Donnelly Centre
for Cellular + Biomolecular Research

UNIVERSITY OF TORONTO

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DONNELLY CENTRE ANNUAL REPORT

2018

The Donnelly Centre for Cellular and Biomolecular Research is an interdisciplinary research institute where scientists make discoveries to improve human health.

Founded in 2005 at the University of Toronto, the Centre has become globally recognized as a leading institute for the study of genome biology. The 2019 will see the launch of the Accelerator for Donnelly Collaboration, an innovation hub dedicated to translating discoveries made by the Centre's investigators into new patient therapies.

With this report, we would like to extend a warm thank you to our visionary donor Terrence Donnelly on his continuous support and all other members of our community whose gifts ensure our researchers remain at the leading edge of discovery.

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Gene interaction map in a cell, Michael Costanzo

Grant Brown's team found that the total number of **protein molecules** in a simple cell is **42 million** to further our understanding of how protein abundance affects health.

Image by Brandon Ho

A Simple Cell Holds 42 Million Protein Molecules, Scientists Reveal

By Jovana Drinjakovic
January 17, 2018.

It's official—there are some 42 million protein molecules in a simple cell, revealed a team of researchers led by **Grant Brown**, a biochemistry professor in the Donnelly Centre. Analyzing data from almost two dozen large studies of protein abundance in yeast cells, the team was able to produce for the first time reliable estimates for the number of molecules for each protein, as revealed in a study published today in the journal *Cell Systems*.

The work was done in collaboration with **Anastasia Baryshnikova**, a U of T alum and now Principal Investigator at Calico, a California biotechnology company that focuses on aging.

Proteins make up our cells and do most of the work in them. This way, they bring genetic code to life because the recipes for building proteins are stored within the genes' DNA code.

Explaining the work, Brown said that given that "the cell is the functional unit of biology, it's just a natural curiosity to want to know what's in there and how much of each kind."

Curiosity notwithstanding, there's another reason why scientists would want to tally up proteins. Many diseases are caused by either having too little or too much of a certain protein. The more scientists

know about how protein abundance is controlled, the better they'll be able to fix it when it goes awry.

Although researchers have studied protein abundance for years, the findings were reported in arbitrary units, sowing confusion in the field and making it hard to compare data between different labs.

"The cell is the functional unit of biology, it's just a natural curiosity to want to know what's in there and how much of each kind"

Many groups, for example, have estimated protein levels by sticking a fluorescent tag on protein molecules and inferring their abundance from how much the cells glow. But the inevitable differences in instrumentation meant that different labs recorded different levels of brightness emitted by the cells. Other labs measured proteins levels using completely different approaches.

"It was hard to conceptualize how many proteins there are in the cell because the data was reported on drastically different scales," says **Brandon Ho**, graduate student in the Brown lab who did most of the work on the project.

To convert arbitrary measures into the number of molecules per cell, Ho turned to baker's yeast, an easy to study single-cell microbe that offers a window into how a basic cell works. Yeasts are also the only organism for which there was enough data available to calculate molecule number for each of the 6,000 proteins encoded by the yeast genome thanks to 21 separate studies that measured abundance of all yeast proteins. No such datasets exist for human cells where each cell type contains only a subset of proteins encoded by the 20,000 human genes.

The wealth of existing yeast data meant that Ho could put it all together, benchmark it and convert the vague measures of protein abundance into "something that makes sense, in other words, molecules per cell," said Brown.

Ho's analysis reveals for the first time how many molecules of each protein there are in the cell, with a total number of molecules estimated to be around 42 million. The majority of proteins exist within a narrow range—between 1000 and 10,000 molecules. Some are outstandingly plentiful at more than half a million copies, while others exist in fewer than 10 molecules in a cell.

Analyzing the data, the researchers were able to glean insights into the mechanisms by which cells control abundance of distinct proteins, paving the way for similar studies in human cells that could help reveal molecular roots of disease. They also showed that a protein's supply correlates with its role in the cell, which means that it may be possible to use the abundance data to predict what proteins are doing.

Finally, in a finding that will rejoice cell biologists everywhere, Ho showed that the common practice of stitching glowing tags onto proteins has little effect on their abundance. While the approach has revolutionized the study of protein biology, netting its discoverers Osamu Shimomura, Martin Chalfie and Roger Tsien the Nobel prize in chemistry in 2008, it also stoked worries that tagging could affect protein durability, which would flaw the data.

"This study will be of great value to the entire yeast community and beyond," said Robert Nash, senior biocurator of the Saccharomyces Genome Database that will make the data available to researchers worldwide. He also added that by presenting protein abundance "in a common and intuitive format, the Brown lab has provided other researchers with the opportunity to reexamine this data and thereby facilitate study-to-study comparisons and hypothesis generation."

Brenda Andrews and Charlie Boone's labs revealed how thousands of genes work together in the cell in the largest study of its kind.
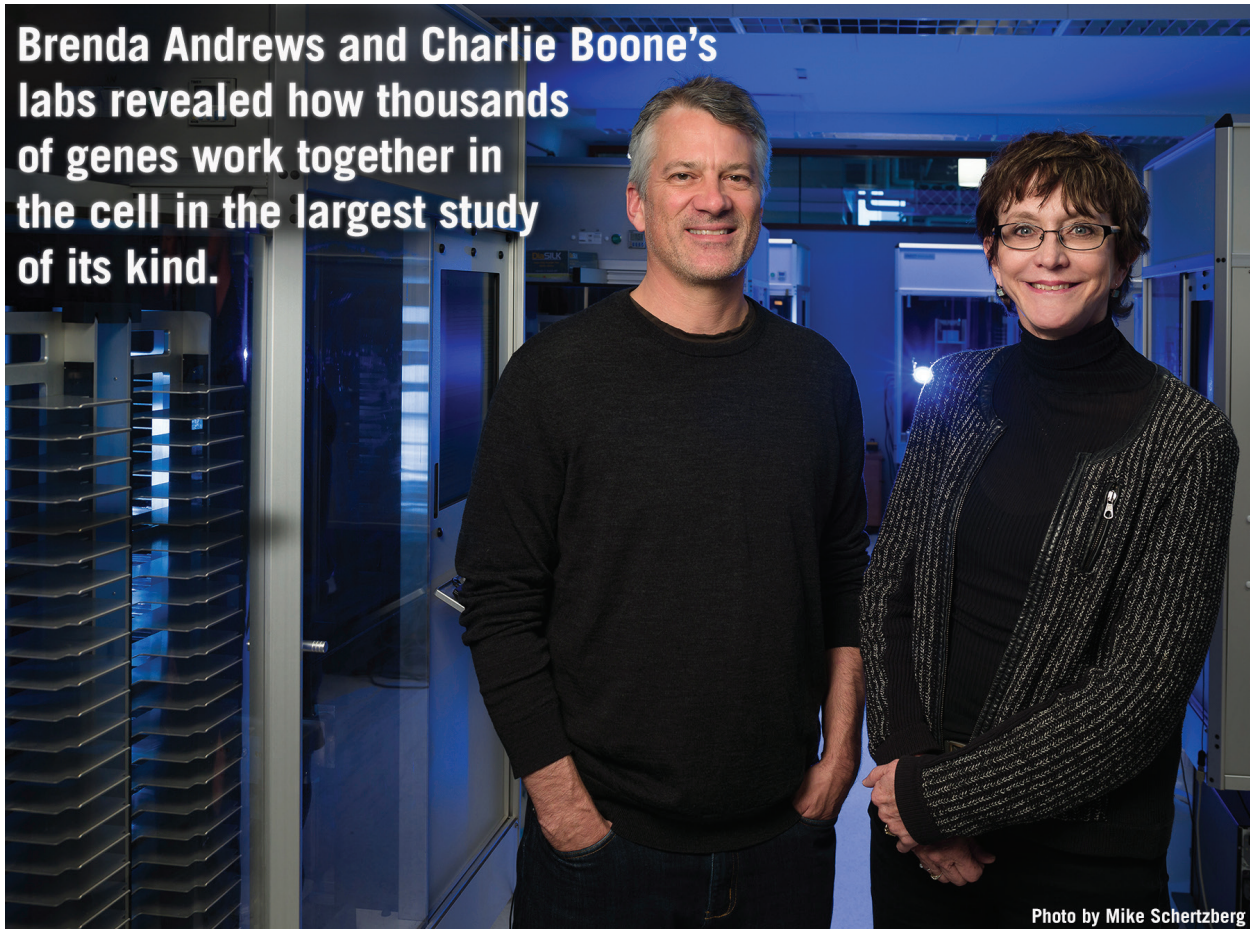
Genome Jenga Study Uncovers Unexpected Gene Alliances in the Cell

By Jovana Drinjakovic
April 19, 2018.

To understand how a cell works, biologists like to take it apart. By removing genes from cells in diverse combinations, researchers have now uncovered how different genes work together to keep cells alive. The research will help scientists understand how faults in multiple genes combine to drive common diseases such as cancer or heart disease.

Led by **Charles Boone**, a professor in the University of Toronto's Donnelly Centre, **Brenda Andrews**, University Professor and Director of the Donnelly Centre, and Professor Chad Myers, of the University of Minnesota-Twin Cities, MN, the research builds

up on the teams' previous work which showed how genes combine in pairs to underpin cell's health. Taking it a step further, the new study examines for the first time how higher-order gene combinations— comprising three genes— help maintain normal cell physiology, as revealed in the journal *Science*.

Boone and Andrews are also professors in U of T's Department of Molecular Genetics and Senior Fellows at the Canadian Institute for Advanced Research (CIFAR) and Myers is a Fellow at CIFAR.

"There's a growing understanding that interactions

between genes can drive inherited disease susceptibility, which is why we have to understand the general principles of these genetic interactions," says Boone.

It's very much like a giant game of Jenga, with thousands of gene blocks that can be removed. While most single blocks can be taken out without compromising the structure, when critical combinations of blocks are removed, the system collapses. Similarly, genes with different roles can combine to keep the cell alive. By unpicking such gene alliances, scientists hope to reveal clues about the foundations of personal health.

It's now clear from genome sequencing studies that each person carries thousands of genetic variants – differences in genes' DNA sequence — that could combine to impact our health. However, these studies do not have the statistical power to predict a person's risk of disease from their unique combination of genetic variants. This poses a major obstacle for personalized medicine which seeks to use genome information to predict risk of disease and tailor treatment.

To uncover the rules of combinatorial gene function, the team previously investigated how genes work in pairs in yeast cells. The yeast is one of biologists' favourite cell models due to its relatively small genome comprising 6,000 genes and an already existing wealth of data. Having previously removed from yeast all possible gene pairs—18 million of them— the team now went a step further to examine what happens when you remove a subset of 36 billion possible trigenic combinations.

They found that, similar to interactions between two genes, trigenic interactions also mainly occur between genes that are functionally related— they code for parts belonging to the same molecular machine or that exist in the same part of the cell, for example.

But with trigenic interactions, the researchers also began to see more surprising partnerships between genes that have unrelated function and are involved in different bioprocesses in the cell.

"Studying genetic networks allows you to see how genes are connected, how biological processes talk to one another and how a cell deals with perturbations in multiple genes," says **Elena Kuzmin**, a lead author on the paper and a previous graduate student in the Boone lab who is now a postdoctoral fellow at McGill University in Montreal. "You get a global view of the cell," she says.

Furthermore, using mathematical modeling the researchers estimate that all genes in the cell have a role to play when trigenic interactions are taken into account. This could finally explain why only a tenth of yeast's 6,000 genes are essential for cell survival, a rule that holds for other cell types including human cells.

Thanks to recent advances in gene editing, it is now possible to remove combinations of genes from human cells, which Boone and Andrews labs are currently doing in collaboration with Jason Moffat's group in the Donnelly Centre to map relationships between disease genes.

"Our yeast work demonstrates how mutations in multiple genes combine to have unexpected effects and is providing a roadmap for understanding genetic interactions in much more complex cells and organisms, including humans." says Andrews. "Identifying combinations of genes that work together to underpin robust biological systems is important for deciphering what goes wrong with its collapse into a disease state."
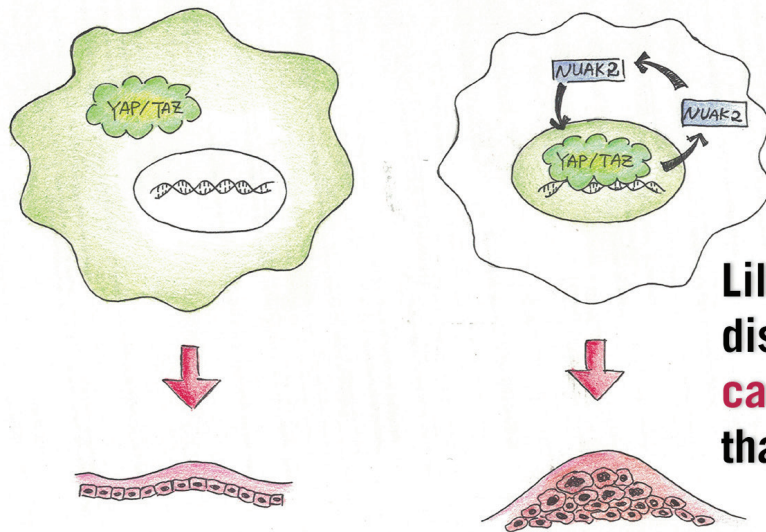
Liliana Attisano's team discovered why some cancers grow faster than others.

Click to learn more

Study Reveals How Some Tumours Fuel Own Growth and Points to New Treatment

By Jovana Drinjakovic
August 28, 2018.

A research team led by **Liliana Attisano** in the Donnelly Centre has identified a protein called NUAK2, which is produced by cancer cells to boost their proliferation and whose presence in tumours is associated with poor disease prognosis. Writing in the journal *Nature Communications*, the researchers show that blocking NUAK2 slows down cancer cell growth raising hopes that a drug could be developed to treat patients.

"We looked at bladder cancer and found that a subset of patients have high levels of NUAK2 protein in their tumours which also happened to be high-grade tumours," says Attisano, who is also a professor in U of T's Department of Biochemistry.

Mandeep Gill, a graduate student in Attisano's lab, first found NUAK2 while looking for a way to block the known cancer-promoting proteins called YAP and TAZ (YAP/TAZ). Highly active in many cancers, YAP/TAZ work by latching onto the DNA to switch on genes that promote cell proliferation. NUAK2 turned out to be one of the genes that was switched on by YAP/TAZ; and unexpectedly it was found to encode a protein that helps shuttle even more YAP/TAZ into the cell's nucleus, where the DNA is stored, to further bolster abnormal cell growth.

Because YAP/TAZ are active in many cancers, including the aggressive forms of breast and bladder cancer, the researchers wondered if NUAK2 too was

elevated in tumour biopsies taken from patients with bladder cancer. They found that NUAK2 was present at high levels in some of the tumours and that those came from patients whose cancer progressed to a more aggressive type.

Professor Liliana Attisano

Fortunately, the flip side is that when NUAK2 is blocked, YAP/TAZ can no longer enter the nucleus. This keeps YAP/TAZ away from the DNA and breaks the vicious cycle by which cancer reinforces itself.

YAP/TAZ belong to the so-called Hippo pathway, a network of proteins that are important for normal cell and tissue growth but which often goes haywire in cancer. The pathway was named after its role in controlling organ size so that organs grow abnormally large, or "hippo-like", when the pathway breaks down.

Although the Hippo pathway, which normally keeps cell proliferation in check, is inactivated in many cancers, so far there was no good way to target it with drugs. The discovery of NUAK2 changes this.

"The ultimate goal is to find a drug that would work on people"

By blocking NUAK2 protein, either by drugs or by muting the gene that encodes it, the researchers were able to slow down expansion of breast cancer cells in the dish and to shrink breast tumours in mice, respectively. A similar approach could target high-grade tumours in patients.

"If you check the patient's tumour and if they have high levels of NUAK2 protein, we could maybe treat them with NUAK2 inhibitors," says Attisano.

In collaboration with **Rima Al-awar**, Director of Drug Discovery Program at the Ontario Institute for Cancer Research, Frank Sicheri and Jeff Wrana at the Lunenfeld-Tanenbaum Research Institute of Mount Sinai Hospital, Toronto, Attisano is working to develop the anti-NUAK2 compound into a form in which it can be used on animals in order to further validate the target.

"The ultimate goal is to find a drug that would work on people," Attisano said.

Grant Brown's team found an unexpected role for a well-known protein machinery in maintaining genome size with implications for cancer and other diseases.

Photos by Tina Sing
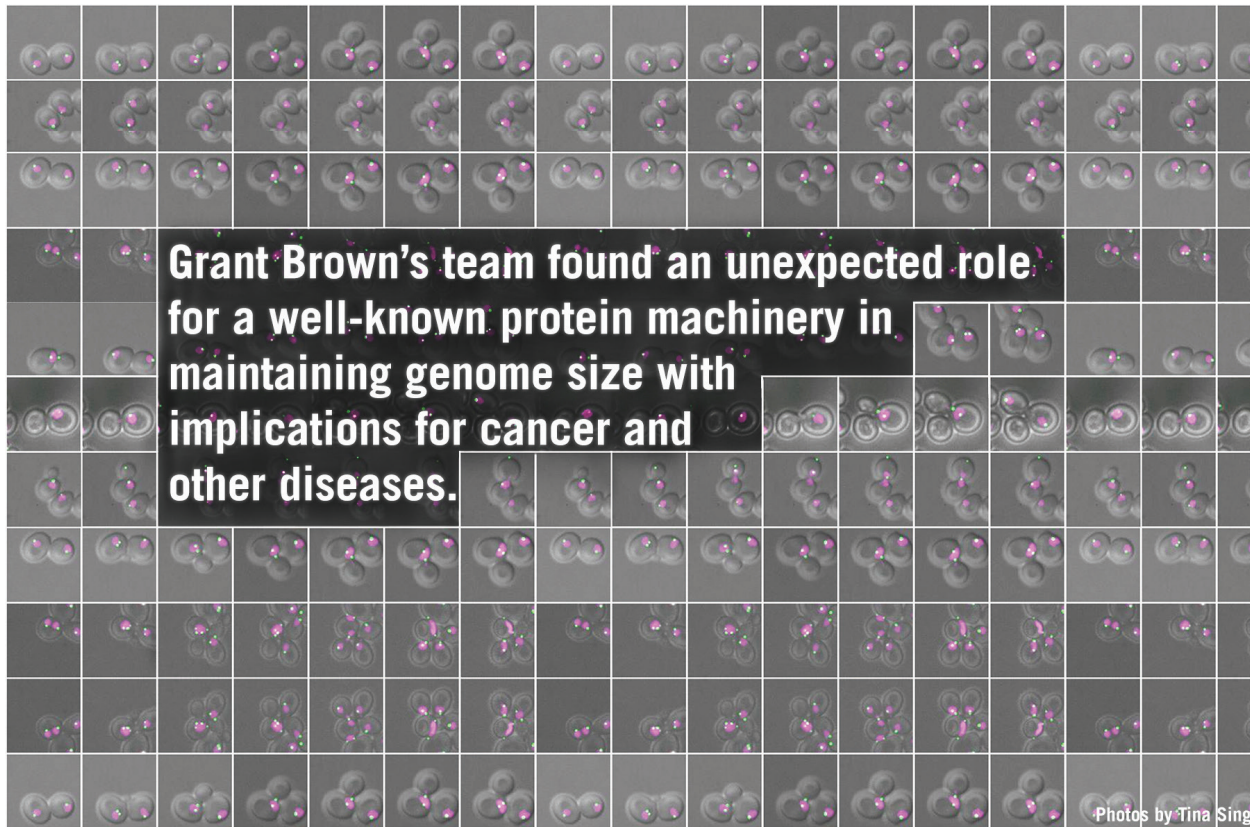
Avoiding Catastrophe: Yeast Study Reveals Clues to Maintaining Genome Size

By Jovana Drinjakovic
June 6, 2018.

As cells divide, they must accurately split their DNA between the two daughter cells or risk having an uneven number of chromosomes which can lead to developmental disorders and cancer. A new Donnelly Centre study uncovers how a key molecular machinery drives this process and gives clues to why some children develop aggressive kidney tumours.

Led by **Tina Sing**, a PhD student in Professor **Grant Brown**'s lab in the Donnelly Centre and Department of Biochemistry, the study's findings are published in *The Journal of Cell Biology*.

Brown likens the genome to an instruction book organized into a set number of chapters, or chromosomes. "It's important that the number of chapters stay constant," he says. "It would be bad if you lack instructions for certain processes but surprisingly it's also bad if you have too many instructions."

Having an extra copy of chromosome 21 leads to Down syndrome, while an absence of one X chromosome will turn females sterile as seen in Turner syndrome. In cancer cells, whole genome duplication followed by haphazard chromosome loss allows tumour cells to accumulate genes which help them outgrow healthy cells.

"When a cell makes a decision to divide it needs to make sure its DNA is equally segregated between both daughter cells," says Sing, who is now a postdoctoral

researcher at the University of California, Berkeley. "The cells must first replicate their DNA and then they have to pull apart these two copies of the DNA so that each daughter cell receives one complete copy of the entire genome."

Sing uncovered a new role for a known protein machinery called RSC, for "remodels the structure of chromatin" and pronounced as "risk", in helping separate the duplicated chromosomes equally between daughter cells. RSC does this by helping the formation of the centrosome, a structure that sprouts tiny filaments which grab each set of chromosomes and pulls them apart. "We found that if cells lack RSC function then this causes abnormal DNA segregation and a spontaneous doubling of chromosome number in cells," says Sing.

> *"It's always surprising to think about how fundamental processes in yeast also take place in humans"*

In their experiments, Sing and Brown used budding yeast—the same single-celled microbe that helps bread rise and beer ferment—which showed uncanny resemblance to cancer cells when RSC is no longer working. Besides having a higher number of chromosomes, yeast cells lacking RSC function also have more centrosomes. Whereas heathy cells typically have two centrosomes during cell division, RSC mutants often had many more, making it difficult for them to segregate their chromosomes properly.

Previously, RSC was known for its role in switching genes on and off. Sing's finding that RSC is also important for DNA segregation was unexpected and ties together with previous findings from other labs to potentially help explain how a form of childhood cancer develops.

Mutations in the human version of RSC also lead to spontaneous increase in chromosome number and have been found in rhabdoid tumours, a highly aggressive form of kidney cancer. Also, if mouse cells lose RSC function, they can turn cancerous. However, there was nothing known about RSC that would suggest its involvement in chromosome segregation. Now, thanks to the insights from yeast cells, it is possible that RSC has a similar role in humans.

"It's always surprising to think about how fundamental processes in yeast also take place in humans," Sing says. "We think that our study gives some insight into this observation in cancer cells and we think it's possible that this complex is also helping with chromosome segregation in human cells."

Sing's finding was serendipitous. When she started working on RSC, her goal was to dig deeper into some of its more conventional roles. It was only after she repeatedly noticed that cells lacking RSC function had twice the normal number of chromosomes that she realized she was onto something unexpected. "The increase in chromosomes was more interesting than what we were looking for," she says. "I think the study is a good example of how sometimes when you set out to study a specific biological problem you can be surprised by the data that you find and sometimes just following your curiosity down a different path can lead to understanding another aspect of biology."

Gary Bader's team helped create the world's first map of the human liver at the molecular level.

Photo by UHN
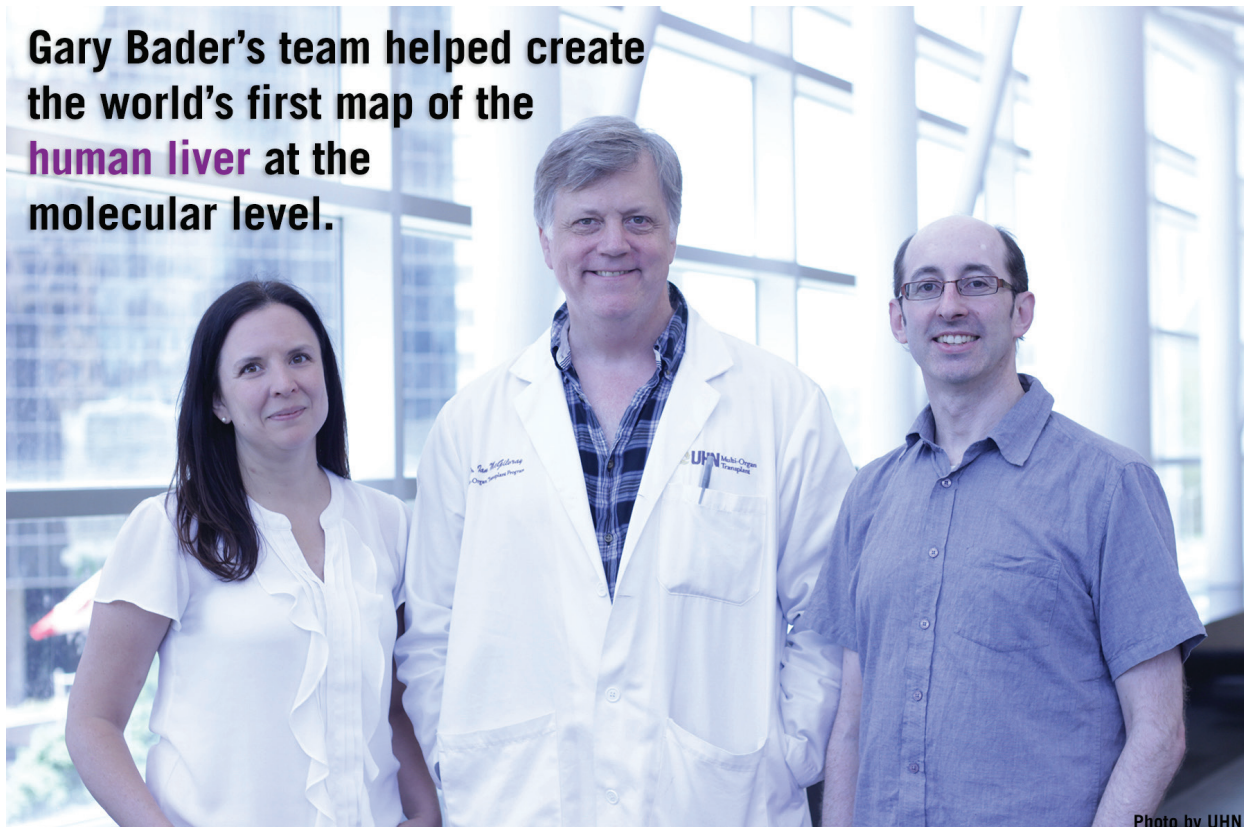
Researchers Create First Map of Human Liver Cells at the Molecular Level

By UHN
October 23, 2018.

A map of the cells in the human liver has been created by University of Toronto researchers and the University Health Network transplant program, revealing for the first time differences between individual cells at the molecular level that can have a profound impact on their behaviour in tissue, tumours and disease.

The researchers, led by Assistant Professor **Sonya MacParland**, of immunology and laboratory medicine and pathobiology in the Faculty of Medicine; Associate Professor **Ian McGilvray** of surgery; and Professor **Gary Bader**, of the Donnelly Centre, mapped out the cellular landscape of 8,444 individual cells obtained from the tissues of healthy deceased donor human livers.

"For the past 20 years, we have studied the liver as a soup of cells as opposed to its individual components. This makes it difficult to target individual cells that are driving liver disease," says lead author MacParland, who is also a scientist at the Toronto General Hospital Research Institute.

By examining the gene expression profiles of each of these cells – about 1,500 active genes per cell – the researchers found 20 distinct cell populations made up of hepatocytes, endothelial cells, cholangiocytes and various immune cells such as B cells, T cells and Natural Killer (NK) cells.

"These evaluations reveal new aspects of the immunobiology of the liver, such as the presence of

two surprisingly distinct populations of liver resident macrophages ("big-eaters" of cellular debris) with inflammatory and non-inflammatory functions," write the authors in their paper published Monday in *Nature Communications*.

"We present a comprehensive view of the liver at single cell resolution that outlines new characteristics of resident cells in the liver, and in particular provides a new map of the human hepatic immune microenvironment," note the authors.

The authors will also make their research available to the Human Cell Atlas Project, an international, open-access, collaborative effort to map all human cells, to help scientists understand how genetic variation impacts disease risk and influences health.

Bader says the creation of the liver map was made possible because of Medicine by Design, a regenerative medicine research initiative at U of T with a mandate to accelerate discoveries and translate them into new treatments for common diseases.

"The liver project came together serendipitously via the Medicine by Design community, and it would not have happened without Medicine by Design,"

says Bader, who is also a member of the organizing committee of the Human Cell Atlas Project.

As the research director of the UHN Transplant Program, McGilvray has performed hundreds of liver transplants and cancer surgeries. In order to advance treatment of liver disease, he says, scientists must understand how the liver functions at the most fundamental level of the single cell.

The variation between cells is huge, McGilvray explains, but in 2018, it is surprising how little we know about the liver's cellular landscape. New treatments, reduction of transplant rejection rates and regenerative medicine solutions can only be found if scientists understand how liver cells develop and work together within tissues and biological systems, he argues.

The urgency to find alternative approaches is spurred on by the increasing burden of liver disease, he says. Up to 23 per cent of obese individuals are at risk of developing fatty liver with inflammation, for example, and more than 70 million people are chronically infected with hepatitis C.

The project could only have been possible with a multidisciplinary team consisting of transplant
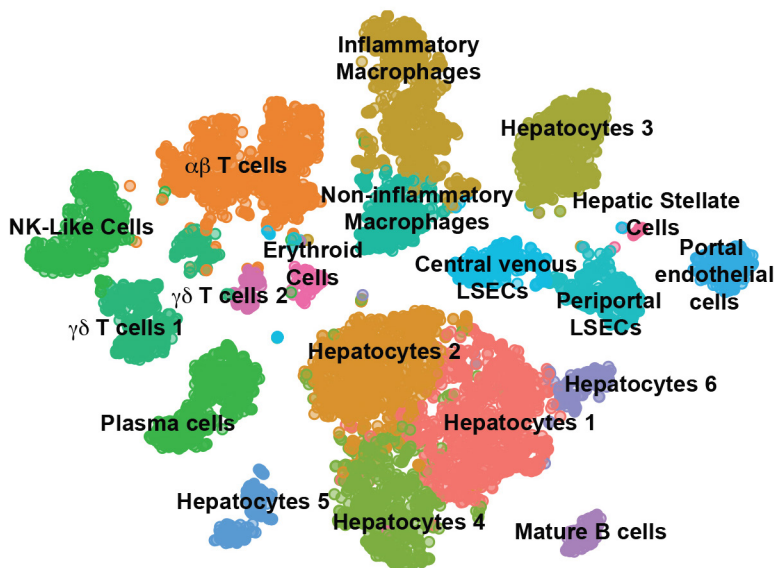
The map has revealed there are more cell types in the human liver than previously thought including two types of immune macrophage cells which researchers think could be harnessed to improve transplant success.

surgeons, immunologists, hepatologists, computer scientists and genomics researchers from different institutions to develop the first-ever map of a solid organ.

"For the past 20 years, we have studied the liver as a soup of cells as opposed to its individual components. This makes it difficult to target individual cells that are driving liver disease"

A major problem in studying the human liver is difficulty in accessing fresh tissue. Samples in the study were collected from deceased donor livers deemed acceptable for liver transplantation, with consent and ethics approvals. This makes it unique in the world, in contrast to the standard method of studying the liver from biopsy samples.

Another challenge was isolating single cells from liver tissue. Liver cells such as hepatocytes and others are delicate and often do not survive standard tissue extraction, which may involve chopping, separating and filtering of tissue into smaller parts. During this process, cells often die.

But with the experience gained in transplantation and painstaking trial and error work of many years, the researchers were able to develop the best protocols using enzyme mixtures to gently dislodge cells embedded in the spider web-like net of connective tissue of the liver, without actually harming the fragile cells themselves.

The latest technological advances helped the team to overcome the limitations of previous techniques such as genomics. Although it can analyze many cell types simultaneously "in bulk", it cannot tease out the critical differences between cells or do so in combination with multiple other data.

The team reached out to colleagues in the Princess Margaret Genomics Centre with their 10X Genomics Chromium system which excels at the analysis of complex tissues and heterogeneous collections of cells, and to the Donnelly Centre's Bader, who developed the state-of-the art data analysis pipeline and custom pathway analysis software for the project. They were then able to map out the genetic and molecular function of each cell and how each one contributes to overall liver function.

"We found some very cool things about the human liver that we did not expect," says McGilvray. "Until this study, very little was known about what the liver macrophage – the 'tank' of the immune system that destroys foreign substances and co-ordinates the immune response – actually is. We found that there are two distinct populations of macrophages in the human liver, one which is pro-inflammatory and the other anti-inflammatory."

This new understanding can help scientists to harness these two contrasting macrophages to, for example, achieve "tolerance" of a new donor organ, says McGilvray. For transplant recipients, he explains, in the future, clinicians may want to downregulate the pro-inflammatory cells and upregulate the anti-inflammatory cells so that the recipient does not reject the new organ, and even may not need to take as many or any immunosuppressive medications.

MacParland adds that the new liver map gives us a new understanding of many more populations of cells found in a normal liver. Eventually, she says, as the map becomes more and more detailed, we can compare these cells to those in a diseased liver.

Then, she says, we can answer the question: "How can we get the liver back to a normal state?"

Ben Blencowe's team uncovered a network of more than 200 genes linked to autism.
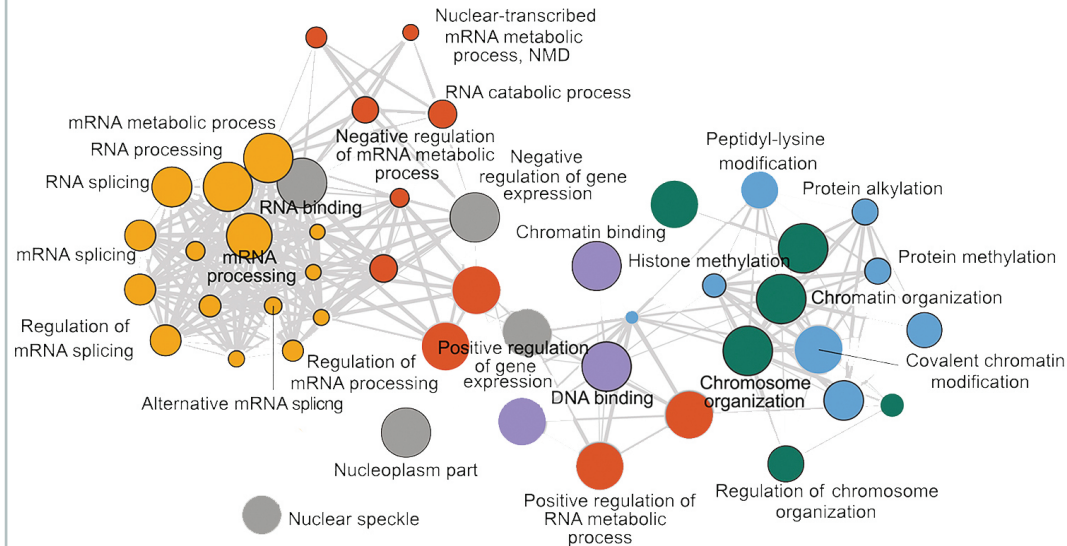
Image by T. Gonatopoulos-Pournatzis

Unraveling a Genetic Network Linked to Autism

By Jovana Drinjakovic
November 2, 2018.

Donnelly Centre researchers have uncovered a genetic network linked to autism. The findings, described in the journal *Molecular Cell*, will facilitate developing new therapies for this common neurological disorder.

As part of a collaborative research program focusing on autism led by Professor **Benjamin Blencowe**, postdoctoral fellow **Thomas Gonatopoulos-Pournatzis**, lead author of the study, uncovered a network of more than 200 genes involved in controlling alternative splicing events that are often disrupted in autism spectrum disorder (ASD). Alternative splicing is a process that functionally diversifies protein molecules—cells' building blocks—in the brain and other parts of the body. Blencowe's laboratory previously showed that disruption of this process is

closely linked to altered brain wiring and behaviour found in autism.

"Our study has revealed a mechanism underlying the splicing of very short coding segments found in genes with genetic links to autism," says Blencowe, who is also a professor in the Department of Molecular Genetics and holds the Banbury Chair of Medical Research at U of T. "This new knowledge is providing insight into possible ways of targeting this mechanism for therapeutic applications".

Best known for its effects on social behaviour, autism is thought to be caused by mishaps in brain wiring laid down during embryo development. Hundreds of genes have been linked to autism, making its genetic

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basis difficult to untangle. Alternative splicing of small gene fragments, or microexons, has emerged as a rare, unifying concept in the molecular basis of autism after Blencowe's team previously discovered that microexons are disrupted in a large proportion of autistic patients.

> *"This new knowledge is providing insight into possible ways of targeting this mechanism for therapeutic applications"*

As tiny protein-coding gene segments, microexons impact the ability of proteins to interact with each other during the formation of neural circuits. Microexons are especially critical in the brain, where they are included into the RNA template for protein synthesis during the splicing process. Splicing enables the utilization of different combinations of protein-coding segments, or exons, as a way of boosting the functional repertoires of protein variants in cells.

And while scientists have a good grasp of how exons, which are about 150 DNA letters long, are spliced, it remained unclear how the much-smaller microexons— a mere 3-27 DNA letters long—are utilized in nerve cells.

"The small size of microexons' presents a challenge for the splicing machinery and it has been a puzzle for many years how these tiny exons are recognized and spliced," says Blencowe.

To answer this question, Gonatopoulos-Pournatzis developed a method for identifying genes that are involved in microexon splicing. Using the powerful gene editing tool CRISPR, and working with **Mingkun Wu** and **Ulrich Braunschweig** in the Blencowe lab as well as with **Jason Moffat**'s lab in the Donnelly Centre, Gonatopoulos-Pournatzis removed from cultured brain cells each of the 20,000 genes in the genome to find out which ones are required for microexon splicing. He identified 233 genes whose diverse roles suggest that microexons are regulated by a wide network of cellular components.

"A really important advantage of this screen is that we've been able to capture genes that affect microexon splicing both directly and indirectly and learn how various molecular pathways impinge on this process," says Blencowe.

Furthermore, Gonatopoulos-Pournatzis was able to find other factors that work closely with a previously identified master regulator of microexon splicing, a protein called nSR100/SRRM4, discovered previously in the Blencowe lab. Working with **Anne-Claude Gingras**' team at Sinai Health System's Lunenfeld-Tanenbaum Research Institute, they identified proteins called Srsf11 and Rnps1 as forming a molecular complex with nSR100.

Knowing the precise molecular mechanisms of microexon splicing will help guide future efforts to develop potential therapeutics for autism and other disorders. For example, because the splicing of microexons is disrupted in autism, researchers could look for drugs capable of restoring their levels to those seen in unaffected individuals.

"We now better understand the mechanism of how the microexons are recognized and spliced specifically in the brain," says Gonatopoulos-Pournatzis, who recently won the Donnelly Centre's newly established Research Excellence Award . "When you know the mechanism, you can potentially target it using rational approaches to develop therapies for neurodevelopmental disorders."

The Hughes lab found that bioactive chemicals in cannabis—THC and CBD—are produced by separate genes which will facillitate the breeding of new medical varieties.

Cannabis Genome Map to Facilitate Breeding of New Medical Strains

By Jovana Drinjakovic
November 23, 2018.

THC and CBD, bioactive substances produced by cannabis and sought by medical patients and recreational users, sprung to life thanks to ancient colonization of the plant's genome by viruses, Donnelly Centre researchers have found.

The finding is only one of the insights revealed by a new cannabis genome map detailing gene arrangement on the chromosomes, published recently in the journal *Genome Research*. Among other revelations are discovery of a gene responsible for the production of cannabichromene, or CBC, a lesser known cannabinoid, as the active substances in cannabis are known, and new insights into how strain potency is determined.

"The chromosome map is an important foundational resource for further research which, despite cannabis' widespread use, has lagged behind other crops due to restrictive legislation," says **Tim Hughes**, a professor in the Donnelly Centre and co-leader of the study. Hughes is also a professor in the Department of Molecular Genetics and Senior Fellow at the Canadian Institute for Advancement of Research.

The researchers expect the map will speed up breeding efforts to create new strains with desired medical properties as well as varieties that can be grown more sustainably, or with increased resistance to diseases and pests.

The study was a three-part collaboration between Hughes' team, with graduate student **Kaitlin Laverty** spearheading the computational work behind genome assembly, and those of Jonathan Page, of Aurora Cannabis and the University of British Columbia , and Harm van Bakel, of the Icahn School of Medicine at Mount Sinai in New York.

Hughes, Page and van Bakel first got together in 2011 when they released the first draft of cannabis genome which was too fragmented to reveal gene position on chromosomes.

The new map reveals how hemp and marijuana, which belong to the same species *Cannabis sativa*, evolved as separate strains with distinct chemical properties. Cannabis plants grown for drug use ("marijuana") are abundant in psychoactive tetrahydrocannabinol, or THC, whereas hemp produces cannabidiol, or CBD, popular of late for its medicinal potential. Some people use CBD to relieve pain and it is also being tested as a treatment for epilepsy, schizophrenia and Alzheimer's.

"This is an important foundational resource for further research which, despite cannabis' widespread use, has lagged behind other crops due to restrictive legislation"

The enzymes making THC and CBD are encoded by THCA and CBDA synthase genes, respectively. Both are found on chromosome 6 of the ten chromosomes the cannabis genome is packaged into. There, the enzyme genes are surrounded by vast swathes of garbled DNA which came from viruses that colonized the genome millions of years ago. This viral DNA, or retroelements as it is known, made copies of itself that spread across the genome by jumping into other sites in the host cell's DNA.

"Plant genomes can contain millions of retroelement copies," says van Bakel. "This means that linking genes on chromosomes is analogous to assembling a huge puzzle where three quarters of the pieces are nearly the same color. The combination of a genetic map and PacBio sequencing technology allowed us to increase the size of the puzzle pieces and find enough distinguishing features to facilitate the assembly process and pinpoint the synthase genes."

The researchers believe that gene duplication of the ancestral synthase gene and expanding retroelements drove ancient cannabis to split into chemically distinct types. Humans subsequently selected for plants containing desirable chemistry such as high THC.

The gene sequences for the THCA and CBDA synthases are nearly identical supporting the idea that they come from the same gene which was duplicated millions of years ago. Over time, one or both gene copies became scrambled by invading retroelements, and by evolving separately, they eventually came to produce two different enzymes - CBDA synthase found in hemp (fibre-type), and THCA synthase in drug-type (marijuana).

Because the enzymes are so similar at the DNA level, until this study it was not even clear if they are encoded by separate genes or by two versions of the same gene. Adding to the confusion was the fact that most strains produce both CBD and THC despite breeders' efforts to grow hemp varieties free from the mind-altering THC for users looking to avoid it.

The chromosome map now clearly shows that two distinct genes are at play which should make it possible to separate them during breeding to grow plants without THC. Some psychoactive effects in medical strains could be coming from CBC, a lesser known cannabinoid that has unusual pharmacology including anti-inflammatory properties. The discovery of the gene responsible for CBC synthesis will make it possible for breeders to tailor its content in future varieties.

"Mainstream science has still not done enough because of research restrictions," says Page. "Legalization and looming ease of research regulation really provide for opportunities for more research to be done. And Canada is leading the way."

MAJOR AWARDS
AND APPOINTMENTS

Order of Canada medals, Office of the Governor General of Canada

University Professors Michael Sefton and Molly Shoichet were inducted into the Order of Canada.

Photos by Calvin Thomas

Michael Sefton and Molly Shoichet Inducted to Order of Canada

By Carolyn Farrell
January 3, 2018.

University Professors Michael Sefton and Molly Shoichet have been named Officers of the Order of Canada, one of the country's most prestigious recognitions. The new appointees were announced last week by Governor General Julie Payette. Both Sefton and Shoichet are faculty members in the Donnelly Centre and professors in the Department of Chemical Engineering and the Institute of Biomaterials and Biomedical Engineering (IBBME).

"Both Professors Michael Sefton and Molly Shoichet are working to undo some of the most devastating diseases of our time using innovative bioengineering approaches. Their research is widely recognized and has helped raise the international standing of Canadian science,"says **Brenda Andrews**, University Professor and Director of the Donnelly Centre. "On behalf of the Donnelly Centre, I extend my warmest congratulations to both on these richly deserved honours."

Michael Sefton

Sefton has made significant contributions to research advances in biomaterials, biomedical engineering and regenerative medicine. He was one of the first to combine living cells with polymers, effectively launching the field now called tissue engineering. More recently, his lab has created biomaterials that actively promote the growth of blood vessels. By producing drug-like activity without any drugs or cells included within the material, these materials

open a new world of possibilities for applications such as wound healing and the development of lab-grown tissues.

A leader in his professional community, Sefton served as president of the U.S. Society for Biomaterials in 2005 and has spearheaded several programs to advance the field, including the Toronto Tissue Engineering Initiative. He has worked with leading clinicians worldwide to advance research on health issues such as cancer and diabetes. From 1999 to 2005, Sefton was director of U of T's IBBME, leading its development into one of the top institutes of its kind in North America. He currently serves as executive director of Medicine by Design, a U of T initiative that is accelerating discoveries in regenerative medicine to improve treatments for conditions such as heart failure, diabetes and stroke.

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

Molly Shoichet

As the Canada Research Chair in Tissue Engineering, Molly Shoichet is pursuing solutions to a critical issue in medicine: treating damage to nerve tissues. Shoichet and her team design and implement novel strategies to promote tissue regeneration after traumatic spinal cord injury and stroke. Her lab is known for its use of materials called hydrogels, which surround and protect stem cells when they are injected in the body. These hydrogels help stem cells survive and integrate into tissues, including tissue damaged by stroke, macular degeneration or other diseases.

Shoichet has published more than 575 papers, patents and abstracts on tissue engineering and regenerative medicine. She is the only person to be elected a fellow of all three of Canada's National Academies and is a foreign member of the U.S. National Academy of Engineering.

In November 2017, Shoichet was named Ontario's first Chief Scientist, with a mandate to advance science and innovation in the province. Earlier this year she was awarded the 2017 Killam Prize in Engineering, Canada's most prestigious engineering award. She is also the recipient of the 2015 L'Oréal-UNESCO For Women in Science Award for North America and the 2013 Queen Elizabeth II Diamond Jubilee Medal. She has been a member of the Order of Ontario since 2011.

Outside of her own research, Shoichet is a passionate advocate for science and engineering and their important role in society. She has provided strategic advice to both the federal and provincial governments through her service on Canada's Science, Technology and Innovation Council and the Ontario Research Innovation Council. In 2014, Shoichet was appointed U of T President Meric Gertler's Senior Advisor on Science and Engineering Engagement.

She is the co-founder of Research 2 Reality, which uses digital media to shine a spotlight on the contributions academic researchers are making to the country. In 2015, she received the Fleming Medal and Citation from the Royal Canadian Institute in recognition of her outstanding contributions to science communication.

Amy Caudy received appointment renewal as **Canada Research Chair** in Metabolomics for Functional Enzyme Discovery.

Amy Caudy's Quest for Metabolism's Missing Links

By Jovana Drinjakovic
May 3, 2018.

Amy Caudy knows all about recycling—"use it up, wear it out, make do or do without" was the family adage on a farm where she grew up in Sunbury, Ohio. Now these same principles are guiding Caudy's study of cell metabolism at the University of Toronto.

"In metabolism, things are getting reused all the time," says Caudy, Associate Professor in the Donnelly Centre and Department of Molecular Genetics. "That reuse of the same enzymes but different substrates, molecules they act on, is providing a greater efficiency for the cell and a regulatory opportunity."

Caudy holds the Canada Research Chair in Metabolomics for Functional Enzyme Discovery, an appointment that has been renewed for another five years as part of the national program that aims to recruit and retain top research talent in the country, the federal government announced today.

Advances in technology have transformed the study of metabolism— the chemical reactions by which cells break down nutrients to fuel growth and repair. But they have also revealed major gaps in our understanding of these processes.

For example, genome sequencing has revealed dozens of genes for "missing enzymes" thought to catalyze the chemical reactions which have not been discovered yet. And, thanks to improved methods

for chemical profiling, researchers are uncovering in cells hundreds of new metabolites, products of chemical reactions, for which they have no clue what they are doing or how they were made.

Caudy is filling these knowledge gaps through her research on yeast and cancer cells with applications that range from clean fuels to drug discovery.
In one recent example, the lab discovered a previously unknown chemical in yeast. In trying to find out how this chemical was made, the team ended up uncovering an entirely new pathway for making isoleucine, a staple amino acid and a building block of proteins—and one that scientists thought they had worked out a recipe for more than half a century ago.

"You can make great drugs by inhibiting cell metabolism"

The alternative pathway had previously been observed only in a handful of rarely studied bacteria and this is the first time that anyone has found it in more complex yeast cells, said Caudy. Unlike bacteria, yeast cells are "eukaryotic" because their DNA is encased by the protein envelope, same as in all plant and animal cells. "The whole thing just underscores that even in yeast, our best-known eukaryote, there are metabolites that require explanation," says Caudy.

One potential application of the discovery is in green energy as one of the products of the new isoleucine pathway looks like a precursor for butanol, a desired biofuel.

Caudy grew up as a single child on a 400 acre family farm where her parents still live. Her mum, a teacher, who also has a masters degree in nutrition, and dad, an engineer, were always supportive of Caudy's inquisitive mind. Also, "school was awesome compared to working on a farm—you go and sit all day instead of having to dig holes and sweat," said Caudy.

In 1999, after graduating from Washington University (WashU) in St. Louis, Caudy joined the lab of Professor **Gregory Hannon** at the Cold Spring Harbor Laboratory (CSHL), for a PhD. There, she began investigating an obscure cellular process known as RNA interference, or RNAi, that had been discovered the year before in worms. RNAi works by silencing gene's messages and it was not before long researchers turned it into a tool for switching off genes at will, netting its discoverers, **Craig Mello** and **Andrew Fire**, the Nobel prize in 2006. During her PhD, Caudy uncovered the key components of the RNAi machinery in human cells and helped build the RNAi-based tool for silencing human genes.

After graduating, Caudy returned to WashU for a brief postdoctoral training in immunology before taking on an independent research position as a Lewis-Sigler Fellow at Princeton University. The prestigious fellowship gave Caudy the freedom to pursue a long-standing interest in metabolic control of cell growth. Working with yeasts, Caudy discovered a role for a "missing enzyme" in a new metabolic pathway for making ribose, a building block of DNA, which had been overlooked for decades.

Finding such missing links in metabolism opens new avenues for drug discovery. "You can make great drugs by inhibiting metabolism," says Caudy. The lab's work in yeasts opens new possibilities for drug discovery. When you know how an enzyme works then you can start engineering molecules that block as is the case with many anti-fungal medicines, said Caudy.

The same approach can be applied to cancer cells. As part of Stand up to Canada Cancer Dream Team, led by Professor **Peter Dirks**, from the Hospital for Sick Children, Caudy is investigating metabolites that are unique to rogue stem cells in the brain that fuel glioblastoma, a highly aggressive form of brain cancer.

"We are profiling these glioblastoma stem cells and finding that they are making new compounds that we don't even know what they are," says Caudy. "And those are exactly the kind of molecules that I want to go after."

Donnelly Centre alum Michael Garton launched his own lab at U of T in a research career spurred by a climbing accident that left him paralysed.

How Michael Garton Forged a Career in Research after being Paralyzed by Climbing Accident

By Jovana Drinjakovic
October 1, 2018.

On a hot July day in 2006, **Michael Garton** was living his dream. Then 24 years old, the British climber was scaling the tallest vertical rock face in Europe – Norway's Troll Wall – hoping to become the first person to reach the top climbing solo.

His bid was all the more audacious in light of the country's no-rescue policy, which said climbers stranded on the notoriously inaccessible wall had to fend for themselves. Garton estimated that if he climbed for up to 18 hours each day, he could reach the peak – about the height of two CN towers – in seven to 10 days.

But then disaster struck as Garton was hit by rock fall, plunging 40 meters down the cliff before getting caught by his climbing equipment. The fall left him paralyzed and all but dead.

The same tenacity that drove Garton up the calamitous mountain 12 years ago has helped him build a successful research career culminating this month with an appointment of an Assistant Professor at the University of Toronto's Institute for Biomaterials and Biomedical Engineering. "When you are climbing and you know you are not going to be rescued if anything goes wrong, there's a feeling

of being super committed and it's totally down to you," he says. "The mindset I built doing that has really helped me doing science."

With climbing, he says, "it is mostly obvious where you have to go – you just have to keep pushing forward." But in science, "it is often difficult to know where to go. Even when you don't feel like you're making any progress, or you're failing at everything, just keep trying, keep thinking about the problem in a different way."

One of the first projects in his lab will be to engineer human cells into a kind that can mend throbbing pain in aging joints. For example, for arthritic knees in which the pain is caused by inflammation, Garton's plan is to take out some knee cells, insert new genetic circuitry encoding components engineered to both sense the inflammation and respond to it by releasing anti-inflammatory molecules, and then put the cells back into the knee.

"I want to develop a basic chassis of the cell that can be fine-tuned to detect and respond to different diseases"

"The cells will respond as and when necessary and you as a patient will never experience the disease as it is being treated by your own tissue," he says. Arthritis will be a test case, but the same principles could then be applied to a variety of diseases. "I want to develop a basic chassis of the cell that can be fine-tuned to detect and respond to different diseases."

Garton says that being at U of T, with "world-renowned experts in various diseases working just across the street or in the next building," will be helpful for establishing the collaborations needed to bring new therapies to patients.

A chemist by training, before the accident Garton thought little about applying his scientific knowledge to better society. But his views shifted during the year-long recovery in the hospital, where he was surrounded by caring staff while grasping the confines of his new reality.

"The thing to do is to apply your passion and drive and hard work to something that is actually going to benefit society and other people and not just yourself "

"I could kind of see that a lot of the staff at the hospital had the same passion for their job as I had for climbing," he says. "I realized then how selfish I've been my whole life by just focusing on how much I could enjoy myself going climbing. It really hit me – that the thing to do is to apply your passion and drive and hard work to something that is actually going to benefit society and other people and not just yourself."

That Garton is alive is only thanks to a chance encounter a few days before his accident. While preparing for the climb, he asked a passerby with a telescope if he could borrow it to make out the safest route and avoid a rockfall. That summer was unusually warm and the heat had melted the ice inside the cracks of the north-facing cliff that glues together loose pieces of rock. The thawing ice released "boulders the size of trucks."

Although Garton tried to avoid the worst areas of rockfall, two days into the ascent a lump of rock came off as he was climbing and knocked him off. The fall left him unconscious and when he woke up, he could not move. "I woke up and had a really excruciating pain in my neck," he says. "That's when I realized I had broken my neck and was paralyzed."

"It was a very odd experience, just being conscious and not being able to fight it, just having to lie there and look at the incredibly serene landscape and just think, 'OK, I only have a few more hours left and then it's death.'"

But what Garton did not know was that the man with

At 1100m, Norway's Troll Wall, on the left, is the tallest vertical rock face in Europe.

the telescope had set up camp with friends to watch him climb. When the campers noticed Garton's body hanging off the cliff, they alerted the authorities, who despite the no-rescue policy sent a Royal Norwegian air force helicopter that was training in the area.

Ten hours passed before help arrived. It was nighttime, and despite the midnight sun, the temperature had dropped below zero. Garton was by then in a state of severe hypothermia and had slipped into a coma. His heart stopped several times, requiring 16 defibrillations to be revived during transport to the hospital, where he stayed on life support for three weeks before coming out of the coma.

In the hospital, Garton had to relearn how to do the most basic things, including how to breathe without

the help of the ventilator. "When you are paralyzed, everything that you have ever learned as a tiny child, down to brushing your teeth, everything is wiped away," he says. "You go from where what you are aiming to do this year is to be the first person to climb the highest cliff in Europe and then a few months later the main thing you are trying to achieve is breathe on your own for 10 seconds."

Garton learned how to control a computer using his voice and in September 2007, just three months after leaving the hospital, he returned to school to earn a master's degree and then a PhD in computational biology at the University of Nottingham.

"I saw disabled people go both ways, a lot of people

give up," he says. You have to make a choice at some point. Do I keep going or do I give up?"

In 2012, he moved to Toronto with his wife Hannah, who is Canadian. After a brief postdoctoral stint in the lab of **Shoshana Wodak**, then at the Hospital for Sick Children, he joined Professor **Philip Kim**'s group at U of T's Donnelly Centre for Cellular and Biomolecular Research. That experience, he says, helped him become a better scientist. "At Donnelly, I wasn't treated any different to anybody else, not like I was anything special for being disabled. I was held to the same standards and that helped me to really up my game and become a much better scientist."

While working with Kim, Garton invented a computational method for designing smart drug molecules that last longer in the body to reduce the frequency of taking medication. The idea came to him after a friend's toddler was diagnosed with Type 1 diabetes and had to receive daily insulin injections. Garton came up with a way to convert natural protein molecules into their mirror-image forms, which retain the same therapeutic properties but are much longer-lasting.

"I like the feeling of being able to invent something to solve the problem. You are not restricted by what nature is doing. You can be somewhat more creative – you are only limited by what you can imagine you can do."

Garton's appetite for "creating new stuff" goes beyond science. Two years ago, he took up stone carving and has created life-sized sculptures of the human ear, eye and the brain. His other hobbies include sailing, but he prefers activities in which he can be fully independent.

Garton started sculpting by mouth after Hannah, who works as a photographer and is also his full-time carer, gave him wooden handled carving tools as a gift. At first, he tried velcroing regular tools to his arms but when that did not work out, he gripped the wooden handled tools with his mouth. With no instructions available on how to do it, he experimented with chipping and scraping until the stone started taking shape.

"Loads of people sculpt, but having been forced to do it by mouth means you are doing something new and I like that," he says. "For me, having a disability is background noise. In some ways it's annoying, but it also makes life interesting."

At times, Garton himself can't quite believe how things have turned out.

"I'm still pinching myself to be honest. Can't feel it but I'm trying", he says with a laugh.

"I like the feeling of being able to invent something to solve the problem. You are not restricted by what nature is doing... you are only limited by what you can imagine you can do"

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Through melding of computer science and biology, Gary Bader helped revolutionise data analysis to become a world's top cited academic.

Photo by Donnelly Centre

Gary Bader Joins the Ranks of World's Top Cited Academics

By Jovana Drinjakovic

November 27, 2018.

Gary Bader learned to code as a young boy so he could play video games on a Commodore 64, the 1980s iconic home computer.

"Commodore 64 was really good because to play a video game you had to type commands first," says Bader, a professor of computational biology at the Donnelly Centre. "It was a good incentive to learn how things worked."

Bader never stopped figuring out how things worked. Leading a team of two dozen computational experts, he is world-renowned for his research that uses machine learning to decode one of biology's greatest mysteries— how genes influence health.

"The ultimate goal of our research is to take all the big human biology data that exists and use it to make predictions about personal health," says Bader, who is also a professor in U of T's Departments of Molecular Genetics and Computer Science, an associate member of the Sinai Health System's Lunenfeld-Tanenbaum Research Institute and holds Ontario Research Chair in Biomarkers of Disease.

Computational advances have revolutionized biomedical research allowing researchers like Bader to gain meaningful insights from a sea of data. But Bader has also played a key role in driving these innovations.

While still a graduate student, in the late 1990s in **Christopher Hogue**'s lab, then at the LTRI, Bader wrote a software that would help change how molecular biologists visualize data. Genomic technologies that were emerging at the time enabled researchers to simultaneously study thousands of genes and their protein products. And while there was a growing awareness that the clues to health and disease lie in the way proteins and other molecules interact with each other, there was no good way to illustrate these networks.

By borrowing from graph theory, used in mathematics for over a century to study a set of nodes and connections between them, Bader wrote one of the first computer systems for storing and depicting interactions between different proteins. The software not only organized the data into a network, but it also placed molecules working closely together into tight clusters. This allowed researchers to make assumptions about, say, genes they knew little about based on their positions in the network.

Called BIND, for Biomolecular Interaction Network Database, Bader's software attracted millions in investments from government and industry. It also helped establish Toronto as one of the few places in the world with expertise in the new field of network biology helping it become a leading biomedical research hub it is today.

In space of a month, Bader's graduate research was part of two papers in *Science* and one in *Nature*, a feat most academics can only dream of. These were first in a string of high-profile publications that make Bader one of the world's most influential researchers in his field. Judged by his papers' citation rate, a measure of how many times other research publications refer to his work, Bader is among the top one percent most cited academics globally, as announced today by Clarivate Analytics, a data company previously owned by Thomson Reuters. Bader made the cut before in 2014.

"It's nice to see that our team's work has impact," says Bader for being on the list.

Two more Donnelly Centre investigators, **Warren Chan** and **Quaid Morris**, are also on the list as well as 30 faculty from other U of T divisions.

More recently, Bader's team helped create the first map of liver cells at the molecular level to serve as a roadmap for developing future cell therapies for liver disease.

The findings are part of the Human Cell Atlas, a large international effort to reveal the molecular makeup of all cells in the human body with Bader as the Canadian representative on the consortium's organizing committee.

Another area of Bader's research is cancer. A few years ago, he helped identify a drug target in the brain tumour of an nine-year-old boy, in a stark example of how computational research can impact health in real life. Working with Dr. **Michael Taylor**, a neurosurgeon at the Hospital for Sick Children, the team was able to source a drug compound targeting a cellular mechanism which Bader's algorithm predicted is critical for the tumour. The drug worked and is now being tested in more patients as part of two clinical trials.

One day he hopes to be able to similarly help patients with breast cancer, as well as with glioblastoma, an aggressive form of brain cancer that strikes adults and for which the prognosis remains grim at around 15 months survival after diagnosis.

"My dream is to help find new treatments for glioblastoma because nothing has changed the survival of that cancer for many years" says Bader who, along with another Donnelly colleague, Professor **Amy Caudy**, is on the Stand up to Cancer Canada's Brain Dream Team led by Drs. **Peter Dirks** of SickKids and **Samuel Weiss** of University of Calgary. "We have so much data, we're getting lots of new interesting insights and I am very excited about spending a number of years really thinking about that," he says.

His video gaming days may be long over, but for Bader, the thrill of figuring out of how things work shows no sign of stopping.

OTHER NOTABLE APPOINTMENTS AND AWARDS:

Warren Chan was named Canada Research Chair in Nanobioengineering and is listed among top one percent of highly cited researchers globally.

Quaid Morris was promoted to the rank of Professor and named an inaugural CIFAR AI Chair. Morris was also listed among top one percent of highly cited researchers in the world.

Ben Blencowe's appointment as Banbury Research Chair was renewed.

Penney Gilbert was promoted to the rank of Associate Professor.

Hannes Röst received the Connaught Fellowship.

The Donnelly Centre in numbers:

Personnel

18 Primary appointed

12 Cross appointed

30 Faculty

43 Research associates

85 Research and admin staff

76 Postdoctoral fellows

74 Undergraduate students

199 Graduate students
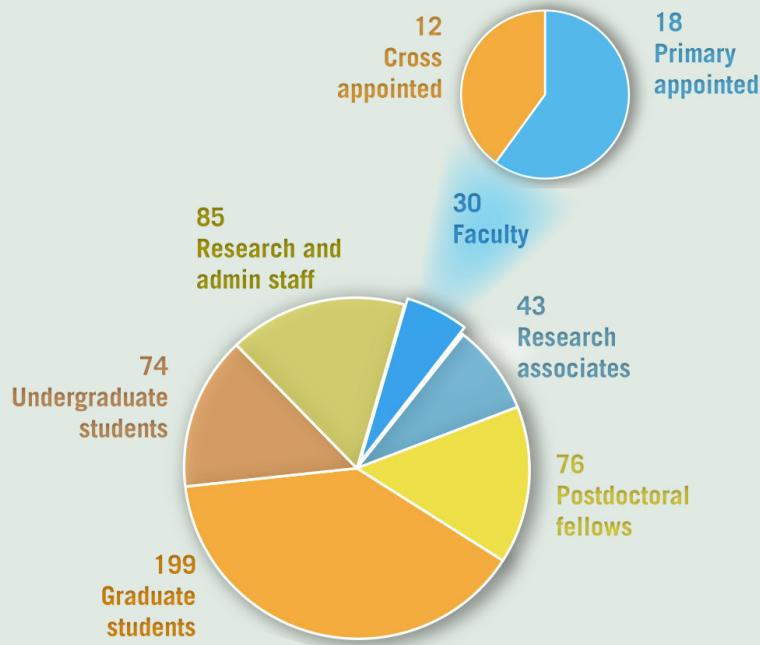
Total 508

Funding
(June 2017-June 2018)

$8.6M Other

$2.7M NIH

$2.2M MRI

$1.7M CFI

$1.6M CRC

$3.3M CFREF

$13.5M CIHR

$1.7M NSERC
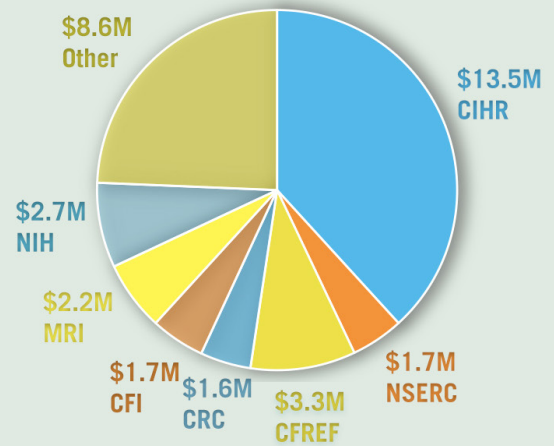
Total $ 35.2M

Faculty

3 Order of Canada medals

5 University Professors
(U of T average is 2% of tenured faculty)

7 Royal Society of Canada Fellows

30 Faculty members

140 Published papers in 2018
(including 32 review articles)

3 Top 1% cited researchers globally

12 Canada Research Chairs

MEET OUR AWARD-WINNING GRADUATE STUDENTS

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Serge Gueroussov from the Blencowe lab won the **Barbara Vivash Award** for the best PhD thesis in U of T's Department of Molecular Genetics.

Photo by Donnelly Centre

Serge Gueroussov Wins Best Thesis Award in Molecular Genetics

By Jovana Drinjakovic
February 27, 2018.

To **Serge Gueroussov**, it all felt "surreal". "During my time as a graduate student, some of the people that I looked up to the most went on to win this award, so to get it myself is very humbling," he says.

Gueroussov is the latest recipient of the Barbara Vivash Award in Molecular Genetics for the most outstanding PhD thesis in the University of Toronto's Department of Molecular Genetics (MoGen).

Established in 2009, the Barbara Vivash Award in Molecular Genetics recognizes PhD research that has significantly advanced our understanding of how biological processes operate on a molecular level.

Past awardees went on to have successful research careers at world's top universities.

The Barbara Vivash Award in Molecular Genetics was borne out of the family's long-standing commitment to the field of genetic medicine, going back four decades to when Mrs. **Barbara Vivash** was involved with establishing the first clinics for genetic counselling in northern Ontario communities so their residents no longer had to travel far for expert advice.

"That early introduction to genetics certainly helped to sustain my interest in this ever expanding field of medicine," says Mrs. Vivash. "So when my husband

John and I discussed setting up an award, there was no doubt in our minds about where we wanted it to go."

"We tremendously appreciate the support from the Vivash family with this gift, which provides important recognition of scientific excellence and promotes the success of the next generation of scientific leaders" said Professor **Leah Cowen**, Chair of Mogen.

Gueroussov has already been successful at every stage of his career, publishing original research he did as an undergraduate with Professor **Alexander Palazzo** at the Department of Biochemistry. But it was his PhD work with Professor **Ben Blencowe** in the Donnelly Centre that revealed groundbreaking new insights about the evolution of cellular complexity. During this time, Gueroussov published seven papers including first author studies in top journals *Cell* and *Science*. "These were absolutely stunning, really original, landmarks studies," said Cowen.

> *"Serge is a remarkably ambitious and gifted young scientist and I fully expect him to continue publishing groundbreaking research in the future"*

"I am very grateful for the opportunity to do my thesis work with Ben in the collaborative environment of the Donnelly Centre", says Gueroussov. "Ben was tremendously supportive throughout my time there and had a great sense of when I needed his mentorship and when to let me explore on my own."

During his PhD, and building on previous work in the lab, Gueroussov uncovered how a cellular process known as alternative splicing could have enabled mammals to evolve more complex brains. Alternative splicing generates greater protein diversity which is thought to be improtant for making more diverse cells types.

Gueroussov found a molecular switch in alternative splicing that only works in the mammalian brain and which has contributed to tissue complexity and possibly also the evolution of advanced cognitive functions.

In another study, Gueroussov revealed a tantalizing possibility that one of the roles for alternative splicing in the brain might be to ward off sticky proteins that form large aggregates and are a hallmark of neurodegenerative diseases such as Parkinson's and Alzheimer's.

"If you have too much protein aggregation, that's linked to neurodegenerative disorders," Gueroussov said during the lecture. "So we could speculate that one purpose for the evolution of this splicing was to limit the extent of aggregation that was taking place."

"Serge has made valuable contributions to our understanding of the regulation, function and evolution of alternative splicing," says Blencowe. "He is a remarkably ambitious and gifted young scientist and I fully expect him to continue publishing groundbreaking research in the future."

Since last September, Gueroussov has been living in Boston, where he is working as a postdoctoral fellow with Professor Feng Zhang, a celebrated researcher who was one of the first to use the gene editing tool CRISPR to edit genes in human cells, at the Broad Institute of MIT and Harvard.

"I was very excited to come here and see what my ultimate potential is as a scientist," Gueroussov says. "So far, I am enjoying it."

Gueroussov is the third student from the Donnelly Centre to win the Barbara Vivash Award. In 2012, the award went to **John Calarco**, who was also in the Blencowe lab and is now Assistant Professor at U of T's Department for Systems Biology. The following year, the winner was **Anastasia Baryshnikova**, who did her PhD with **Brenda Andrews**, University Professor and Director of the Donnelly Centre. Baryshnikova was Assistant Professor at Princeton before becoming a principal investigator at Calico, a California biotechnology company focusing on aging.

Mohsen Afshar, Eesha Sharma and Alexander Vlahos won the Jennifer Dorrington Research Award which recognizes outstanding students in U of T's Faculty of Medicine.

Dorrington Award Recognizes Graduate Research in Bioengineering, Genome Mapping and Transplantation

By Jovana Drinjakovic
February 21, 2018.

Most people don't ponder about chemical processes playing out in their muscles while they exercise, yet that's all **Mohsen Afshar** thinks about. A tennis enthusiast and tissue engineer, Afshar grows mini muscles in the dish that allow him to study how muscles form and work at a level of detail previously impossible.

Along with **Eesha Sharma** and **Alexander Vlahos**, Afshar is this year's recipient of the Jennifer Dorrington Doctoral Research Award, awarded annually to outstanding graduate students in the Faculty of Medicine doing research in the Donnelly

Centre. The award was established in 2007 as a tribute to Dr. **Jennifer Dorrington**, who was a professor in the Banting and Best Department of Medical Research. Dorrington's pioneering research greatly advanced our understanding of reproductive biology and ovarian cancer.

"The award was highly competitive this year as we had 50 per cent more applicants than usual," says **Gary Bader**, Chair of the award committee with **Liliana Attisano**, **Henry Krause** and **Cindi Morshead** as members. All are Principal Investigators in the Donnelly Centre. "These excellent students are

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highly deserving of the Jennifer Dorrington Award for having made important contributions to their respective fields of research, and I have no doubt that ahead of them lies a bright future as independent investigators," says Bader.

The muscles Afshar grows are tiny, no larger than a pencil tip, but they twitch just like real muscles do.

"Using the right biomaterials and extracellular matrix proteins, we can now grow human skeletal muscle in a dish in a way that mimics muscles in the body and how they respond to stimuli," says Afshar, a fifth year PhD candidate in the group of **Penney Gilbert**, Assistant Professor in the Institute of Biomaterials and Bioengineering (IBBME) and Principal Investigator in the Centre. The new tissue platform allows the team to study in exquisite detail how muscles that help us move form and work.

Mohsen Afshar

It took Afshar a lot of work to get to this point. He gets scraps of adult muscle tissue from biopsies taken during surgery by Gilbert's clinical collaborators at the nearby St. Michael's Hospital. To watch muscle fibers form from scratch, Afshar first had to isolate muscle stem cells from the donated tissue and then, using molecular tricks, coax these cells to grow into elongated muscle cells that eventually come together to form contractile fibers. The whole process takes about a fortnight.

"It's all very well to have a tissue model, but it's what you do with it that counts," says Afshar. "That's

what's great about Penney's lab. She always pushes us to think about how we can use our model to learn more about the science."

One research avenue Afshar is pursuing is to figure out how nerves interlace with muscles to form the neuromuscular junction (NMJ) through which electrical impulses flow and tell the muscle to contract. Thanks to his mini muscles, he can now study this process for the first time in a three-dimensional space, similar to how it occurs in the body.

To do this, Ashfar grows muscle fibers alongside stem cell-derived nerve cells, which then self-organize into the NMJ within a custom-made 3D scaffold.

Another advantage of Ashfar's complex tissue platform is that it is more similar to the adult NMJ than any other available models, which more closely resemble the immature NMJ in the embryo. This means that the team can now use the platform to study in a dish neuromuscular diseases such as myasthenia gravis or amyotrophic lateral sclerosis (ALS), which cause, respectively, weakness of skeletal muscles and the death of neurons controlling them, as they appear in real life.

Afshar says his research would not have been possible without support from colleagues in the lab and across the Donnelly Centre. "Ever since I started here, people have been so welcoming and collaborative," he says. "I got a lot of help from **Peter Zandstra**'s lab when I first started setting up the tissue culture platform. And **Jason Moffat**'s lab helped me overcome hurdles when working with viruses used to deliver genes to cultured muscle cells."

Five floors up from Afshar's bench, Eesha Sharma is investigating the uncharted territory of the cell. A self-professed physics nerd, she became fascinated with biology during high school after learning about a study in which scientists took a fluorescent protein from jellyfish and put it into a cat so it could glow in the dark. "This was mind-blowing to me," she said. "This Nobel-winning biomedical tool revolutionized our ability to view the inner workings of the cellular machinery. I thought, if this is what we can do with

biology, then that's what I want to be doing."

Today, Sharma is illuminating the cell not with a fluorescent protein, but with sequencing technology. Now in her final year of graduate studies in the Department of Molecular Genetics (MoGen) and working with Professor **Benjamin Blencowe**, Sharma has pioneered a new method that allows researchers to investigate parts of the cell that were previously out of reach.

Eesha Sharma

One of the biggest surprises from the sequencing of the human genome was that of six billion DNA letters that make up our genome, only about two per cent encodes for proteins, molecules that do most of the work in the cell. Historically, this is what most research focused on. One of the biggest unchartered territories in biology is this other 98 per cent of sequence information. It is now clear that a lot of this non-protein coding DNA is copied into RNA molecules—same as the coding fragments. But instead of serving as templates for making proteins, non-coding RNAs (ncRNA) can be important in their own right in development and disease.

With the pressing need to come up with a way to study ncRNAs on a large scale, Sharma developed a method called LIGR-Seq. The technology captures the pairing between ncRNA and other RNA molecules, which in turn sheds light on their possible function in the cell.

"Before, there were only ways to do this one RNA at a time, using methods developed in the 1960s," says Sharma. "These are beautiful techniques but very laborious. So, we tweaked it, harnessed some clever molecular tools and combined it with the powerful high-throughput sequencing technology we have today so that we could look systematically at thousands of interactions in a single experiment", says Sharma.

Sharma's technology is based on the fact that RNA molecules can stick together like Velcro, so long as their sequences are sufficiently matched to support the pairing. By surveying thousands of interactions between different RNA molecules, Sharma was able to uncover new roles for ncRNA. Her work was published in 2016 in *Molecular Cell*, a prestigious journal in the field and continues to be highly cited by the research community.

She is now working to detect and uncover the meaning of the so-called secondary structures in RNA molecules, which occur when an RNA loops in on itself. Sharma recently uncovered a new role for a ring-like structure or circular RNA in acting like an "off" switch for a gene that has been linked to a rare blood disorder. "Circular RNAs are a new concept and we've been able to use our data to define an interesting point of control for this mRNA, which has been linked to a blood disease called Diamond Black-fan anemia. It's pretty fascinating what we are able to find given a fresh perspective on the cell," she said.

Sharma credits her PhD supervisor for her success. "Ben has been an excellent mentor," she says. "You never feel like you work for him, you work with him and that's a very empowering thing. He is really good at drawing the strengths of his people and I don't think I would have been able to accomplish as much as I had if I had been in another lab," she said.

The Dorrington Award will help Sharma to attend a workshop in Israel on the role of ncRNAs in embryo development at which she has been selected to give a talk on her findings. "I'm really looking forward

to getting feedback from the community on the latest stories I've been working on and finding out what cutting-edge techniques in the field are being developed. With the gene-editing CRISPR system and its variations it's a really exciting time to be in the field."

While Afshar and Sharma are focusing on uncovering new biology, Alexander Vlahos' goal is to develop better transplantation methods for the treatment of diabetes. The decision to take on the project was partly personal, he said.

"My father has type 2 diabetes and my grandfather died of pancreatic cancer so maybe there is subconsciously some gravitation towards looking at the pancreas," says Vlahos.

But he was also in the right place at the right time— five years ago, he joined University Professor **Michael Sefton**'s lab as a PhD candidate at IBBME. The team already had a long expertise in using bioengineering approaches to boost blood vessel growth in the body. This would turn out to be critical for Vlahos' success in showing that type 1 diabetes (T1D), in which the body is unable to produce insulin, can be treated— in mice at least— by transplanting the insulin-producing cells, sourced from the pancreas of a healthy donor, right beneath the skin. The findings were published last year in the *Proceedings of the National Academy of Sciences* (PNAS).

If the procedure could be applied to people, it would be far less invasive than the current gold standard method in which pancreatic cells are transplanted into the patient's liver.

"Our approach also has the advantage of being retrievable— in case something were to go wrong, the cells could be easily removed," says Vlahos.

Vlahos is now working to improve the underneath-the-skin transplantation method so that it requires fewer pancreatic cells, which are hard to come by.

For the graft to take, the transplant site needs to be rich in blood vessels so they can support the survival of pancreatic cells. The space underneath the skin is poorly vascularized, however, and this presented a main obstacle to transplantation. Vlahos was able to clear this hurdle by co-implanting with pancreatic cells, collagen rods and cells that line the blood vessels which spurred the growth of capillaries around the graft, boosting its survival.

He is now exploring a related approach in which he vascularizes the transplant site before implanting the pancreatic cells. His other project involves developing a new technology for engineering insulin-producing microtissues. Both of these approaches focus on reducing the number of donated pancreatic cells required to have a therapeutic effect, thereby increasing the efficacy of these rare cells.
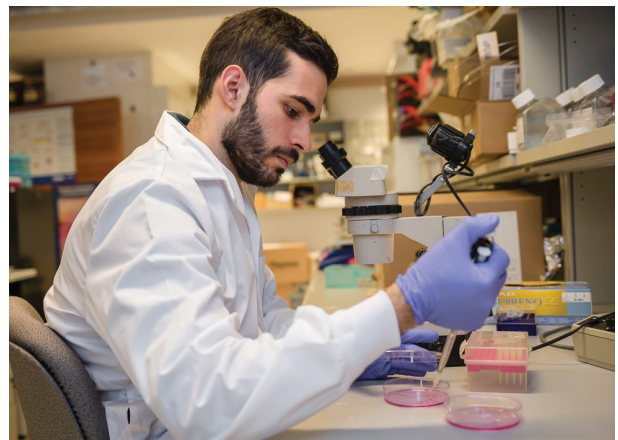
Alexander Vlahos

Vlahos' success has taken the lab on a new path. When he started his PhD, Vlahos was the only person on the team working on the project. Thanks to his data, the lab has secured a $1.1M in funding from the JDRF, a leading world organization focusing on T1D research, and there are now five students working on transplanting pancreatic islets underneath the skin.

After his PhD, Vlahos wants to get postdoctoral training in order to become an independent investigator. He believes the Dorrington Award will help him reach this goal. "Looking at the past students who had won this award, they are doing very successful things," says Vlahos. "I am humbled to be considered part of that group."

Oren Kraus from the Andrews lab won the Donnelly Thesis Prize.

Photo by Donnelly Centre

Computer Vision Research Wins Oren Kraus Donnelly Thesis Prize

By Jovana Drinjakovic
April 4, 2018.

Oren Kraus was awarded the Donnelly Centre Research Thesis Prize, an annual award given to an outstanding PhD student in the Donnelly Centre whose completed thesis has achieved the highest standards of quality, originality and research significance, it was announced this week.

In his PhD, Kraus developed a computer vision software to make cell image data analysis faster and more accurate,

Dubbed DeepLoc, and based on deep learning, a form of artificial intelligence, the software quickly sifts through reams of microscopy data to pick out subtle differences between cells and sort them into distinct categories. Faster and more accurate than the human eye, the algorithm is vastly accelerating research that aims to understand how thousands of genetic mutations and drugs affect cell health to, for example, spot early signs of cancer and develop more precise treatments.s

"On behalf of the award committee, I would like to congratulate Oren on this deserving award," says Professor **Jason Moffat**, chair of the award committee that counts Professors **William Ryu**, **Ben Blencowe**, **Derek van der Kooy** and **Aaron Wheeler** as members.

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All are principal investigators in the Donnelly Centre. "This was a very competitive year with amazing candidates but Oren's deep learning research stood out in its potential to accelerate science and help us glean new insights from microscopy data," added Moffat.

Co-supervised by **Brenda Andrews**, University Professor and Director of the Donnelly Centre and a pioneer of large scale microscopy research, and **Brendan Frey**, a professor in the Department of Electrical and Computer Engineering, who is applying deep learning to solving problems in biology, Kraus was immersed in the cutting-edge research in both fields that ultimately allowed him to develop the long-awaited data analysis tool.

Both Andrews and Frey are Senior Fellows at the Canadian Institute for Advanced Research.

"In Andrews and Frey labs, we really started the deep learning revolution in microscopy data"

"I am very thankful to my supervisors for providing me with the opportunity to work on exciting research problems at the intersection of computer vision, machine learning, cell biology, and genetics," says Kraus. "As world-renowned scientists in these fields, they helped me make novel research contributions in deep learning and high-content screening analysis and helped me develop lasting relationships with these communities."

From social media to online banking, computer vision has all but permeated the every-day life. But in biology labs across the globe, its absence is glaring, as researchers still mainly examine cell images by eye.

These images hold clues about what makes cells healthy and how they change during disease but thanks to rapid advances in automated microscopy, the researchers can acquire the data much faster than they can analyse it.

With DeepLoc in hand, Kraus and **Jimmy Ba**, who was a graduate student in the Frey lab and is now Assistant Professor in Vector Institute for Artificial Intelliegence, has helped bring down the time of data analysis from weeks and months to hours. Working with **Benjamin Grys**, another student in the Andrews lab, Kraus trained DeepLoc on millions of images of yeast cells until it learned to recognize slight changes between the cells. When they ran it on the real data set, DeepLoc was able to sort the cells into 22 distinct groups, whereas the human eye could only distinguish between 15 categories.

The beauty of the algorithm is that it is not confined to analyzing yeast cells and it can be quickly retrained to work on any type of cells including human.

Knowing that there is a great need for computer vision in both academic and industry research, Kraus launched Phenomic AI a startup that uses AI to develop cancer drugs for which he secured the seed fund of $500,000 with the help of Creative Destruction Lab (CDL) at U of T's the Rotman School of Management. Expecting to graduate during a convocation ceremony in June, Kraus is now focused on growing the company with collaborations in academia and industry and setting up an independent lab.

"In Andrews and Frey labs, we really started the deep learning revolution in microscopy data and there's been a lot of interest from pharma and biotech companies since," says Kraus. "Leaving that behind following my PhD seemed to be kind of waste, so the motivation was really to continue leading the field and to use these technologies to accelerate drug discovery."

Ten PhD candidates from diverse undergraduate backgrounds won the Cecil Yip Doctoral Research Award in support of interdisciplinary research.
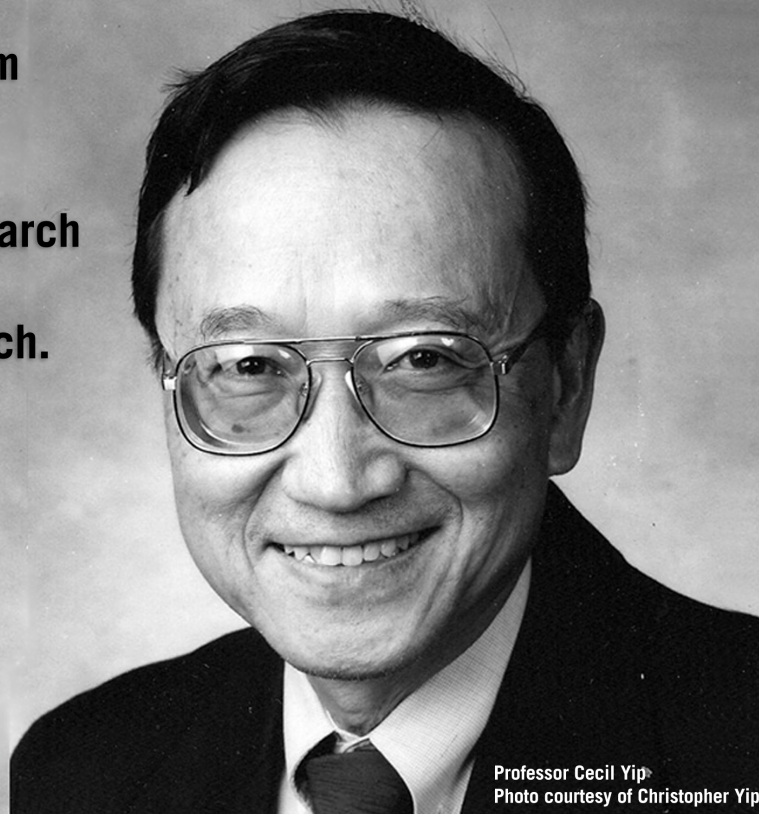
Professor Cecil Yip
Photo courtesy of Christopher Yip

Meet Winners of 2018 Cecil Yip Doctoral Research Award

By Jovana Drinjakovic
August 13, 2018.

We're thrilled to announce winners of the Cecil Yip Doctoral Research Award, awarded annually to first year graduate students who are doing interdisciplinary research in the Donnelly Centre.

Coming from diverse undergraduate backgrounds, with bachelor degrees in life sciences and engineering, these young scientists aim to uncover new biological insights that could pave the way for future advances in medicine.

"On behalf of the award committee, I would like to congratulate the winners of the Cecil Yip Doctoral Research Award," says **Christopher Yip**, Chair of the award committee and Principal Investigator in the

Donnelly Centre. Yip is also Associate Vice-President, International Partnerships and Professor in the Department of Chemical Engineering and Applied Chemistry and in the Institute of Biomaterials and Biomedical Engineering. "These are exciting times for interdisciplinary, biomedical research. I look forward to following the progress of this year's recipients as they start their research journey," says Yip.

Other members of the award committee were: Professors **William Ryu**, **Quaid Morris** and **Igor Stagljar**, who are all Principal Investigators in the Donnelly Centre.

Some of today's most exciting advances in biomedicine occur at the intersection of biology and computer science in which advanced algorithms help researchers extract meaningful insights from a growing mountain of data. **Shubham Gupta** (Mogen/Röst lab) is creating a computational pipeline to analyze thousands of protein molecules in over 900 blood samples taken over time from more than 100 individuals to find biomarkers which herald diabetes. The study is part of a collaboration with Professor Michael Snyder, of Stanford University, and paves way for more personalized approaches in predicting risk of disease.

"These are exciting times for interdisciplinary, biomedical research. I look forward to following the progress of this year's recipients as they start their research journey"

Cadia Chan (Mogen/Zhang lab) is leading computational analysis in a collaborative project between the Zhang lab in the Donnelly Centre and the group of **Michael Wilson**, Senior Scientist at the Hospital for Sick Children, to uncover how diet influences puberty offset. Chan will do this by analyzing how gene activity changes in parts of the brain involved in regulation of puberty in response to low and high-fat diets.

And **Owen Whitley** (Mogen/Bader lab) has a task of integrating diverse sets of molecular profiling data from brain tumours to find genes involved in cancer onset and progression. In particular, he is focusing on the glioblastoma cancer stem cells which are thought to seed some of the hardest-to-treat brain tumours as part of a large Stand Up to Cancer Canada/Brain Dream Team which includes over a dozen labs in Canada.

Also working with stem cells is **Justin Belair-Hickey** (Mogen/van der Kooy lab) whose focus is on the stem cells in the eye. Belair-Hickey wants to uncover how these stem cells turn into diverse types of retinal cells, such as light-detecting photoreceptors, during development. Also, in collaboration with Professor **Molly Shoichet**, an expert in bioengineering whose lab is also in the Donnelly Centre, Belair-Hickey is looking to develop a method that would allow him to grow photoreceptors from stem cells in the lab as transplant tissue for future cell therapies.

One of the outstanding questions in biology is how cells handle proteins that are faulty. **Kyle Wang** (Mogen/Andrews and Boone labs) wants to shed light on this process by identifying genes that regulate proteins' three-dimensional shape which is crucial for their function. Wang is taking advantage of the powerful large-scale genetics platform in the Donnelly Centre which uses yeast cells to uncover global genetic networks behind basic cellular processes.

Urvi Bhojoo (Mogen/Andrews and Boone labs) is also working with yeast cells but her goal is to develop a new technology for matching drug compounds to their target molecules in the cell. Finding how drugs work on the molecular level is a major challenge in pharmaceutical industry and Bhojoo's approach, based on the gene editing technology CRISPR, has the potential to accelerate discovery of new medicines.

Even when promising drugs have been identified, getting them into the right place in the body can be difficult. Nanoparticles have the potential to overcome this obstacle by delivering drugs directly into tumours for example, and other hard-to-reach parts of the body. However, once infused into the bloodstream, these synthetic vesicles don't behave as expected because they get coated by plasma proteins. **Yuwei Johnny Zhang** (Chemistry/Chan lab) will identify the proteins that interfere with nanoparticle function to help improve their design.

The Cecil Yip Doctoral Research Award was established in 2015 as a tribute to Professor **Cecil Yip**, who was the former Vice-Dean, Research in the Faculty of Medicine and a key player in both the ideology and eventual realization of the Donnelly Centre as an interdisciplinary institute at the forefront of biomedical research.

MEET OUR OUTSTANDING POSTDOCTORAL FELLOWS AND RESEARCH ASSOCIATES

Meet Jiabao Liu from Henry Krause's lab who won the Charles H. Best Postdoctoral Fellowship.

Photo by Donnelly Centre

Meet Jiabao Liu, the 2018 Charles H. Best Fellow

By Jovana Drinjakovic
February 5, 2018.

Jiabao Liu is not one to shy away from a challenge. After graduating in pharmaceutical science with honours from Harbin University of Commerce, in north east China, Liu decided he wanted to get a PhD. But instead of casting a wide net by applying to several graduate schools, Liu applied to only one— Peking Union Medical College, the most prestigious of its kind in China. If he did not get in, he would have to wait another year to reapply, his family repeatedly pointed out to no avail. In the end, Liu fought off fierce competition and made history as the first student from his university to go to the nation's top medical school.

Liu is this year's winner of the Charles H. Best Postdoctoral Fellowship, awarded annually by the Charles H. Best Foundation to an exceptional postdoctoral researcher in the Donnelly Centre.

"It is a great honour for me to get the Best award. It will inspire me to continue discovering new and key molecules for life," Liu said.

Eight years after graduating from university, Liu is facing a different kind of challenge. As a postdoctoral researcher in Professor **Henry Krause**'s lab, his goal is to shed light on molecules called nuclear receptors

(NRs) which have been linked to a range of diseases, from hormonal and immune disorders to biological clock misregulation, obesity, diabetes and fatty liver disease. Despite their vital role in health, exploring NRs on a molecular level has been difficult because the right technology was lacking. But with skill and a little luck, Liu reckons he can now make headway.

In the two years since joining Krause's lab, using the know-how acquired during graduate training in medicinal chemistry, Liu has vastly improved the method for isolating NRs from living tissue in order to study them in more detail.

"Jiabao came to my lab with a very sophisticated knowledge of drug like molecules, how they behave and how to isolate and identify them," says Krause. "When put together with his incredible drive and intuition, he was able to develop powerful new methods that are now identifying exciting new hormones and potential drugs."

" The Best Fellowship will inspire me to continue discovering new and key molecules for life"

Of the 48 human NRs, only about half have been studied in depth. This knowledge has already led to new treatments, such as tamoxifen for example, which acts on estrogen receptor to halt breast cancer. Cellular processes controlled by other, less well studies NRs open the door to finding new medicines for some of the most prevalent diseases of our time, such as diabetes and obesity.

It's only fitting that the Best fellowship was awarded to a researcher following in the steps of Charles Best whose co-discovery of insulin with Frederick Banting in Toronto, in 1921, saved millions of lives of people suffering from childhood diabetes, in which the body does not produce insulin. Almost a century later, however, cases of insulin resistance—as in type 2 diabetes in which the body fails to normally respond to insulin—continue to soar due to unhealthy lifestyle, which calls for new medications.

Like all molecular receptors, NRs directly receive and transmit signals telling cells to alter gene expression in order to grow, divide or change their physiology in any way. But unlike the majority of receptors, which are found on cell surface and rely on molecular middlemen to pass on the signal to the cell's interior, NRs reside inside cells, in the vicinity of the DNA. This means that they can quickly latch on to DNA to turn genes on or off as needed.

Liu's goal is to isolate molecules that bind and activate NRs linked to metabolic disorders, such as insulin resistance, and which could give clues to how these NRs can be targeted by drugs. This type of research is usually done in cultured human cells, which often yields flawed data because cells grown in plastic dishes do not replicate normal body physiology.

To overcome this hurdle, Liu has tuned to zebrafish. The staple aquarium pet is also a coveted research tool— it has a spine, and therefore a similar body plan and physiology as a human, but is at the same time a relatively simple animal and easy to work with in the lab. Previously, the Krause team genetically engineered zebrafish strains so that they express human NRs in their tissue. This allows Liu to use human NRs as bait in order to capture associated molecules in their intact physiological environment.

Despite the challenging project, science does not keep Liu awake at night. His eight-month-old son does. Being a postdoctoral father can be exhausting but Liu remains unfazed about the prospect of his research. "I just don't have free time anymore, and new NR biology is waiting to be discovered" he says, eager to get back to work.

Photo by Thomas Lewandovski

Thomas Gonatopoulos-Pournatzis from the Blencowe lab and Wei Zhang from the Sidhu lab won the inaugural Research Excellence Awards.

Inaugural Research Excellence Awards Recognise Collaborative Science

By Jovana Drinjakovic
September 20, 2018.

The Donnelly Centre is delighted to announce that **Thomas Gonatopoulos-Pournatzis** and **Wei Zhang** are the inaugural recipients of Donnelly Centre Research Excellence Awards. The prize, which will be awarded annually, recognizes outstanding postdoctoral researchers pursuing collaborative and interdisciplinary research.

"We established the Research Excellence Awards to recognize our top postdoctoral fellows and research associates who are tackling important questions in biology through collaborative research both within the Centre and in the wider research community," says **Brenda Andrews**, University Professor and Director of the Donnelly Centre. "Thomas and Wei

are highly deserving first recipients of this award - both have pursued exciting research projects in the Donnelly, which I am confident will form the basis for successful careers as independent researchers."

The decision to reward Gonatopoulos-Pournatzis and Zhang was made by the Selection Committee, whose members are: **Charlie Boone**, Principal Investigator, **Ulrich Braunschweig**, Research Associate in Ben Blencowe's lab, **Laura Prochazka**, **Punit Saraon** and **Nick Stepankiw**, Postdoctoral Research Fellows in **Peter Zandstra**, **Igor Stagljar** and **Tim Hughes**' labs, respectively.

"I'm very honoured that I have been selected for a

Donnelly Centre Excellence Award. It is wonderful to receive this recognition based on highly productive collaborative research projects I have enjoyed working on during the past several years in the Donnelly Centre," says Gonatopoulos-Pournatzis, a postdoctoral research fellow in the Blencowe lab who plans to establish an independent research career to study the genetic basis of brain development and disorders.

During his postdoc, Gonatopoulos-Pournatzis developed a much-needed CRISPR-based tool to study the differential functions of multiple products of genes and to explore the functional relationship between different genes. Thanks to a process known as alternative splicing, there are many more gene products (RNA and protein variants) in the cell than there are genes in the genome. During alternative splicing, segments of the RNA produced from a gene are spliced together in diverse combinations so that one gene can give rise to multiple and functionally distinct protein products. Up until now, there was no effective way to systematically study the function of protein variants but thanks to Gonatopoulos-Pournatzis's new tool this is now possible.

Gonatopoulos-Pournatzis developed the method while working with other labs in the Centre and across U of T. "The best thing about the Donnelly Centre is its highly collaborative atmosphere," says Gonatopoulos-Pournatzis. "My research has highly benefited from a strong collaboration I have established with **Jason Moffat**'s lab. This collaborative environment does not stop at the door step of the Donnelly Centre but expands into the neighbouring institutes," he added referring to his work with **Anne-Claude Gingras**, **Sabine Cordes** and **Graham Collingridge**, Senior Investigators at Sinai Health System's Lunenfeld-Tanenbaum Research Institute and **Melanie Woodin**, Professor at U of T's Department of Cell and Systems Biology.

Gonatopoulos-Pournatzis credits his advisor, Ben Blencowe, for his success. "Ben is a remarkable scientist and also a great mentor," he says.
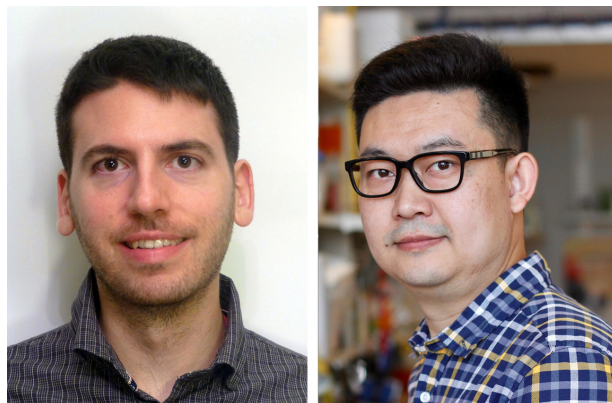
Thomas Gonatopoulos-Pournatzis and Wei Zhang

"In Ben's lab I learned to focus on important and timely research questions and to establish collaborations so as to bring expertise from different fields into my own research as required."

Wei Zhang won the Research Excellence Award for the research conducted jointly in Professors **Sachdev Sidhu** and Jason Moffat's labs where he was first a postdoctoral research fellow and then a research associate. As a protein engineer, Zhang developed a new tool that allowed him to target precise proteins in cells to, for example, spur enzymes into action or switch them off altogether. The tool has already shown promise in creating potential new anti-viral and anti-cancer therapeutics.

During postdoc, Zhang received prestigious awards for his protein engineering work, including a Mitacs Outstanding Innovation Award and a Next Generation of Scientist award from the Cancer Research Society and forged a number of collaborations in Canada and abroad.

Zhang has since moved on to the University of Guelph where he established an independent research group in which he will continue to apply protein engineering to studying cancer and developing new therapeutics.

NEW TOOLS FOR DETECTING AND TREATING DISEASE

Cancer cells, National Cancer Institute
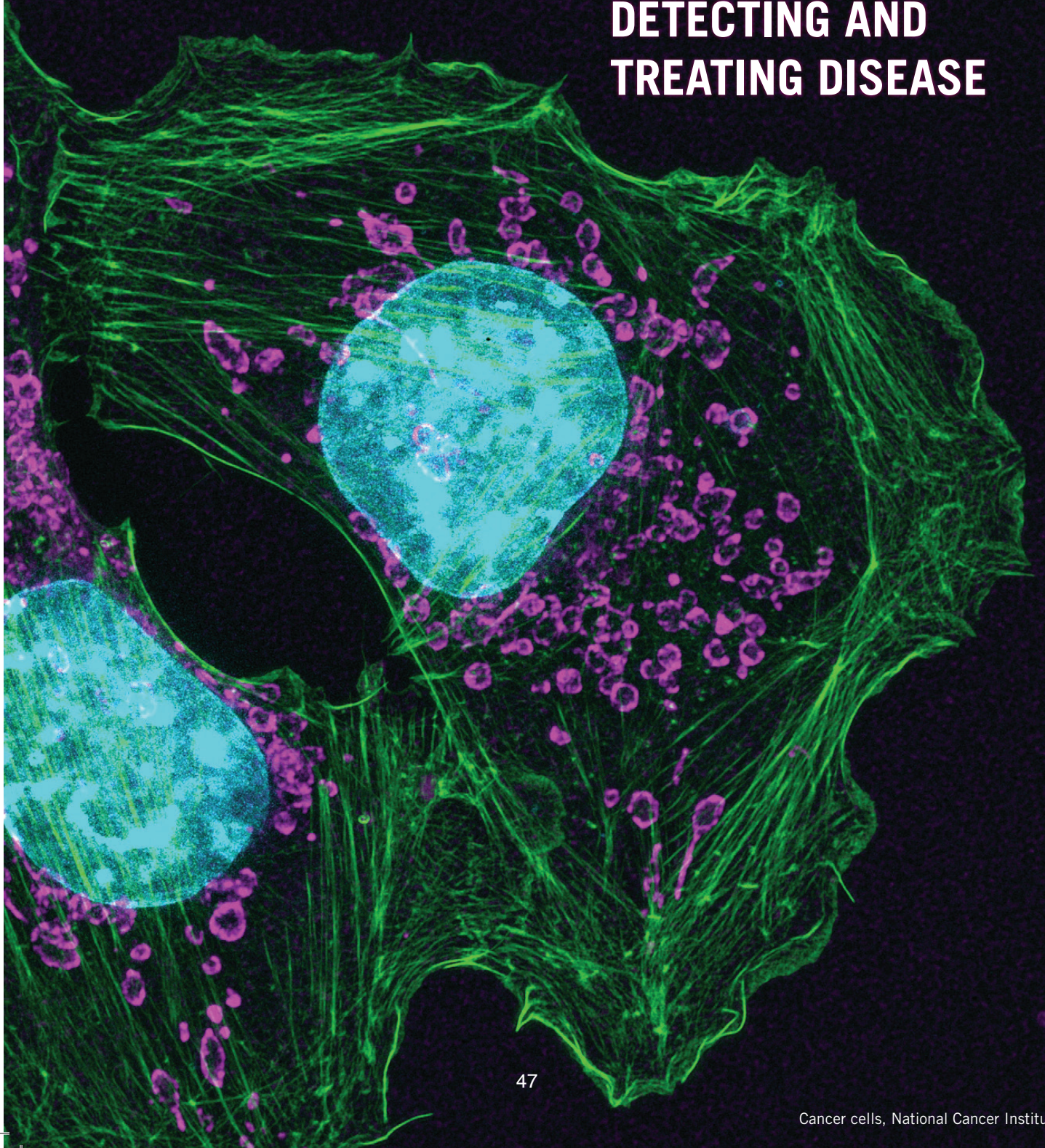
U of T's Faculty of Medicine has designated research space for the Accelerator for Donnelly Collaboration dedicated to translating discoveries made in the Centre into new patient therapies.

Terrence Donnelly's Gift Comes to Life as Construction Begins on New Biotech Hub

By Jovana Drinjakovic
December 20, 2018.

A revamped research space at the heart of the main University of Toronto campus will house the Accelerator for Donnelly Collaboration (AcDC), a state-of-the-art catalyst hub for biotechnology innovation and commercialization.

"The Accelerator for the Donnelly Centre enhances our capacity to continue advanced biomedical research and to increase the number of world class researchers at the Donnelly Centre," says **Terrence Donnelly**, whose generous $10 million gift is helping fund its construction and whose initial gift helped found, in 2005, the Centre as an interdisciplinary biomedical research institute.

By providing a home to startup companies, and for scientists collaborating with Donnelly investigators, the AcDC will accelerate translation of research discoveries made in the Centre into new therapies while helping boost innovation, create jobs and retain research talent in Canada.

"The Toronto community is comparable to biotech hubs like Boston and the San Francisco's Bay Area in terms of its academic research strength, but more programs are needed to help build and sustain a vibrant biotechnology sector," says **Brenda Andrews**, University Professor and Director of the Donnelly Centre. "The AcDC will house key technology platforms established by Donnelly investigators, and provide space for interested scientists from

the biotech sector to work directly with Donnelly scientists on new research projects".

"By bringing together the very best of private enterprise and academia, the AcDC will speed up breakthroughs in research leading to new drugs for today's patient population and generations to follow"

The AcDC was also made possible thanks to U of T's Faculty of Medicine, which designated a space for it on the fourth floor of the Medical Sciences Building, adjacent to the Centre. The existing research space is being renovated to convert it to the CL2 safety level for mammalian cell culture work and to accommodate robotics and other key infrastructure, with construction work ending by spring 2019.

In the 13 years since the Donnelly Centre was founded, its scientists have made important insights into how genes influence health. This research is helping pave the way for personalized medicine in which a person's genetic make-up can be used to predict risk of disease and tailor treatment that's right just for them. For example, using genome data, Donnelly Centre researchers have already developed a more effective way of targeting under-treated and highly lethal pancreatic cancer, and have provided compelling data that has set the stage for potential human trials. The AcDC will catalyze these types of discoveries, which promise to produce tangible advances that will help patients.


Mr. Terrence Donnelly

Part of the income generated by the AcDC thorough industry partnerships will feed back into the Donnelly Centre, ensuring that its scientists can continue to make important foundational discoveries and recruit the best researchers.

The AcDC will also provide space to the Toronto Recombinant Antibody Centre (TRAC) and Platform for Advanced Cell Engineering (PACE), the Centre's flagship technology platforms for antibody and cell engineering, respectively. As a result, many groups that are working with the TRAC and the PACE will now have a rapid means to continue translational research through the AcDC.

"This new Accelerator means the distance between research bench and patients' bedside will be shortened again. By bringing together the very best of private enterprise and academia, the AcDC will speed up breakthroughs in research leading to new drugs for today's patient population and generations to follow," says Donnelly.

Logo of the Donnelly Centre's biotechnology hub expected to launch in 2019.
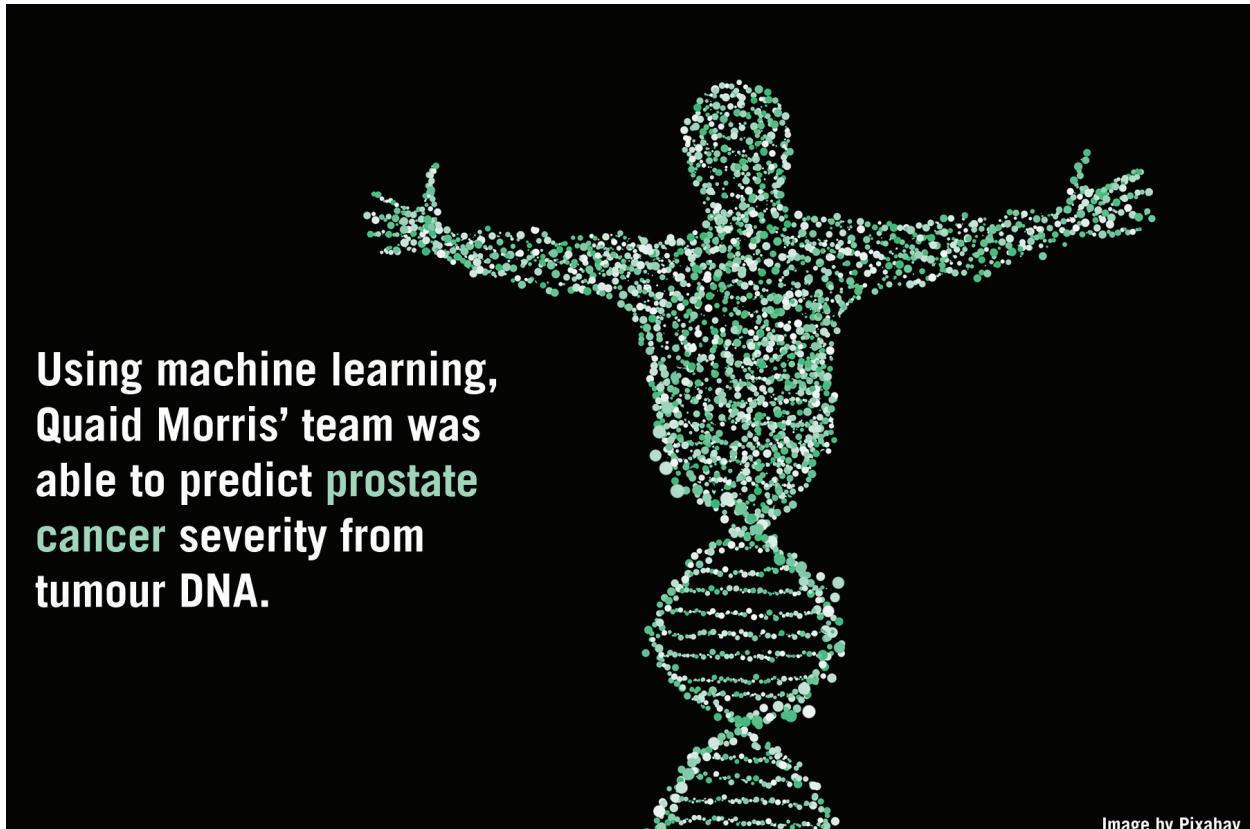
Using machine learning, Quaid Morris' team was able to predict prostate cancer severity from tumour DNA.

Machine Learning Links Tumour Evolution to Prostate Cancer Severity

By Ontario Institute for Cancer Research and Prostate Cancer Canada
April 19, 2018.

Findings from Canadian Prostate Cancer Genome Network (CPC-GENE) researchers and their collaborators, published today in *Cell*, show that the aggressiveness of an individual prostate cancer can be accurately assessed by looking at how that tumour has evolved. This information can be used to determine what type and how much treatment should be given to each patient, or if any is needed at all.

The researchers analyzed the whole genome sequences of 293 localized prostate cancer tumours, linked to clinical outcome data. These were then further analyzed using machine learning, a type of statistical technique, to infer the evolutionary past of a tumour and to estimate its trajectory. They found that those tumours that had evolved to have multiple types of cancer cells, or subclones, were the most aggressive. Fifty-nine per cent of tumours in the study had this genetic diversity, with 61 per cent of those leading to relapse following standard therapy.

"Tumours are a community of related cancer cells, and by examining their DNA using machine learning, we can gain insight into how they evolved from normal cells. In this paper, we show that the past evolutionary history of a tumour helps predict whether that tumour will progress into an aggressive form," says Professor **Quaid Morris**, of the Donnelly Centre, who collaborated with the CPC-GENE team on the study.

"By incorporating time into the context of the existing knowledge we have about where a tumour is

at diagnosis we were able to very accurately identify those patients whose prostate tumours needed no treatment, those men who could be cured by existing treatments, and those men who had very aggressive tumours and may have benefitted from novel therapeutic options," says **Paul Boutros**, Principal Investigator, Ontario Institute for Cancer Research and leader of CPC-GENE.

"Clinical decision making in treating prostate cancer can be very difficult. These findings pave the way for a new tool to improve our ability to determine the best approach for each individual patient, including sparing patients from unnecessary treatment or over-treatment and the associated side effects," says Professor **Robert Bristow**, Director of the Manchester Cancer Research Centre at the University of Manchester U.K., formerly of the Princess Margaret Cancer Centre in Toronto.

"These findings pave the way for a new tool to improve our ability to determine the best approach for each individual patient, including sparing patients from unnecessary treatment or over-treatment and the associated side effects"

"Prostate cancer is the most common cancer among men," says **Reza Moridi**, Ontario's Minister of Research, Innovation and Science. "Ontario congratulates this research team, whose work is pointing the way toward improved testing and treatment."
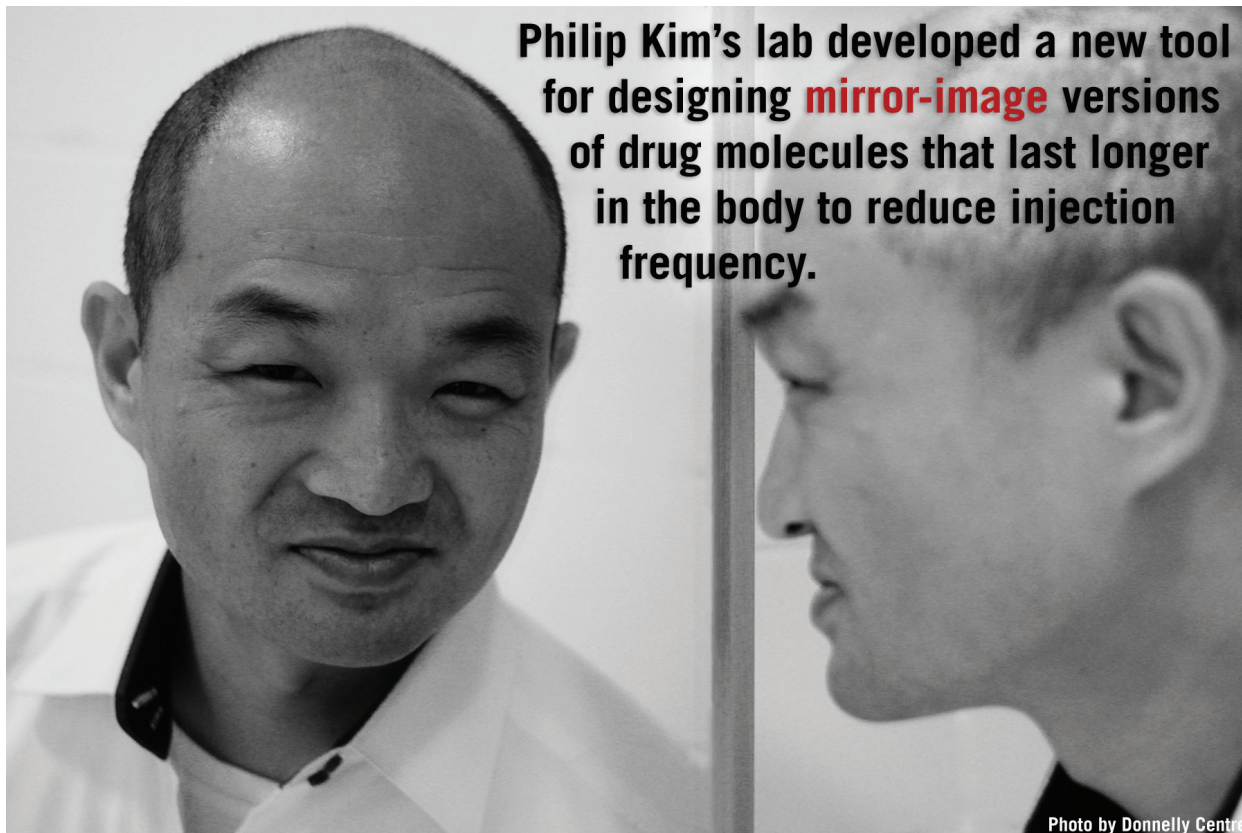
The study's findings are not its only contributions to prostate cancer research. The sequencing data generated during the course of the study are now freely available online to researchers worldwide to carry out further analyses, becoming the largest prostate cancer genomics resource available to-date.

Professor Quaid Morris, Donnelly Centre

CPC-GENE is a team of multidisciplinary researchers from across Canada working to crack the genetic code of prostate cancer. Through funding of approximately $20 million, research of this magnitude has been made possible through a partnership between the Movember Foundation, Prostate Cancer Canada, and the Ontario Institute for Cancer Research. Dr. **Stuart Edmonds**, Vice-President of Research, Health Promotion and Survivorship at Prostate Cancer Canada, has released the following statement:

"From the tireless work of researchers to the selfless giving of donors, we applaud the efforts of everyone who has played a role in helping make CPC-GENE possible. Since its beginnings as an ambitious undertaking that was massive in scope, the goal of this project has been to greatly improve personalized care for men with prostate cancer. The findings published in *Cell* – widely considered one of the most prestigious and highest impact medical journals – represent a monumental stride towards that goal. Together, we will continue to advance this important work on behalf of the one in seven Canadian men who will be diagnosed with prostate cancer and their families."

Philip Kim's lab developed a new tool for designing mirror-image versions of drug molecules that last longer in the body to reduce injection frequency.

Photo by Donnelly Centre

Through the Looking Glass: Scientists Create Mirror-Image Molecules to Develop Better Medicines

By Jovana Drinjakovic
January 29, 2018.

When Alice stepped through the looking glass, she discovered a fantastical world. Unlike that dream world in Lewis Carrol's novel, the world of mirror-image molecules is very much real and it could lead to better medicines.

Mirror-image versions of existing drugs last longer in the body because they are harder to digest. For patients, this would mean less frequent drug injections and more medicines could potentially be made available as pills.

Designing these drugs has been tricky, however.

Now a team of researchers led by **Philip Kim**, a professor of computer science and molecular genetics in the Donnelly Centre, has developed a new technology for making mirror-image peptides, which bind and activate receptors on the surface of cells. They created mirror-image versions of two blockbuster drugs, a diabetes medication called glucagon-like-peptide 1 (GLP1) and parathyroid hormone (PTH), a common treatment for osteoporosis. In studies, both mirror-image counterparts had longer effects on cells than the existing drugs.

The findings are described in a study published

today in an early online edition of the Proceedings of the National Academy of Sciences.

"Mirror image peptides are not recognized and degraded by enzymes in the stomach or bloodstream and therefore have a long-lasting effect," says Kim. The other advantage, he said, is that mirror-image peptides also get overlooked by the immune system, which often mistakes natural peptides for foreign invaders and thus limits drug efficacy.

> *"For frequently dosed medication, mirror-image peptides are of great interest, as taking a pill is much easier than having an injection"*

Peptides are made from molecules called amino acids. For reasons that are not fully understood and which go back to the origin of life, almost all amino acids in the natural world occur in one geometric form. Their atoms are arranged in such a way that makes the entire amino acid molecule appear left-handed, or "L" for short, which means that natural peptides are also left-handed. Because peptides produced by microbes, plants and animals can be harmful, the human body has evolved efficient ways to purge them.

But if you inverse a peptide, by making a mirror-image of it, it can still bind correct receptors while sliding unnoticed past the body's defense mechanisms. Mirror image peptides can be made in the lab from synthetic right-handed amino acids, which are also known as "D" for dextrorotary.

Unlike straight L peptides, which can be fairly easily converted to a D form, most biologically active peptides are twisted into helices, and so far there has been no good way to design their mirror-image counterparts on a large scale, said Kim.

Using a purely computational approach, Kim's team was able to clear this obstacle. They started with the largest public database which contains structural information for three million helical peptides. They then created an algorithm to flip these peptides into their D versions. Finally, the team looked in this new virtual library of mirror-image peptides for those that best matched GLP1 and PTH.

Once they found the match, the researchers had the D-peptides synthesized and tested for their ability to activate their receptors on the cell's surface. They found that both D-GLP1 and D-PTH elicited cellular responses similar to their natural counterparts but had a longer-lasting effect.
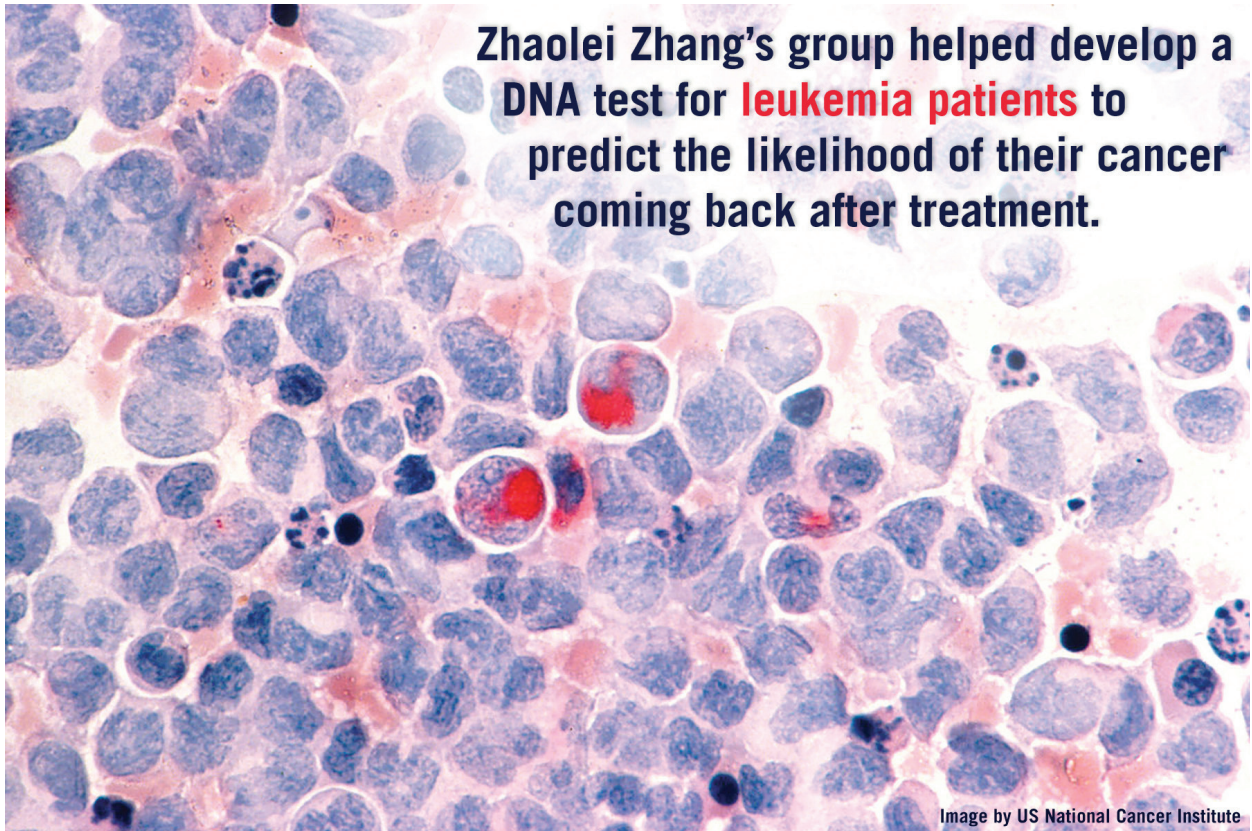
"We are now investigating whether the D-PTH could be orally delivered because it is avoiding breakdown in the stomach", says Kim. "For frequently dosed medication, this is of great interest, as taking a pill is much easier than having an injection. This could lead to many more peptide drugs being taken as pills".

Currently, patients who take GLP1, which was discovered at U of T by Professor **Daniel Drucker**, of the Department of Medicine and Sinai Health System, or PTH, must inject these drugs on a daily basis.

Kim is working with the U of T patent office to protect his technology as he explores opportunities to partner with the pharmaceutical industry to commercialize the research. He is also developing mirror-image versions of peptides that work against the Dengue and Zika viruses in order to make them more durable in the bloodstream.

"We are testing our approach on as many interesting peptides as we can," Kim said.

Zhaolei Zhang's group helped develop a DNA test for leukemia patients to predict the likelihood of their cancer coming back after treatment.

Image by US National Cancer Institute

DNA Test Predicts Likelihood of Leukemia Relapse After Bone Marrow Transplant

By Jovana Drinjakovic
Sep 6, 2018.

Donnelly Centre researchers have helped develop the first DNA-based test that will allow physicians to tell which patients with acute myeloid leukemia, or AML, will relapse after receiving full treatment consisting of chemotherapy and a bone marrow transplant. The findings, published recently in the journal *Blood*, could help doctors improve patient outcome by changing the treatment before cancer has returned in full force.

"We can detect mutations in patients' bone marrow cells three weeks after the transplant and based on that predict the likelihood of their relapse," says **Zhaolei Zhang**, Principal Investigator in the Donnelly Centre and a professor in the Departments

of Molecular Genetics and Computer Science, who co-led the study.

AML is the most common type of leukemia in adults, comprising about one quarter of all cases. It affects the bone marrow, the spongy tissue inside the bone where all blood cells are made. The disease stems from an overproduction of immature blood cells which over time outgrow normal blood cells. It's a type of cancer which starts suddenly and progresses quickly, requiring urgent treatment.

Treatment involves chemotherapy to wipe out the diseased bone marrow, followed by a bone marrow transplant to reconstitute the patient's blood with

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cells from a healthy donor. While most patients go into remission after chemotherapy, about one third will relapse three to six months after receiving the transplant.

"In AML, it is very important to predict who is going to relapse, "says **Dennis Kim**, of the Princess Margaret Cancer Centre, at the University Health Network (UHN) and Associate Professor in U of T's Department of Medicine and a co-leader of the study. "If we are able to identify someone who is at high risk of relapse then we can do therapeutic intervention earlier which can improve their outcome in the long run."

"We can detect mutations in patients' bone marrow cells three weeks after the transplant and based on that predict the likelihood of their relapse"

Until now, there was no good way to detect the trace amounts of leukemia cells which resisted the treatment and which drive relapse. By the time these cells are picked up by available methods, the cancer is usually already at an advanced stage.

Using new DNA sequencing technology called next generation sequencing, or NGS, the team was able to identify the treatment-resistant leukemia cells, or clones, even when they make up a tiny proportion of all cells in the bone marrow. The nature of mutations reveals further clues about how best to target the disease with drugs.

"With our method, not only can we say that this patient will relapse, but we can also say their relapsing clone contains certain mutations which can be a target for therapeutic compounds that can be used to treat the patient," says Kim.

For the study, the researchers collected 529 bone marrow samples from 104 AML patients who underwent chemotherapy and bone marrow transplant. The samples were collected at different time points: at the time of diagnosis, during the chemotherapy-induced remission, and three weeks after the bone marrow transplant. A subset of patients also gave samples three, six and twelve months after the transplant. Some samples were also taken from bone marrow donors to rule out the possibility that the leukemia cells were introduced by the transplant.

The researchers then identified DNA mutations which were present at the time of diagnosis and looked for those same mutations at each sampling point. They found that while chemotherapy and bone marrow transplant eliminated most leukemia cells, revealed by a drop in detectable harmful mutations, some disease driving mutations still lingered three weeks after the transplant, indicating the presence of treatment-resistant cells. Further analysis revealed that the same cancerous cells that started the leukemia are also responsible for the disease comeback.

Data analysis required Zhang's team to develop new computational tools to parse the leukemia-driving mutations from a sea of DNA sequence data. This allowed them to identify low residual mutation frequency of 0.2 per cent to use as a surrogate marker for giving a personal chance of relapse.

"Patients who had a mutation burden greater than 0.2 per cent were four times more likely to relapse than patients who had a lower burden or no mutation burden," says **TaeHyung (Simon) Kim**, a computer science graduate student in Zhang's lab who analyzed the data.

The researchers hope their DNA-based test will become routine for monitoring disease prognosis although they say this could take five to ten years.

A lab-on-a-chip device developed by Aaron Wheeler's group brought vital molecular diagnostics to rural Kenya.

Photo by Alphonsus Ng

Lab-on-a-Chip Delivers Critical Immunity Data for Vulnerable Populations

By Marit Mitchell
April 26, 2018.

For millions of displaced people around the world — many of them refugees, living in temporary shelters under crowded conditions — an outbreak of disease is devastating. Each year, the measles virus kills more than 134,000 people globally, and another 100,000 children are born with defects caused by congenital rubella syndrome. Both diseases are preventable by vaccination.

Now, a team of researchers from the University of Toronto, including Donnelly Centre and IBBME alumni **Alphonsus Ng** and **Ryan Fobel**, has applied a hacker mentality to developing a portable, reconfigurable lab-on-a-chip diagnostic platform and field-tested the system in remote Kenya. Their validated platform can gauge the level of immunity

to vaccine-preventable diseases among vulnerable populations. Their work appears today in the journal *Science Translational Medicine*.

"We found that our low-cost device matched the international laboratory-standard reference tests of the Kenyan Medical Research Institute for 86 per cent of measles samples, and 91 per cent of rubella samples," says **Darius Rackus**, one of the authors of the paper.

These results underscore their platform's potential to help identify populations susceptible to epidemics in remote or under-resourced locations.

"Our platform is inexpensive, fast and flexible —
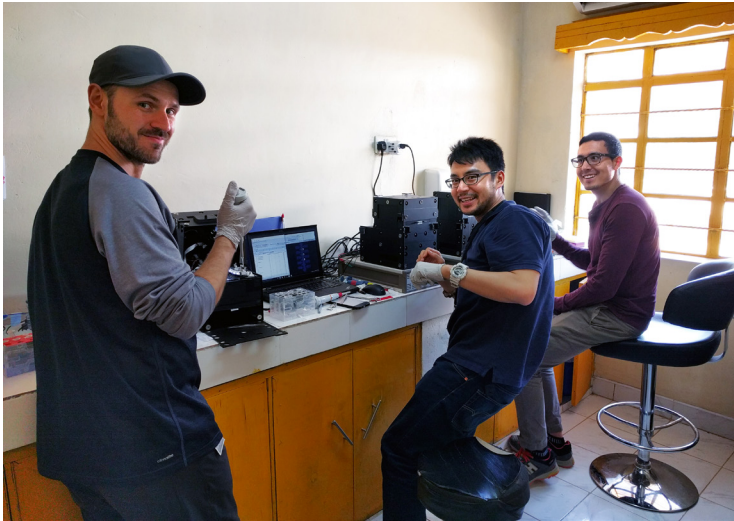
Members of the "Away Team" Christian Fobel, Alphonsus Ng and Julian Lamanna run blood tests on their portable lab-on-a-chip instruments, called the MR Box, in their temporary lab at the Kakuma refugee camp in Kenya.

there's nothing like it out there," says Rackus. "We see it as a powerful tool for public health workers on the front lines, who have no access to health records, or may be dealing with humanitarian emergencies."

Rackus and his team, led by **Aaron Wheeler**, a professor in the Donnelly Centre, U of T Chemistry and IBBME, are world leaders in the area of digital microfluidics, a technique used to move, split, recombine and mix miniscule droplets of liquid all on a tiny 'chip.' The chips are made using low-cost fabrication techniques such as ink-jet and 3D printing, and the droplets are controlled by applying electrical signals to different electrodes.

In June 2016, four members of the Wheeler Lab travelled to the Kakuma refugee camp in northwestern Kenya to validate their platform, dubbed the MR Box — a desktop lab the size of a toaster oven configured to test for measles and rubella.

They arrived in Kakuma following a massive public-health immunization campaign and tested hundreds of children and their caregivers for the presence of molecular markers indicating disease immunity. They then sent their samples to the Kenyan Medical Research Institute national laboratory in Nairobi for validation.

"For the first time taking digital microfluidics out

of the lab, this is phenomenal result," says Julian Lamanna, one of the paper's authors and a member of the team who was on the ground in Kakuma. "In future, with simple statistical analyses our point-of-care system could be used to monitor the levels of immunity within dynamic populations, helping prevent outbreaks before they happen."

"If you could distribute these devices at airports or points of entry around the world, they could become a powerful tool for disease surveillance and monitoring," adds Rackus. "They also have the potential to significantly reduce the burden on expensive and sophisticated diagnostic labs that currently do all these epidemiological tests."

Since the trip to Kakuma, the team has taken MR Boxes for additional testing in the Democratic Republic of the Congo. They are also developing new chips to test for different markers and diseases, including zika and malaria.

"What we've demonstrated is a universal platform — our microfluidic chips are relatively generic, and highly customizable," says Wheeler. "Now that we've seen how practical it is in the field, we want to adapt it to as many diseases and environmental conditions as we can."

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

Donnelly grad's startup **Phenomic AI** raised US$1.5 million to bring computer vision to drug discovery.

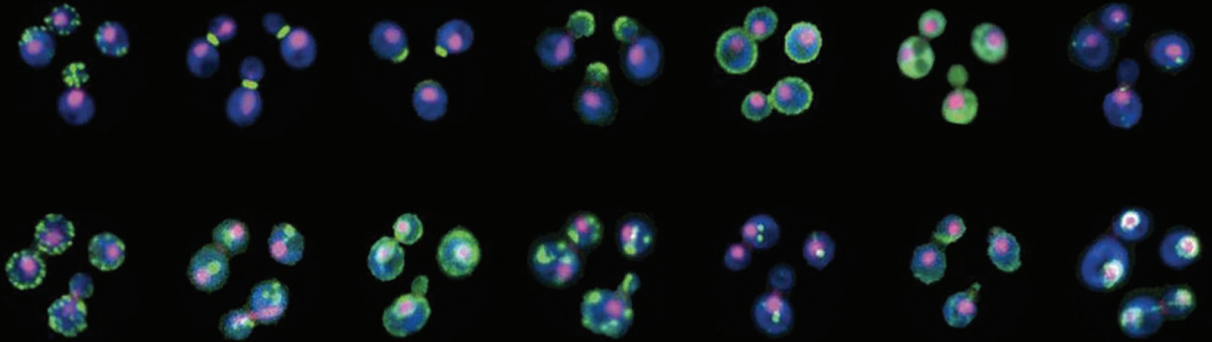## Donnelly Grad's AI Startup Raises US$1.5 Million to Accelerate Cancer Drug Discovery

By Jovana Drinjakovic
June 19, 2018.

Oren Kraus took up coding because, by his own admission, he was not cut out for doing experiments in the lab. Now his artificial intelligence-powered startup has raised US$1.5 million to transform biomedical research and drug discovery.

Called Phenomic AI, the startup develops computer vision tools for a faster and more accurate analysis of microscopy data. Its name comes from the word "phenotype," which biologists use to describe how a cell – and its inner parts – look. The tools developed will help researchers spot subtle differences between cells that could be early signs of disease and identify promising drugs.

"We're able to apply deep learning to microscopy datasets," says Kraus, who will receive his PhD on Tuesday. His graduate research was co-supervised by University Professor **Brenda Andrews**, who is also Director of the Donnelly Centre and a pioneer in large-scale cell microscopy research, and Professor **Brendan Frey**, of the department of electrical and computer engineering. Frey is also a founder of Deep Genomics, a startup using AI for interpretation of genome data.

"Our method can be used to distinguish between cells that are growing normally from those that are not, but also for finding out whether or not a drug

is working when applied to cells in culture," says Kraus. "The great thing is that our technique can be widely applicable to almost any type of disease."

Launched in 2017, the company already has several partnerships with academia and industry. Working with Ran Kafri, a scientist at the Hospital for Sick Children and assistant professor in the department of molecular genetics, Kraus and the team are developing an algorithm that can recognize slight changes in cells as they become cancerous. They are also helping a major microscope manufacturer improve its widely used data analysis software.

"We're excited about the potential of AI-based technologies to accelerate drug discovery and lead to much needed medicines for devastating diseases"

In deep learning, a form of artificial intelligence, computers learn to recognize patterns from reams of data – millions of images in the case of computer vision. Images of cells hold clues about what makes them healthy and how they change during disease. However, advances in automated microscopy preceded those in computer vision, which means that researchers are able to acquire the data much faster than they can make sense of it. As a result, in many labs across the world researchers still analyze their data by eye, which can take months.

Phenomic AI seeks to bridge the gap between the time it takes to gather the data and draw insights from it. The company's technology is based on a software called DeepLoc, which Kraus created during his PhD. Faster and more accurate than the human eye, the algorithm can quickly sort cells into distinct categories based on how protein molecules are distributed inside the cells. For his research, Kraus won a prize for the best doctoral thesis in the Donnelly Centre.

"I am very thankful to my supervisors for providing me with the opportunity to work on exciting research problems at the intersection of computer vision, machine learning, cell biology, and genetics," says Kraus. "In Andrews and Frey labs, we really started the deep learning revolution in microscopy data and there's been a lot of interest from pharma and biotech companies since."

"Leaving that behind following my PhD seemed to be a waste, so the motivation was really to continue leading the field and to use these technologies to accelerate drug discovery."

After launching Phenomic AI, Kraus secured seed funding of US$500,000 and entered the mentorship program at the Creative Destruction Lab (CDL) at U of T's Rotman School of Management. **Sam Cooper**, another co-founder, joined Kraus in Toronto last October after completing a PhD at the Institute for Cancer Research in London, U.K. The pair had met in 2016 during a workshop at Harvard University that brought together the small community of researchers – about two dozen – who were working at the crossroads of computer vision and microscopy.

Kraus and Cooper recently secured support from several AI and biotechnology investors to boost the total investments to US$1.5 million.

Phenomic AI, which started with a couple of guys working in Kraus' living room, now has nine employees, five of whom are recent U of T grads. In May, the company moved to JLABS, the biotechnology incubator founded by the pharmaceutical giant Johnson & Johnson, which provides research space and infrastructure to startups at the Toronto MaRS Discovery Tower.

"It's amazing to have the opportunity to continue developing the pioneering research conducted during my PhD," says Kraus. "Doing so with the talented interdisciplinary team we've built is even more rewarding. We're excited about the potential of AI-based technologies to accelerate drug discovery and lead to much needed medicines for devastating diseases."

COLLABORATION HIGHLIGHTS

A spotlight on recent technology upgrades that will ensure our researchers stay at the leading edge of discovery.

Photo by Tom Arban

Spotlight on Major Technology Upgrades in Donnelly Centre

By Jovana Drinjakovic
December 20, 2018.

In 2018, the Donnelly Centre acquired new high-end DNA sequencing instruments and microscopes and also launched the facility for mass-spectrometry analysis. While ensuring the Centre's researchers remain at the leading edge of discovery, these advances also present new opportunities for collaboration within the Centre and other research labs in Toronto.

Donnelly Sequencing Centre gets state-of-the-art new sequencer

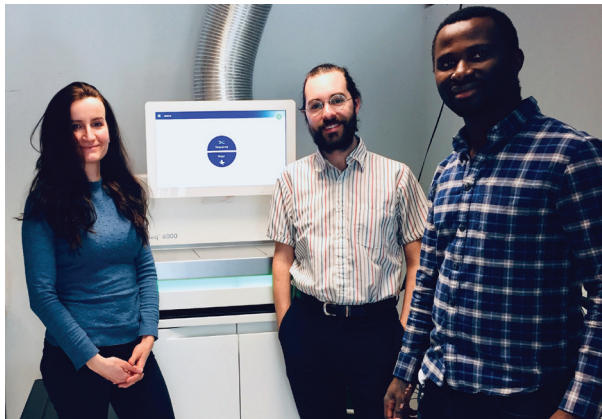Founded in 2010, the Donnelly Sequencing Centre provides broad expertise in DNA and RNA sequencing technologies to labs in the Centre and external collaborators. The facility operates at cost and is the only Illumina Certified Service Provider of Next Generation Sequencing in Toronto. .

Thanks to a $5.6M grant from the Canada Foundation for Innovation and the Ontario Research, awarded to Donnelly Centre Director **Brenda Andrews**, the Centre was able to add a NovaSeq6000 system, a top of the line sequencer, to its suite of instruments consisting of Illumina HiSeq2500, NextSeq500, and MiSeq platforms. The new instrument can sequence 60 complete human genomes in 44 hours, at a cost of $1,500 CAD each. The DSC has also recently purchased 200 TB of additional computer server space to handle the substantial amount of increased

data produced by the DSC with its new infrastructure.

"As Director of the DSC I am very proud of the outstanding team we have assembled, including **Tanja Durbic** (DSC Coordinator), **Kyle Turner** and **Michael Forbiteh**, who have produced high quality sequencing data for over a hundred sequencing projects during the past year, and with record turnaround times," says Professor **Ben Blencowe**, DSC Director. "A unique capability of the DSC is its ability to work with clients to develop custom sequencing protocols to foster innovative research projects. As an example, the DSC has developed custom sequencing protocols to enable new genome-wide CRISPR-based screens and this area will represent an ongoing major focus of the Centre's work during 2019."

Tanja Durbic, Kyle Turner and Michael Forbiteh with the NovaSeq6000 at Donnelly Sequencing Centre.

In 2018 alone, the DSC helped researchers: discover a network of more than 200 genes linked to autism, through a project led by **Thomas Gonatopoulos-Pournatzis** in the Blencowe lab; assemble the world's first cannabis chromosome map, led by **Kaitlin Laverty** in the Hughes lab; and map epigenetic changes linked to telomere maintenance and cancer, in collaboration with **Uri Tabori**'s lab at the Hospital for Sick Children. Overall, the DSC has ongoing projects with 22 research groups in the Centre with more than 120 external collaborations.

Other contributions, from **Aaron Wheeler** and **Fritz**

Roth, of the Donnelly Centre, and **Brian Cox**, of U of T's Department of Physiology, have brought in another Illumina MiSeq instrument to complement the NovaSeq6000 system, allowing the DSC team to accommodate users with smaller-scale projects, and extended the lifespan of the existing infrastructure.

"These new developments in the DSC have allowed us to simultaneously expand the scale of sequencing projects, reduce costs and turnaround times, and as a consequence maintain our competitive edge in the broader community," says Durbic.

New imaging equipment

Donnelly investigators also leveraged the infrastructure grant described above to acquire two new live-cell imaging instruments: a fully automated Opera Phenix microscope for high throughput imaging studies and a VT-iSIM high speed super-resolution imaging system for visualizing intracellular compartments.

These new instruments, together with existing infrastructure, allow Donnelly researchers to capture thousands of images in a single day to study how genetic mutations, drugs or other environmental changes, such as nutrient availability or temperature, affect basic processes in cells: from protein trafficking, to cell aging and death. For example, the Centre's researchers now have the ability to screen the entire genome-wide collection of yeast mutants— about 6,000 of them— in a single day under the same experimental conditions to ensure robust data collection. In addition to yeast work, ongoing studies also include work on mouse and human cells.

Previously, an older version of the Opera system enabled the Andrews and Boone labs to complete a landmark study that revealed where in the cell each of ~4,000 yeast proteins — almost all proteins produced by yeast— is localized and how it moves about in response to different stimuli. These large-scale image datasets have catalyzed significant collaborations with between computational and experimental biologists, to develop automated methods, involving the latest artificial intelligence algorithms, to identify key features in cell images.
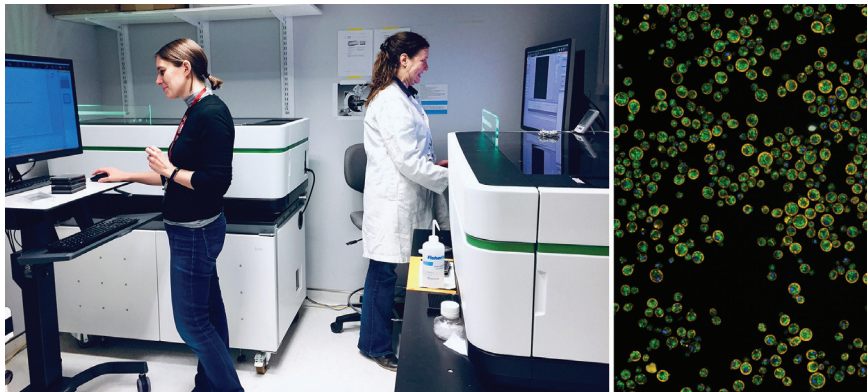
Mojca Mattiazzi Usaj and Helena Friesen working with the two Opera systems, on the left. On the right are yeast cells captured with the new Opera-Phenix that allows simultaneous imaging in four channels— blue, green, red, and far red— to highlight diverse subcellular compartments (Image by Dara Lo).

The new VT-iSIM super-resolution microscope allows zooming in on subcellular structures of interest with a spatial resolution of up to 100nm, about a thousand times smaller than the width of human hair. "This new machine is also faster than standard confocal microscopes, producing images at up to 1000 frames per second, allowing us to monitor multiple fluorophores in real-time," says **Mojca Mattiazzi Usaj**, a research associate in the Andrews lab who is studying how genetic and environmental changes influence morphology of the cell and more than a dozen of its inner compartments.

Newly launched Donnelly Centre facility for mass-spectrometry

Launched earlier in the year, the facility offers expertise in available mass spectrometry technologies and new method development and is open to both Donnelly Centre researchers and external collaborators. The facility is directed by Donnelly Centre researchers, Univeristy Professor **Jack Greenblatt** and Assistant Professor **Hannes Röst**, who are leading experts in mass spectrometry methods and data analysis, while **Edyta Marcon** oversees its daily operations.

"Our aim is to allow different research groups to get access to high-end mass spectrometry instruments as well as expertise and knowledge that we have in the Donnelly Centre to help them answer interesting and complicated questions," says Röst. Ongoing projects include understanding how Epstein-Barr virus infects cells, in collaboration with Lori Frappier,

of U of T's Department of Molecular Genetics, as well as detection of biomarkers for vascular disease, mapping of protein interactions in cells and detection of chemical modifications on proteins that can have profound effects on their function. Greenblatt and Röst are also working to develop methods for detecting chemical modifications on RNA molecules, which help bring DNA code to life, and which have so far remained elusive.

The facility operates at cost and has two first-rate mass spectrometry instruments which can be reconfigured for diverse research needs. With such in-house knowledge, the Centre's researchers no longer have to seek external help making their research faster and cost-effective.

Edyta Marcon pictured beside a mass spectrometry instrument.

A scientific retreat in Niagara-on-the-Lake was an opportunity for Donnelly Centre researchers at all stages of their careers to exchange ideas and build new collaborations.

Highlights from Donnelly Centre's Annual Scientific Retreat

By Jovana Drinjakovic
May 16, 2018.

In early May, Donnelly Centre faculty and trainees traveled to Niagara-on-the-Lake for a two-day retreat, which took place in Queen's Landing, a hotel located by the town's marina. Despite a gloomy weather forecast, the sun welcomed the researchers to a great start.

The goal was to bring together researchers at all stages of their careers in an informal setting in which they can learn about each other's science from across diverse areas of biomedicine and brainstorm ideas for future collaborative projects.

One hundred graduate students and postdoctoral fellows presented their work, 15 of whom gave research talks while the rest were poster presentations spread across two poster sessions. Topics ranged from uncovering fundamentals of genetics and cell biology to drug discovery targeting a variety of diseases: from autism, to parasitic infections to cancer.

This year we had not one but two keynote speakers! Professor **Thomas Nyström**, of the University of Gothenburg in Sweden, gave the first keynote lecture about his research on the molecular basis of aging, which is thought to be driven by accumulation of damaged proteins in the cell. Using an elegant approach in yeast cells, developed by the lab, Nyström's team uncovered previously unknown genes involved in abnormal protein accumulation

with implications for neurodegenerative diseases such as Alzheimer's and Parkinson's.

The second keynote speaker was **Gordon Keller**, Director of McEwen Centre for Regenerative Medicine and a professor in U of T's Department of Medical Biophysics. Keller's talk covered some of his seminal research of working out how to mimic heart development in the dish in order to spur stem cells to form a variety of heart cell types for future application in regenerative medicine. The painstaking work has paid off and Keller is now trying to scale up the production of heart muscle cells, backed by BlueRock Therapeutics, a company he co-founded, so they can be used as transplant tissue for heart damage repair.

Keller was also a member on the science career development panel alongside Donnelly Centre Director and University Professor **Brenda Andrews**, Professor **Philip Kim**, of the Donnelly Centre, and **Dorothea Maetzel**, Senior Scientist at Northern Biologics, a biotechnology company co-founded by Professor **Sachdev Sidhu**, of the Donnelly Centre, which took place on the second day of the retreat.

"Anyone who's enthusiastic and has passion for science has a good chance of succeeding in academia," said Keller, who began his scientific career at the University of Saskatchewan after which he moved several times to Switzerland, Austria and the US, before returning to Canada ten years ago. Andrews urged trainees who wish to remain in academic research to embrace the changing environment and learn new tools as well as take the opportunity to travel to other countries and labs to expand their horizons. "Cultivate your network of mentors, it is always good to have recommendation letters from diverse people," Andrews also said.

Maetzel, who joined Northern after a postdoc at the Whitehead Institute in Boston, MA, emphasized the importance of being a team player when working in industry. The panel agreed that while Toronto lags far behind Boston and San Francisco in terms of

Conference room at Queens Landing Holtel in Niagara-on-the-Lake during a research presentation session.

career opportunities in biotechnology, this is slowly changing.

Kim, who worked for McKinsey & Company consultancy group for two years between his PhD and postdoc, said that the experience allowed him to test the waters of the corporate world with all its pluses, such as salary, and minuses, including the work/life balance. He also said that it's possible to return to research so long as the hiatus is not a long one.

After the gala dinner, Andrews presented the Donnelly Centre awards to outstanding students and postdocs, including the Cecil Yip Doctoral Research Awards, awarded to 10 students in their first year of graduate program who are pursuing highly collaborative research, Jennifer Dorrington Graduate Research Awards, awarded to three students in the Faculty of Medicine working in Donnelly Centre labs, Donnelly Centre Research Prize, awarded for the best doctoral thesis in the past year, and the Charles H. Best Postdoctoral Fellowship, awarded annually to one postdoctoral fellow.

Inspiring the Next Generation of Scientists

By Jovana Drinjakovic
December 15, 2018.

"You mean you can do this as a job?", asked a wide-eyed sixth grader after a fun-filled day of learning about biology at the Donnelly Centre. Her next question was, "How can I become a scientist?"

Sparking an early interest in science is why we run our youth outreach program that draws dozens of primary and high school students to the Centre each year. Among other events, this year the Centre hosted 30 students in sixth grade from Fossil Hill Public School in Toronto. The event was made possible thanks to our graduate students and postdoctoral fellows who took time away from their experiments

to engage with our young visitors, talk about science and help with hands-on activities.

The day kicked off with **Deb Ray** (Hughes lab) giving a fun lecture about the research process itself. Deb stressed the importance of making mistakes—and learning from them— as a driving force of discovery.

The visitors also did their own experiments to learn about genetics. Working with **Yuko Arita** (Boone lab), **Brandon Ho** (Brown lab) and **Clarence Yeung** (Andrews lab), the schoolchildren performed a mating experiment with two different strains of yeast

Fossil Hill students (on the left) and Deb Ray giving an inspiring presentation (on the right).

cells, where each strain was expressing a protein that glowed either green or red. From this emerged baby yeast cells that glowed both green and red in an example of how parental traits mix in the next generation.

Our guests also learned about different cells and tissues in the body. **Nancy Liu** (Morsehead lab) talked about stem cells and how they build different parts of the body, and how researchers like her are working to replicate this process in the lab to grow replacement tissue to treat disease.

Furthermore, our guests learned that studying simple animals can teach us a lot about how the human body works. **Jannatun Wnaiza** and **Jiabao Liu**, both from the Krause lab, brought zebrafish larvae and fruit flies which they, and others in the lab, use in their experiments to glean insights about important

molecules in cells. And, by comparing normal animals with genetic mutants, such as spotted and completely see-through zebrafish larvae, or flies with red and white eyes, the students appreciated the power of genes in determining what the body looks like— and by extension, the health of an organism.

Among other events, we took part in U of T's Bring Our Children to Work Day, an annual event open to our researchers and staff' children in grade four and above. The day provided an opportunity for the kids to isolate their own DNA, while learning about the importance of basic research as a foundation for better medicine and society as a whole.

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

Schoolchildren isolating their own DNA during Bring Our Children to Work Day.

SELECT 2018 NATIONAL AND INTERNATIONAL MEDIA HIGHLIGHTS FEATURING DONNELLY CENTRE RESEARCHERS

- Scientists calculate proteins in a single cell and find 42 million - **CBC News**
- How many protein molecules in a single cell? Go on, guess - **Cosmos**
- Por fin sabemos cuántas moléculas hay en una célula - **El Mundo**
- Simpele gistcel bevat 42 miljoen eiwitmoleculen - **New Scientist** (Dutch edition)

- Mirror Image Compounds Could Help Drugs Last Longer - **Futurism**
- KSIDC to set up bio-park with focus on cancer therapy - **The Hindu Business Line**
- Developing advanced therapeutics for cancer - **The New Indian Express**
- Q&A: Meet Ontario's first Chief Scientist - **Canadian Geographic**

- Repairing the most complex network of all - **Research 2 Reality**
- How Many Genes Do Cells Need? Maybe Almost All of Them - **Quanta Magazine**
- Network of 200 genes linked to autism - **AutismEye**
- Quaid Morris discussed machine learning in cancer research on **Integrate.AI** podcast

- Portable test helps identify refugees at risk of outbreaks - **Washington Post**
- Lab-on-a-chip test could help prevent disease outbreaks in remote regions - **National Post**
- Shoebox-sized lab can diagnose infectious diseases from a drop of blood - **STAT News**
- Aaron Wheeler appeared on **CTV News** to talk about their new diagnostics technology

- It's Like Google Maps, but for Your Cells - **Research 2 Reality**
- Researchers uncover why some cancers grow faster than others - **News Medical**
- Cancro, svelata la proteina che rende i tumori più aggressivi e letali: è un nuovo bersaglio - **Fanpage.it**

- Scientists develop first DNA-based test for predicting risk of leukemia relapse - **News Medical**
- DNA-Test ermittelt Rückfall-Risiko bei Blutkrebs - **Bild**

- Researchers smoke out the genes that give cannabis its kick - **Toronto Star**
- Ancient Viruses Are Probably Why Weed Has THC and CBD - **Vice|Motherboard**
- Ancient viruses inspired THC production in marijuana plants - **United Press International**
- Así es como la marihuana consiguió sus canabinoides - **La Vanguardia**

Dorrington family members visited the Donnelly Centre and met with graduate students who won the Jennifer Dorrington Research Award.

Photo by Nick Moshenko

Donors Meet Students Thriving on Their Gift

By Jovana Drinjakovic

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Research labs do not usually stir up memories of childhood but that's what happened to **Jon Dorrington** and his sister **Emma Karpfinger** on their recent visit to the Donnelly Centre.

As kids, they would often accompany their mom, U of T Professor **Jennifer Dorrington**, to the lab on the weekends as she looked after research animals. Now they were back in the lab albeit a more high-tech one than the antiquated space they remember from decades ago.

Vancouver-based Jon and his wife **Jodie**, got together with Emma, who lives in Germany, in Toronto this past August to meet the 2018 winners of the Jennifer Dorrington Graduate Research Award. Jon and Emma established the award in 2007 in memory of their mother, who passed away in 2001, to recognize outstanding students in U of T's Faculty of Medicine doing research in the Donnelly Centre.

"It was an honour to finally meet Jon and Emma in person," says Professor **Tim Hughes**, who welcomed the donors as the then Acting Director of the Donnelly Centre. "We are grateful for their generous gift that allows us to recognize our students and help them achieve their career goals."

Dr. Dorrington was a professor in the Banting and Best Department of Medical Research, founded in

U of T Professor Jennifer Dorrington with Jon and Emma as children (photo courtesy of Jon Dorrington).

great discussions on the translational potential of our work."

Afshar, who is in Professor **Penney Gilbert**'s group, showcased a device that allows him to study muscle contraction in a dish by measuring tension in stem cell-derived muscles. And Sharma, whose PhD advisor is Professor **Ben Blencowe**, took the visitors to the Center's recently upgraded DNA sequencing center, a key facility she uses often in her research on how cells interpret information in the genome. "It was great talking to the donors about our work and seeing them really excited about it," says Sharma. "And it was great to hear about Dr. Dorrington. She was an inspiring figure and clearly her influence has gone beyond her lifetime."

"It was a great reminder of why we set-up the award – to continue our Mom's spirit of supporting graduate students and their research"

1930 by **Frederick Banting** on the heels of his and **Charles Best**'s discovery of insulin and Banting's Nobel win in 1923. The BBDMR was the first U of T Department relieved from teaching duty allowing its faculty to solely focus on research, something that Dr. Dorrington embraced when she arrived in 1971. Described by her children as extremely passionate about science and hard-working, Dr. Dorrington made foundational discoveries in ovarian physiology and co-founded and directed a company to apply her research.

BBDMR stayed active until the early 2000s when many of its faculty moved to the newly founded Donnelly Centre that was built as a state-of-the-art research institute fit for 21st century biomedical science.

During their visit to the Centre, the donors met with this year's Dorrington award winners: **Eesha Sharma**, **Alexander Vlahos** and **Mohsen Afshar**, who talked about their research projects supported by the Dorrington gift. Vlahos works in University Professor **Michael Sefton**'s lab on a transplantation strategy to counter diabetes. "The donors were fantastic," says Vlahos. "They were very engaging and they stimulated some

"It was a great experience to meet some of the amazing students who have benefited from the award and listen to their passion as they described the incredible innovations driving their research at the Donnelly Centre," says Jon Dorrington. "The experience was a great reminder of why we set-up the award – to continue our Mom's spirit of supporting graduate students and their research."

Over the past 10 years, the Jennifer Dorrington Award has provided nearly $38,000 in financial support for 25 scientists, many of whom went to do postdoctoral training in leading research institutions in the world. These scientists come from a range of research backgrounds with the goal of making discoveries which can transform our understanding of biology and medicine.

WE WISH TO EXPRESS OUR THANKS TO THE FOLLOWING DONORS WHOSE GIFTS HELP ADVANCE OUR WORK:

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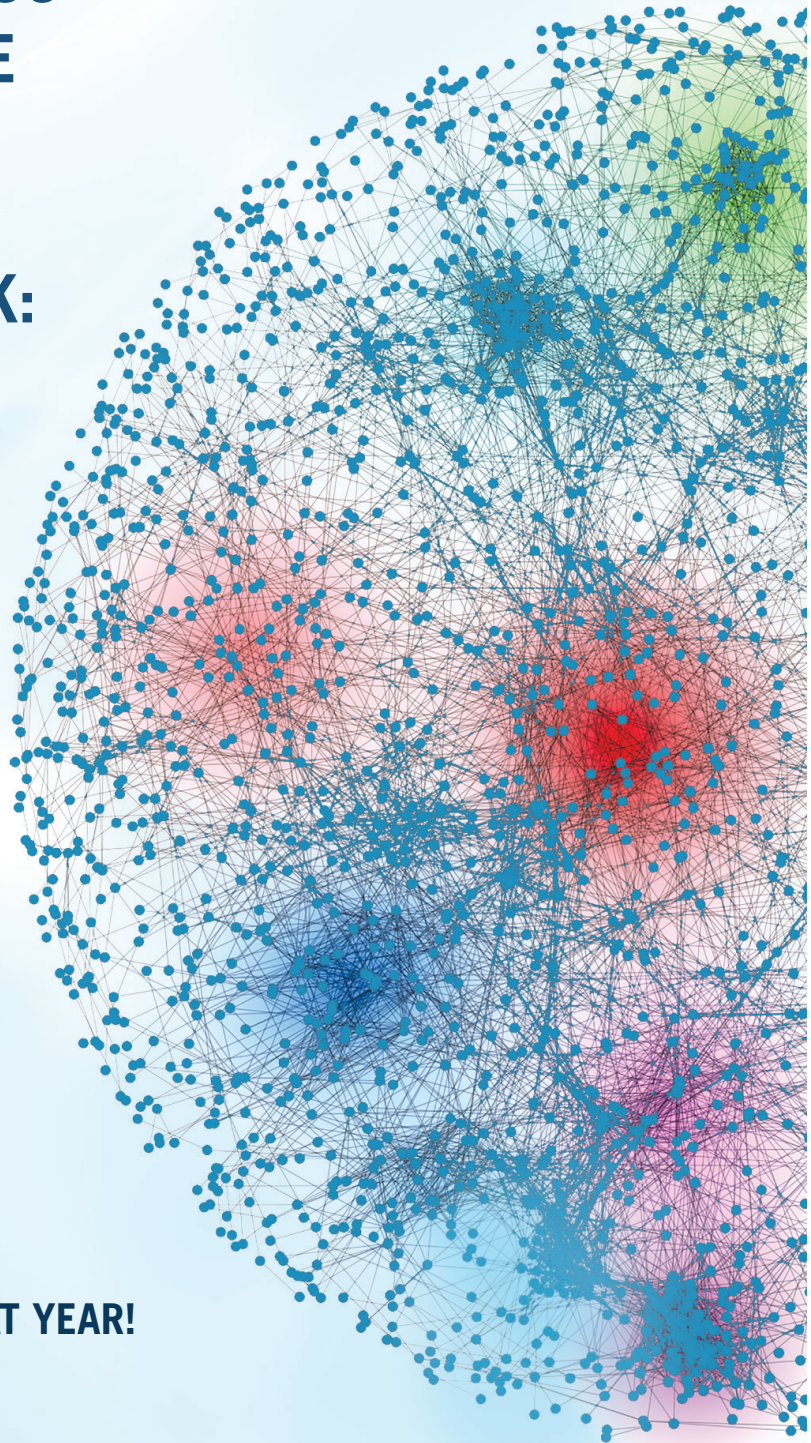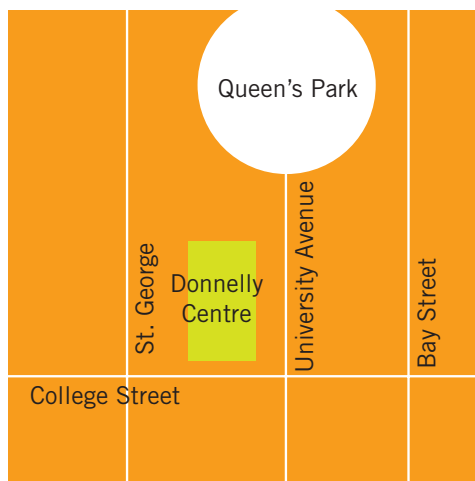
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