Donnelly Centre 2021

Annual Report

Donnelly Centre
for Cellular + Biomolecular Research

TEMERTY FACULTY OF MEDICINE
UNIVERSITY OF TORONTO

View of the Toronto skyline with the Donnelly Centre on the right (Erin Howe).

The Donnelly Centre for Cellular and Biomolecular Research is a research institute where scientists from diverse fields make discoveries to improve health.

Founded in 2005 at the University of Toronto, the 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 a visionary philantropist Dr. Terrence J. Donnelly.

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Director's Welcome

It is my great pleasure to introduce the 2021 Annual Report on behalf of everyone at the Donnelly Centre — and my first since assuming the role as Director, on September 1, 2021.

Since its inception in 2005, the Centre has become a globally renowned hub for research in biomedicine in large part thanks to a bold leadership of my predecessor and the Centre's inaugural director Dr. Brenda Andrews. During this time, the Centre's investigators have transformed our understanding of cellular processes and how they contribute to health and disease.

This progress has continued unabated despite significant personal challenges posed by the ongoing coronavirus crisis. Many labs have even expanded their research programs with a swathe of new projects that take aim at Sars-CoV-2 and other pathogens.

The Centre currently houses over 500 occupants, comprising 30 faculty members and over 300 students and trainees in the areas of integrative and systems biology, bioengineering, regenerative medicine and models of disease. Our faculty are emerging and world-leading experts in their fields who are developing and applying state-of-the-art technologies in a highly collaborative environment. Last year alone, the Centre's investigators raised more than $35M in competitive research funding from government and other sources to support their work—a remarkable achievement for a relatively small research community. Their work has led to new insights that could lead to better treatment for ailments ranging from cancer to blindness, as well as safeguard us from future pandemics to name a few.

With this report, we bring you a selection of stories about Donnelly science and scientists that we produced over the past year. As we face mounting global challenges, from infectious diseases to climate change, it is more important than ever for scientists to share their research with the public and inspire an interest in science among younger generations. 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

About Dr. Stephane Angers, Director of Donnelly Centre

Stephane Angers was appointed Director of the Donnelly Centre for Cellular and Biomolecular Research on September 1, 2021. He is a professor of biochemistry in the Temerty Faculty of Medicine and in the Leslie Dan Faculty of Pharmacy at the University of Toronto. He joined U of T in 2006 and previously served as Graduate Coordinator and Associate Dean of Research in U of T's Leslie Dan Faculty of Pharmacy. In 2019 he co-founded PRiME, the University of Toronto Precision Medicine Strategic Initiative.

Professor Angers has been named the Charles H. Best Chair in Medical Research. The distinguished appointment celebrates the long history of discovery at the University and it was established in 1981 in memory of the insulin co-discoverer and Nobel laureate Charles H. Best. The chair was initially associated with leadership at the historic Banting and Best Department of Medical Research and, following its dissolution, with the Donnelly Centre as its modern-day successor.

Angers is a world leader in understanding cellular mechanisms governing stem cells during development, tissue regeneration and cancer. He has made fundamental discoveries in how cells respond to the Wnt family of growth factors that enabled the development of innovative therapeutic agents that are advancing towards the clinic both as anti-cancer treatments and as regenerative medicine strategies. He co-founded two biotech companies, ModMab Therapeutics and AntlerA Therapeutics, which are pursuing clinical translation of his research.

Angers, who previously held a Canada Research Chair II in functional architecture of signal transduction, has received more than $10 million in peer reviewed research support and has published more than 100 peer-reviewed publications in top-ranked journals. He also received the Early Researcher Award from Ontario government, the GSK Early Career Award from the Canadian Society for Pharmaceutical Sciences as well as the Professor of the year award from the Leslie Dan Faculty of Pharmacy.

Angers received a B.Sc in Biochemistry from McGill University and a Ph.D in Biochemistry from the Université de Montreal. He completed post-doctoral training at the University of Washington in Seattle.

Brain Cancer Linked To Tissue Healing

By Jovana Drinjakovic

Brain tumours might arise when tissue does not heal properly. The finding opens up new ideas about how cancer develops — and how to combat it.

The healing process that follows a brain injury could spur tumour growth when new cells generated to replace those lost to the injury are derailed by mutations, Donnelly Centre investigators have found with collaborators. A brain injury can be anything from trauma to infection or stroke.

The findings were made by an interdisciplinary team of researchers from the University of Toronto, The Hospital for Sick Children (SickKids) and the Princess Margaret Cancer Centre who are also on the pan-Canadian Stand Up To Cancer Canada Dream Team that focuses on a common brain cancer known as glioblastoma.

"Our data suggest that the right mutational change in particular cells in the brain could be modified by injury to give rise to a tumour," says Dr. **Peter Dirks**, Dream Team leader who is the Head of the Division of Neurosurgery and a Senior Scientist in the Developmental and Stem Cell Biology program at SickKids.

Gary Bader, Professor of molecular genetics and computer science in the Donnelly Centre for Cellular and Biomolecular Research at U of T's Temerty Faculty of Medicine and **Trevor Pugh**, Senior Scientist at the Princess Margaret Cancer Centre, also led the research which has been published today in the journal *Nature Cancer.*

The findings could lead to new therapy for glioblastoma patients who currently have limited treatment options with an average lifespan of 15 months after diagnosis.

"Glioblastoma can be thought of as a wound that never stops healing," says Dirks. "We're excited about what this tells us about how cancer originates and grows and it opens up entirely new ideas about treatment by focusing on the injury and inflammation response."

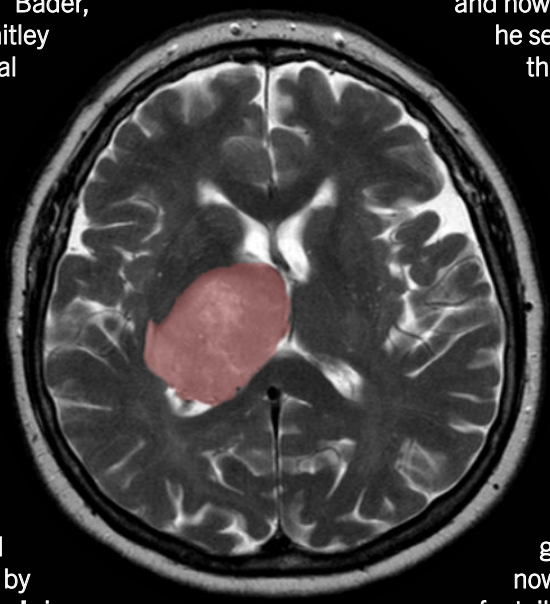
The researchers applied the latest single-cell RNA sequencing and machine learning technologies to map the molecular make-up of the glioblastoma stem cells (GSCs), which Dirks' team previously showed are responsible for tumour initiation and recurrence after treatment.

They found new subpopulations of GSCs which bear the molecular hallmarks of inflammation and which are comingled with other cancer stem cells inside patients'

tumours. It suggests that some glioblastomas start to form when the normal tissue healing process, which generates new cells to replace those lost to injury, gets derailed by mutations, possibly even many years before patients become symptomatic, Dirks said.

Once a mutant cell becomes engaged in wound healing, it cannot stop multiplying because the normal controls are broken and this spurs tumour growth, according to the study.

"The goal is to identify a drug that will kill the glioblastoma stem cells," says Bader, whose graduate student Owen Whitley contributed to the computational data analysis "But we first needed to understand the molecular nature of these cells in order to be able to target them more effectively."



The team collected GSCs from 26 patients' tumours and expanded them in the lab to obtain sufficient numbers of these rare cells for analysis. Almost 70,000 cells were analyzed by single-cell RNA sequencing which detects what genes are switched on in individual cells, an effort led by the graduate student **Laura Richards** in Pugh's lab.

The data confirmed extensive disease heterogeneity, meaning that each tumour contains multiple subpopulations of molecularly distinct cancer stem cells, making recurrence likely as existing therapy can't wipe out all the different subclones.

A closer look revealed that each tumour has either of the two distinct molecular states—termed "Developmental" and "Injury Response"— or somewhere on a gradient between the two.

The developmental state is a hallmark of the glioblastoma stem cells and resembles that of the rapidly dividing stem cells in the growing brain before birth.

But the second state came as a surprise. The researchers termed it "Injury Response" because it showed an upregulation of immune pathways and inflammation markers, such as interferon and TNFalpha, which are indicative of wound healing processes.

These immune signatures were only picked up thanks to the new single-cell technology after being missed by older methods for bulk cell measurements.

Meanwhile, experiments done by **Stephane Angers'** lab, then at the Leslie Dan Faculty of Pharmacy and now in the Donnelly Centre where he serves as Director, established that the two states are vulnerable to different types of gene knock outs, revealing a swathe of therapeutic targets linked to inflammation that had not been previously considered for glioblastoma.

Finally, the relative comingling of the two states was found to be patient-specific, meaning that each tumour was biased either toward the developmental or the injury response end of the gradient. The researchers are now looking to target these biases for tailored therapies.

"We're now looking for drugs that are effective on different points of this gradient", says Pugh, who is also the Director of Genomics at the Ontario Institute for Cancer Research. "There's a real opportunity here for precision medicine— to dissect patients' tumours at the single cell level and design a drug cocktail that can take out more than one cancer stem cell subclone at the same time."

In addition to funding from the Stand Up To Cancer Canada Cancer Stem Cell Dream Team: Targeting Brain Tumour Stem Cell Epigenetic and Molecular Networks, the research was also funded by Genome Canada, the Canadian Institutes for Health Research, the Ontario Institute for Cancer Research, Terry Fox Research Institute, the Canadian Cancer Society and SickKids Foundation.

The image shows a brain scan with a glioblastoma tumour coloured red. (Wikimedia Commons)

New Antibody Therapy Holds Hope For Eye Diseases

By Eileen Hoftyzer

Antibodies engineered by the Angers and Sidhu teams may reverse diabetic retinopathy and other eye conditions.

The life-saving diabetic medication insulin, developed at the University of Toronto 100 years ago, was the first biologic therapy — a protein to treat disease. A century later, a new biologic therapy also developed by researchers at U of T has potential to reverse a common complication of diabetes.

A team led by **Stéphane Angers**, who was a professor and associate dean of research at the Leslie Dan Faculty of Pharmacy and is now director of the Donnelly Centre, and **Sachdev Sidhu**, professor of molecular genetics in the Centre, has developed a synthetic antibody as a promising treatment for diabetic retinopathy, which causes blindness and affects about 30 per cent of diabetes patients.

The researchers tested the antibody in both cell cultures and mice, and published their findings in the journal *EMBO Molecular Medicine*.

“This study has shown that these antibodies are very attractive therapeutics to restore blood-retina barrier defects,” said **Rony Chidiac**, a postdoctoral fellow in the Angers lab and lead author of the study. “It gives new hope for the treatment of eye diseases like diabetic retinopathy and macular degeneration.”

Angers and his team are experts in the Wnt cell signalling pathway, which is crucial for the formation and maintenance of the blood-retina barrier, a physiological barrier that prevents molecules from entering the retina.

When the signalling pathway is disrupted — which can occur because of genetic mutations in rare eye conditions such as Norrie disease, or when tissue oxygen is low, as in diabetic retinopathy — the blood vessels can become leaky, causing damage in the eye.

In previous research, Angers had collaborated with Sidhu to develop a catalogue of synthetic antibodies that could activate Wnt signalling.

Their new publication describes how one of the antibodies, specifically activating the Frizzled4-LRP5 receptor complex, successfully stimulated Wnt signalling in the blood-retina barrier and effectively restored barrier function.

The antibody attaches to two key cell surface receptors (Frizzled4 and LRP5) bringing them close together, and this induced proximity activates the Wnt pathway that maintains the blood vessels.

The team first tested the antibody in cell cultures and found that it was a highly precise way to trigger the signalling pathway and restore barrier function. They then tested the antibody in different mouse models in collaboration with Harald Junge at the University of Minnesota and AntlerA Therapeutics, a start-up company founded by Angers and Sidhu. One model represented a genetic eye condition and one represented diabetic retinopathy.

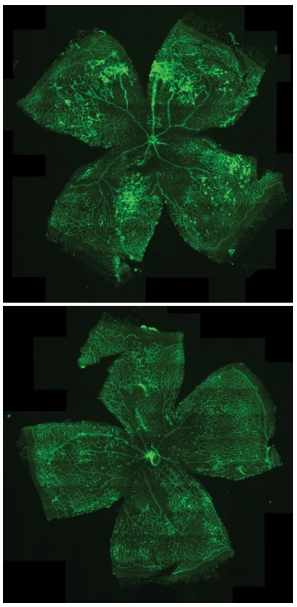
Remarkably, the antibody restored the barrier function and corrected retinal blood vessel formation in these mice. In addition, it normalized the pathological formation of new blood vessels, one of the consequences of a leaky blood-retina barrier that causes further eye damage.

With the antibody's promising preclinical results, AntlerA Therapeutics will now lead the commercialization and translation to clinical studies.

While the current study's results are focused on eye conditions, the similarities between the blood-retina barrier and blood-brain barrier mean that its applications could be much broader than eye conditions.

"The retinal vasculature was the first indication, and we have new funding to explore the role of this pathway in other contexts," said Angers. "For example, we are testing whether this antibody could have implications in the blood-brain barrier and whether it could repair the barrier in the context of stroke."

"We've found a way to activate Wnt signalling very precisely in order to have a viable therapeutic opportunity and actually treat these diseases," added Chidiac. "We anticipate that this could have enormous impact in diverse applications in regenerative medicine."



Antibody injection prevents pathological vascularisation in the mouse eye. Image at the top shows untreated mouse retina with overgrown blood vessels visible as green patches. These are absent from the retina into which the antibody was injected (bottom image). From Chidiac et al., 2021, EMBO Molecular Medicine.

This story first appeared in Research News on the website of U of T's Leslie Dan Faculty of Pharmacy.

“Firefly” Test For Measuring COVID-19 Immunity

By Jovana Drinjakovic

A new test developed by the Stagljar lab uses a protein from the firefly to count coronavirus antibodies in a drop of blood in under one hour.

gor Stagljar made his career building molecular tools to combat cancer. But when the pandemic hit last March, he aimed his expertise at a new adversary, SARS-CoV-2.

Stagljar is a professor of biochemistry and molecular genetics in the Donnelly Centre for Cellular and Biomolecular Research at U of T’s Temerty Faculty of Medicine. Last spring, with support from U of T’s Toronto COVID-19 Action Fund, his team began developing a new method for measuring immunity to coronavirus in those who recovered from COVID-19.

They are now ready to reveal their creation — a pinprick test that accurately measures in under one hour concentration of coronavirus antibodies in blood. And it’s cheap, costing a toonie or about tenth of the cost of the market gold standard.

Their method has been published in the journal *Nature Communications*.

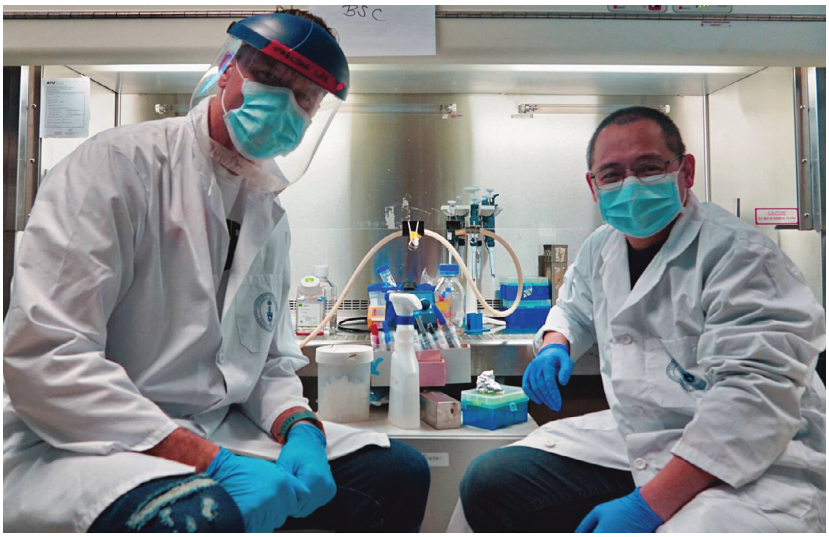
“Our assay is as sensitive, if not better than any other currently available assay in detecting low levels of IgG antibodies, and its specificity, also known as false-positive rate, is as good as the best antibody test on the market,” said Stagljar who collaborated with public health agencies and blood banks from across Canada to have the test validated on blood samples taken from former COVID-19 patients.

Serological tests detect antibodies, protein molecules in blood that recognize and neutralize Sars-CoV-2 to prevent infection. Such tests are seen as a key tool for public health experts wanting to measure population immunity to be better able to manage the ongoing pandemic.

According to a January report by the national COVID Immunity Task Force, the majority of Canadians remain vulnerable to coronavirus infection with less than two percent testing positive for antibodies.

Population level studies can also help reveal duration of coronavirus immunity across patients who had different experiences of disease, from asymptomatic to severe.

Professor Igor Stagljar and Research Associate Zhong Yao pictured in a tissue culture room wearing PPE. Yao spearheaded the development of the new rapid antibody test.



They also have the potential to reveal threshold antibody level required for protection after natural infection and vaccination.

"That level is still to be determined, but we do know that people who have been infected with SARS-CoV-2 have very diverse levels of antibodies, and it would not be surprising to find that below some baseline level they might not be protective," said **Zhong Yao**, senior research associate in Stagljar's lab and co-inventor of the method.

Several serological tests have received regulatory approval with ELISA-based methods as the gold standard when it comes to measuring antibody concentration as a strength of individual immune response. But it comprises several laboratory steps that take six hours to complete, making it unsuitable for rapid diagnostics. Simpler methods using test strips, similar to pregnancy tests, provide fast results but are not quantitative and are less reliable.

The new method is called SATiN, for Serological Assay based on split Tripart Nanoluciferase. It is the first COVID-19 serology test that uses highly sensitive protein complementation chemistry in which a light-emitting luciferase protein, originally from the firefly, is reconstituted from separate fragments as test readout.

Luciferase is initially supplied in fragments that cannot not glow on their own. One piece is attached on the viral spike protein, which antibodies bind to neutralise the virus, while another is hooked to a bacterial protein that antibodies also interact with. By binding simultaneously to the coronavirus spike protein and the bacterial protein, the antibody helps lock luciferase pieces together into a whole molecule. A flash of light ensues whose intensity is detected and converted into antibody concentration by a plate reader instrument. All reagents can be prepared from scratch and in bulk and this keeps the cost down.

Stagljar is now working with U of T's intellectual property office and Toronto Innovation Acceleration Partners to find industry partners that would help make the method widely available. He is also collaborating with Dr. **Prabhat Jha**, Director of the Centre for Global Health Research at St. Michael's Hospital and a professor at U of T's Dalla Lana School of public Health, who is leading a long-term study to establish duration of immunity across 10,000 Canadians. In another project, Stagljar is working with Dr. **Allison McGeer**, Senior Clinician Scientist at Sinai Health System and also a professor at Dalla Lana, to assess antibody levels in people after vaccination.

"It's really useful to have that quantitative ability to know what someone's antibody status is, whether it's from a past infection or a vaccination. This will be of crucial importance for the next stage of the pandemic, especially now when governments of all countries started with mass vaccinations with recently approved anti-COVID-19 vaccines", Stagljar said.

Not A Living Fossil: How Coelacanths Gained Dozens Of New Genes

By Jovana Drinjakovic

The bodies of ancient coelacanth fish may have changed little over tens of millions of years, but their genomes tell a different story.

The capture of the first living Coelacanth, a mighty ocean predator, off the coast of South Africa caused quite a stir in 1938 — 65 million years after its supposed extinction. It became known as a "living fossil" owing to its anatomy looking almost identical to the fossil record. But while the Coelacanth's body may not have changed much, its genome tells another story.

Donnelly Centre scientists have now revealed that the African coelacanth, *Latimeria chalumnae*, gained 62 new genes through encounters with other species 10 million years ago. Their findings were reported in the journal *Molecular Biology and Evolution*.

What's even more fascinating is how these genes came about. Their sequences suggest they arose from transposons, also known as "selfish genes". These are parasitic DNA elements whose sole purpose is to make more copies of themselves, which they sometimes achieve by moving between species.

The findings show the dramatic effect the traveling transposon DNA can have on gene birth. They also provide a glimpse into some of the forces that shaped the genome of one of the most ancient and mysterious organisms.

"Our findings provide a rather striking example of this phenomenon of transposons contributing to the host genome," says **Tim Hughes**, senior author of the paper and professor of molecular genetics in the Donnelly Centre.

"We don't know what these 62 genes are doing, but many of them encode DNA binding proteins and probably have a role in gene regulation, where even subtle changes are important in evolution," said Hughes, who holds Canada Research Chair in Decoding Gene Regulation.

Transposons are also called "jumping genes" because they can switch locations in the genome, thanks to a self-encoded enzyme which moves its own DNA code via a "cut and paste" mechanism. New copies can arise through

Preserved specimen of Coelacanth at the Natural History Museum, Vienna, Austria. Alberto Fernandez, Wikimedia Commons

serendipitous jumps during cell division when the whole genome is replicated. Over time, the enzyme's code drifts into disrepair and the jumping ceases. But if the altered sequence confers even subtle selective advantage to the host, it can begin new life as a *bona fide* host gene.

There are myriad examples of transposon-derived genes across species, including humans, but coelacanths stands out for the sheer scale of it.

"It was surprising to see coelacanths pop out among vertebrates as having a really large number of these transposon-derived genes because they have an undeserved reputation of being a living fossil," said graduate student **Isaac Yellan** who spearheaded the study. "The Coelacanth may have evolved a bit more slowly but it is certainly not a fossil," he says.

Yellan made the discovery while looking for counterparts in other species of a human gene he was studying. He knew that the gene, CGGBP1, had arisen from a particular type of transposon in the common ancestor of mammals, birds and reptiles. It was named after the protein it encodes, which binds CGG-containing DNA sequences, but it was difficult to study partly because it has no counterpart in other commonly researched species, such as fruitfly.

After scanning all available genomes, Yellan was able to find related genes, but their distribution across species was patchy and not what you would expect from common ancestry. In addition to the single CGGBP-like gene in all mammals, birds and reptiles, Yellan found copies in some, but not all, fish he looked at. He also found copies in in lamprey, a primitive vertebrate, and a type of fungus. Worms, molluscs, and most insects had none. And then there were 62 in the African coelacanth, whose genome became available in 2013.

With common ancestry ruled out, it appears instead that the transposons came into various lineages at different times by being carried between species through what's known as horizontal gene transfer.

"Horizontal gene transfer fuzzies up the picture of where the transposons came from but we know from other species that it can occur via parasitism," says Yellan. "The most likely explanation is that they were introduced multiple times during evolutionary history."

It remains unclear what the genes are doing but several lines of evidence point to a finely-tuned role in gene regulation. Computational modeling and test tube experiments established that the genes encode proteins that bind unique sequence signatures on the DNA, suggesting a role in gene expression. Furthermore, the genes are varyingly switched on across a dozen or so coelacanth organs for which data exist, suggesting finely-tuned roles that are tissue-specific.

The research was supported by the National Science and Engineering Council and the Canadian Institutes of Health Research.

Lab-Grown Muscles Aid Study Of Muscle Disorder

By Paul Fraumeni

Miniature muscles have been derived in a laboratory from patients with Duchenne muscular distrophy to help develop treatments for the genetic disorder.

Inside a Petri dish in a lab at the University of Toronto is a muscle – made from scratch using human stem cells – that has Duchenne muscular dystrophy (DMD).

To study the biological properties of DMD, a degenerative muscle disorder that mainly affects males, U of T researchers obtained cell lines from people living with the condition and used them to create miniature muscles in a dish. Now, they're helping other researchers and industry partners develop and test new treatments that may help the boys and young men who are afflicted with DMD.

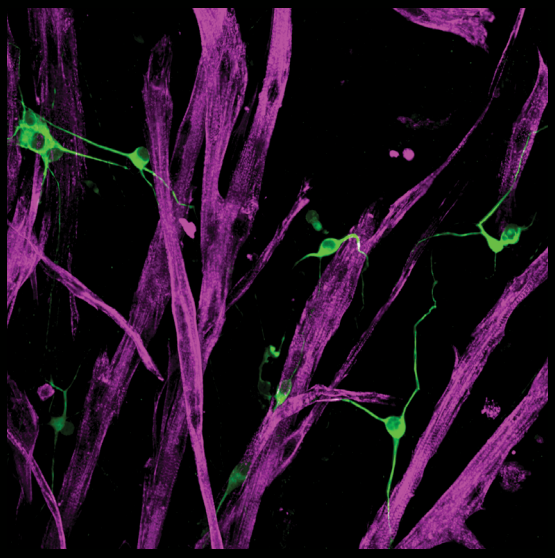
The research team is led by **Bryan Stewart**, professor of biology at U of T Mississauga, and **Penney Gilbert**, associate professor in the Institute of Biomedical Engineering and at U of T's Donnelly Centre for Cellular & Biomolecular Research. Stewart specializes in the physiology of neurons and muscles. Gilbert, a cell biologist, specializes in restoring skeletal muscle (the muscles attached to bone) by using stem cells. They decided to collaborate after meeting at a research leadership workshop organized by University Professor **Molly Shoichet** about six years ago.

"We learned we were both studying skeletal muscle," says Gilbert. "Bryan's lab was using fruit flies to understand the muscle-nerve connection, which enables the brain to tell, for example, our arm to move.

"My lab was creating human tissue to make models of the muscle-nerve connection. Together, we realized our unique tools and methods could enable us to look at DMD in a different way from, literally, any group in the world."

DMD is caused by a gene mutation that prevents the body from producing dystrophin, the protein that enables muscles to function. It is a rare condition – occurring in one out of 3,500 to 5,000 male children worldwide – but it is devastating. Starting around age five, DMD progressively damages and weakens the muscles, including the heart. Most children with DMD will have to use a wheelchair. And most will die before they reach 30.

Gilbert says the biomedical innovation of creating muscle "means that for the first time ever it is actually possible to study DMD and the nerve-muscle connection outside of the body.



Human nerve cells (green) created from pluripotent stem cells making connections with human skeletal muscle cells (purple) (Erik Jaques).

"This gives us the opportunity to revisit observations that had been made decades ago that seemed to suggest that the muscle-nerve connection in DMD might be impaired," she says. "Now, we will see if this can be observed in our model. And if we do see it, could we try to use that as a starting point to find molecules that might improve the muscle-nerve connection?"

The team is working to make its 3D muscle models more representative of what is actually found in humans. They are especially paying attention to the variation in muscle structure and function that can exist in people who have DMD. Gilbert and Stewart note the expertise brought to the work by post-doctoral researchers Christine Nguyen and Majid Ebrahimi.

Stewart emphasizes that while the team is not directly creating drugs or therapies, their work will be an important foundational system for other researchers to use in developing pharmaceutical treatments or for testing the gene therapy experiments that will soon move to clinical trials.

Michael Rudnicki, a noted Canadian stem cell expert, agrees.

"The DMD pre-clinical assays being developed by Gilbert and Stewart are a critical facet of the translational pipeline, making it possible to test current and future therapeutics in the context of human cells," says Rudnicki, senior scientist and director of the regenerative medicine program and Sprott Centre for Stem Cell Research at the Ottawa Hospital Research Institute.

"There is a wealth of great work being done on DMD around the world," says Stewart. "Penney and I knew when we met at that workshop that there could be a lot of power in merging our two groups.

"I think we are at a point where we can help to launch a new surge in testing and discovery that will begin to benefit the people and families living with DMD."

This story first appeared in U of T News in a series featuring researchers working on medical and health innovations for the future.

Researchers Pursue Treatment For Vision Loss

By Paul Fraumeni

A multidisciplinary team of researchers seek to reverse eye damage caused by age-related macular degeneration.

It takes only a fraction of a second for light to travel through your eye to create an image in the brain, enabling you to see these words on your screen.

This ability, however, can be weakened – sometimes resulting in total blindness – when key structures in the eye are lost due to conditions such as age-related macular degeneration (AMD), which affects millions of people, and retinitis pigmentosa (RP), one of the most common inherited diseases of the retina.

But an interdisciplinary team of scientists, funded by the University of Toronto's Medicine by Design initiative, believes there is a possibility this outcome can be changed. Their plan: use retinal stem cells to restore vision.

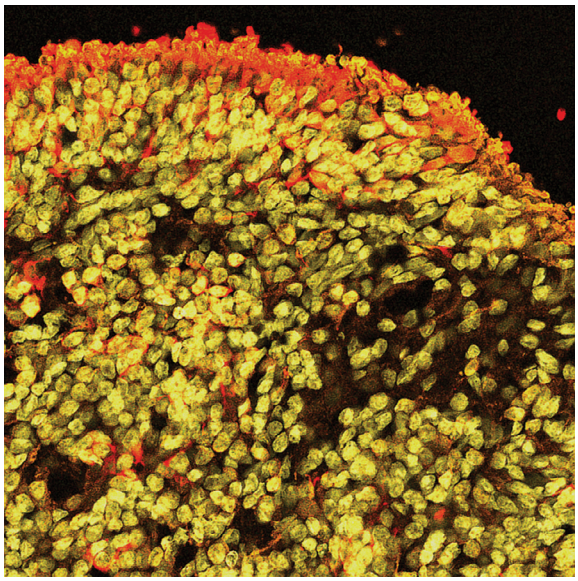
"This is extraordinarily difficult research, but we've seen some progress in restoring some vision in mice," says Molly Shoichet, a University Professor in the department of chemical engineering and applied chemistry in the Faculty of Applied Science & Engineering and the Institute of Biomedical Engineering and Principal Investigator in the Donnelly Centre.

"Now, by bringing together an integrated team of experts, we think we can take the next big step."
Shoichet's team includes **Derek van der Kooy**, also Principal Investigator in the Centre, **Valerie Wallace**, a senior scientist at the Krembil Research Institute at University Health Network, and **Julie Lefebvre**, a scientist in the neuroscience and mental health program at The Hospital for Sick Children (SickKids).

The team is one of 11 that is sharing nearly $21 million in funding from Medicine by Design over three years. Funded by a $114-million grant from the Canada First Research Excellence Fund, Medicine by Design is a strategic research initiative that is working at the convergence of engineering, medicine and science to catalyze transformative discoveries in regenerative medicine and accelerate them toward clinical impact.

To appreciate the challenges the team faces, first you need to understand just how our eyes see.

Light passes through your eye and hits the retina. Photoreceptor cells in the retina absorb light and convert the energy into electrical signals that go to the brain, enabling vision. The photoreceptors have a symbiotic relationship with the retinal pigmented epithelium (RPE), where the RPE cells support photoreceptor survival and function.
Age-related macular degeneration and retinitis pigmentosa, however, cause the photoreceptors and RPE



Human eye tissue derived from stem cells. Such retinal organoids can be harnessed as a source of light-sensing photoreceptors (orange rim) for transplantation to restore vision lost to age-related eye decay. (Margaret Ho)

to die. Without them, we can't see.

But could the photoreceptors and RPE be created from stem cells, then transplanted into eyes to restore the lost vision?

"We have been able to transplant photoreceptors and RPE cells into the eyes of mice that have lost their vision in a model of AMD," says Shoichet. "We have observed some vision repair, which is exciting. But at the same time, most of the transplanted cells perish and some of the ones that survive seem to transfer their proteins to the mouse photoreceptors in a process that Wallace and her team describe as material transfer."

The researchers came upon the material transfer problem when they used green fluorescently-labeled photoreceptors for transplantation. Doing this enabled the team to follow integration of the photoreceptors more easily – or so they thought.

"We saw many green cells in the retina after transplantation, which we thought meant that our stem cells were taking root in the retina. That made us feel good," says Shoichet.
But Wallace soon discovered something was amiss.
As it turned out, the green colour wasn't coming from the transplanted cells. Rather, it was being taken up by existing cells.

"That is the material transfer that Dr. Wallace's lab identified," Shoichet explains. "One photoreceptor transfers its material – in this case the green fluorescent protein – to another. We thought the transplanted cells were integrating, but now it was not clear that all of them were."

It was a frustrating moment for the team. Then they realized they could, in Shoichet's words, "turn lemons into lemonade and build on what we've learned."

The scientists now propose taking cell transplantation a step further and actually manipulating material transfer to overcome the mutations prevalent in RP, which is a genetic disease.

With that as the goal, each scientist is concentrating on a distinct task as part of an overall plan. Lefebvre's team has designed a tool that will enable them to evaluate the success of getting the cells to survive and integrate into the neural circuitry that sends visual signals to the brain. Wallace's group, meantime, will go deeper in studying the material transfer process and how to manipulate genes to overcome mutations like RP. And van der Kooy's lab will work on developing a source of photoreceptors from human stem cells.

Shoichet's lab will focus on making the retina more receptive to transplanted cells using innovative protein delivery strategies coupled with cell transplantation. She and van der Kooy recently published a paper where they showed, for the first time, that by transplanting RPE and photoreceptors together, some vision is restored.

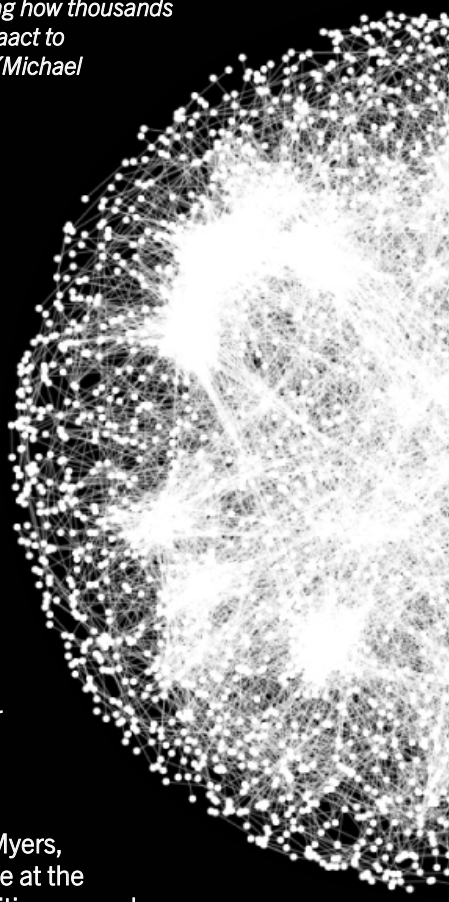
"There is certainly a tough challenge to this work, but our integrated team approach makes us much more likely to achieve the result we want as opposed to working separately," says Shoichet.

She praises Medicine by Design for its support and for the inspiring challenge that came from executive director and Donnelly Centre investigator **Michael Sefton**.

"Michael asked us all to conduct research that is truly transformative," Shoichet says. "Medicine by Design is funding a new way of thinking about cell therapy by supporting our work. It's exciting to do these studies and think about moving from mouse models to one day restoring vision in humans."

This story first appeared in Medicine by Design News.

Cells Are More Resilient Than Previously Thought



Global map depicting how thousands of yeast genes interaact to sustain cellular life (Michael Costanzo).

By Jovana Drinjakovic

The yeast study is the first to evaluate how environmental conditions affect the genetic program behind cellular sustenance.

Cells are more resilient to environmental perturbations than previously thought, Donnelly Centre investigators have found. It means that observations of the effects of drugs or mutations on cells grown in a lab setting stay strong despite external influences, making it easier for scientists to translate them as they seek to develop new diagnostics and treatments.

Writing in the journal *Science*, the group reported that the Baker's yeast cells employ the same network of gene interactions to coordinate cell growth in response to a wide range of different environments.

"We wanted to test in an unbiased way how the reference genetic network of a model cell changes in different environments," said **Brenda Andrews**, University Professor and former director of the Donnelly Centre who co-led the research. "And we found that the network is highly resilient and remains broadly the same, which means that a single reference condition provides us with a nearly complete view of the molecular wiring of a cell."

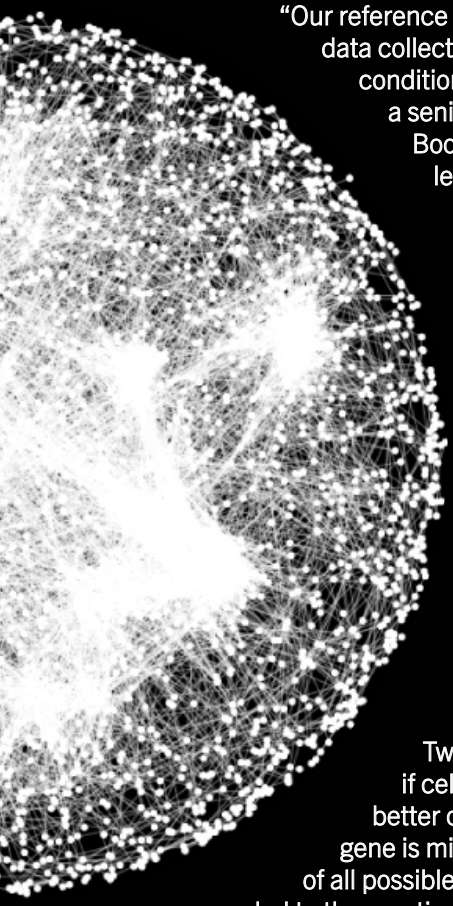
Charles Boone, a professor of molecular genetics and Chad Myers, a professor of computer science at the University of Minnesota-Twin Cities, were also senior authors on the paper.

The work builds on their previous research, published in *Science* in 2016, which established how all of yeast's ~6000 genes form a network of ~900,000 interactions. Yeast cells are similar to human cells but they are easier to study thanks to having smaller genomes and well-stablished techniques for genetic manipulations, which is why scientists have been using them as a research model to study the the molecular foundations of life.

As the only genome-wide map of genetic interactions for any cell, the global yeast genetic network is a unique

reference resource. The connections between genes hold clues about their function, and they can also reveal how mutations combine to produce cellular defects behind diseases. And, a robust reference map is also key for identifying the best genes to target therapeutically.

There was a concern, however, that genes might change their interacting partners depending on the cells' environment, which would complicate things because it would mean the molecular wiring is dynamic, like a moving target.



"Our reference map was constructed from data collected under standard laboratory conditions," said **Michael Costanzo**, a senior research associate in the Boone and Andrews labs and co-lead author on the paper.

"If you alter the conditions, maybe that would cause massive rewiring of the network."

Others have reported that the environment has the ability to rewire the connections within a select group of genes involved in a specific cellular process such as DNA repair, but its impact across the genome had not been assessed systematically.

Two genes are said to interact if cells lacking both genes grow better or worse than when either gene is missing on its own. The testing of all possible pairwise interactions that led to the creation of the reference map took over 15 years and cost tens of millions of dollars in research funding. Since it would have been impossible to replicate this tour de force under multiple conditions, the researchers selected a representative set of genes which span all major biological processes. In total, 30,000 genome-wide interactions were tested under 14 diverse environments, including an alternate food source, osmotic pressure, as well as various drugs. The vast majority—more than 90 percent—of the interactions first identified in the reference map remained present across all the conditions. Only seven percent of the interactions were novel, meaning they were detected for the first time and only in some environments. These novel interactions typically occurred between genes involved in different cellular processes, showing that external stimuli have the power to forge more distant genetic connections.

"Our study tells us that reference maps are useful, but they also highlight that keeping your eyes open for some rare but new connections in modified conditions may lead us into completely new territory," says Andrews.

The team, including **Jason Moffat**, a professor of molecular genetics at the Centre, are now working to create the first human reference map — a huge task given the larger number of human genes (~20,000) and the 200 million possible interactions between them. But the researchers say that based on their yeast work they can be confident that the human map will equally capture the fundamental biology regardless of variables such as cell type or growth conditions.

"People have been concerned that there is too much variability between different human cell lines to make accurate predictions about the effects of drugs, for example," said **Jing Hou**, co-lead on the paper and Donnelly postdoctoral fellow who will soon be starting her own lab at the French National Centre for Scientific Research in Strasbourg.

"If we know that the global human network is stable, we can be confident about the interactions we see, and based on our yeast data across vastly different environments we expect that to be the case," she said.

In addition to Costanzo and Hou, postdoctoral fellow **Vincent Messier** along with PhD students Justin Nelson and Mahfuzur Rahman, both from the Myers lab, equally contributed to the paper.

The study was funded by research grants from the Canadian Institutes of Health Research and the National Institutes of Health in the U.S.

Rapid Point-of-Care Diagnostics

By Qin Dai

Researchers have developed a quantum dot smartphone device to diagnose and track COVID-19.

Researchers at the Donnelly Centre in collaboration with Sunnybrook Health Sciences Centre, Public Health Ontario, and Mt. Sinai Hospital have engineered a diagnostic test that makes use of a smartphone camera to surveil and track COVID-19 patients.

This finding could significantly improve the turnaround time and efficiency for infectious disease diagnosis, both for COVID-19 and beyond. The research was published in the June 2020 issue of *Nano Letters*.

"The goal of the study is to make COVID-19 antibody tests more accessible." said **Johnny Zhang**, a PhD candidate at the Institute of Biomedical Engineering and Department of Chemistry, and one of the co-first authors of this publication. "The end result is that the patients can take a self-diagnosis for COVID-19 with their phone, and that data can be immediately accessed digitally by medical professionals."

In a traditional infectious disease diagnostic testing workflow, the clinical sample is obtained from the patient, sent to a laboratory for diagnostic testing, and the result is distributed to clinical personnel for decision making. These processes are often detached in operation and have a long turn-around time.

The researchers engineered quantum dot barcoded microbeads and a secondary label to search for antibodies against COVID-19 antigen in the patient's blood. Finding the antibodies leads to a change in microbead emission colour.

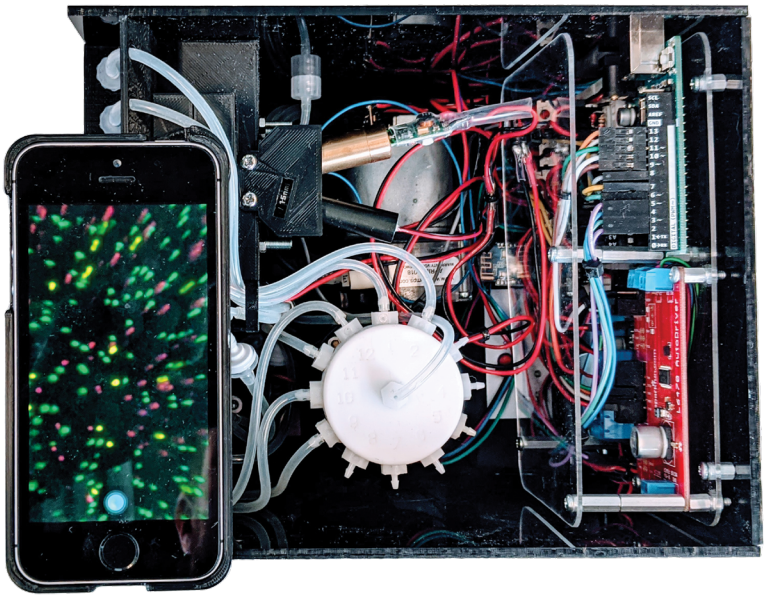
The beads are then loaded into the device, 'activated' with a laser, and the signal is imaged using a smartphone camera. An app is designed to process the image to identify the bead's emission change. Lastly, the data are interpreted and transmitted remotely across the world for data collection and decision making.

"The beauty of the system is that everything is integrated into one portable unit." said Zhang.

This technology, by which quantum dot microbead detection can measure minuscule amounts of key biomarkers in blood, has been in development for the past 10 years.

"We really wanted to improve the performance and utility of the technology this time around," said **Ayden Malekjahani** (BME PhD candidate), the other co-first

The quantum dot-powered smartphone device developed by the Chan lab for the detection of various antibodies in response to viral infections. Antibody detection emits a colour signal which is captured by the smartphone camera. (Matthew Osborne)



author of this study.

"Being able to detect traces of target in patients is not enough. We wanted to add more functions to the device. We designed the device to simultaneously detect multiple antibodies from different sample types, so each test run is packed with information. The results are then uploaded to an online dashboard where medical professionals and the public can see trends in real time."

The researchers tested this device with forty-nine patient blood samples where varying degrees of COVID-19 infection were present, and were able to achieve 84-88% sensitivity. Although this result is not as high as traditional tests it is still approximately three times higher than lateral flow assays, which are currently the most commonly available portable antibody tests.

This result also means detecting COVID-19 antibody can now be done outside of the centralized facilities without a big drop in accuracy.

This research was a collaboration with the Public Health Ontario, Sunnybrook Hospital and Mount Sinai Hospital, where clinical samples were provided to the researchers to test and evaluate this new system.

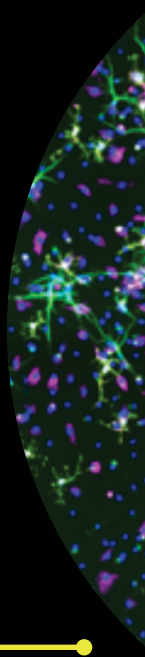
"This device can be a game-changer in the way we monitor the spread of infectious diseases and a patient's response to vaccines," said **Warren Chan**, Director at the Institute of Biomedical Engineering and Donnelly Centre investigator who led the research.

> ***"This device can be a game-changer in the way we monitor the spread of infectious diseases and a patient's response to vaccines.***
>
> **Warren Chan**, Director of U of T's Institute of Biomedical Engineering and Principal Investigator in the Donnelly Centre

This story first appeared on the website of U of T's Institute of Biomedical Engineering.

Protecting Juvenile Brains From Radiation Effects

By Julie Crljen



Differentiating neurons (green) that had been derived from stem cells. Metformin has the ability to promote stem cell differentiation into brain cells (Daniel Derkach).

New research shows diabetes drug could provide brain protection to children who get radiation for brain tumours.

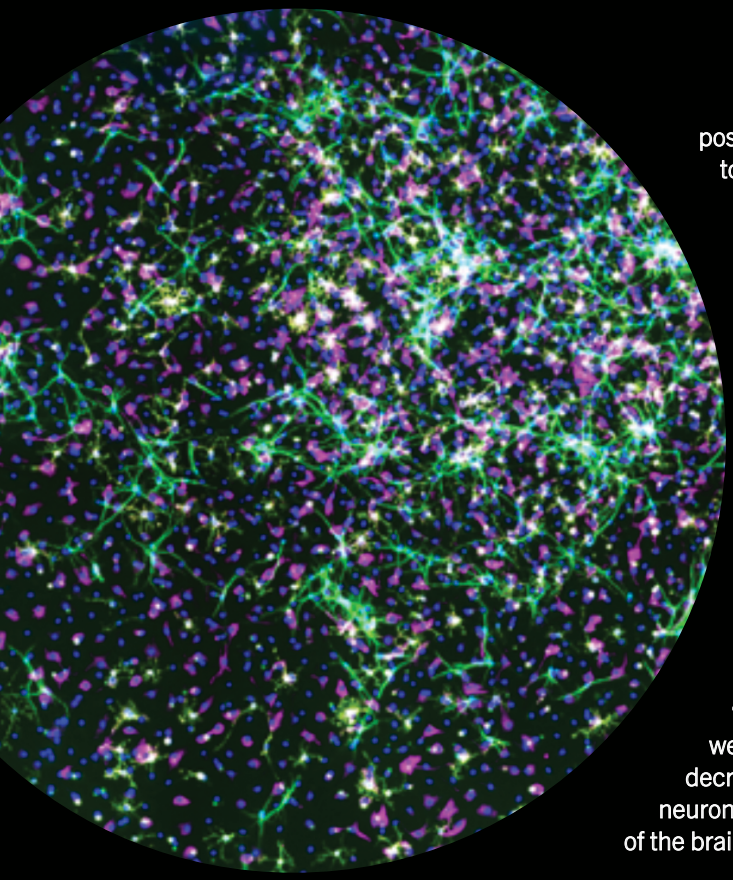
Radiation can be life-saving for a child with a brain tumour. But this therapy can also cause damage to the brain that leaves the child with deficits in cognitive function, including learning and memory challenges.

Now, thanks to funding from Medicine by Design, a University of Toronto scientist and her team are closer to finding a way to protect the brain from damage for children who must be treated with cranial radiation.

"We found that if we gave metformin, which is an approved, safe drug used to treat diabetes, as a pre-treatment in animal models, we could actually stop the damage from happening," says **Cindi Morshead**, a professor and chair of the Division of Anatomy in the Department of Surgery and a principal investigators in the Donnelly Centre.

This study, published in *Cell Reports Medicine*, builds on previous work done with metformin. Last summer, Morshead and researchers from The Hospital for Sick Children (SickKids) showed that metformin administered after cranial radiation encouraged neurogenesis, or the process of making new neurons in the brain.

Morshead says that given the safety of metformin, this new research will hopefully proceed quickly to clinical trials. "Anything we can do to stop children from having these long-term impairments would be very



positive. For children with brain tumours who need cranial radiation, to be able to do something that would ensure their brain is damaged less in the first place, rather than try to repair it after the fact, would be life-changing for these children and their families."

Notably, the previous metformin study, which looked at administering the metformin after the cranial radiation and once the damage had already occurred, found that the benefits of metformin were seen only in juvenile females. Morshead says that today's study showed no sex-specific effect, which indicates that pre-treating children with Metformin could provide additional benefit.

Cognitive deficits from radiation can result from killing newborn neurons that underly learning and memory. Morshead says this study shows that metformin offers neuroprotection to animals who were given the drug prior to the cranial radiation.

"Radiation is an insult on the brain, and our study showed that we're able to protect the micro environment because the metformin decreases brain inflammation. After the drug treatment, newborn neurons were not lost and could keep making new connections in the part of the brain that is important for olfactory memory."

Morshead, whose lab is located at the Donnelly Centre for Cellular and Biomolecular Research, says that, for this project, the researchers taught animals where to find a food reward based on a particular smell. One type of scent belonged to a dish that had a hidden treat, and another type of smell belonged to a dish that had no hidden treat. Only mice that had the metformin treatment before radiation could remember which scent was associated with the treat.

"It was really quite a striking effect. The ones that were not administered the metformin prior to radiation couldn't remember the association," Morshead says. "The ones that were given the metformin remembered the association weeks after the radiation. So we concluded that the mice that were not treated with the metformin had an impairment in long-term memory, and metformin protected against this impairment."

This study is part of a large team project funded by Medicine by Design, led by **Freda Miller**, an adjunct scientist in the Neurosciences & Mental Health program at SickKids. Miller's research team, which includes eight labs at U of T and SickKids, is taking a wide-ranging approach to promoting self-repair in the brain and muscle. Miller and her colleagues at SickKids made the discovery that metformin had potential to be used for self-repair in the brain. Morshead's metformin research builds on this original finding.

Morshead credits funders including Medicine by Design for being strong supporters of this and other promising metformin work. "My lab — as well as the labs of Freda Miller and Don Mabbott at SickKids and others — are grateful to have the opportunity to do this research. Being able to show these positive results using a drug that we know is safe, approved and accessible is really the best-case scenario. Our hope is that this is one day a low-risk solution for children who would otherwise be living with cognitive deficits after surviving a brain tumour."

This story first appeared in Medicine by Design News

Sars-CoV-2 Neutralizing Compounds Created

By Jovana Drinjakovic

Researchers have developed mirror-image peptides which can neutralize Sars-CoV-2, raising hopes of new treatments.

Professor Philip Kim

Postdoctoral Fellow Pedro Valiente

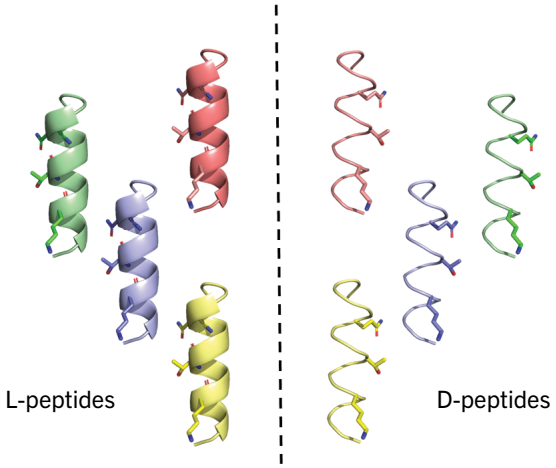
Donnelly Centre researchers have created first in class chemical compounds which can neutralize Sars-CoV-2 and several of its variants. Known as mirror-image peptides, the compounds have chemical properties that make them suitable for the development of low-cost antiviral therapeutics.

"A big advantage of mirror-image peptides is their long stability and that they are relatively cheap to produce," says **Philip Kim**, senior author of the study and a professor of molecular genetics and computer science at the Donnelly Centre for Cellular and Biomolecular Research at U of T's Temerty Faculty of Medicine.

"You could imagine them being formulated as a nasal spray to take prophylactically to prevent infection from occurring."

In a paper published in the *Journal of Medicinal Chemistry*, the researchers report the creation of D-peptides that neutralize the virus and stop infection of cultured human cells.

Peptides are similar to proteins in that they are composed of the same amino-acids building blocks although they are smaller than protein molecules. They can be designed to bind virtually any molecular target and with a greater specificity than small molecule drugs which reduces risk of side effects. In this regard, peptides are similar to antibodies but are at least a hundred times cheaper to produce thanks to their small size. The low cost and easy scaling of manufacturing makes peptides attractive options, in



Mirror-image peptides (D-peptides on the right) engineered by Donnelly Centre investigators neutralized Sars-CoV-2 and prevented infection of cultured human cells (Pedro Valiente).

particular for low-income countries.

There's a caveat, however. Peptides are rapidly degraded in the body by enzymes evolved to stamp out harmful peptides produced by bacteria and other pathogens. But science has found a solution in mirror-image peptides that are resistant to degradation.

For reasons that remain unclear, all naturally occurring amino-acids exist in a left-handed configuration, as defined by the direction in which they rotate plane polarized light. Consequently, all proteins and peptides are also left-handed — and known as L-peptides.

A few years ago, Kim's team developed a computational tool for the design of so-called D-peptides that have inverse geometry. These mirror-image molecules are manufactured from synthetic D-amino-acids strung together in the same way as their left-handed counterparts. And using Kim's design method, they can be engineered to bind the same targets with undiminished specificity. The main difference is that their unusual geometry makes them resistant to enzymes in the bloodstream that break down normal L-peptides.

The prospect on working with D-peptides is what enticed postdoctoral researcher **Pedro Valiente** to join Kim's lab in the first place. When the pandemic hit, he realized they could apply their tool to try to make antivirals for COVID-19. By May 2020, Valiente had already created the compounds that would prove to be potent inhibitors of the virus, although it took another year to verify that they work as expected in human cells. The delay was caused by an overwhelmed capacity of high security labs for study of dangerous pathogens as scientists around the globe rushed to study the novel coronavirus.

Valiente designed several D-peptides that mimic the region of the virus spike that binds the ACE2 receptor on the surface of cells. He reasoned that the peptides will bind to the receptor before the virus makes contact with it therefore preventing infection. This was later confirmed by the experiments with cultured human cells that were carried out by collaborators at two high security labs in the Republic of Korea.

What's more, the peptides worked equally well against the Alpha, Beta and Gamma variants, which wreaked havoc over the past year after appearing in the UK, South Africa and Brazil, respectively.

"While we focused on the variants that were circulating at the time when we were doing this work, the peptides should work on Delta as well based on the similarity with its receptor binding domain," said Kim.

Valiente, who joined Kim's lab a year before the pandemic, said that the experience was especially gratifying as he was able to create a potential therapeutic at record speed during the first lockdown when most of the world was at a standstill.

By the time the researchers published their findings however, several treatments have become available, including antiviral medications, antibody cocktails and vaccines. Prompted by these global advances, the team has shifted focus from COVID-19 to trying to create compounds that target all coronaviruses, including SARS and MERS in a bid to design a universal therapeutic as safeguard from future pandemics. To this end, Kim has partnered up with a Boston biotech company Decoy Therapeutics to commercialize the research.

Funding Highlights

During the period from June 2020 to July 2021, Donnelly Centre investigators have raised more than $35 million in research funding from federal and provincial governments and other sources. Notable funding news are highlighted below.

Professor Charlie Boone

Accelerator for Donnelly Collaboration

Charlie Boone, a professor of molecular genetics at the Centre, won $1.9M from the Canadian Foundation for Innovation for upgrades to the Accelerator for Donnelly Collaboration (AcDC), a biotechnology hub dedicated to the translation of the Centre's discoveries. The funding will enable an expansion and consolidation of two existing platforms, with an emphasis on academic-industry partnerships.

The first platform is the Toronto Recombinant Antibody Centre, led by Professor **Sachdev Sidhu** and focused on development of humanized antibodies. The second is the Platform for Advanced Cell Engineering, a technology for genome editing developed by Professor **Jason Moffat** based on CRISPR-Cas9 and lentiviral pooled screening.

The new funding will allow Donnelly researchers to create an Editing and Infrastructure Technology (EDIT) lab to help map genetic networks and profile human cells through chemical genomics. It will also bring new infrastructure to TRAC and enable a Protein-Protein Interaction (PPI) Disrupt pipeline to support technologies developed in Professor **Igor Stagljar**'s lab for screening and validation of new drug targets.

"We've seen great progress toward personalized medicine, with the complete genotyping of individuals and effective treatments for some specific conditions," said Boone. "But to realize the potential in those advances, we need better datasets to interpret genome variation, functionally annotate the human genome and potentially translate these findings into new therapeutics," Boone said. "This new infrastructure will help get us there."

Associate professor Mikko Taipale

Professor Frederick (Fritz) Roth

Genetic Variation Effect Mapping

Mikko Taipale and **Frederick Roth**, both professors of molecular genetics, won $1.9 M from the National Human Genome Research Institute U.S. to shed light on how variation in our genomes affects disease risk and severity in a bid to improve interpretation of personal genome information.

The research is part of a newly launched multimillion dollar initiative in the U.S., the Impact of Genomic Variation on Function Consortium, which brings together scientists and clinicians from all over the world to advance an understanding of genome function and how it contributes to health and disease. The total funding awarded for the project is $8.3M (U.S.) or $10.5M (CAD) and it is directed by Marc Vidal, Director of the Center for Cancer Systems Biology (CCSB) at Dana-Farber Cancer Institute and Professor of Genetics at Harvard Medical School.

Over the next five years, the researchers will develop a catalog of experimental data to assist in the classification of missense variants—alterations in the DNA code which change the amino-acid composition of the encoded protein—as either pathogenic and capable of causing disease, or benign and harmless. For the majority of missense variants, their impact on health remains unknown which is why they are called variants of unknown significance, or VUS. A genetic test with a VUS result can be agonizing for patients as it leaves them no wiser about its meaning.

“When people get a genetic diagnostic test and find a variant in their gene, a genetic counselor has to interpret it — and a VUS result is essentially throwing up their hands and saying we don’t know,” says Roth who is also a professor of molecular genetics and computer science at U of T and a senior investigator at the Lunenfeld-Tanenbaum Research Institute at Sinai Health.

“The promise of personalized medicine based on your personal genome sequence comes to a grinding halt when the majority of the variants that are found can’t be interpreted,” he said.

The researchers will investigate around 75,000 variants in about 1000 genes with known links to genetic disorders, such as Cystic fibrosis and Duchenne muscular dystrophy and for which dozens of variants have already been documented across patient populations. This is key because sufficient numbers of known pathogenic and benign variants are required for VUSs to be compared to and classified accordingly.

For each gene, the researchers will compare across several lab tests how dozens of its encoded protein variants, perform at the cellular level. The work will reveal mechanistic insight into variant protein function in health and how it goes awry in disease. It will also enable the classification of VUSs by comparing them to their benign and pathogenic counterparts.

Transplantation Treatment for Diabetes

University Professor Michael Sefton

University Professor and world-renowned tissue engineer **Michael Sefton** won a grant of almost $430,000 from international diabetes foundation JDRF. The funding will support ongoing efforts in the lab towards developing a transplantation-based treatment for type 1 diabetes. It follows the $1.1M grant Sefton received in 2016, also from JDRF, which enabled the team to begin to explore an experimental treatment that involves transplanting healthy pancreatic cells which produce insulin into patients living with the disease. The team is looking to transplant islets under the skin because it is considered a less hostile environment to prevent graft rejection.

The new funding will help the researchers address several hurdles standing in the way of transplant success, including a limited supply of islets from donors. Working with **Maria Cristina Nostro**, Senior Scientist at McEwan Stem Cell Institute at the University Health Network, they are trying to create insulin-producing cells from stem cells, which provides an unlimited supply.

The researchers are also looking to boost graft survival by co-implanting a material containing methacrylic acid (MAA) which they think will prevent graft rejection. “We believe that the MAA has properties that will work on the skin’s dendritic cells to be tolerant of the pancreatic cells. We don’t want to suppress the immune system, because that is dangerous for the patient. We want to fool it into accepting the new pancreatic cells as if they are part of the patient’s body. And if we can do that, we’ll have taken a huge step forward,” said Sefton in a *U of T News* story

Tackling Diversity Gap in Mass Spectrometry

Assistant Professor Hannes Röst

Hannes Röst, an assistant professor of molecular genetics and computer science, received funding from the Chan Zuckerberg Initiative to create an outreach and training program that will enhance diversity in computational mass spectrometry and equip a wider group of researchers with the advanced tools for data analysis.

A lack of role models has meant that female researchers and researchers from other under-represented groups are facing hurdles beyond their control in learning the programming skills that would help them advance their research. “We hope to change that by educating a generation of future leaders and role models who can pay forward and multiply the effects,” said Röst.

The program will teach a wider research community how to use and adapt Open MS, a leading software in the field developed by the Röst lab, for their specific research questions. The first step will be to hire a community manager whose role will be to seek out researchers from underrepresented groups wishing to advance their data analysis skills. The training will be delivered through online and in-person workshops, for which travel grants will be available.The best trainees will be offered internships in the labs of renowned mass spectrometry experts with all research and accommodation costs covered.

Faculty Appointments & Awards

As globally recognized leaders in their fields, Donnelly Centre investigators are bestowed some of the most prestigious honours reserved for top scholars. Highlighted below is a selection of distinguished appointments won by our faculty in the past year.

Founded in 1882, the Royal Society of Canada recognizes Canada's leading intellectuals, scholars, researchers and artists.

Derek van der Kooy, Fellow of the Royal Society of Canada

Professor of molecular genetics **Derek van der Kooy** has been named fellow of the Royal Society of Canada, considered one of Canada's major accomplishments for scholars.

Van der Kooy is world renowned for making foundational discoveries in neurobiology, from the neural basis of motivation and addiction, as well as learning and memory, to stem cells and nervous system regeneration. His discovery of stem cells in the adult mammalian eye opened the door to research in regenerative medicine in pursuit of treatment for blindness. His team is at the forefront of these efforts as they work to develop strategies to harness stem cells for the replacement of retinal tissue damaged by injury or disease. At the same time, his discoveries in opiate responses hold potential for treatments for drug and other addictions.

He has published more than 270 papers in high impact journals and his work has been cited more than 35,000 times. He is a founding member of the Canadian Stem Cell Network and was the initiator of the Toronto stem cell initiative, which evolved to be the Ontario Institute of Regenerative Medicine.

Although Donnelly Centre faculty make up a tiny proportion of professional academics nationally, they amass an outsized share of the most prestigious honours in Canada. These inlcude:

3
Order of Canada medals

7
Royal Society of Canada fellows

1
Gerhard Herzberg Gold medal

11
Canada Research Chairs

4
University Professors

Brenda Andrews, Canada Research Chair in Systems Genetics & Cell Biology

University Professor and founding director of the Donnelly Centre **Brenda Andrews** was named Canada Research Chair in Systems Genetics & Cell Biology. The appointment comes with research funding that will help shed light on how disease unfolds at the level of individual cells.

Work is already underway in Andrews' lab to understand why cells that have the same alterations in their genetic codes don't always develop the same defects. This phenomenon is known as incomplete penetrance and it is common in human diseases, since people with the same disease-causing gene variant can experience different disease symptoms and severity.

"We are beginning to appreciate that any kind of genetic perturbation can have a highly variable penetrance and there's a large cell-to-cell variability," said Andrews. "And that has implications for understanding the mechanisms of disease, and for thinking about potential treatments."

Over the last decade, Andrews' team built a fully automated high-throughput platform to collect measurements from millions of individual cells in a mixed population using automated microscopy. Coupled with computer vision tools and artificial intelligence, the platform will reveal the bioprocesses behind cell-to-cell variability.

"We can look at all kinds of different mutant scenarios and measure how that affects cellular traits at the single cell level," says Andrews. "It gives us a lot more information so that we can begin to unpick the mechanisms behind disease penetrance."

A pioneer of functional genomics, Andrews has received numerous national and international awards. She was named Companion of the Order of Canada, the highest national honor that can be bestowed on any citizen, fellow of the Royal Society of Canada, an international member of the U.S. National Academy of Sciences and holds the highest academic rank of University Professor, among other honors and appointments.

Established in 2000, the Canada Research Chair program seeks to attract and retain top minds in Canada, supporting research in natural sciences, health sciences, engineering, humanities and social sciences.

Grant Brown, Canada Research Chair in Genome Integity

Grant Brown is a professor of biochemistry in the Centre where he studies how cells maintain their genomes intact. Whenever a cell copies its DNA, copying errors inevitably appear but in most cases repair enzymes swiftly correct them. External insults such as UV light from the sun or tobacco smoke, as well as internal factors, such as mutations in cancer genes, further increase the number of mutations tilting the balance to where the cell is no longer able repair its DNA. When repair is overwhelmed, this can lead to cancer and other diseases.

CRC funding will support two kinds of projects in Brown's lab. The first are foundational projects in which the team will try to understand the basic cellular processes that prevent mutations from arising—and that repair them when they do arise—using yeast cells as a model. The second are projects that aim to reveal how cancer develops and find new ways to treat it. To this end, the team will identify the genes that cause loss of genome integrity in human cancer cells, and in cancer cells that have been treated with therapeutic drugs.

Rafael Montenegro-Burke, Connaught Young Investigator

Assistant professor **Rafael Montenegro-Burke** was awarded a Connaught New Researcher award from the University of Toronto, which provides support for new faculty members at the start of their careers.

Montenegro-Burke joined the Donnelly Centre for Cellular and Biomolecular Research as a principal investigator in fall of 2020 and built a research program in metabolomics — an emerging field that draws on molecular biology, engineering, computer science and other areas to illuminate metabolites, which are small chemical compounds produced by the body that influence health and disease.

The funding will support the development of new chemistry approaches for the identification of scarce lipid molecules that have been linked to inflammation in the gut known as irritable bowel syndrome.

He has also won the John Evans Leaders Award from the Canadian Foundation for Innovation which will allow him to obtain a state-of-the-art mass spectrometry instrument for the detection of small molecules in cells and tissue samples.

Research Excellence Awards

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

Ulrich Braunschweig

Hunting down genetic miscues in the brain

The brain's ability to process information is in part borne out by a startling diversity of protein species unrivaled by any other organ in the body. This is thanks to a process known as alternative splicing (AS) whereby different protein variants are encoded by the same gene— and which has been the focus of Braunschweig's research.

Braunschweig is a research associate in Professor **Ben Blencowe**'s lab known internationally for their work on AS. During splicing, the genes' coding fragments, or exons, are variably spliced into messenger RNA molecules which serve as templates for building proteins. The lab previously showed that AS is tightly regulated during brain development and that miscues in this process can lead to neurological disorders such as autism. But it remains unclear how splicing is regulated in different cell types and at different time points.

Braunschweig helped develop a method called SPAR-Seq, for Systematic Parallel Analysis of Endogenous RNA Regulation Coupled to Barcode Sequencing, which allowed him to identify novel splicing regulators. Because SPAR-Seq can be used to study splicing across cell types and cellular processes, Braunschweig established multiple collaborations across U of T and internationally to address other research questions.

He also found that some splicing errors are more common than previously thought, and that these miscues have been co-opted by cells for gene regulation. When the genes' noncoding segments, or introns, are erroneously spliced into

mRNA transcripts, this prompts transcript degradation to prevent malfunctioning proteins from being made. But in some cases, intron retention serves to ensure that a right protein is made at the right time. Working with John Rinn's lab at the University of Colorado, Braunschweig found that intron retention in a cancer gene called TERT ensures that the transcripts are kept in the cell nucleus where they can't be translated into proteins until a time when the TERT protein is needed, at which point the correct splicing kicks back in.

When the coronavirus pandemic hit in March 2020, Braunschweig was quick to join the effort between the Blencowe lab and **Jeff Wrana**'s team at the Lunenfeld-Tanenbaum Research Institute, at Sinai Health System, to adapt SPAR-Seq into a more efficient method for detecting Sars-CoV-2 from patient samples. The method eventially became a key tool for new variant detection and surveillance in samples collected at Toronto's Mount Sinai hospital.

> ***Ulrich and Muhammad have developed novel technologies in their fields that allowed them to gain insights that were not possible before. I can hardly wait to see what they will achieve next!***
>
> **Charlie Boone**, Professor of molecular genetics and former interim director of the Centre.

Muhammad Rizwan

Engineering liver tissue for transplants

About half a billion people globally are living with liver disease and for many of them a liver transplant is the only hope of recovery. But with donor organs in short supply, Rizwan and scientists like him are trying to grow functional liver tissue in the lab that can be used for transplants.

Rizwan is a research associate in University Professor **Molly Shoichet**'s lab and his focus has been on creating bile ducts, tubular structures inside the liver which secrete bile and digestive juices. Diseases affecting bile ducts are the reason behind two thirds of liver transplants each year.

Material scientist by training, Rizwan created a biomaterial known as hydrogel, which mimics the liver's natural microenvironment to support bile duct self-assembly in a laboratory dish. He collaborated with the group of **Gordon Keller**, Director of the McEwen Stem Cell Institute at University Health Network, which previously developed a method for growing bile duct cells from stem cells.

Rizwan cross-linked the hydrogel with a photoactivatable form of Jagged-1, a molecule which triggers a molecular pathway required for bile duct formation. Using a laser beam, he was able to activate Jagged-1 in the same spatial pattern in which it is expressed during liver development. He was also able to tweak hydrogel's viscoelasticity properties to match those of the real human liver to support bile duct self-assembly in a defined culture medium.

This research has established the minimal components required for bile duct formation which should facilitate regulatory approval of potential therapy with lab-grown bile ducts. It will also aid further research into the mechanics of bile duct formation and how it goes awry in disease.

Charles H. Best Postdoctoral Fellowship

2021 Charles H. Best Fellow Marina Musa, PhD, is studying parasite metabolism, in the lab of Prof. Andy Fraser, in search of new treatments.

Things did not go according to plan for **Marina Musa** when she arrived in Toronto in March 2020 for a postdoctoral stint. As the country shut down in the wake of the coronavirus pandemic, she spent the next three months confined to an unfamiliar apartment thinking about science instead of doing it.

"It was not a great time," she says of the first lockdown. "But there was time to narrow down what we need to prioritize and how to go about things, so once the labs reopened it was full steam ahead."

Such determination is only fitting for a Charles H. Best Fellow, a recognition Musa won after a competitive selection process. The prestigious fellowship is awarded annually by The Charles H. Best Foundation to a postdoctoral researcher in the Donnelly Centre whose research has the potential to benefit society.

"I feel very fortunate and honoured, first by the chance to work with Dr. **Andy Fraser** and then by this fellowship," says Musa. "It's a great encouragement to tease apart this biological puzzle of how the host, the parasite and the microbiome affect each other. I am very excited to see where this project takes us in the future."

The award decision was made by the fellowship committee co-chaired by Donnelly Centre Interim Director **Charles Boone** and Director of Research Operations & Strategy **Sara Sharifpoor**, with Centre's investigators **Brenda Andrews**, **Peter Roy**, **Tim Hughes**, **Hannes Röst** and **Mikko Taipale** as members.

Musa joined the lab of **Andy Fraser**, a professor of molecular genetics, to study the metabolism of parasitic round worms, also known as helminths, which infect the guts of about one billion people worldwide. Infections occur paredominantly in the developing world and, if left untreated, can impair development and health in the long term. New drugs are urgently needed due to a growing resistance among the parasites to existing medications.

She is approaching the problem from a new angle. She is investigating how the bacteria in the worm gut—the worm microbiome— contribute to infection. Her goal is to identify the chemicals produced by the bacteria that are essential for the parasites' survival in the low oxygen environment inside the host gut.

The team previously uncovered a metabolic process that allows parasites to survive without oxygen for long periods of time. Moreover, they were able to mimic this airless environment with cyanide, a drug that prevents oxygen from being used for respiration. This let them activate the same metabolic pathway in a nonparasitic worm known as *Caenorhabditis elegans* which is widely used in research, allowing them to study a key aspect of parasite biology in a lab dish.

"Parasites are difficult to study, because one would need to study them inside the host, so we would be dealing with two organisms in addition to a complex microbiome," says Musa. "In the context of our project it would be nearly impossible to work directly on parasites. That is why we use *C. elegans* — we can see the same metabolic process in worms crawling in the dish."

The secret behind the parasites' ability to survive without oxygen lies in a molecule called rhodoquinone, or RQ. Musa will investigate how the worm's gut bacteria affect the RQ metabolism. Because RQ is present only in the parasites and not in their hosts, this opens a way to specifically target the parasites without harming the infected humans.

Although Musa will study this in worms in a dish, the human gut is more like a jungle, teeming with different bacteria. If changing these bacteria, the so-called human gut microbiome, can alter the way the parasites can make and use RQ, this opens up a new way of targeting the parasites through changes in the host microbiome.

Donnelly Research Thesis Prize

Keith Lawson (MD, PhD) won the best thesis prize for his research on genetic interactions in cancer conducted with Prof Jason Moffat.

As a clinician scientist, **Keith Lawson** has feet in two worlds, splitting his time between seeing patients and inventing better treatments for them. Blending science with medicine can offer a unique perspective.

"I think it's important for clinicians to stay engaged in discovery science where we are not just trying to apply the things that other people discovered," said Lawson, now a senior resident at the university's urology clinic. "Having our perspective is important right from the discovery side of things and I think that helps us ask clinically meaningful questions."

Lawson cut his research teeth in the Donnelly Centre where he investigated how cancer becomes resistant to treatment. He was a doctoral student in the lab of **Jason Moffat**, a professor of molecular genetics, as part of his medical training in the Surgeon Scientist Program at U of T's Department of Surgery.

He received the Donnelly Centre Thesis Prize, awarded annually to the best doctoral graduate in the Centre. The decision was made by the award committee members and the Centre's investigators, **Molly Shoichet**, **William Ryu** and **Aaron Wheeler**.

"Keith was an outstanding student with an incredible drive to use systematic genetics approaches for clinically relevant questions related to cancer," said Moffat, who chairs the award committee, although he recused himself from voting to avoid conflict of interest.

"As a surgeon scientist in training, Keith was passionate about kidney cancer and made important discoveries related to lipid metabolism and cytotoxic T lymphocyte killing of cancer cells."

"His finding that autophagy plays a major role in cancer evasion of the immune system has now been observed in many different labs throughout the world, providing new insight for the field of immuno-oncology," says Moffat.

Personal effort notwithstanding, Lawson puts his research success down to team diversity.

"Team diversity is important and that's something that is celebrated in the Donnelly Centre with people from multidisciplinary backgrounds getting involved in projects together," said Lawson.

"We had people from the industry, we had people that were academics and then we had people like myself who have a strong clinical background. And the way we think and approach problems is different and complementary and I think that helps steer the project in a way that kept it very clinically relevant, but also technologically savvy and focused," he said.

Lawson first investigated what happens to cancer cells when they lack key nutrients needed to sustain rapid proliferation. His focus was on fat molecules, or lipids, whose biosynthesis has emerged as a promising therapeutic target. Drugs designed to block lipid production—and starve cancer—are advancing through human trials. But Lawson discovered that when cancer cells can't make their own lipids, they import them from outside the cell. As well as revealing a likely mechanism for treatment evasion, the study, which was published in the journal *Nature Metabolism*, also points to a way of improving therapy by blocking lipid synthesis and import at the same time.

His second project focused on cancer's evasion of the immune system. Immunotherapies, in which the patient's immune cells are reprogrammed to attack cancer, hold great promise but they do not work for everyone for reasons that are not clear. Lawson identified almost 200 genes that are involved in the interaction between the immune killer T cells and cancer cells, publishing the findings in *Nature*. Many of these genes also play a role in autophagy, a process by which cells recycle their own components, suggesting that targeting it could improve immunotherapy success.

Now in the final year of urology residency, Lawson takes care of patients and performs urinary tract surgery. He is also a team lead on a new research initiative that is applying the latest genomic technologies to profile patients' kidney tumours and find new therapeutics for them.

"I think that the integration of new genetic technologies such as CRISPR-screens and single-cell genomics with improved patient-derived models of cancer will facilitate a rapid expansion in new drug targets for cancer, particularly immunotherapies," said Lawson.

"Establishing multi-disciplinary teams to enable and translate this kind of science will become more important than ever before."

Jennifer Dorrington Graduate Research Awards

Can global food supply be protected from parasites? Can we spot diabetes before symptoms appear? How can drugs be delivered directly into cancer cells? Answering these questions is no small feat but three students are making progress and reaping prizes along the way.

Jessica Knox, **Shubham Gupta** and **Jamie Wu** are the recipients of the 2021 Jennifer Dorrington Graduate Research Award, which recognizes students enrolled in graduate programs at the Temerty Faculty of Medicine who are doing research in the Donnelly Centre.

> ***We were really impressed by the exceptionally strong pool of candidates this year. Jessica, Shubham and Jamie have made great progress and their research will have an important impact on peoples' lives.***
>
> **Gary Bader**, a professor of computational biology and molecular genetics in the Donnelly Centre and Chair of the award committee.

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.

Safeguarding global food supply

Jessica Knox is a fourth year PhD student in molecular genetics in Professor **Peter Roy**'s lab, where she is searching for chemicals that can kill nematode worms which feed on crops. It has been estimated these parasites cause a 12 per cent drop in global crop yield, or over 150 billion U.S. dollars in damage every year.

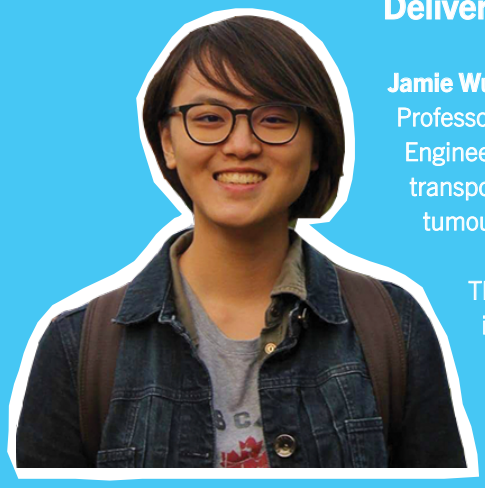
The lab previously discovered drug compounds which can kill the standard nematode model, *Caenorhabditis elegans*. Supported by a Burroughs Wellcome Fund travel award, Knox tested these compounds in a real-life scenario at the U.S. Department of Agriculture research centre in Corvallis, Oregon. She discovered potent nematicide against the tomato parasite, *Meloidogyne incognita.* She is now investigating how the compounds work at the molecular level.

Predicting diabetes before it strikes

Shubham Gupta is a fourth year PhD student in molecular genetics in Professor **Hannes Röst**'s group where he is developing computational tools for the analysis of protein content in blood to find the early biomarkers of diabetes.

Blood is brimful with thousands of proteins whose levels change depending on person's health, but current methods can only detect a handful at a time. Gupta has been able to incrase throughput to 300 proteins per hour, opening the door to large scale data analysis. Working with collaborators at Stanford University, he is analysing blood samples which had been collected over time from 100 prediabetic individuals, some of whom went on to develop type 2 diabetes, in search of protein signatures predictive of the disease years before symptoms appear.

Delivering drugs directly into tumours



Jamie Wu is in her third year of PhD in biomedical engineering in the group of Professor **Warren Chan**, who is also Director of U of T's Institute of Biomedical Engineering. Wu's goal is to learn how medication-carrying nanoparticles are transported from the bloodstream into tumours in a bid to enhance targeted tumour drug delivery.

The lab previously showed that only a fraction of nanoparticles injected into the bloodstream reach tumours through as yet unindentified receptors, rather than leaking passively out of blood vessels as previously thought. Wu is using a combination of genetic approaches and optical and electron microscope imaging to identify the cellular components involved in the transport.

Cecil Yip Doctoral Research Awards

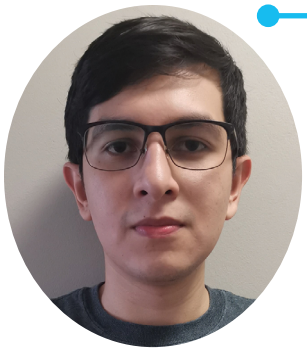
Established in 2015, the Cecil Yip Doctoral Research Awards recognize students in their first year of graduate programs who are engaged in multidisciplinary research in Donnelly Centre labs.

The 2021 Yip awardees come from various graduate programs at U of T: molecular genetics (Mogen), biomedical engineering (BME) and chemical engineering and applied chemistry (ChemE). Their projects seek to uncover fundamental cell and genome biology, and how it is linked to disease, as well as explore bionegineering approaches for the treatment of ailments ranging from blindness to muscle repair.

> ***Despite the complex challenges of the pandemic year, the awardees have made huge strides in their projects. So many inspiring and exciting research projects underway in the Centre!***
>
> **Christopher Yip**, Dean of Applied Science & Engineering, Chair of Yip Award committee and son of Prof Cecil Yip.

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



Adrian Granda Farias (Mogen) in Prof Jason Moffat's lab is hunting down the genes allowing cancer cells to evade the immune system as potential targets for cancer immunotherapy.

Shamira Tabrejee (Mogen) in Prof Tim Hughes' lab is investigating how the genome's 3D architecture affects gene expression.

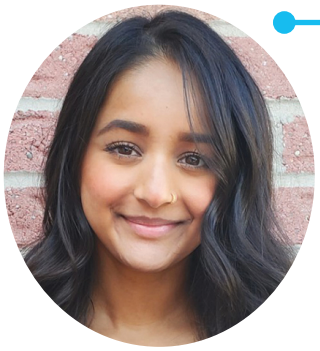
Sara Pour (Mogen) in Prof Tim Hughes' lab is trying to pin down the exact sequences which mark the genes' ends using deep learning computational approaches.

Steven Dupas (Mogen) in Prof Ben Blencowet's lab is studying how brain cells diversify their protein content and how errors in this process contribute to neurological disorders.

Brandon Lieng (Mogen) in Profs Rafa Montenegro-Burke and Hannes Rost's labs is developing software tools for the identification of small molecules produced by metabolic reactions in cells.

Michael Dang (ChemE) in Prof Molly Shoichet's lab is creating a gel-like biomaterial that can be infused with an antimicrobial drug to treat eye infections.

Arianna Skirzynska (ChemE) in Prof Molly Shoichet's lab is developing a brain-on-a-chip platform to search for compounds which could be developed into treatments for brain cancer.



Heta Lad (BME) in Prof Penney Gilbert's lab is investigating if circulating factors in the blood contribute to muscle weakness in ICU patients.

Carolina Chavez Madero (BME) in Prof Penney Gilbert's lab is growing human muscles in a dish to study the molecular factors important for regeneration after injury or disease.

Art Exhibit Pulls Curtain On Molecular Science

A remarkable collection of images —normally reserved for the eyes of scientists—is now available to the U of T community in an exhibition celebrating cutting-edge research in biomedicine at the university.

The recently unveiled installation features stunning data visualizations and microscopy images created by researchers working in the fields of genomics, computational biology and bioengineering in the Donnelly Centre for Cellular and Biomolecular Research at the Temerty Faculty of Medicine.

Envisioned as a single art piece, the installation comprises ten images depicting diverse research projects pursued by the Centre's investigators. These include the world's first complete genetic network of a cell resembling a dandelion brimful of wishes, grown-from-scratch human nerve fibers lacing the surface of a Petri dish that hold potential for regenerative medicine and the world's first map of the human liver at the molecular level that could unlock future treatments.

With the individual pieces laser-printed on aluminum panels, which heightens image quality and preserves colour from fading, the exhibit offers visitors a chance to revel in technicolour delight of the world less seen, as well as learn about ongoing research in the Centre.

"As scientists it's our job to make sense of data patterns and of what we capture under the microscope and it's easy to overlook the sheer beauty of biology," said **Brenda Andrews**, former and founding director of the Centre who commissioned the exhibit.

"We wanted to share this beauty with the public and to use the artwork to tell stories about some of the discoveries that have made the Centre globally known as a leading hub for research in biomedicine," she said.

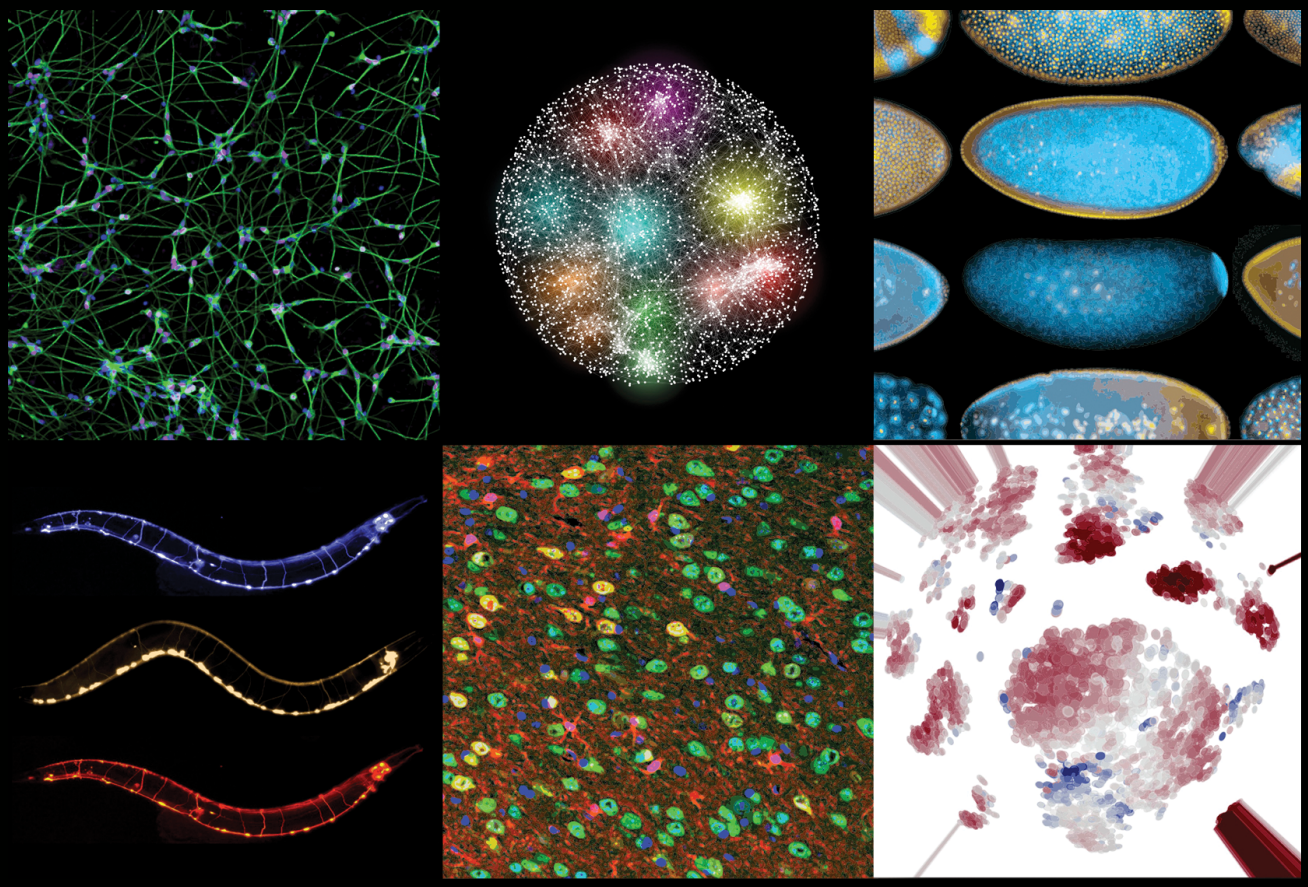
The exhibition was to mark the 15th anniversary of the Donnelly Centre, but its realization got delayed due to the coronavirus pandemic.

Founded in 2004, the Centre brought under one roof researchers from across scientific disciplines to harness genomic technology for the advancement of science, medicine and health. During this time, the Centre's investigators carried out landmark studies that have transformed our understanding of cellular function and how it is linked to disease.

Andrews helmed the Centre from its founding through three consecutive terms before stepping down in Summer 2020 after completing her final term. Public outreach also blossomed under her leadership, with multiple initiatives aimed at instilling curiosity and the love of science among Canadians of all ages, especially schoolchildren.

For the scientist and artist **Ronit Wilk** who created the piece, the exhibit is a dream come true. Wilk, who was previously a research associate in the Centre and performed a lot of microscopy, always wanted to bring the "magical world" of cells to a wider audience.

Wilk obtained her Phd at U of T in the lab of Professor **Howard Lipshitz** at the department of molecular genetics, followed by a postdoctoral stint at the Hospital for Sick



Top, L to R: human nerve fibers in a Petri dish, global genetic network of a eukaryotic cell, RNA localisation patterns in fruit fly embryos; Bottom, L to R: Lit up portions of the nervous system in nematode worms, neural stem cells in the brain, human liver map at the molecular level.

Children before joining the Centre in 2009.

"You transform into this tiny being looking around a cell that is colour-coded for you," said Wilk, referring to fluorescent markers scientists use to label various structures inside cells.

To prepare the exhibit, Wilk solicited scientific images from all 30 Donnelly Centre labs. She then selected the final 10 based on their theme, colour and composition to create a collage that captures the diverse research landscape in the Centre. Wilk also artistically rendered each image using image-processing software before printing.

One panel in particular holds special value for Wilk. It shows exquisite patterns of RNA localization in fruit fly embryos, which Wilk herself took when she worked in Professor **Henry Krause**'s lab in the Centre. The lab was the first to show that the majority of genes' messages, transcribed into intermediate RNA molecules, show specific and dynamic localization within the embryo— and even inside individual cells— which helps ensure that the encoded proteins are made at the right place and time.

Although Wilk has moved on from the lab, she remains a staunch supporter of science, donating ten per cent of her artist fee to foundational research.

"Basic research gets overlooked and usually there's excitement about discoveries that can be applied right away," says Wilk.

"But people don't realize that by studying, for example, how RNA works, what is controlling it— those types of questions can lead to amazing discoveries later on, like we've seen with the first RNA-based vaccines in this pandemic."

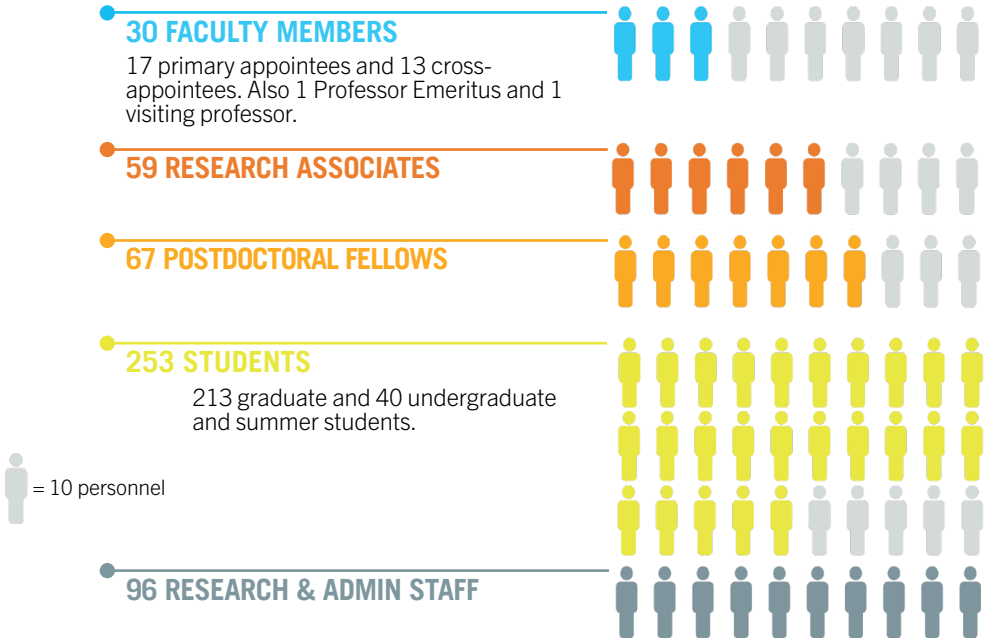
The exhibit is displayed in the Donnelly Centre lobby adjacent to the Medical Sciences Building.

Donnelly in Numbers

507 Total Personnel

Personnel

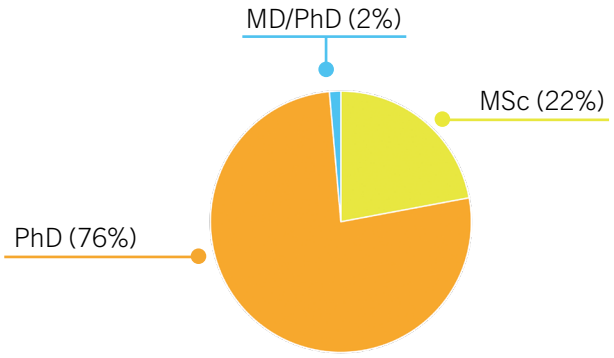
The Donnelly Centre currently houses a total of 507 occupants, representing scientists at all stages of their careers as well as members of research and administrative staff.



Graduate Students

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

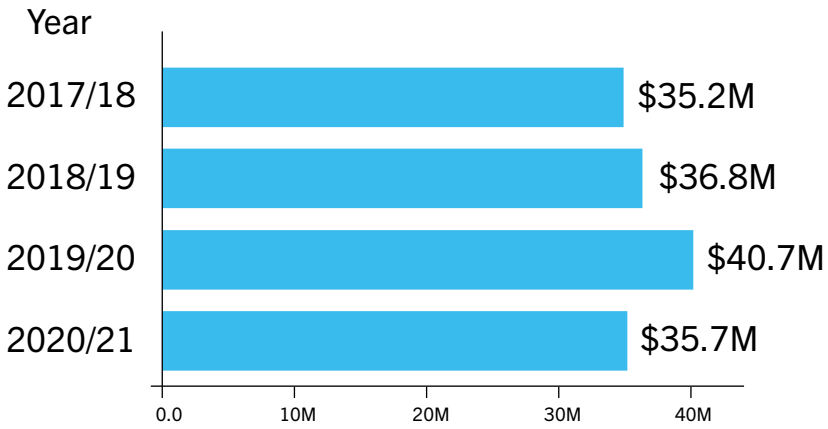
Biochemistry (18)
Cell & Systems Biology (1)
Chemical Engineering (14)
Chemistry (5)
Computer Science (11)
Institute of Medical Science (9)
Institute of Biomedical Engineering (51)
Medical Biophysics (2)
Molecular Genetics (113)
Pharmacology & Toxicology (2)
UG-Anatomy (1)



162 students (76%) are PhD candidates, 47 (22%) are pursuing a Masters degree and 4 (2%) are in the MD/PhD program.

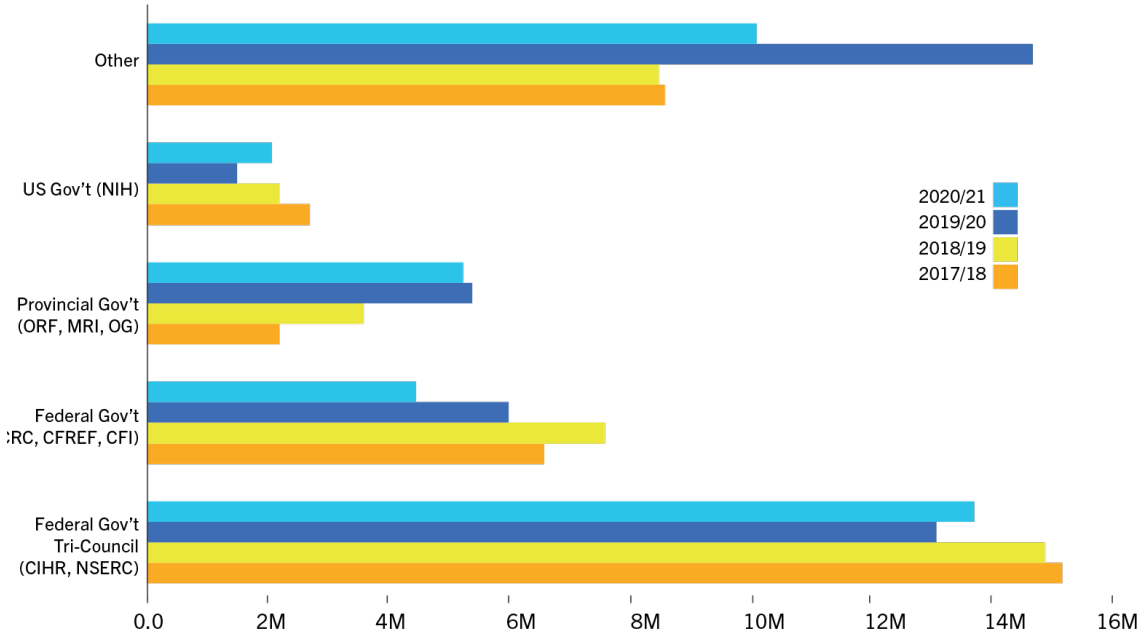
Research Funding

The number on the right of the bar represents the total funding raised by primary and cross appointed faculty for the respective academic year.



Funding Sources

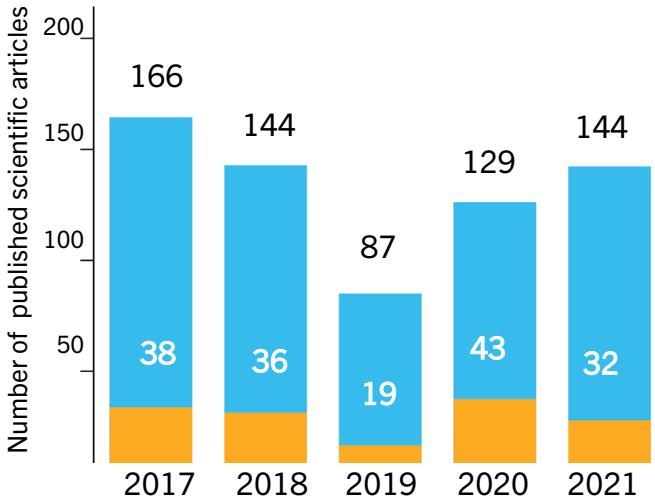
The majority of the funding for infrastructure, research and personnel is supported by the grants from the Canadian federal government. Shown here is a breakdown of total research grants raised by primary and cross appointed faculy. “Other” sources of funding represent other federal and provincial grants as well as support from foundations.



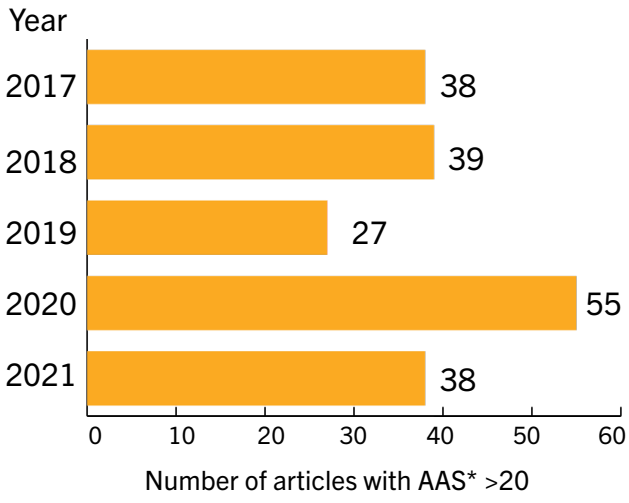
Funding agency abbreviations: CIHR (Canadian Institutes of Health Research), NSERC (National Science and Engineering Research Council), CFREF (Canada First Research Excellence Fund), CRC (Canada Research Chair Program), CFI (Canada Foundation for Innovation), MRI (Ministry of Research and Innovation),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

Publication Output

Donnelly Centre investigators regularly publish their findings in peer-reviewed academic journals, with 144 articles published in 2021, 32 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*.

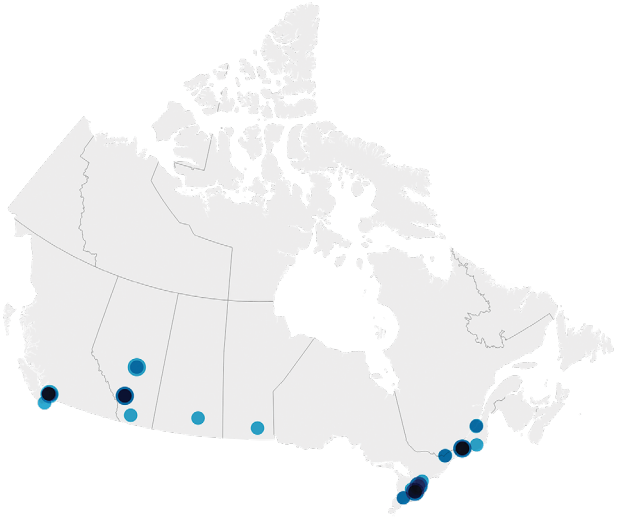


The graph on the left shows the number of scientific articles authored by Donnelly Centre investigators that received notable media coverage, with Altmetric Attention Score* greater than 20.

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

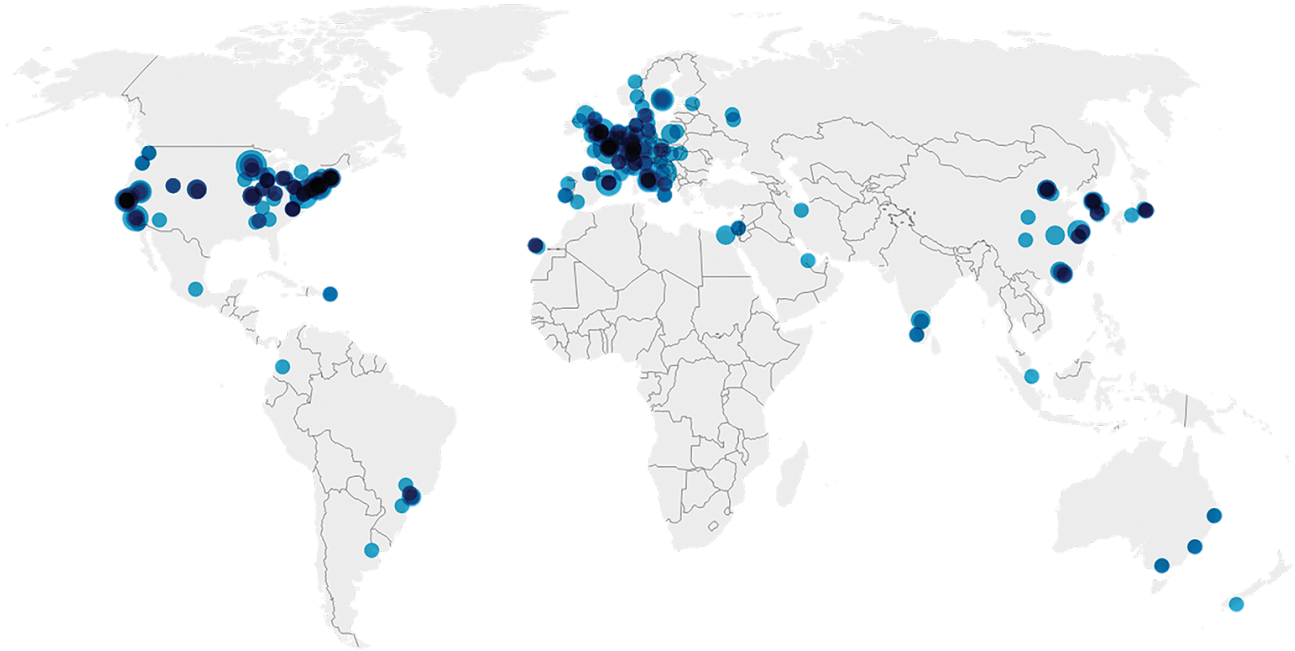
Scientific collaboration

Donnelly Centre investigators collaborate with scientists from all over Canada and around the world.



Blue circles on the maps 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 the Canadian and global research hubs. The maps were created using Datawrapper with 2021 publication data data from Pubmed.

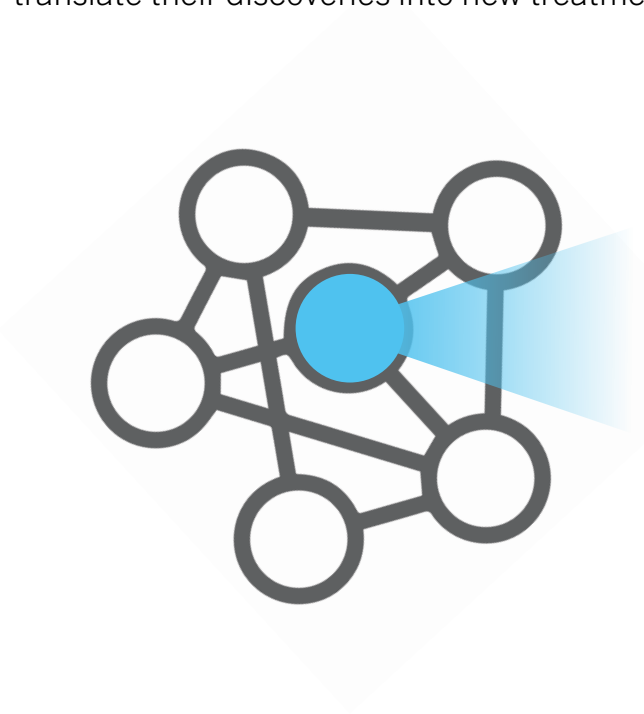
Click here for an interactive map to view the names of collaborating institutions in Canada.



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

Industry collaboration

Donnelly Centre investigators have partnerships with various biotechnology companies at home and abroad as they work to translate their discoveries into new treatments.

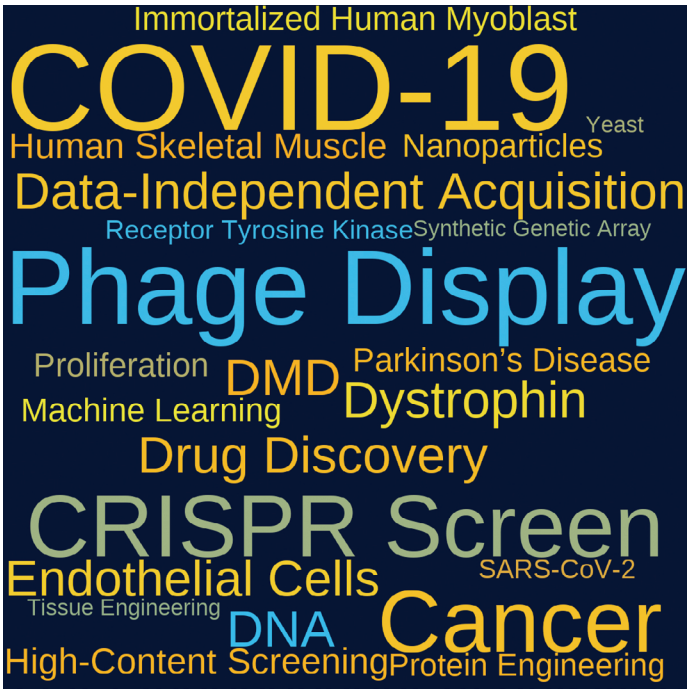


32

The number of biotechnology companies with whom the Centre's investigators co-published research articles during 2021.

Research Themes

Researchers in the Donnelly Centre work on diverse topics, with many teams collaborating across scientific disciplines. The map on the right representes the top 23 words that appeared at least twice across 144 scientific articles that were published by Donenlly Centre faculty during 2021. 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.



Donnelly in the Media

Donnelly Centre investigators and their research feature regularly in the Canadian and international media seeking to bring the latest impactful discoveries to the public.

Listed below is a selection of news stories that have appeared in mainstream and science media in the past year. Click on the links to view the stories.

100 years after insulin treatment was invented, researchers hope to ditch needles once and for all, *Quirks and Quarks, CBC*
100 years since insulin discovery, Canadian scientists push for new diabetes treatments, *Global News*
Out of the lab, into the marketplace: How one of Canada's most celebrated scientists, Molly Shoichet, is bringing her key discovery to market, *The Globe and Mail*
'Firefly' test aims to shed light on COVID-19 vaccine endurance, *The Globe and Mail*
Toronto researchers develop "firefly" method to measure COVID-19 immunity, *CityNews*
'Firefly' test aims to shed light on COVID-19 vaccine endurance, *Rogers radio*
Low-Cost Pinprick Test Measures COVID-19 Immunity in Under One Hour, *Technology Networks*
I wonder if I had COVID when I was sick in January 2020. Why widespread antibody testing can't come soon enough for my family, *Toronto Star*
Canada's scientists are elucidating the dark metabolome, *Nature*
U of T researchers discover a new way to take on COVID-19. Could it change the way we combat cancer?, *Toronto Star*
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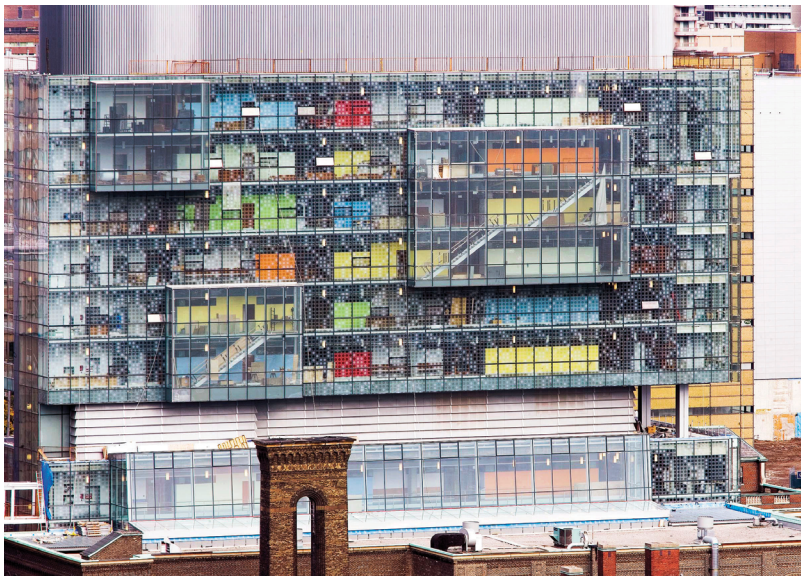

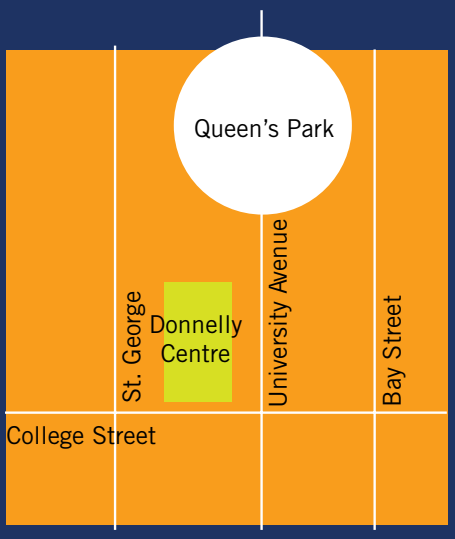

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