programs who are engaged in multidisciplinary research projects that seek to improve medicine and health.

This year's winners are enrolled in graduate programs at the Department of Molecular Genetics (Mogen) and the Institute of Biomedical Engineering (BME). Their research projects attempt to answer some of the biggest outstanding questions in human biology with implications for neurological disorders, infectious disease, regenerative medicine and cancer.

The award was established by the Yip family in memory of Cecil Yip, former vice-dean of research at U of T's Faculty of Medicine and co-founder of the Donnelly Centre. Prof Yip championed the idea of collaborative science which is enshrined in the Centre's mandate.

Photo courtesy of Christopher Yip

Jack Dayang Li (Mogen) is in Dr. **Ben Blencowe**'s lab where he is researching the regulatory mechanisms behind alternative splicing, a process by which cells diversify their protein content. The lab previously showed that AS is essential for normal brain development and that miscues in this process can lead to neurological disorders such as autism. Working with the proteomics expert Dr. **Mikko Taipale**'s lab at the Centre, Li is developing an unbiased method using a CRISPR-based technology for hunting down novel protein factors that regulate AS.

Nicholas Sar Ly (Mogen) is working with Dr. **Rafael Montenegro-Burke** to develop new mass-spectrometry methods for the identification of the key molecules that are required for self-renewal of the hematopoietic stem cells (HSCs). HSCs give rise to all blood cells and hold potential for treatment of various blood disorders and cancers. Their wider clinical application has been hampered by a scarce availability of these cells and by a lack of understanding of the molecular differences between individual HSCs, which can impact their function. Ly is collaborating with Dr. **Stephanie Xie**, at the Princess Margaret Cancer Centre.

Travis Tribble (Mogen) in Dr. **Mikko Taipale**'s lab is working to establish the most comprehensive atlas to date of the protein factors produced by viruses and bacteria to help them invade and multiply in human cells. In collaboration with Alex Stark, at the Research Institute for Molecular Pathology in Vienna, Austria, they seek to map how thousands of pathogen produced proteins behave in human cells. A better handle on the biological outcome of human-pathogen protein interactions will increase our understanding of infectious disease and could also reveal novel targets for therapeutics.

Bram Bussin (BME) is in Dr. **Warren Chan**'s lab where he is investigating tumour drug delivery using nanoparticles. The lab previously showed that far more nanoparticles get taken up by the liver than reach tumours. They think this could be caused by the particles becoming coated with various proteins as they travel through the bloodstream. Bussin is developing methods to identify which proteins on the nanoparticles interact with receptors on the liver cells in a bid to engineer them better for tumour delivery. He is collaborating with functional genomics expert Dr. **Jason Moffat**, formerly at the Donnelly Centre and now at the Hospital for Sick Children, and liver immunologist **Sonya MacParland**, at the Toronto General Research Institute.

Qin Ji (BME) is also in Dr. Chan's lab focusing on the interaction between the nanoparticles and tumours. He is building on their previous research that showed that the particles do not passively leak from the blood vessels into tumours, as previously thought. Instead, they are transported in an active process but the mechanism remains unclear. Ji has set out to probe if tumour metabolism might be linked to nanoparticle accumulation in a bid to develop new ways to improve targeted delivery.

Donnelly Research Thesis Prize

By Jovana Drinjakovic

Computational biologist **Nil Sahin** is the 2022 winner of the Donnelly Research Thesis Prize, awarded annually to a top graduate student in the Centre whose PhD project crosses scientific disciplines while meeting the highest standards of excellence.

Sahin obtained her PhD in the laboratory of **Brenda Andrews**,University Professor and founding director of the Centre. She was co-supervised by **Quaid Morris**, AI expert and former investigator at the Centre, now at the Memorial Sloan Kettering Cancer Centre in New York.

Sahin investigated how genetic mutations affect cellular morphology using the single-celled Baker's yeast, *Saccharomyces cerevisiae*, as a model system. The Andrews lab is renowned for its pioneering work that established how a full complement of genes in a genome interact to sustain the life of yeasts. They also pioneered automated microscopy allowing them to collect images of millions of cells that are either healthy or carry genetic mutations.

Sahin is delighted that the analysis pipeline she built is helping her old colleagues and other researchers, in the Andrews lab and beyond, address their specific questions.

"The greatest joy for me as a computational scientist is to design software that helps researchers obtain knowledge from data in a fast and reliable way," she said.

> *"Nil's pioneering work in AI-assisted computer vision has opened new avenues for exploring how genetic mutations and other perturbations affect cellular morphology, with wider implications for understanding the molecular mechanisms of disease.*
>
> **Jason Moffat**, Chair of the award committee and U of T Prof of molecular genetics

She also added that she is grateful to her mentors who provided more than scientific advice.

"In addition to providing guidance on my project, Brenda made me feel like I could always count on her. Being an international student, she made me feel like the lab was my second home."

Sahin previously won two flagship Donnelly Centre awards for graduate students, the Cecil Yip Doctoral Research Award for 2017, and the Jennifer Dorrington Graduate Research Award for 2020.

Youth Outreach

It's often said that you can't be what you can't see and we all rely on examples to help us visualize career possibilities.

Science may especially appear far flung to girls and disadvantaged youth, who are under-represented in labs across the country.

To help counter these disparities, the Donnelly Centre has established a vibrant and inclusive outreach program that seeks to instill curiosity and a love of science among Ontario elementary and high school students. In 2022, the Centre welcomed 20 grade 7/8 students from the King Edward Public School and 40 students from the Mayfield Secondary School for a day of learning about biology through seminars and hand-on activities in the lab. The students heard about possibilities for discovery in biology and medicine that have been enabled by genome sequencing technologies and got to isolate their own DNA from their cheek cells as well as perform experiments with yeast cells and worms.

We also held an online seminar for girls through our partnership with the Canadian Association for Girls in Science. Presented by graduate students in the Centre, the seminar covered the intricate biology of the human eye and our ability to see the world around us and how the Centre's researchers are working to develop treatments for vision loss.

During March Break, the Centre hosted eight students in grades 10 to 12 as part of Research Exploration Program by Stem Fellowship, a non-profit promoting STEM among disadvantaged youth. Each student was placed in a lab of their choice where they spent a week learning basic laboratory techniques as well as handling advanced equipment such as mass spectrometers and robots for plating yeast strains on media plates. The students also learned about their mentors' research projects, and they attended lab meetings and other seminars.

Grade 7 & 8 students from King Edward Public School looking down microscopes. Image in the corner shows yeast colonies growing in the shape of a smiley face after a student a streaked a yeast strain on a plate.

> *"I was blown away by the robots which I got to use. It was amazing for a high school student to experience that!*
>
> **2022 REO Participant**

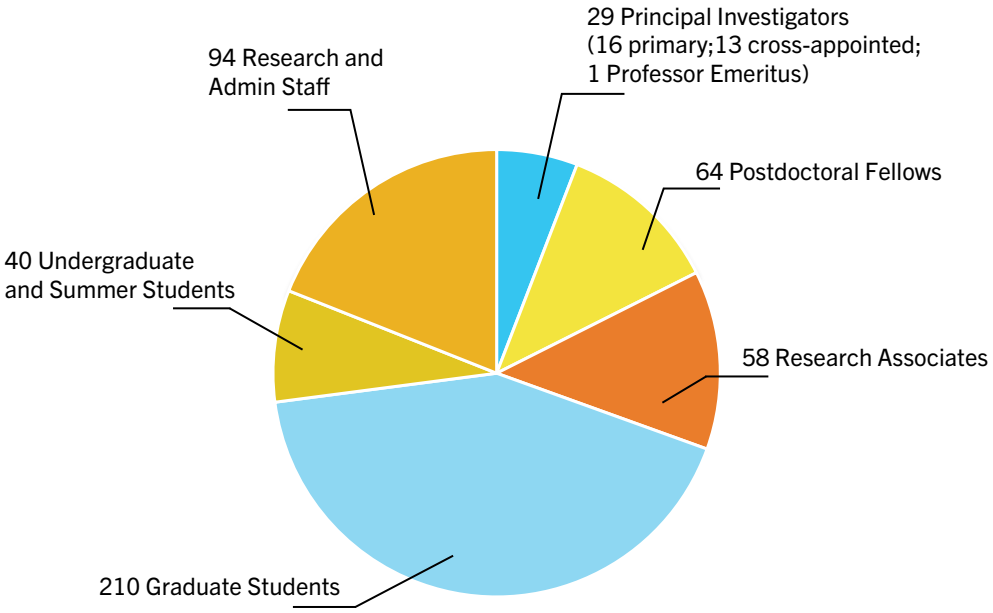
Grade 11 & 12 students from Mayfield Secondary School

> *"I found that the experience at the Donnelly centre was amazing and full of knowledge. The staff, professors, and students there were so nice and made all of us feel very welcome. I would love to go back if I'd have the chance!!*
>
> **Mayfield SS student**

Donnelly in Numbers

Personnel

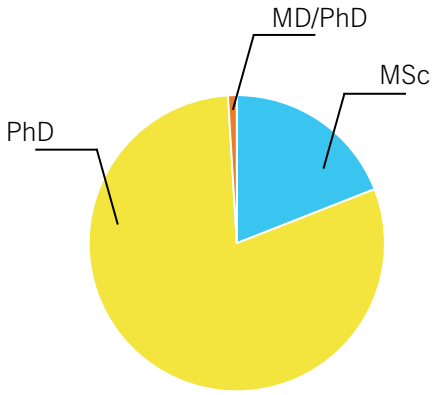
At the time of the last personnel survey conducted in the summer of 2022, the Centre comprised a total of 492 occupants, representing scientists at all stages of their careers as well as members of research and administrative staff.



Graduate Students

Our graduate students come from 14 U of T departments, shown by the numbers in brackets:

Biochemistry (16)
Cell & Systems Biology (1)
Chemical Engineering (9)
Chemistry (5)
Computer Science (11)
Institute of Medical Science (8)
Institute of Biomedical Engineering (55)
Medical Biophysics (2)
Molecular Genetics (97)
Pharmacology & Toxicology (1)
Pharmacy (5)
Physics (1)
Physiology (1)
UG-Anatomy (1)

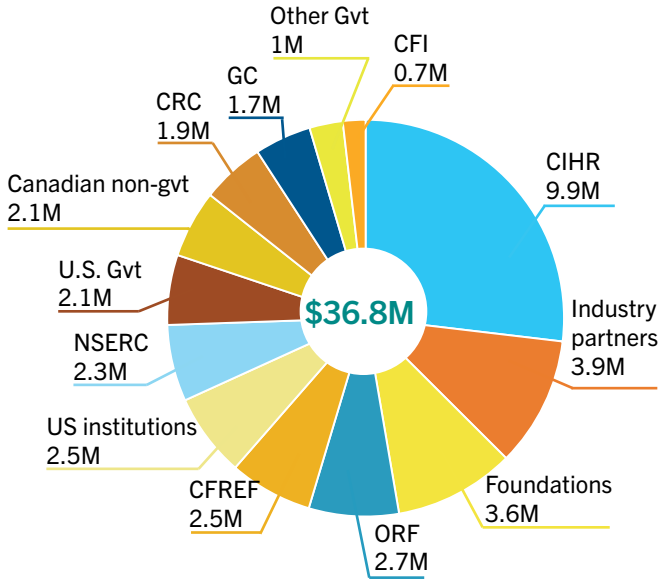


168 students (76%) are PhD candidates, 40 are pursuing a Masters degree and 2 are in the MD/PhD program.

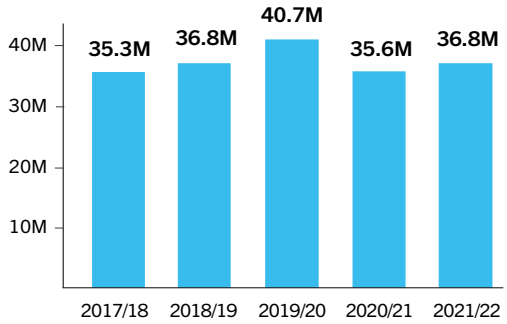
Research Funding

The majority of the funding for infrastructure, research and personnel is supported by the grants from the Canadian federal government. Shown below are sources of funding for 2022 as well as total funding and major sources of funding over the last five years.

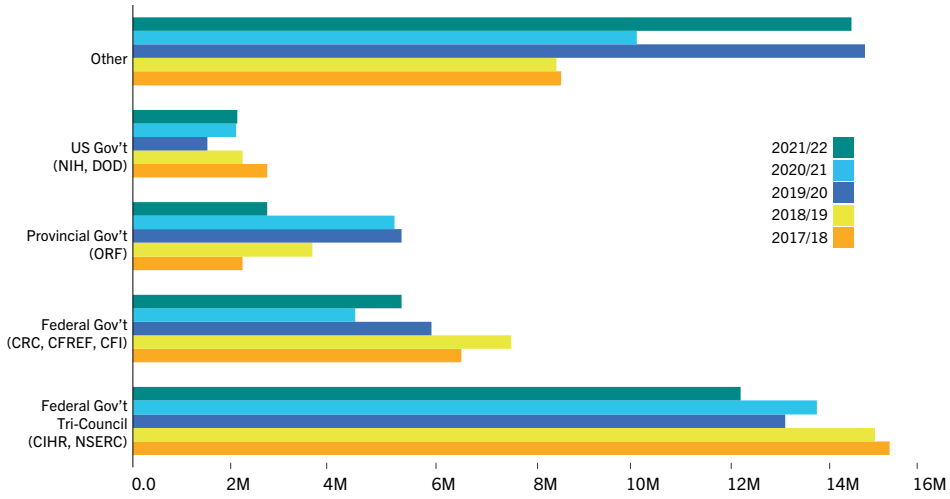
Funding sources 2022



Total funding 2017-2022



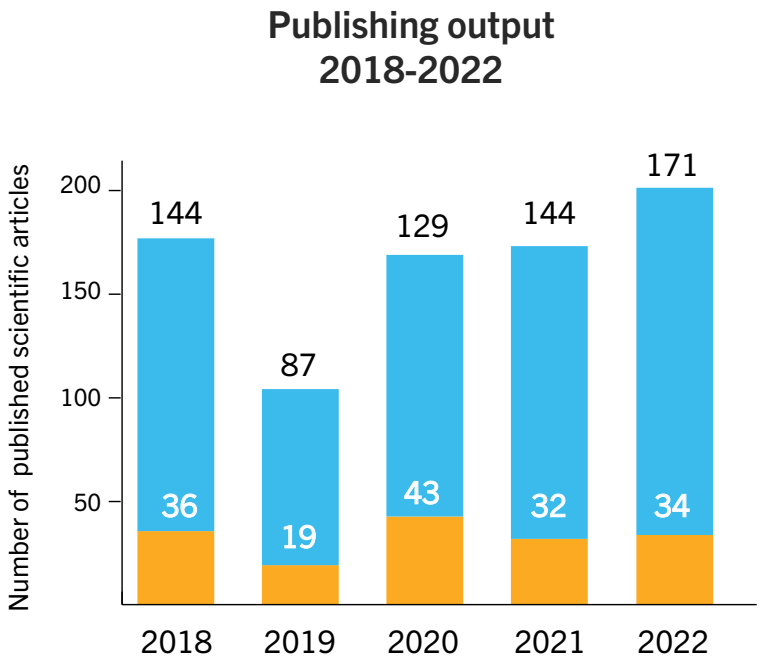
Funding sources 2017-2022



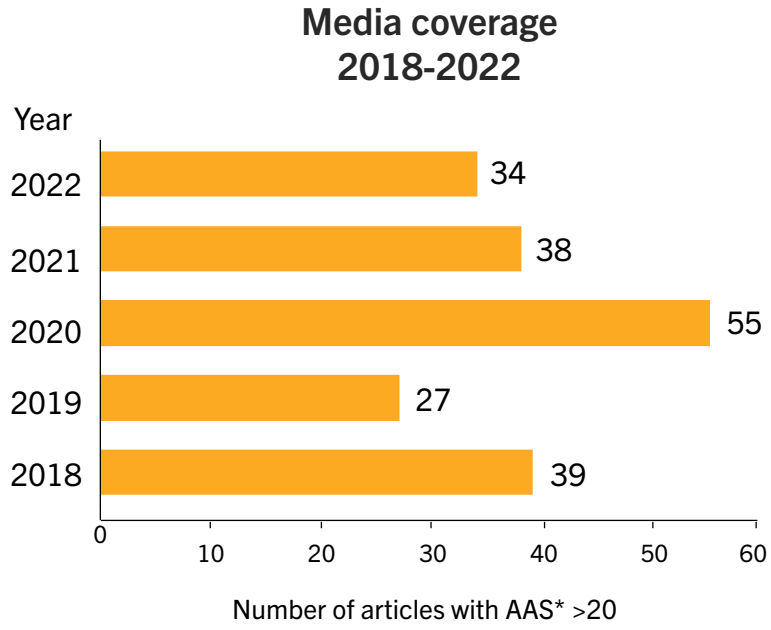
Funding agency abbreviations: CIHR (Canadian Institutes of Health Research), NSERC (National Science and Engineering Research Council), CFREF (Canada First Research Excellence Fund), CRC (Canada Research Chair Program), CFI (Canada Foundation for Innovation), DOD (U.S. Department of Defence), GC (Genome Canada) ORF (Ontario Reserach Fund), NIH (U.S. National Institutes of Health).

Publication Output

Donnelly Centre investigators regularly publish their findings in peer-reviewed academic journals, with 171 articles published in 2022, 34 of which appeared in high impact journals*. The graph on the right shows the total number of publications (blue bars and the numbers above them) and those in high impact journals (orange bars with numbers in white) for each year.



*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*.



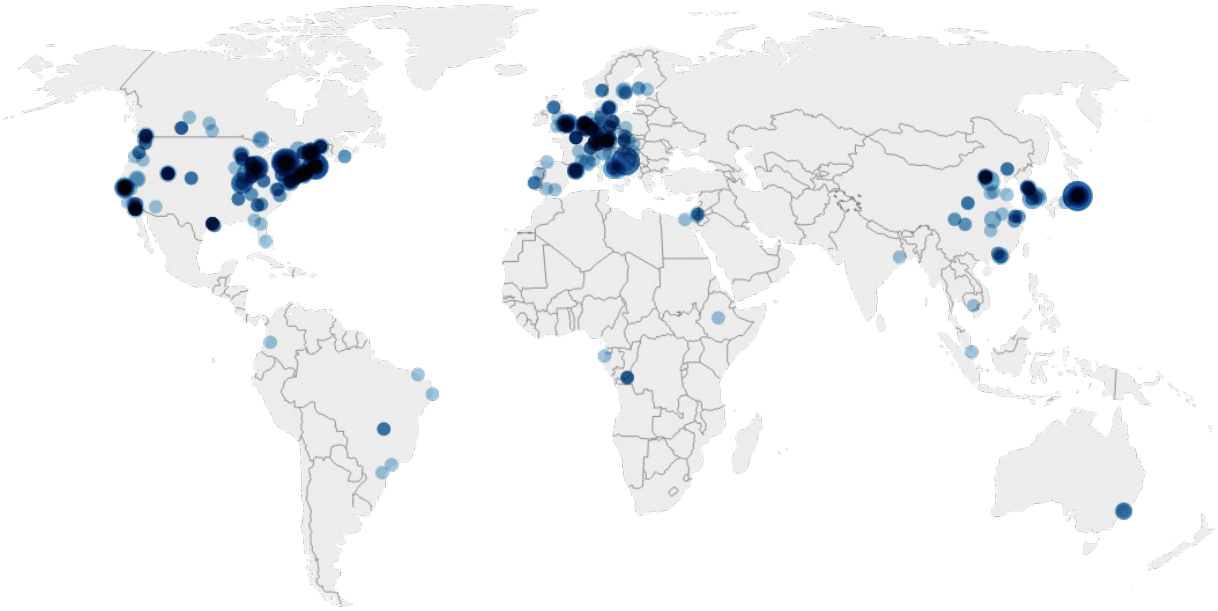
The graph on the left shows the number of scientific articles authored by Donnelly Centre investigators that received notable media coverage, with Altmetric Attention Score* greater than 20.

*Altmetric Attention Score is a weighted count of the attention that a scholarly article has received including mentions in mainstream and social media.

Scientific Collaboration

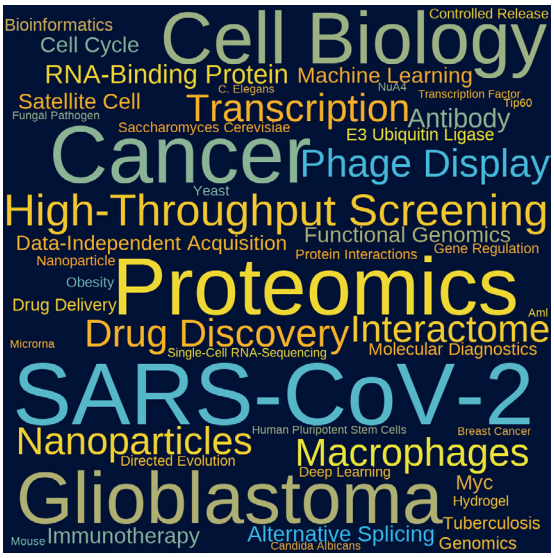
Donnelly Centre investigators collaborate with scientists from all over Canada and around the world. Blue circles on the map show the location of the researchers working in academia and industry who have co-authored peer-reviewed scientific articles with the Centre's investigators. Overlapping circles appear darker highlighting global hubs for research and innovation. The map was created using Datawrapper with 2022 publication data data from Pubmed.

Click here for an interactive map to view the names of collaborating institutions across the world.



Research Themes

Researchers in the Donnelly Centre work on diverse topics, with many teams collaborating across scientific disciplines. The map on the right represents the top 50 words that appeared at least twice across 171 scientific articles that were published by Donenlly Centre faculty during 2022. The visualisation was generated using WordCloud for Python by Andreas Mueller. The font size represents the relative frequency with which a given keyword or phrase appears.



Research Commercialization

Donnelly Centre investigators are among the most entrepreneurial at the university as they seek to translate their discoveries into tangible advances for patients. Featured here is a selection of startups founded by the Centre's investigators and their trainees.

Pursuing exciting molecules for oncology targets by combining novel modular antibody platforms toward next generation antibody-drug conjugates and immune cell engagers. Co-founded by former Donnelly investigator Dr. **Sachdev Sidhu**.

Transforming therapeutics with a unique, injectable hydrogel platform for localized, sustained drug delivery across multiple therapeutic areas. Co-founded by Dr. **Molly Shoichet**.

Developing regenerative medicine treatments through precision protein engineering. Co-founded by Donnelly Centre director Dr. **Stephane Angers** and former investigator Dr. **Sachdev Sidhu**.

Enabling synthetic biology by unlocking access to genes with unparalleled accuracy. Co-founded by Dr. **Andrew Fraser**.

Developing immunotherapies to address treatment-resistant forms of cancers. Co-founded by former Donnelly investigator Dr. **Jason Moffat** and acquired by Century Therapeutics in 2020.

Delivering molecules and bioengineering solutions to expand stem and immune cells for therapeutic use. Co-founded by former Donnelly investigator Dr. **Peter Zandstra**.

Developing products and solutions for nanomedicine and biomedical research. Founded by Dr. **Warren Chan**.

Transforming healthcare by capturing a rich snapshot of your personal metabolism. Co-founded by Dr. **Andrew Fraser**.

Developing novel therapeutic antibodies for the treatment of human diseases in oncology and fibrosis. Co-founded in 2014 by former Donnelly investigators Drs. **Jason Moffat** and **Sachdev Sidhu** and acquired by Boehringer Ingelheim in 2020.

Developing precision therapies that modulate protein-protein interactions with a focus on undrugged cancers. Co-founded in 2022 by Dr. **Igor Stagljar**.

Applying machine learning to improving patient outcomes with new medicines targeting tumour stroma, a barrier that surrounds cancer and stops today's medicines working. Co-Founded by **Oren Kraus**, former graduate student in Dr. Brenda Andrews' lab.

Developing a gel for effective and safe treatment of skin wounds. Co-founded by Dr. **Milica Radisic**

Offering innovative next-generation sequencing DNA and RNA library preparation methods Co-founded by former Roth lab member **Joseph Mellor**.

Developing solutions to use wearable devices to monitor individual's physiological data in a bid to aid diagnosis of neurological diseases and real-time monitoring of patient's health. Co-founded by Dr. **Zhaolei Zhang**.

Harnessing human biology and data to transform cardiac drug discovery. Co-founded by Dr. **Milica Radisic** and acquired by Valo Health in 2022.

Developing new, safe and effective chemical tools to control plant parasitic nematodes and safeguard global food security.Co-founded by Dr. **Peter Roy**.

Research Events

Over the past year, the Donnelly Centre brought the wider research community together through its External Speaker Series. This lecture series featured emerging and leading experts from across the world who are working at the intersection of molecular genetics, engineering and computational biology. A total of 15 internationally recognized speakers presented their latest findings that have the potential to improve health of people around the world. The speakers and their talk titles are listed below.

George Church, PhD, Founding Core Faculty & Lead, Synthetic Biology, Wyss Institute at Harvard University | Professor of Genetics, Harvard Medical School | Professor of Health Sciences and Technology, Harvard and MIT | *Exponential tech applied to pathogens, aging & ecosystems* | Hosted by Fritz Roth

Xin Wang, PhD, Senior Scientist, Statistical Genetics, 23andMe, Inc. | *Scale and diversity power novel genetic discovery at 23andMe* | Hosted by Charlie Boone

Michael Tyers, PhD, Principal Investigator, Systems Biology and Synthetic Biology Research Unit, IRIC | Professor, Department of Medicine, Faculty of Medicine, U Montréal | *The human genetic interaction landscape through a chemical looking glass* | Hosted by Charlie Boone

Pascal Falter-Braun, PhD, Professor & Director, Institute of Network Biology (INET), Microbe-Host Interactions, Faculty of Biology, Ludwig Maximilian University of Munich | *Using interactome networks to understand microbe-host interactions from plants to humans* | Hosted by Fritz Roth

Pedro Beltrao, PhD, Associate Professor, Department of Biology, ETH Zurich | *The genetics of human traits across the scales of biological organisation* | Hosted by Mikko Taipale

Francesco Iorio, PhD, Research Group Leader, Fondazione Human Technopole, Milan, Italy | *Tools for optimisation and drug-discovery oriented analyses of CRISPR screens* | Hosted by Jason Moffat

Benjamin F. Cravatt, PhD, Professor, Department of Chemistry, The Scripps Research Institute, La Jolla | *Activity-based proteomics – target and ligand discovery on a global scale* | Hosted by Charlie Boone

Jacques Corbeil, PhD, Infectious and Immune Diseases Axis, CHUL, Canada Research Chair in Medical Genomics, Professor, Department of Molecular Medicine, Faculty of Medicine, Université Laval | *Metabolomics and machine learning: a great pairing* | Hosted by Rafael Montenegro Burke

Paola Picotti, PhD, Associate Professor, Molecular Systems Biology, Institute of Molecular Systems Biology, ETH Zurich | *Proteomes in 3D: Structural barcodes to probe protein functional alterations* | Hosted by Hannes Röst

Joshua Pan, PhD, Broad Institute of MIT and Harvard | *Sparse dictionary learning recovers pleiotropy from human cell fitness screens* | Hosted by Mikko Taipale

Molly Przeworski, PhD, Professor of Biological Sciences and of Systems Biology, Columbia University, New York, NY | *Causes and consequences of recombination hotspot evolution in vertebrates* | Hosted by Fritz Roth

Hartland W. Jackson, PhD, Investigator, Lunenfeld-Tanenbaum Research Institute, Associate Scientist, Ontario Institute for Cancer Research, Assistant Professor, University of Toronto | *New tools, model systems, and multiplexed imaging for the study of multi-cellular tumour environments* | Hosted by Gary Bader

Georg Winter, PhD, Principal Investigator, Chemical Biology of Oncogenic Gene Regulation, Research Center for Molecular Medicine of the Austrian Academy of Sciences, CeMM, Vienna | *Disrupting oncogenic gene control via targeted protein degradation* | Hosted by Mikko Taipale

Debora S. Marks, PhD, Associate Professor, Systems Biology, Harvard Medical School Associate Member, Broad Institute of Harvard and MIT | *Predicting and designing biology using machine learning* | Hosted by Gary Bader

Yevgeny Brudno, PhD, Assistant Professor, University of North Carolina at Chapel Hill | North Carolina State University | Joint Department of Biomedical Engineering | Pharmacoengineering Track | *Biomaterial solutions for refillable drug depots and CAR T cells manufacturing* | Hosted by Molly Shoichet

Donnelly in the Media

Listed below is a selection of news stories from the past year featuring Donnelly Centre researchers in the Canadian and international media.

If you got COVID early this year, you can get reinfected now, U of T study finds, ***Toronto Star***

What COVID-19 health advice can Canadians follow for the summer surge that's upon us? ***The Globe and Mail***

U of T research team develops new test to detect immunity against COVID-19 variants, ***CityNews***

Older antibodies no longer effective, ***CTV News***

Studies unravel SARS-CoV-2 protein interactions with human proteins, ***Genomeweb***

Wie kommuniziert SARS-CoV-2 mit menschlichen Körperzellen? ***MTA Dialog*** (German)

Por qué la comunicación entre el COVID y las células puede ser determinante en el desarrollo de tratamientos, ***Infobae*** (Spanish)

Researchers hopeful about new treatment for deadly paediatric brain cancer, ***RTT News***

Enzyme that drives growth of medulloblastoma may hold the key to future treatment, ***The Medical News***

Worms have the ability to identify thousands of different smells; scientists discover mystery behind this sniffing skill, ***The Science Times***

Thousands of different scents – scientists solve a 30-year-old mystery, ***SciTech Daily***

Forscher lüften 30 Jahre altes Geheimnis der Geruchsveränderung bei Würmern, ***Nach Welt*** (German)

Research helping stroke patients, ***CTV News***

How cell therapies can help with brain injuries, ***CP24***

Interview with Molly Shoichet, Woman Of Science, ***Canadian Living***

With therapeutic protein delivery strategy, researchers pave way for degenerative eye disease treatments ,***Technology Org***

'Feasible science fiction': Toronto researchers team up to advance treatments to repair the brain, ***Toronto Star***

There are no overnight successes in science: medical research needs more stable funding, ***The Hill Times***

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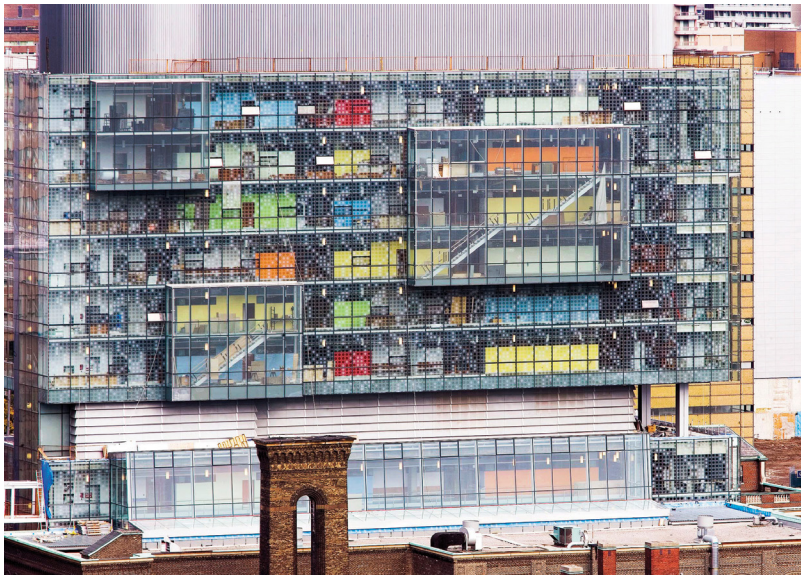

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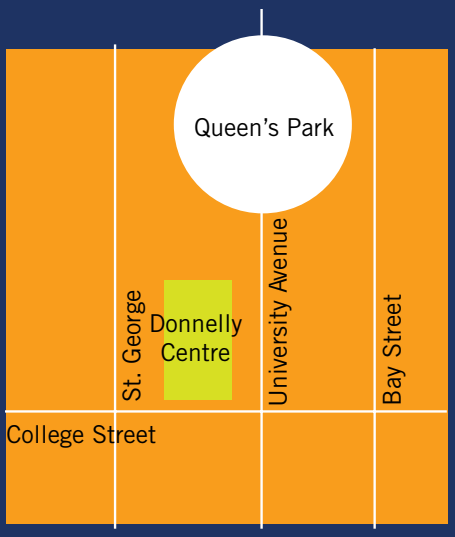

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