Donnelly Centre
for Cellular + Biomolecular Research
UNIVERSITY OF TORONTO

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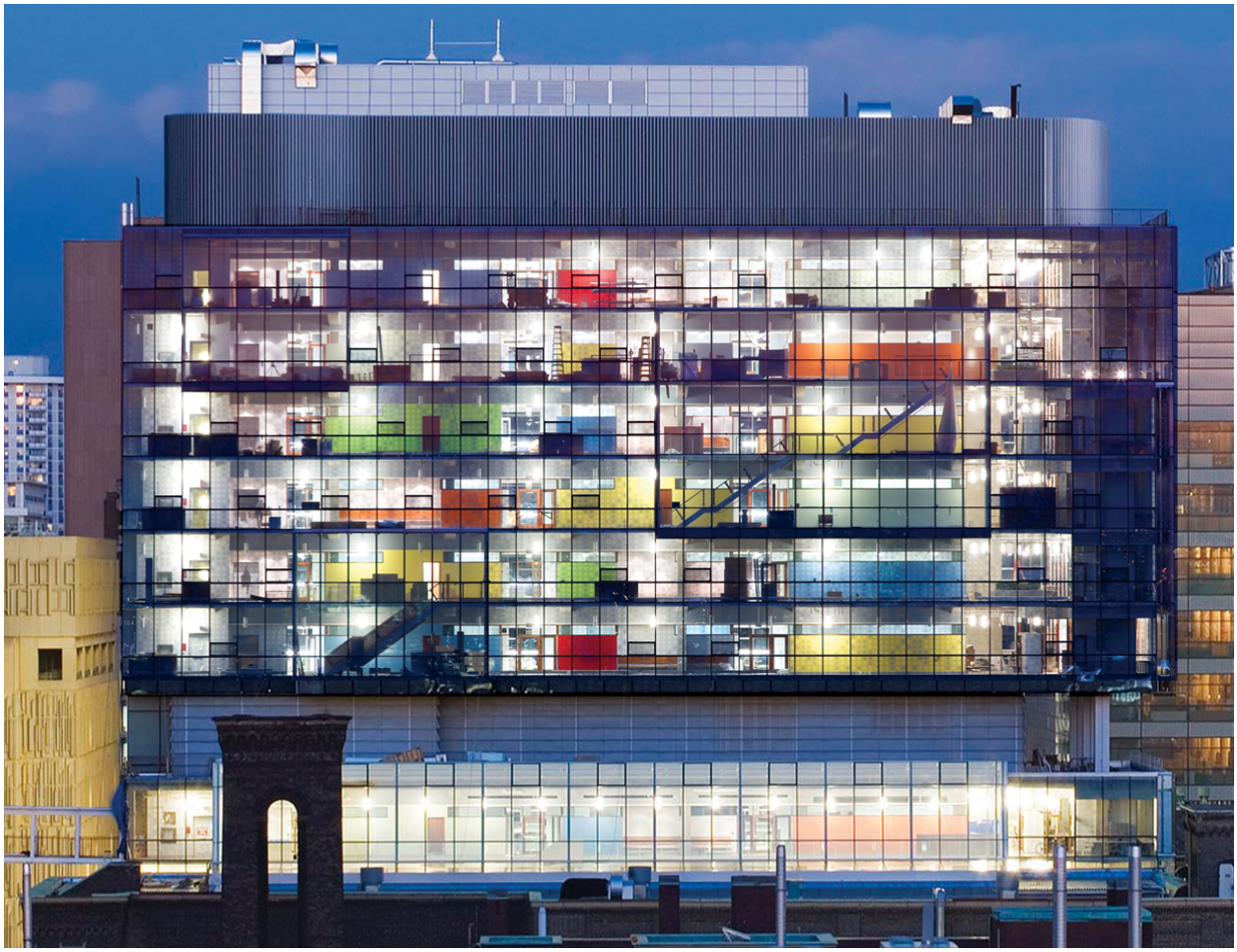
DONNELLY CENTRE 2015 ANNUAL REPORT



2015 was a big year for us!

We celebrated our 10th anniversary knowing that in a short time the Donnelly Centre has become recognized as a major hub for biomedical research. Led by Professor Brenda Andrews, who was named Companion to the Order of Canada for her leadership and scientific legacy, the Centre continues to champion cutting-edge research through collaboration among scientists from different fields and at all stages in their careers.

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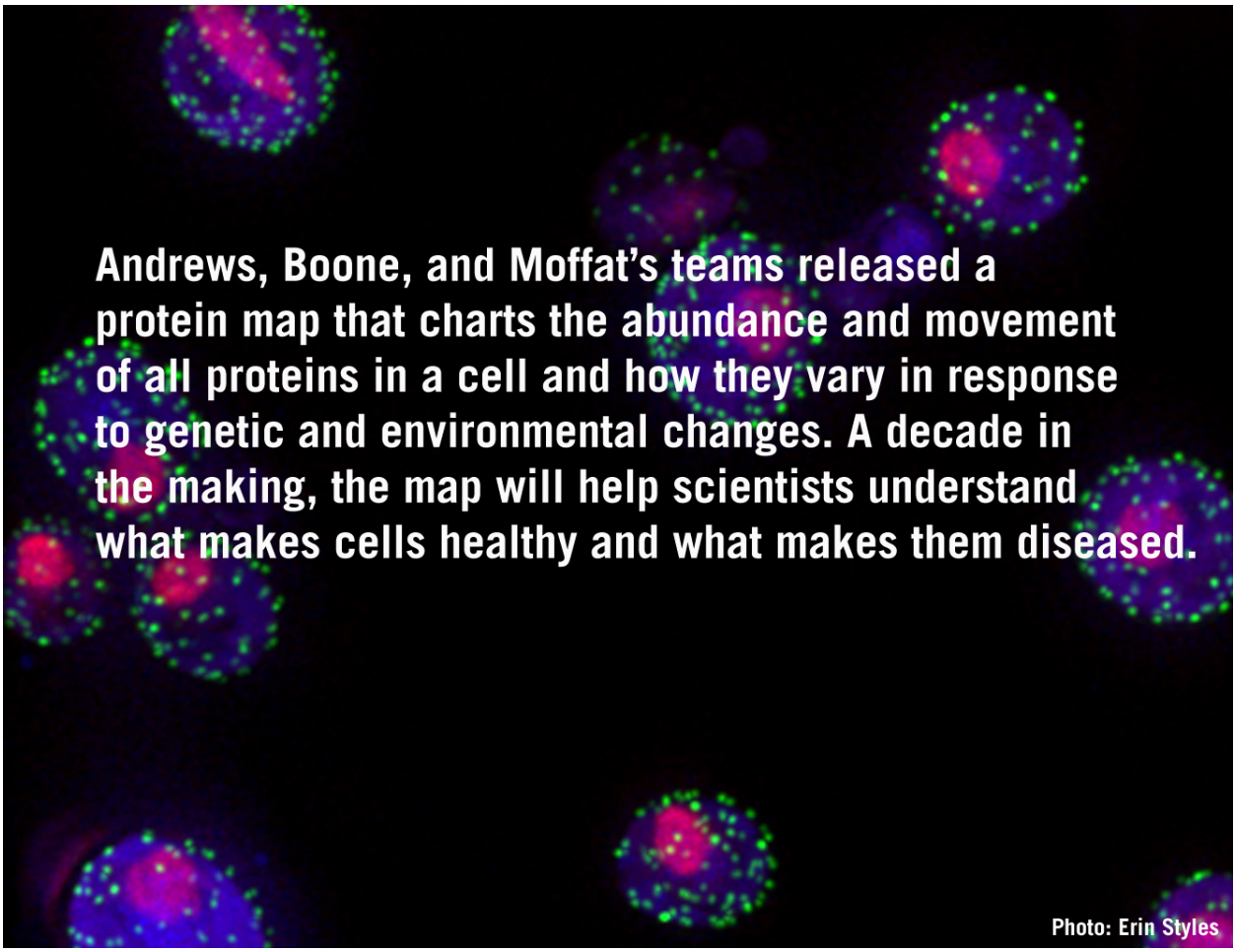


New Map Uncovers the Traffic of Life in a Cell

By Jovana Drinjakovic

Donnelly Centre scientists have recorded, in unprecedented detail, the locations of all proteins in a cell. This new protein map allows scientists to look much more closely into what happens in a cell when disease strikes, and will also help find better treatments.

Led by Professors **Brenda Andrews**, **Charles Boone**, and **Jason Moffat**, the team built a state-of-the-art automated pipeline to monitor where proteins sit in the cell and to see how they move in response to genetic or environmental perturbations. The study was published in *Cell* on June 4, 2015.

The detailed database of protein locations will be made available, also this month, through *G3: Genes|Genomes|Genetics*, the official journal of the Genetics Society of America, so that anyone can look up location and movement of their protein(s) of interest.

The findings were featured in *The Globe and Mail* and *Vice|Motherboard*.

As cells do their jobs, such as making, maintaining and repairing our bodies, they continuously shuttle proteins – genes' products that are responsible for all workings of the cell. But scientists understand very little about how this traffic occurs inside our cells. This is about to change as the new map, which charts protein movement and abundance, becomes available. Much as the shipping or airline routes give insights into the state of world economy, so this new protein map will help scientists understand better what happens in cells when they are healthy and what goes wrong in a disease.

"A lot of the regulation that happens within cells, which is critical for the basic functioning of the human body, influences where individual proteins are localized and how they move around. It is very important to understand how this regulation happens if we are going to be able to understand why cells are healthy and why they are sometimes diseased," says **Brenda Andrews**, who is also a professor in U of T's Department of Molecular Genetics.

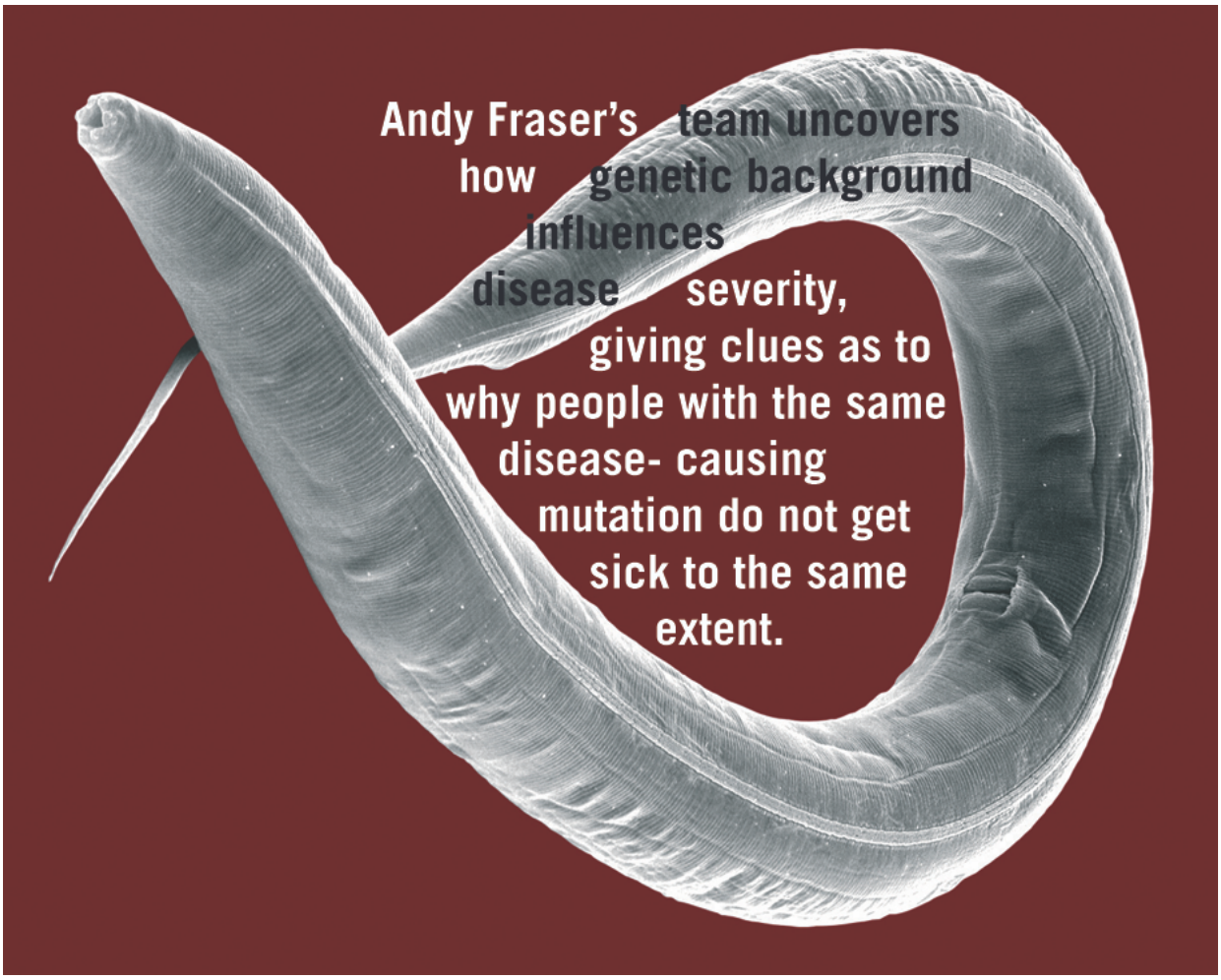
To visualize and count as many as half of the roughly 6000 proteins in the cell, the researchers collected data for mind-boggling 20 million cells. For more than a decade, the scientists worked closely together with robotic engineers, who built machines to handle the cells, and software writers who designed artificial intelligence-based algorithms to process the vast amount of data. "**The reason we need to do it on a large scale is because there simply are so many proteins**," says **Andrews**, who uses baker's yeast as a model to understand human cell biology.

Yeast cells work in very similar ways to human cells but have fewer proteins, around a quarter the number that exist in more complex human cells. This relative simplicity has allowed researchers like Andrews and Boone to use yeast to make many fundamental insights into how both yeast and human cells work.

Their team not only charted protein movement and abundance in normal cells, but they also looked at what happens when cells carry a mutation, which could lead to a genetic disease, for example, or when they are exposed to different drugs. "**We've developed methods that allow scientists to examine all of proteins in the cell and how they change in response to any kind of perturbation**," says **Andrews**.

Next, the researchers will use this powerful pipeline to investigate how proteins move in human cells, such as cancer cells, to understand better the origin of the disease, but also to search for new treatments.

"**We want to understand how all proteins are moving, at a systems level, in cancer cells upon, say, a treatment with a drug or genetic perturbation, so that we can identify vulnerabilities in cancer cells, in terms of protein localization and abundance, and start thinking about how to best target those changes**," says **Moffat**, also a professor in U of T's Department of Molecular Genetics.



Why Bad Genes Don't Always Lead to Bad Diseases

By Jovana Drinjakovic

That two people with the same disease-causing mutation do not get sick to the same extent has been puzzling scientists for decades. Now Professor **Andy Fraser** and his team have uncovered a key part of what makes every patient different.

"**We have shown how genetic background – that is, the unique set of DNA letters present in any person's genome – influences the severity of any genetic disease**," says **Fraser**, a professor in the University of Toronto's Donnelly Centre.

The finding, published in *Cell* on July 16, 2015, advances our ability to predict how severe any inherited genetic diseases will be in each affected person, a key insight into human disease.

The onset and severity of genetic diseases can vary widely. For example, people who carry mutations in a gene called CFTR will go on to develop cystic fibrosis (CF), a lung disease

where mucus build-up makes breathing difficult and leads to life-threatening infections. But while some patients are diagnosed as newborns, others do not show any signs of the disease until adulthood. Predicting disease severity is critical because often the uncertainty can be almost as frightening as the diagnosis.

"At present we can tell little more than that someone will get a genetic disease, but cannot tell them how bad this might be. This is a bit like telling someone that they will have a car crash but not whether this will be a mild bump or a major crash. Changing this uncertainty helps patients greatly and also lets doctors focus on those likely to be most severely affected," says Fraser, who is also a professor in the Department of Molecular Genetics.

Disease-causing mutations mainly strike at a gene's function – they change the order of DNA letters so that a gene's product, that is, protein, ends up faulty and unable to do its job in a cell.

Genetic background influences how much protein gets made, finely tuning genes like dimmer switches. This means that every person ends up having their own unique amount of thousands of different proteins.

If a person carries a disease-causing mutation, the resulting faulty protein will lead to a disease. Fraser's team found that if the levels of that faulty protein just happen to drop below a threshold, that's when things start to get worse as the effect of the mutation becomes more severe.

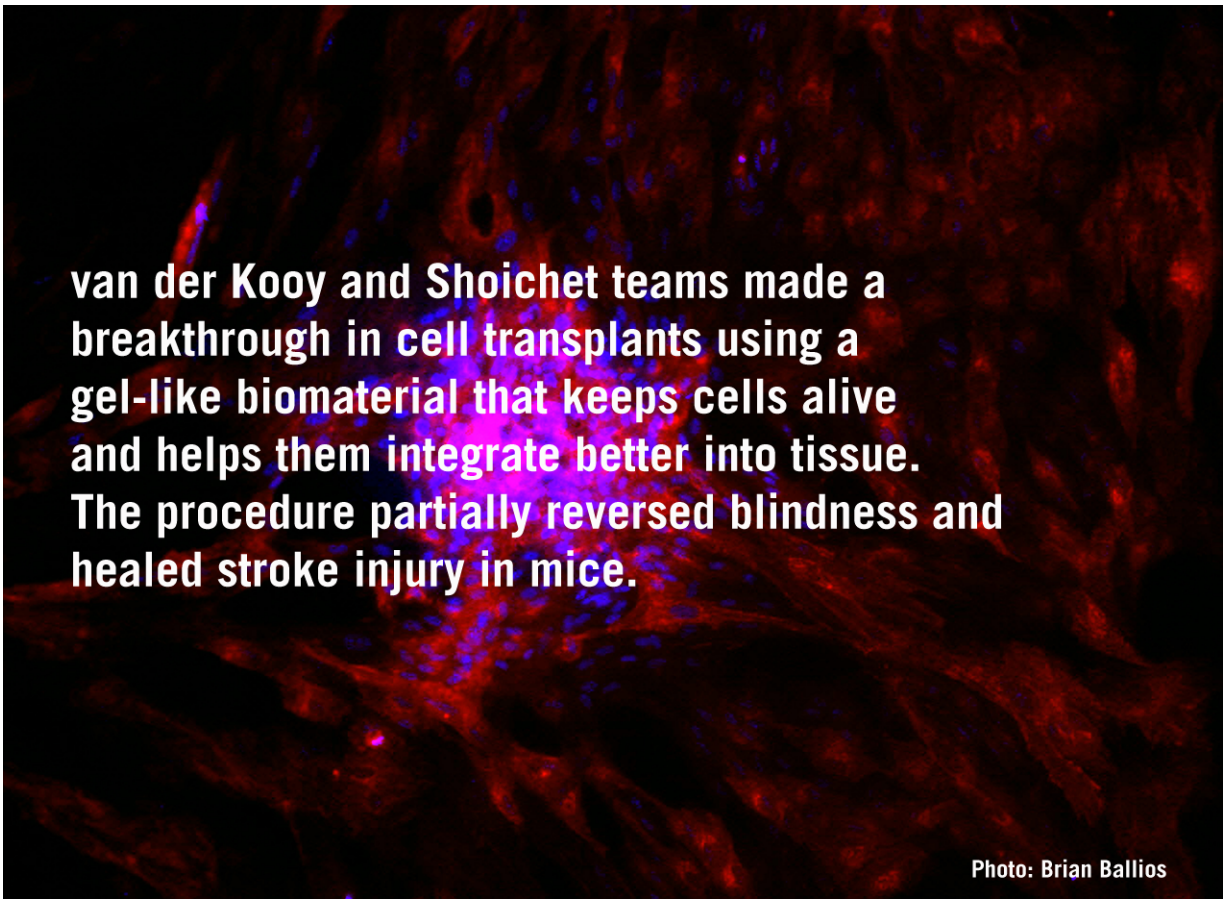
This important insight into human disease came from a powerful experimental organism - a lowly worm.

"Worms are the only animals in which we could do this massive scale of experiments to investigate how genetic background affects the severity of genetic disorders," says Fraser.

Following initial experiments that saw a quarter of million worms scrutinized for the effects of genetic mutations, the data were then validated in human cells with the same take-home message: the severity of a disorder is a combination between the fault in the protein and its amount in each individual.

Of the three billion DNA letters that make up human genome, an astonishing three million are different between any two people. This genetic variation is great for our lives, underpinning our looks, talents and social interaction. But there is also a more sinister side to this hodgepodge of DNA, as it determines what disease we get and how bad they might turn out to be.

"Now for the first time we can begin to predict disease severity for each affected person by measuring their unique personal gene activity," says Fraser. "We hope that this will eventually lead to new therapies aimed at turning down the severity of genetic diseases, a new way to tackle these life-threatening conditions."



Hydrogels Boost Ability of Stem Cell to Restore Eyesight and Heal Brains

By Jovana Drinjakovic

Led by University of Toronto Professors **Molly Shoichet** and **Derek van der Kooy**, together with Professor **Cindi Morshead**, the team encased stem cells in a "hydrogel" that boosted their healing abilities when transplanted into both the eye and the brain. These findings are part of an ongoing effort to develop new therapies to repair nerve damage caused by a disease or injury.

Conducted through the U of T's Donnelly Centre, their research was published in June 9, 2015, issue of *Stem Cell Reports*, the official scientific journal of the International Society for Stem Cell Research and caught the attention of *The Globe and Mail* where it was featured as "Injectable gel makes inroads against blindness and stroke".

Stem cells hold great therapeutic promise because of their ability to turn into any cell type in the body, including their potential to generate replacement tissues and organs. While scientists are adept at growing stem cells in a lab dish, once these cells are on their own—transplanted into a desired spot in the body—they have trouble thriving. The new

environment is complex and poorly understood, and implanted stem cells often die or don't integrate properly into the surrounding tissue.

Shoichet, a bioengineer who recently won the prestigious L'Oreal-UNESCO for Women in Science Award, and her team created the hydrogel several years ago as a kind of a bubble wrap to hold cells together during transport and delivery into a transplant site.

"**This study goes one step further, showing that the hydrogels do more than just hold stem cells together; they directly promote stem cell survival and integration. This brings stem-cell based therapy closer to reality**" says **Shoichet**, a professor whose affiliations span the Donnelly Centre, the Department of Chemical Engineering and Applied Chemistry and the Institute of Biomaterials & Biomedical Engineering at U of T.

In addition to examining how the stem cells benefit from life in hydrogels, the researchers also showed that these new cells could help restore function that was lost due to damage or disease.

One part of the Stem Cell Reports study involved the team injecting hydrogel-encapsulated photoreceptors, grown from stem cells, into the eyes of blind mice. Photoreceptors are the light sensing cells responsible for vision in the eye. With increased cell survival and integration in the stem cells, they were able to partially restore vision.

"**After cell transplantation, our measurements showed that mice with previously no visual function regained approximately 15% of their pupillary response. Their eyes are beginning to detect light and respond appropriately**," says Dr. **Brian Ballios**, an expert in stem cell biology and regenerative medicine for retinal degenerative disease, who led this part of the study.

Ballios' background as an engineer stimulated his interest in biomaterial-based approaches to therapy in the eye. He recently completed his MD and PhD under the supervision of Shoichet and van der Kooy, and he'll be continuing his medical training as an ophthalmologist, hoping to apply some of his research insights in the clinic one day.

In another part of the study, Dr. **Michael Cooke**, a postdoctoral fellow in both Shoichet's and Morshead's labs, injected the stem cells into the brains of mice who had recently suffered strokes.

"**After transplantation, within weeks we started seeing improvements in the mice's motor coordination**," says **Cooke**. His team now wants to carry out similar experiments in larger animals, such as rats, who have larger brains that are better suited for behavioral tests, to further investigate how stem cell transplants can help heal a stroke injury.

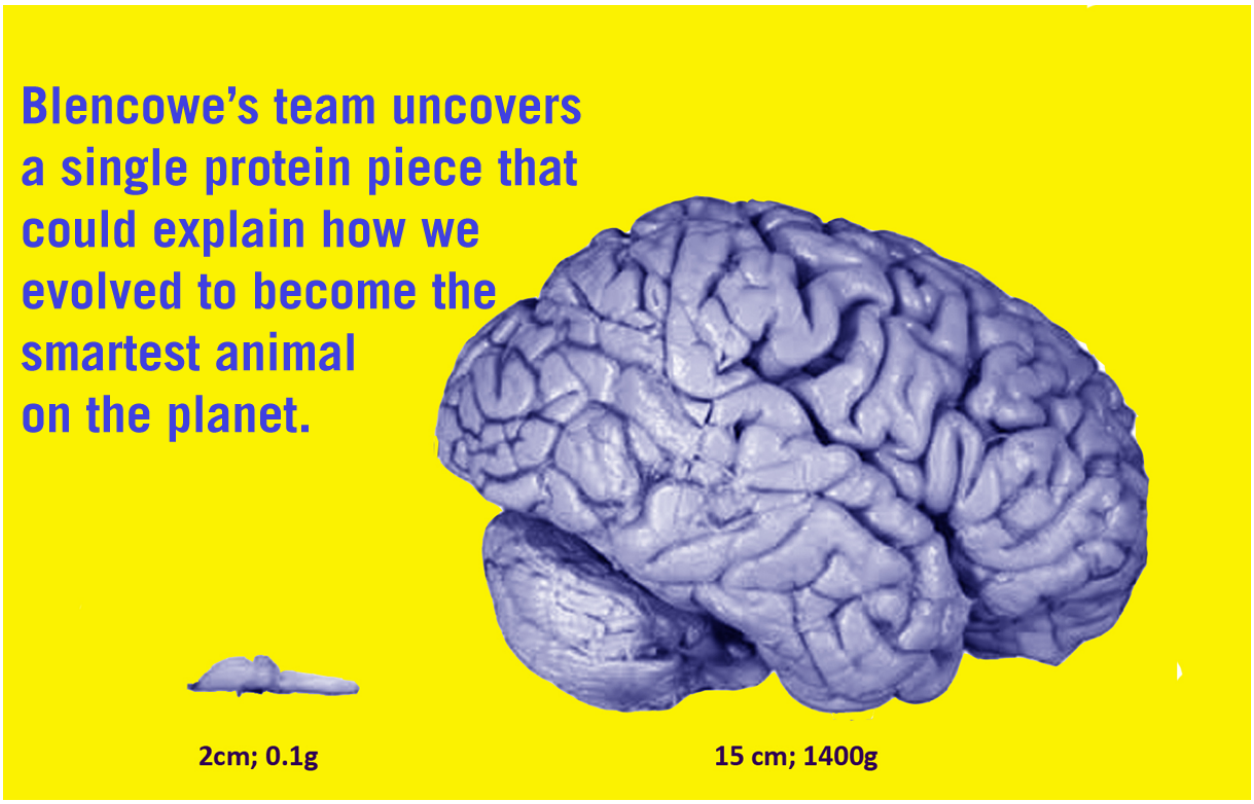
Leveraging engineering techniques—such as the design and manufacture of new biomaterials—to develop new stem-cell based therapies using hydrogels has always been on Shoichet's mind.

"I always think that in engineering our raison d'être is to advance knowledge towards translation," says Shoichet.

Because the hydrogel could boost cell survival in two different parts of the nervous system, the eye and the brain, it could potentially be used in transplants across many different body sites. Another advantage of the hydrogel is that, once it has delivered cells to a desired place, it dissolves and is reabsorbed by the body within a few weeks.

This remarkable material has only two components—methylcellulose that forms a gel and holds the cells together, and hyaluronan, which keeps the cells alive.

"Through this physical blend of two materials we are getting the best of both worlds," says Shoichet.



Protein Piece May Hold Key to How a Mammalian Brain Evolved

By Jovana Drinjakovic

Dr. **Benjamin Blencowe**, a professor in the Donnelly Centre and Banbury Chair in Medical Research, and his team have uncovered how a small change in a protein called PTBP1 can spur the creation of neurons – cells that make the brain – that could have fuelled the evolution of mammalian brains to become the largest and most complex among vertebrates.

The study was published in the August 20, 2015, issue of *Science*, grabbing headlines in media worldwide, including *International Business Times*, *El Pais* and *RaiNews*.

Greater protein diversity fuels brain complexity in higher vertebrates Brain size and complexity vary enormously across vertebrates, but it is not clear how these differences came about. Humans and frogs, for example, have been evolving separately for 350 million years and have very different brain abilities. Yet scientists have shown that they use a remarkably similar repertoire of genes to build organs in the body.

So how is it that a similar number of genes, that are also switched on or off in similar ways in diverse vertebrate species, generate a vast range of organ size and complexity?

The key lays in the process that Blencowe's group studies, known as alternative splicing (AS), whereby gene products are assembled into proteins, which are the building blocks of life. During AS, gene fragments – called exons – are shuffled to make different protein shapes. It's like LEGO, where some fragments can be missing from the final protein shape.

AS enables cells to make more than one protein from a single gene, so that the total number of different proteins in a cell greatly surpasses the number of available genes. A cell's ability to regulate protein diversity at any given time reflects its ability to take on different roles in the body. Blencowe's previous work showed that AS prevalence increases with vertebrate complexity. So although the genes that make bodies of vertebrates might be similar, the proteins they give rise to are far more diverse in animals such as mammals, than in birds and frogs.

And nowhere is AS more widespread than in the brain.

"We wanted to see if AS could drive morphological differences in the brains of different vertebrate species," says Serge Gueroussov, a graduate student in Blencowe's lab who is the lead author of the study. Gueroussov previously helped identify PTBP1 as a protein that takes on another form in mammals, in addition to the one common to all vertebrates. The second form of mammalian PTBP1 is shorter because a small fragment is omitted during AS and does not make it into the final protein shape.

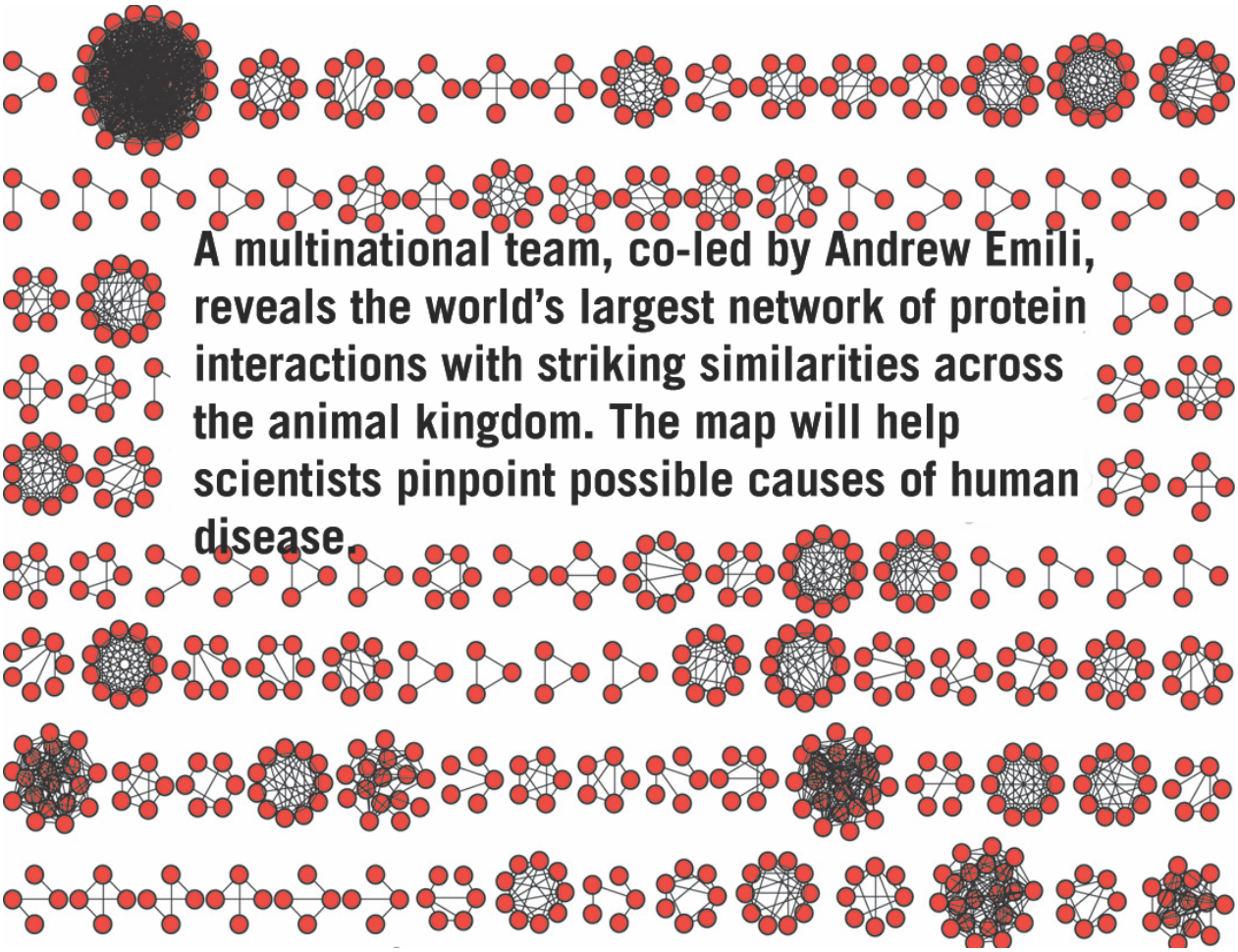
Could this newly acquired, mammalian version of PTBP1 give clues to how our brains evolved? PTBP1 is both a target and major regulator of AS. PTBP1's job in a cell is to stop it from becoming a neuron by holding off AS of hundreds of other gene products.

Gueroussov showed that in mammalian cells, the presence of the second, shorter version of PTBP1 unleashes a cascade of AS events, tipping the scales of protein balance so that a cell becomes a neuron. What's more, when Gueroussov engineered chicken cells to make the shorter, mammalian-like, PTBP1, this triggered AS events that are found in mammals.

"One interesting implication of our work is that this particular switch between the two versions of PTBP1 could have affected the timing of when neurons are made in the embryo in a way that creates differences in morphological complexity and brain size," says Blencowe, who is also a professor in the Department of Molecular Genetics.

As scientists continue to sift through countless molecular events occurring in our cells, they'll keep finding clues as to how our bodies and minds came to be.

"This is the tip of an iceberg in terms of the full repertoire of AS changes that likely have contributed major roles in driving evolutionary differences," says Blencowe.



Tree of Life Study Unveils Inner Workings of a Cell

By Jovana Drinjakovic

A multinational team of scientists have sifted through cells of vastly different organisms, from amoebae to worms to mice to humans, to reveal how proteins fit together to build different cells and bodies.

This *tour de force* of protein science, a result of a collaboration between seven research groups from three countries, led by Professor **Andrew Emili** from the Donnelly Centre and Professor Edward Marcotte from the University of Texas at Austin, uncovered tens of thousands of new protein interactions, accounting for about a quarter of all estimated protein contacts in a cell.

When even a single one of these interactions is lost it can lead to disease, and the map is already helping scientists spot individual proteins that could be at the root of complex

human disorders. The data will be available to researchers across the world through open access databases.

The study was published in *Nature* on September 7, 2015.

While the sequencing of the human genome more than a decade ago was undoubtedly one of the greatest discoveries in biology, it was only the beginning of our in-depth understanding of how cells work. Genes are just blueprints and it is the genes' products, the proteins, that do much of the work in a cell.

Proteins work in teams by sticking to each other to carry out their jobs. Many proteins come together to form so called molecular machines that play key roles, such a building new proteins or recycling those no longer needed by literally grinding them into reusable parts. But for the vast majority of proteins, and there are tens of thousands of them in human cells, we still don't know what they do.

This is where Emili and Marcotte's map comes in. Using a state-of-the-art method developed by the groups, the researchers were able to fish thousands of protein machineries out of cells and count individual proteins they are made of. They then built a network that, similar to social networks, offers clues into protein function based on which other proteins they hang out with. For example, a new and unstudied protein, whose role we don't yet know, is likely to be involved in fixing damage in a cell if it sticks to cell's known "handymen" proteins.

This landmark study gathered information on protein machineries from nine species that represent the tree of life: baker's yeast, amoeba, sea anemones, flies, worms, sea urchins, frogs, mice and humans. The new map expands the number of known protein associations over 10 fold, and gives insights into how they evolved over time.

"For me the highlight of the study is its sheer scale. We have tripled the number of protein interactions for every species. So across all the animals, we can now predict, with high confidence, more than 1 million protein interactions – a fundamentally 'big step' moving the goal posts forward in terms of protein interactions networks," says Emili, who is also Ontario Research Chair in Biomarkers in Disease Management and a professor in the Department of Molecular Genetics.

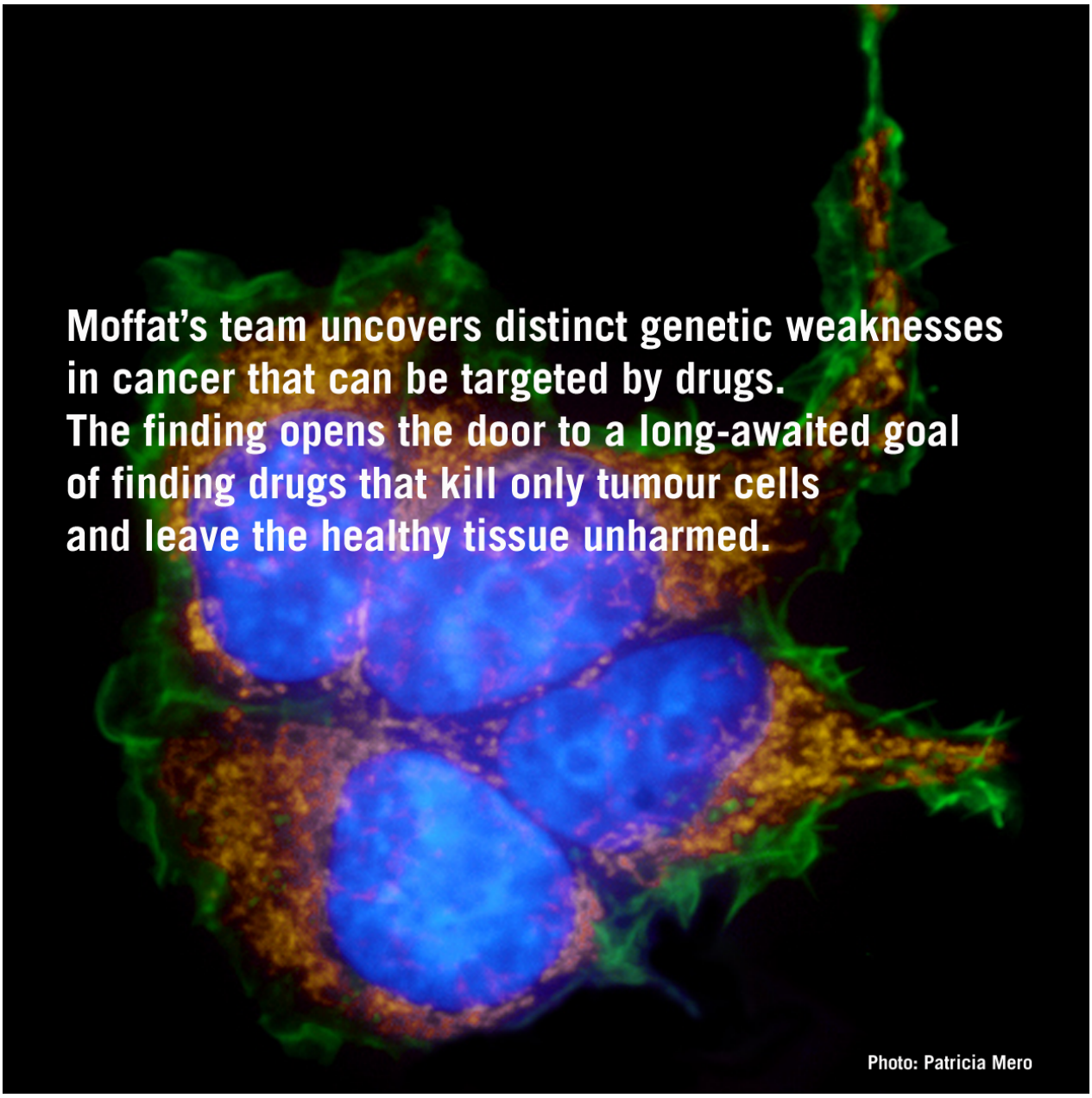
The researchers discovered that tens of thousands of protein associations remained unchanged since the first ancestral cell appeared, one billion years ago (!), preceding all of animal life on Earth.

"Protein assemblies in humans were often identical to those in other species. This not only reinforces what we already know about our common evolutionary ancestry, it also has practical implications, providing the ability to study the genetic basis for a wide variety of diseases and how they present in different species," says Marcotte.

The map is already proving useful in pinpointing possible causes of human disease. One example is a newly discovered molecular machine, dubbed Commander, which consists of about a dozen individual proteins. Genes that encode some of Commander's components had previously been found to be mutated in people with intellectual disabilities but it was not clear how these proteins worked.

Because Commander is present in all animal cells, graduate student Fan Tu went on to disrupt its components in tadpoles, revealing abnormalities in the way brain cells are positioned during embryo development and providing a possible origin for a complex human condition.

"With tens of thousands of other new protein interactions, our map promises to open many more lines of research into links between proteins and disease, which we are keen to explore in depth over the coming years," concludes Emili.



New Gene Map Reveals Cancer's Achilles Heel

By Jovana Drinjakovic

Scientists have mapped out the genes that keep our cells alive, creating a long-awaited foothold for understanding how our genome works and which genes are crucial in disease like cancer.

A team of Toronto researchers, led by Professor **Jason Moffat** from the University of Toronto's Donnelly Centre, have switched off, one by one, almost 18,000 genes — 90 per cent of the entire human genome — to find the genes that are essential for cell survival.

The data, published in *Cell* on November 25, 2015, revealed a "core" set of more than 1,500 essential genes. This lays the foundation for reaching the long-standing goal in biomedical research of pinpointing a role for every single gene in the genome.

The study grabbed headlines in *The Atlantic*, *Maclean's* and *VICE|Motherboard*.

By turning genes off in five different cancer cell lines, including brain, retinal, ovarian, and two kinds of colorectal cancer cells, the team uncovered that each set of cells relies on a unique set of genes that can be targeted by specific drugs. The finding raises hope of devising new treatments that would target only cancer cells, leaving the healthy tissue unharmed.

"**It's when you get outside the core set of essential genes, that it starts to get interesting in terms of how to target particular genes in different cancers and other disease states**," says **Moffat**, who is also a professor in the Department of Molecular Genetics and a Senior Fellow at the Canadian Institute For Advanced Research (CIFAR).

Sequencing of the human genome 12 years ago allowed scientists to compile a list of parts – our 20,000 genes – that make up our cells and bodies. Despite this major achievement, we still didn't understand the function of each gene, or how some genes make us sick when they go wrong. To do this, scientists realized they would have to switch genes off, one by one across the entire genome to determine what processes go wrong in the cells. But the available tools were either inaccurate or too slow.

The recent arrival of the gene editing technology CRISPR has finally made it possible to turn genes off, swiftly and with pinpoint accuracy, kicking off a global race among multiple competing research teams. The Toronto study, along with the paper from Harvard and MIT, published recently in *Science*, found that roughly 10 per cent of our genes are essential for cell survival.

These findings show the majority of human genes play more subtle roles in the cell because switching them off doesn't kill the cell. But if two or more of such genes are mutated at the same time, or the cells are under environmental stress, their loss begins to count.

Because different cancers have different mutations, they tend to rely on different sets of genes to survive. Moffatt's team have identified distinct sets of "smoking gun" genes for each of the tested cancers – each set susceptible to different drugs.

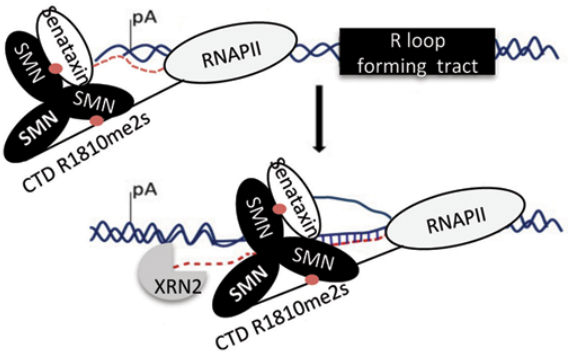
"**We can now interrogate our genome at unprecedented resolution in human cells that we grow in the lab with incredible speed and accuracy. In short order, this will lead to a**

functional map of cancer that will link drug targets to DNA sequence variation," says Moffat.

His team has already shown how this can work. In his study, Metformin, a widely prescribed diabetes drug successfully killed brain cancer cells and those of one form of colorectal cancer — but was useless against the other cancers he studied. However, the antibiotics chloramphenicol and linezolid were effective against another form of colorectal cancer, and not against brain or other cancers studied. These data illustrate the clinical potential of the data in pointing to more precise treatments for the different cancers – and show the value of personalized medicine.

"The Moffat group has developed a powerful CRISPR library that could be used by investigators around the world to identify new treatment strategies for the treatment of cancer," says Dr. Aaron Schimmer, a professor in the Department of Medical Biophysics and a medical oncologist at Princess Margaret Cancer Centre in Toronto, who was not involved in the study. "I would be interested in using this tool to identify new treatment approaches for acute myeloid leukemia – a blood cancer with a high mortality rate."

Jack Greenblatt's team discovers a molecular switch that links the genome-reading machinery to neuro-degenerative disorders, shedding light on how some of these devastating diseases may begin.



Untangling Neurodegenerative Disease

By Jovana Drinjakovic

Understanding the ins and outs of transcription - a process by which cells read the genome – has been a life-long cause for University Professor **Jack Greenblatt** of the Donnelly Centre. His latest research, out in *Nature* on December 23, 2015, uncovered a tantalizing link between the key enzyme RNAPII and disorders such as spinal muscular atrophy (SMA) and amyotrophic lateral sclerosis (ALS).

Instructions for making our bodies are stored in genes, but the genetic code is only a blueprint and of little use on its own. In fact, scientists still can't make complete sense of it. This is because the valuable text is interspersed with gibberish, all spelled out in the many combinations of DNA letters that only cells know how interpret. Cells interpret the code to turn genes into proteins, which are the building blocks of life.

Protein making begins with transcription that, akin to a cell's Rosetta stone, turns the enigmatic genetic code into a more useful form – genes are transcribed into string-like RNA molecules that then serve as templates for building proteins. Cells have evolved a great number of molecular switches which ensure that transcription runs smoothly. Now Greenblatt and colleagues have discovered a crucial new switch that brings transcription to an end once the RNA has been synthesized.

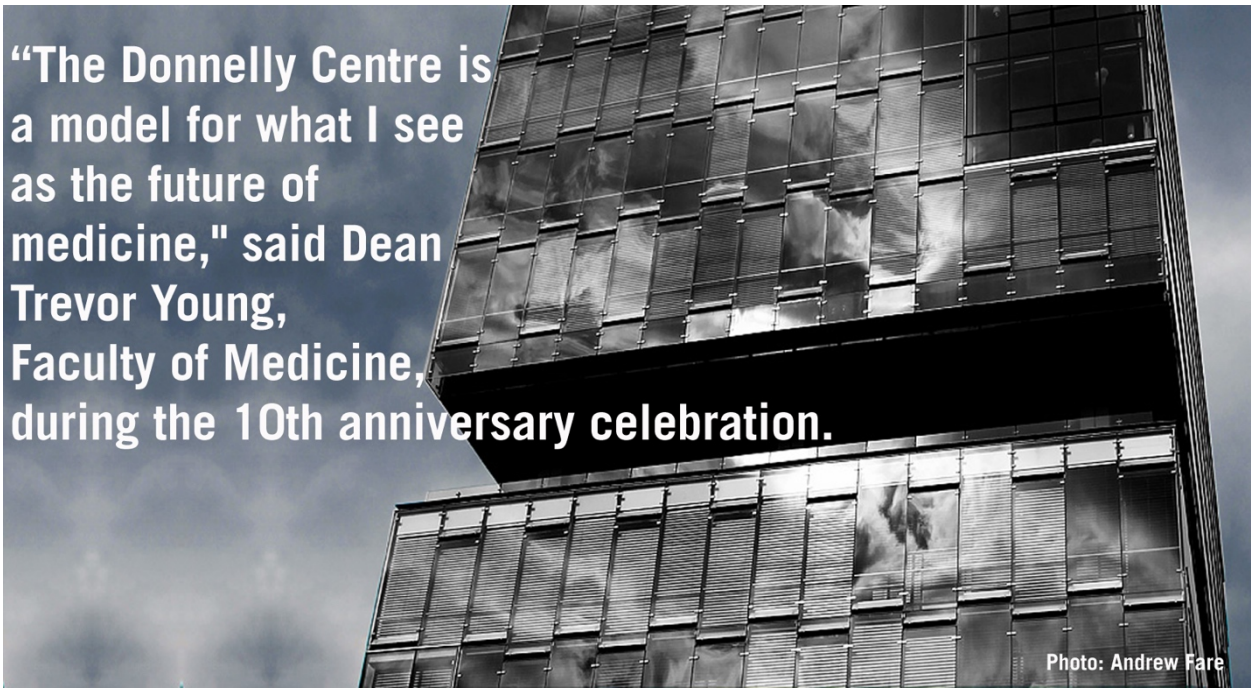
The researchers found that RNA polymerase II (RNAPII), the key enzyme that puts the RNA together, becomes adorned at a particular place with chemical tags called methyl groups. In the absence of these tags, RNAPII can't work with other proteins that help disengage the newly synthesized RNA molecule from the DNA original. This results in the snarling of the DNA and RNA strands, known as R-loops. If left unresolved, R-loops can lead to genome damage. In addition, they can also affect other steps in protein production such as RNA splicing, a process that brings the correct protein-coding parts together in the transcribed RNA. Failure to do so would cause ripples of badly formed proteins that would be damaging to the cell.

Greenblatt's team found that methyl groups on RNAPII help the enzyme recruit a protein called SMN, known to be involved in SMA, a fatal motor neuron degenerative disease of infancy, and senataxin, which is sometimes mutated in ALS, a motor neuron disease that affects speaking, swallowing and eventually breathing. SMN and senataxin help untangle R-loops and release RNA from DNA so that protein synthesis may proceed.

"We've discovered a pathway that leads from modifications of RNAPII to how transcription is regulated, and remarkably it involves proteins involved in neurodegenerative disorders, suggesting that there is a link between the regulation of transcription and these diseases," says Greenblatt, who is also a professor in the Department of Molecular Genetics.

This fascinating discovery is the first known link between a single molecular switch on the RNAPII and disease, opening the door to further research into understanding the causes of neurodegenerative disorders.

WE CELEBRATED OUR 10TH ANNIVERSARY!



A Decade of Breakthroughs

By Jovana Drinjakovic

The Faculty of Medicine at the University of Toronto celebrated the 10th anniversary of the Donnelly Centre for Cellular and Biomolecular Research on October 15. Led by Professor Brenda Andrews, the Centre has quickly established itself as a major international hub for biomedical research.

"**The Centre wonderfully embodies the values and aspirations that animate the University's research enterprise, including a fervent desire to extend the boundaries of knowledge and an unceasing quest to provide answers to some of the world's most important questions**," said Professor **Vivek Goel**, Vice-President of Research and Innovation at U of T.

The Centre was made possible by the investment from the Government of Canada, private sector contributions and a visionary philanthropist Dr. Terrence Donnelly, whose gift helped complete the state-of-the-art building in the heart of Toronto.

In the past decade, Donnelly Centre researchers have made a number of breakthroughs in our understanding of genes and how they influence health and disease. These insights are

already paving the way for personalized medicine, where treatment will be tailored to an individual's genetic make-up.

Donnelly Centre 10th Anniversary gala. From left to right: Ms. Mitze Mourinho, Dr. Lee Errett, Professors Catherine Whiteside and Sachdev Sidhu, Dr. Terrence Donnelly, Professors Brenda Andrews and James Friesen, Mrs. Jackie Nasso, Mr. Jim Nasso and Professor Alan Bernstein

The 10th anniversary celebration event included a lively discussion on the promise and pitfalls of personalized medicine by a panel of Donnelly Centre researchers that included: Professor Gary Bader, a computational scientist, Professor Molly Shoichet, a chemical engineer, Professor Sachdev Sidhu, a biochemist and Professor Andrew Fraser, a geneticist.

The panel's interdisciplinary nature reflects that of the Centre, where experts from different fields of science work side by side in an open concept space that fosters creativity and exchange of ideas.

"**Essentially, the Donnelly Centre is a model for what I see as the future of medicine. We need to break out of traditional disciplines and other boundaries. We need to discover new scientific insights and then apply them**," said Dean **Trevor Young**, U of T's Faculty of Medicine.

Such interdisciplinary approach was a revolutionary idea in the mid 1990s, when U of T professors and visionaries James Friesen and Cecil Yip first began to plan the Centre.

Professors Friesen and Yip recognized, ahead of many, that the advances in genomic technologies would enable gathering data on an unprecedented scale, calling for a paradigm shift in biomedical research. This posed a challenge of how best to analyze the vast amounts of data that could not be met by one field alone – collaboration would become necessary.

"I find it remarkable, that Jim and Cecil recognized, that in order for the University to be ahead of the game now in 2015, we really had to start thinking then how to build this type of research environment," said Professor Andrews.

Today the Donnelly Centre houses 35 principal investigators and 500 trainees and staff, who explore fundamental principles of biology, be it at the level of genes, proteins or cells. The Centre provides a unique teaching environment to students who have come from 20 different U of T departments, helping raise a new generation of scientists who think outside the confines of single research fields.

OUR SCIENTISTS WERE RECOGNIZED BY PRESTIGIOUS AWARDS

Brenda Andrews Named to the Order of Canada

By Jovana Drinjakovic

Professor **Brenda Andrews**, Director of the Donnelly Centre, has been appointed Companion to the Order of Canada, the highest level of the Order which recognizes national pre-eminence or international service or achievement. This was announced on December 30, 2015, by His Excellency the Right Honourable David Johnston, Governor General of Canada.

"**It feels incredible to be awarded this honour, given all the other people who have been honoured by the Companion to the Order of Canada. I am humbled**," says **Andrews**.

Andrews is being recognized for her globally significant research in systems biology and for developing and nurturing prominent scientific communities in molecular genetics.

"**I am thrilled to congratulate Professor Andrews on this wonderful and deserved honour. Brenda is well known at home and internationally for her high-impact research, as well as her leadership, which is reflected in the mounting successes of the Donnelly Centre. Only a decade after its founding, the Donnelly has become one of the world-leading institutes for biomedical research**," says **Dean Trevor Young**.

Andrews, who is also a professor in the Department of Molecular Genetics, is a Fellow of the Royal Society of Canada, a Senior Fellow of the Canadian Institute for Advanced Research and holds the Charles H Best Chair of Medical Research at the University of Toronto. Andrews' more recent awards also include:

- JJ Berry Smith Doctoral Supervision Award, School of Graduate Studies, University of Toronto, 2013 (inaugural award)
- The Emil Christian Hansen Award for Microbiology, The Carlsberg Foundation, Copenhagen (with Charles Boone), 2013
- Fellow, American Academy of Microbiology, 2012
- Fellow of the American Association for the Advancement of Science, 2011
- Ira Herskowitz Award, Genetics Society of America, 2010

After completing her PhD in molecular biology and biochemistry with Dr. Paul Sadowski at the University of Toronto, Andrews obtained her postdoctoral training in genetics with Dr. Ira Herskowitz at the University of California, San Francisco (UCSF). Andrews returned to U of T as an Assistant Professor in the Department of Medical Genetics to start her own research group and was elected Chair of Department in 1999.

Around this time, Andrews began to collaborate with Professor Charles Boone to lay the backbones of the emerging field of genetic networks that aims to understand how genes work co-operatively, rather than as single players, to determine cells' health and behaviour.

When the Faculties of Medicine, Pharmacy and Engineering founded the Donnelly Centre in 2005 as an interdisciplinary hub for the study of genome biology, Andrews was appointed Director and has been at the helm ever since. The Centre houses 35 research investigators and over 500 staff and trainees who work side by side in an open-concept space to tackle some of the biggest questions in biology.

As a firm supporter of collaborative research, Andrews continues to work with Boone and other scientists to drive innovation in large-scale genetics and computational methods.

"Many of the problems at the cutting edge of modern biology are too vast for a single group to tackle. The collaborative nature of the Donnelly Centre lets us pull together as a team to address these new frontiers," says Andrews. "This is where the future of biology lies and we are excited to be driving that forward".

Dev Sidhu Won Protein Society's Christian B. Anfinsen Award

By Jovana Drinjakovic

Dr. **Dev Sidhu**, a Professor in University of Toronto's Donnelly Centre, has won the Christian B. Anfinsen Award from the Protein Society, recognizing significant technological advances in protein science. What does it mean to Sidhu?

"**It means you're a musician's musician, so that's good**," he quips. So in other words, Sidhu is to proteins what Hendrix was to electric guitar.

One of Sidhu's most significant achievements was adapting a technology known as "phage display" to build vast collections of man-made antibodies that could revolutionize medicine. Sidhu, who is also a Professor in the Department of Molecular Genetics, is already putting his tools to good use through the Donnelly-based Centre for Commercialization of Antibodies and Biologics (CCAB). The Centre's goal is to turn promising lab findings into future drugs.

Antibodies help fend off illnesses by spotting and sticking to special molecular shapes, called antigens, on the surfaces of bacteria and viruses. Antibodies can also stick to antigens residing on proteins that drive diseases, and they have been used as medicines to treat ailments such as cancer and blindness. But making antibodies was costly and took a long time, which slowed their development.

Thanks to Sidhu adaptations, he found a way to use a phage display — which was first developed in the '80s for studying proteins — to produce antibodies faster and on an unprecedented scale.

Phage display uses tiny viruses, called phages, as antibody-making machines. Antibodies, like any other proteins, are products of genes. The first step is to introduce into the phages packages of antibody-coding DNA. With recent technology advances, phages can be genetically altered to make countless kinds of antibodies. The researchers then look for an antibody that sticks the most to a given disease antigen. The goal is to find drugs with minimum side-effects by identifying antibodies that bind to, and block, antigens for a specific disease or illness, like cancer cells, for example.

Sidhu began working on phage display at Genentech, a leading drug company in San Francisco. Sidhu improved the technology to create a staggering 100 billion different antibody shapes, surpassing what our bodies are capable of and reaching the limit of what is physically possible.

In 2008, Sidhu left sunny California for the Donnelly Centre in Toronto to be at the forefront of genomics research and use its insights to find medically useful antibodies from the deluge produced by phage display.

"**But clever science is only 10 per cent of getting a drug that can cure people**," says **Sidhu**, who is also Senior Investigator in Ontario Institute for Cancer Research. All too often, promising research findings from the lab never make it to the clinic.

"**Academics are still thinking that the industry's job is to make new drugs, and that our job is to discover targets. And a target in the industry is not a target until it is highly validated; people in academia often forget that**," says **Sidhu**.

This is certainly the case in Toronto, which has struggled to make its name in drug development despite its world-leading biomedical research.

To change this, Sidhu established CCAB to pose as a middleman between academia and the pharmaceutical industry. Its mandate is to turn promising antibodies into commercial products for drug companies to further develop and bring to market.

Together with Professor **Jason Moffat**, also at the Donnelly Centre and Senior Fellow at the Canadian Institute for Advanced Research, Sidhu co-founded Northern Biologics, a small

drug company that will advance four antibodies from CCAB's current pipeline of 100 molecules.

"The goal is to have a drug in the clinic by 2018," says Sidhu.

He hopes that further partnerships with industry will ensure CCAB — and U of T — get a bigger share in the emerging market of "biologics," which are drugs made by living organisms. After all, this is where Drs. Frederick Banting and Charles Best developed the first biologic — insulin — in 1921. Almost a century later, Sidhu is ensuring Toronto is back in the game.

Brendan Frey Elected Fellow of the Royal Society of Canada

By Carolyn Farrell from U of T Engineering

Engineering professors **Levente Diosady** (ChemE) and **Brendan Frey** (ECE) have been elected fellows of the Royal Society of Canada (RSC) on the basis of their exceptional contributions to Canadian intellectual life.

The Society's mission is to recognize scholarly, research and artistic excellence, to advise governments and organizations, and to promote a culture of knowledge and innovation in Canada. Fellowship in the RSC is one of the highest honours that Canadian researchers can achieve.

"**Professors Levente Diosady and Brendan Frey are trailblazing researchers who are expanding our understanding of what is possible and improving lives**," said Dean **Cristina Amon**. "**They exemplify the very best of engineering innovation and the outstanding calibre of research conducted at our Faculty; we are extremely proud that they are being recognized for their extraordinary achievements**."

Diosady and Frey were among 13 new fellows elected from the University of Toronto. Across Canada, 87 new fellows were named in 2015.

About Brendan Frey

Over the past twenty years, Brendan Frey has played a key role in the emergence of new areas of research and application in machine learning and genome biology. He was one of the first researchers to successfully train a deep neural network, and he was a pioneer in inventing message-passing algorithms, which are now widely used. He is a co-inventor of the affinity propagation algorithm and of the factor graph notation for graphical models.

Frey also co-developed the long-sought-after 'splicing code' for determining how genes are expressed and introduced a new approach to understanding the genetics of disease. His technique has successfully identified previously unknown genetic determinants of major human disorders, including autism, certain cancers and spinal muscular atrophy. Frey recently cofounded the start-up Deep Genomics, developing deep learning technologies to predict the consequences of genomic changes.

He has served on the technical advisory board of Microsoft Research, holds seven patents and has served as an expert witness in patent litigation. Professor Frey is a fellow of the American Association for the Advancement of Science, the Canadian Institute for Advanced Research (CIFAR) and the Institute of Electrical and Electronics Engineers. His many research awards include the NSERC E.W.R. Steacie Fellowship and the NSERC John C. Polanyi Award. He holds the Canada Research Chair in Biological Computation.

Aaron Wheeler Named to the Royal Society College

By Jovana Drinjakovic

Professor **Aaron Wheeler** was inducted into The College of New Scholars, Artists and Scientists of The Royal Society of Canada. This division of the 133-year old RSC recognizes high achievement, and especially interdisciplinary work, by Canadians and permanent residents at an early stage of their career. Members represent the emerging generation of scholarly, scientific and artistic leadership in Canada and are inducted within 15 years of earning their doctorates.

Professor Wheeler, who is also a professor in U of T's Department of Chemistry, has been recognized for his work on lab-on-a-chip technology and the development of microfluidic schemes for combinatorial peptide synthesis. Wheeler's recent work includes the development of microfluidic schemes for combinatorial peptide synthesis, a new paradigm for mammalian cell culture and analysis, and a potentially transformative approach to quantifying molecular markers for cancer in tiny tissue samples.

Molly Shoichet Receives National Fleming Medal

By Luke Ng from U of T Engineering

University of Toronto engineering professor **Molly Shoichet** (The Donnelly Centre, ChemE, IBBME) has received the 2015 Fleming Medal and Citation from the Royal Canadian Institute in recognition of her outstanding contributions to the public understanding of science.

Shoichet joins the prestigious ranks of other distinguished recipients, including environmental activist David Suzuki, U of T chemistry professor and Nobel Prize winner John C. Polanyi and astronaut Chris Hadfield.

Among her many science outreach activities, in May Shoichet founded the groundbreaking initiative Research2Reality (R2R), which uses digital media to communicate cutting-edge research performed in Canada and spark nationwide awareness. R2R hosts more than 70 short videos featuring some of the country's top research scientists and engineers describing their work in accessible terms. The initiative has garnered more than 1,000 social media followers in five months.

A world-renowned expert in tissue engineering and regenerative medicine, Shoichet holds a Canada Research Chair in Tissue Engineering and is a University Professor, the highest

academic rank at the University of Toronto. She also serves as the senior advisor on science and engineering engagement to U of T President Meric Gertler.

"Research is the heart of invention, invention leads to innovation, and innovation is the core of our future," said Shoichet, who was also named one of five 2015 L'Oréal-UNESCO for Women in Science Award Laureates from around the world earlier this year. "This is an opportunity to use modern communications tools to ignite a national discussion and inspire the next generation of researchers to invent the future."

"On behalf of the IBBME Faculty, I want to congratulate Professor Molly Shoichet on this tremendous honour," said Dean Cristina Amon. "As a world-leading researcher and educator with a remarkable record of innovation and discovery, she is an exemplary ambassador for the vital importance and impact of scientific research on our society, our well-being and our future prosperity."

Research2Reality is supported by six research-intensive universities to date, along with the Ontario government and Discovery Science Channel, where some of the videos are televised.

Other Notable Awards:

- **Aaron Wheeler** was awarded E.W.R. Steacie Memorial Fellowship for work on digital microfluidics.

- **Molly Shoichet** was North American Laureate of the L'Oréal-UNESCO For Women in Science Award.

- **Derek van der Kooy** received the Canadian College of Neuropsychopharmacology Heinz Lehmann Award.

- **Igor Stagljar** and postdoctoral fellow **Julia Petschnigg** were elected among U of T Inventors of the Year.

- **Warren Chan** won Kabiller Young Investigator Award.

OUR DISCOVERIES ARE BECOMING TANGIBLE ADVANCES IN MEDICINE

Antibody Network, Celgene Partner to Develop Cancer Drugs

From U of T's Media Centre

A new collaboration between **Celgene Corp**. and the **Recombinant Antibody Network (RAN)**, a consortium comprising research groups from UC San Francisco, the University of Chicago, and the University of Toronto, will support the development of next-generation, antibody-based cancer therapies.

In this first industry partnership for the RAN, Celgene will provide $25 million in funding over the next three years and will have the option to enter into an exclusive license agreement to develop and commercialize promising therapeutic antibodies to cancer-related targets.

"The RAN consortium has developed an automated, antibody engineering pipeline that enables high-throughput generation and validation of high-performance recombinant antibodies at an unprecedented scale" said James Wells, PhD, one of the founding members of the RAN and a professor of pharmaceutical chemistry in the UCSF School of Pharmacy.

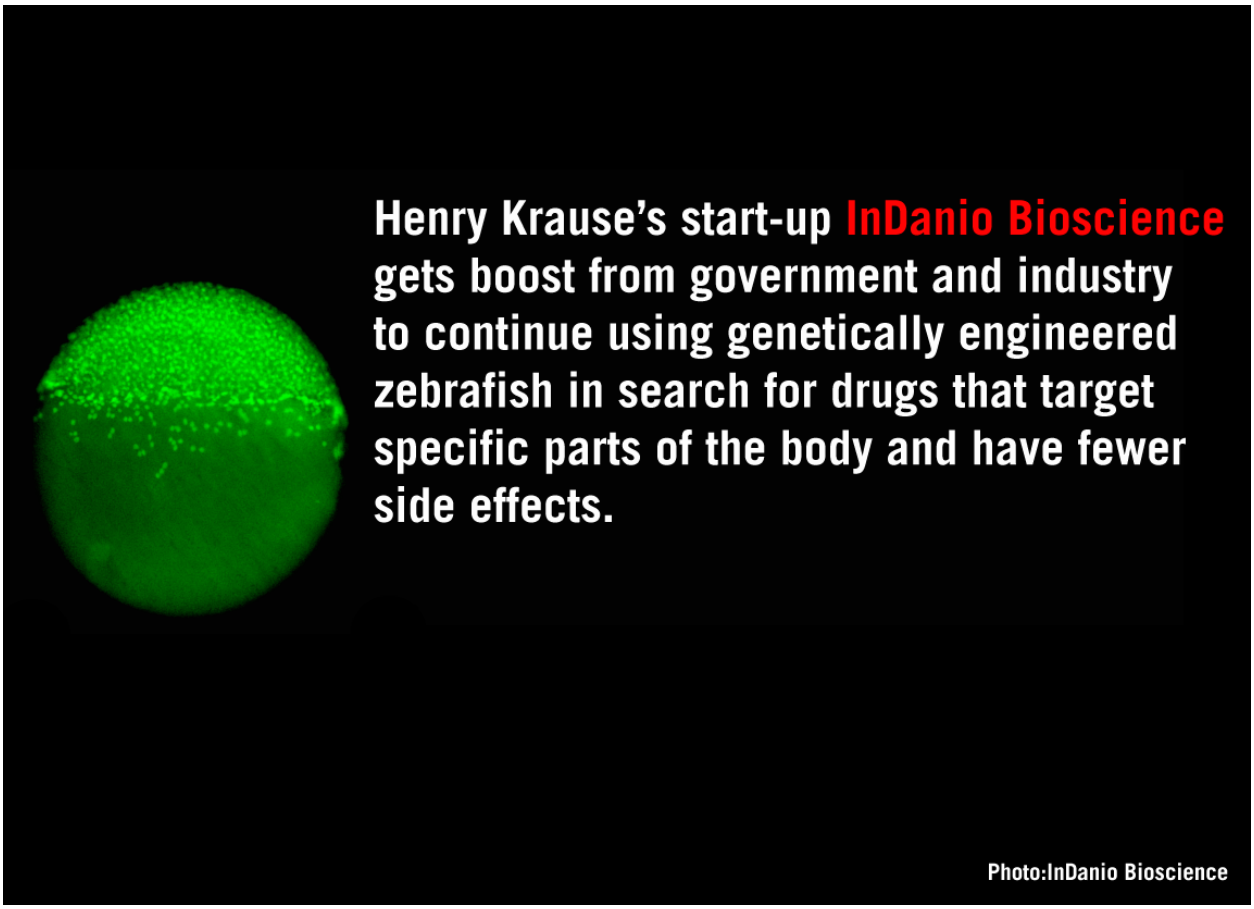
Over the past decade, antibodies have emerged as the major breakthrough in targeted cancer therapy and are now the fastest growing class of therapeutic molecules. Unfortunately, antibody development remains an imprecise science, conducted on a case-by-case basis.

To address the unmet need for an efficient pipeline for renewable antibody discovery, Wells co-founded the RAN with two other veterans from the former Protein Engineering Department at Genentech Inc. Sachdev Sidhu, PhD, now a professor in the University of Toronto's Donnelly Centre, and Anthony Kossiakoff, PhD, professor of biochemistry and molecular biology at the University of Chicago, have teamed with Wells to make automated, large-scale antibody production a reality. The RAN generates recombinant antibodies from cloned synthetic genes that are selected for high performance.

"Through this partnership, we are taking a giant step forward in the ultimate goal of the RAN: the systematic targeting of the "extra-cellularome," the cell-surface proteins that control cancer and other diseases," said Sidhu, who also leads the University of Toronto's Centre for the Commercialization of Antibodies and Biologics. "In the near future, we envision that we will be able to precisely target any cancer at the molecular level, which will provide better therapies for patients and greater peace of mind for their families."

During the past decade, the researchers have developed new methods to rapidly and reliably produce large libraries of recombinant antibodies, which are tailored, synthetic antibodies created in vitro that consistently show high performance. Using funding from the National Institutes of Health, the RAN has completed an ambitious project that has provided thousands of high-quality antibodies targeting hundreds of human transcription factors – the signaling molecules that cells use to control when and how their genes produce proteins — which previously have been particularly challenging to target with antibodies. The robotic RAN system enables researchers to select these antibodies efficiently at a broad scale to begin to approach the level of the proteome – the full system of proteins found in a human or organism.

On the heels of this success, the collaboration with Celgene will apply this systematic approach to signaling proteins on the cell's surface that drive cancer and immunological disease. The RAN also will leverage collaborations with academic groups to engineer antibodies for basic biological research and for developing novel treatments for cancer and other devastating diseases.



See-through Fish Offer Clear Advantages to Drug Researchers

By Joseph Hall, *Toronto Star*, Mon., Nov. 9, 2015

Genetically modified zebra fish whose organs glow fluorescent green will help pharmaceutical researchers test new products, say scientists at the University of Toronto.

When it comes to drug development, nothing is ever quite clear.

Will the compound you're testing actually hit the diseased organ you're aiming for? If it does, is it also having an impact on other tissues, perhaps with harmful or toxic side-effects? Researchers looking for novel pharmaceuticals have long sought a testing model for new medicines that can — at the earliest stages — make such drug effects transparent.

Well, how about using a see-through fish?

How about using a see-through fish whose heart, brain, or liver glows a fluorescent green when hit by a tested drug?

A team of scientists at the **University of Toronto's Donnelly Centre for Cellular and Biomolecular Research** are developing just such a spectral drug-screening platform.

In hundreds of bubbling tanks jamming two rooms at the College St. facility, the scientists are creating dozens of lines of genetically modified zebra fish that will aid in new drug testing.

Henry Krause, a scientist at U of T's Donnelly Centre, is developing zebra fish that carry human DNA segments known as nuclear receptor genes. The transparent fish glow green when a particular organ is hit by a drug being tested.

"**With a (see-through) animal you know right away if (a potential drug) is going to be toxic**," says **Henry Krause**, a biochemist at the centre.

"**You know if it's going to make it through to the tissue that you want it to and how many different tissues are going to be hit**."

These homely creatures are guppy-size and greyish, except for the faintly coloured lines that have earned them their zebra sobriquet.

But these horizontal lines only appear at maturity. As they develop through their embryonic stages, the fish are translucent with their internal organs clearly visible.

In Krause's lab, the team is also modifying the fish to carry human DNA segments known as nuclear receptor genes.

Nuclear receptor genes produce proteins that help control such critical things as tissue development and metabolism. Mutations in these genes can promote a plethora of ailments — from diabetes to cancers to liver disease. Medicines that target their master protein products, then, could have profound effects on these maladies.

The lab implants the genes in progenitor zebra fish. The scientists then selectively breed these piscine patriarchs together until — over several generations — all of their teeming descendants carry that human, "transgenic" content within their zebra fish genomes.

So far, the lab has created zebra fish lines carrying 36 of the 48 human nuclear receptors and it is on its way to producing all of them.

And here's the neat trick.

Alongside each human gene they insert into a fish line, the scientists add another DNA segment — one that produces a green fluorescent glow when a drug interacts with its twinned nuclear receptor.

"We've rigged the fish so they turn on a fluorescent signal that we can easily see," says Krause, who helped found a U of T spinoff company — InDanio Bioscience Inc. — to market his new screening process.

With this glowing green function in place, researchers can literally peer inside the transparent fish embryos under a microscope to see if and where a drug has triggered a nuclear receptor response.

Krause's team is testing thousands of candidate medicines in this way — compounds often culled from pharmaceutical catalogues of promising or discarded chemicals.

The scientists simply place the transparent fish embryos in dimpled trays and bathe them with the candidate medicines to see which organs light up.

"It tells us if (the chemical) is functioning everywhere or just some specific tissue," Krause says.

This is where the largest payoff from Krause's fish lies: All of our genes — some 20,000 of them — are present in almost every cell in our bodies, but each one can take on profoundly different duties depending on the tissue in which it's situated.

Look at the well-known estrogen receptor genes involved in many breast cancers, Krause says.Drugs that are capable of blocking these receptors have been among the most successful in combating the disease.

"So if you want to treat breast cancer, you can do it by trying to knock down the activity of the estrogen receptor in the tissue where the cancer is," Krause says.

In hundreds of bubbling tanks jamming two rooms at the College St. facility, the scientists are creating dozens of lines of genetically modified zebra fish that will aid in new drug testing.

"But … estrogen is doing a lot of things in a lot of places — it has control of behaviour in the brain, (it affects) bone density — so if you knocked out its activity everywhere, people would not be very healthy."

However, drugs that could control estrogen balances in breast tissue alone were discovered by chance. With Krause's fish, researchers can see well in advance which drugs might impact a nuclear receptor in a specific organ — and if that impact is localized to that tissue or spread throughout the body.

This transparent testing will allow researchers to reject countless chemicals quickly, without bringing them up the hugely expensive drug-trial chain into rodent models or beyond.

It will also allow researchers to more quickly flag those drugs that might have the best shot at safely and effectively treating the myriad ailments associated with nuclear receptor actions.

The fish platform "allows you to expedite the drug discovery process and expedite the preclinical activities," says Anne Cheung, CEO of InDanio.

"You can potentially shave (off) maybe one year, one and a half years, and that's huge. That translates into huge cost shavings."

The Donnelly fish may also usher in new uses for old or discarded drugs.

Indeed, they have already produced a potential new use for a failed Alzheimer's disease medication. The drug, they found, was not making its way into the zebra fish brains.

It was being blocked in their livers, where it was helping to control the lipid deposits associated with fatty liver disease.

New Company Will Benefit Patients Undergoing Transplants for Leukemias

From ExCellThera's Media Room

Patients suffering from acute myeloid leukemia (AML), who require stem cell transplantation as part of their treatment, may now benefit from a new best-in-class process that improves the viability and success of cord blood stem cell transplantation.

ExCellThera, a spin-off company launched by the Institute for Research in Immunology and Cancer – Commercialization of Research (IRICoR), and the Centre for Commercialization of Regenerative Medicine (CCRM) is based on novel proprietary intellectual property related to the expansion of stem cells developed by Dr. Guy Sauvageau at Université de Montréal's (UdeM) Institute for Research in Immunology and Cancer (IRIC), and Dr. **Peter Zandstra** at the University of Toronto's Donnelly Centre and Institute of Biomaterials and Biomedical Engineering.

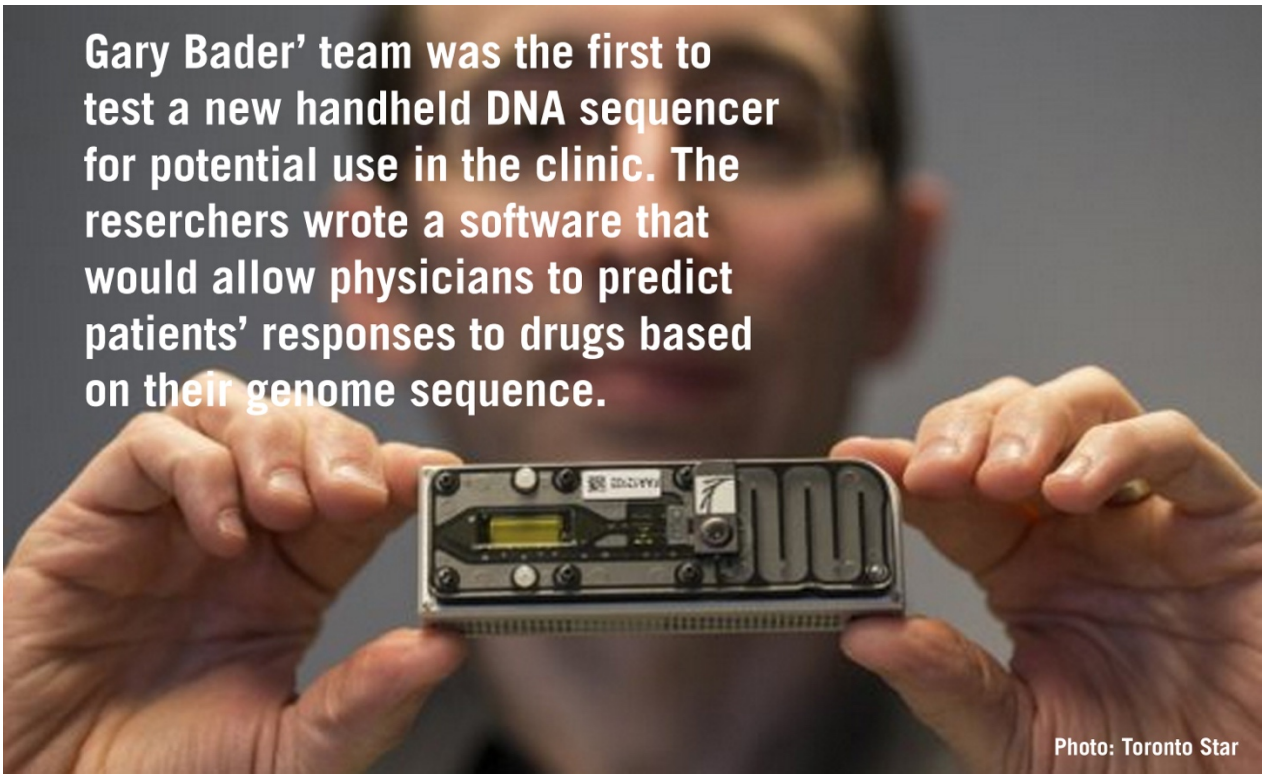
"**We are excited to be working with CCRM to launch this new IRICoR spin-off company located in Montréal, which includes novel stem cell-expanding molecules that were initially identified and funded at IRIC via an early-stage investment from IRICoR**," commented Michel Bouvier, CEO of IRICoR. "**Our unique expertise in stem cell biology, coupled with a strong medicinal chemistry team has allowed us to advance this program rapidly towards the clinic. By working closely with CCRM, and combining our intellectual property, we have**

been able to leverage the expertise and technology of both IRICoR and CCRM to demonstrate the value of strong partnerships between Montreal and Toronto."

A Phase I and II clinical trial designed to test the ability of ExCellThera's stem cell expansion approach is slated to begin this year at the Maisonneuve-Rosement Hospital in Montreal, and will also include Sainte-Justine Hospital and other centres in the near future. The trial will enroll up to 25 patients suffering from AML who require stem cell transplantation for the treatment of their disease.

"CCRM is thrilled to be announcing its first spin-off company and working in partnership with IRICoR," says Michael May, President and CEO of the Centre for Commercialization of Regenerative Medicine. "In only four years, CCRM has already achieved an important goal to advance regenerative medicine technologies to the market to meet the needs of patients. We look forward to launching a portfolio of regenerative medicine companies in the future through similar collaborations."

Approximately 60,000 people in Canada and the United States are expected to be diagnosed with leukemia in 2015. The success rate of blood system transplantation is strongly correlated to the number of cells used, making ExCellThera's process a valuable breakthrough for clinical application. ExCellThera is also developing related gene therapy products.



A Hand-held Device That Can Read Your DNA

By Joseph Hall, *Toronto Star*, Fri., Feb. 13, 2015

University of Toronto team creates first app for the MinION, an inexpensive device that can read any segment of your genetic material that a doctor may want to examine.

Sitting on a bench in a sixth-floor University of Toronto lab on College St., a pair of suitcase-sized genomic sequencers flaunt the high-tech gleam and heft befitting their $750,000 price tags.

Across the hall, **Gary Bader** holds up a dinky device in the palm of his hand that can also read your DNA. Price tag: $1,000.

"**This is the potential next generation (of sequencer) technology, this thing right here**," says the University of Toronto computational biologist, brandishing a rectangular contraption the size of a Swiss army knife. "**This is a glimpse of the future that we have in our hand.**"

Bader's team at the U of T's Donnelly Centre for Cellular and Biomolecular Research has become the first in the world to create a proven software app for the emerging technology.

Appropriately dubbed the MinION, the puny machine hasn't the brute power of its cross-corridor cousins to sequence the entire three-billion base pairs that make up the human genome.

What it can do, however, is accurately read any segment of your genetic material that a physician or researcher may want to examine. Bader says the device, if it proves itself, could be a boost for the emerging field of individualized medicine, which looks at a patient's own DNA profiles to determine best treatments.

"That's like a hard drive that's 300-gigabyte," Bader says, referring to one of the larger machines across the hall. "Whereas this is like a one-gigabyte USB key, or something."

But what it lacks in power, the device makes up for in the breadth of smaller sequencing chores it can undertake.

Built by the U.K.'s Oxford Nanopore Technologies, the MinION is an app-dependent device. And around the world, several hundred researchers are currently developing applications software that will allow it to scan many of the 22,000 human genes spread sparingly along the human genome for such things as diseases, genetic risks and drug tolerances.

Company officials say the device is "blind" to the species of DNA it's sequencing, so MinION apps for such things as veterinary and botanical research are also under development.

"You can get started with quite a lot of interesting applications," says Bader, who has been working with the MinION since last June. "You don't need that big beast to get a lot of things done."

In January, Bader and Ron Ammar, a U of T postdoctoral fellow, became the first of the scientists working with the device to publish a study on a MinION app. The study concerns three genes that are responsible for some of the liver's major drug processing capacities.

The program — which runs off a laptop mated to the MinION — prods the tiny sequencer to scan for common mutations along these genes. In their paper, the U of T pair show the device can be used to accurately predict a patient's ability to process codeine and several other medications.

"Just like different people react differently to alcohol, it's genetic whether they can tolerate (codeine) or not," Bader says.

Based on slight variations in the DNA base pairs that make up the CYP2D6 gene responsible for processing the painkiller, the ability of patients to tolerate codeine can vary significantly. Roughly 30 per cent of people who take codeine have a problem with the

standard prescription dose, Bader says. The CYP2D6 gene helps the liver metabolize codeine into morphine, which is the active analgesic agent.

Patients with versions that prompt an unusually rapid metabolization of the drug can run the risk of a morphine overdose. For those with versions that convert it too slowly, the drug would have few painkilling benefits.

Such apps, which might also look for the critical genetic variations in cancers that dictate treatment alternatives, can be used by physicians to help find best treatments for patients. The U of T app also analyzes genetic material that metabolizes the popular blood thinner Warfarin.

Apps are also being developed to seek out the genetic signatures of viruses and bacteria to allow quick diagnoses of infectious ailments. Importantly, such MinION apps can give physicians access to rapid and low-cost genetic readings, especially in regional or remote hospitals that lack the resources for more powerful sequencers, Ammar says.

Users will also have access to a cloud-based analyzing system – known as Metrichor and developed by the manufacturer — to boost their computational power. The MinION will analyze strands of DNA isolated and prepared from blood or other tissues and injected directly onto a tiny receptacle impregnated with the protein tubes on the device's inner surface.

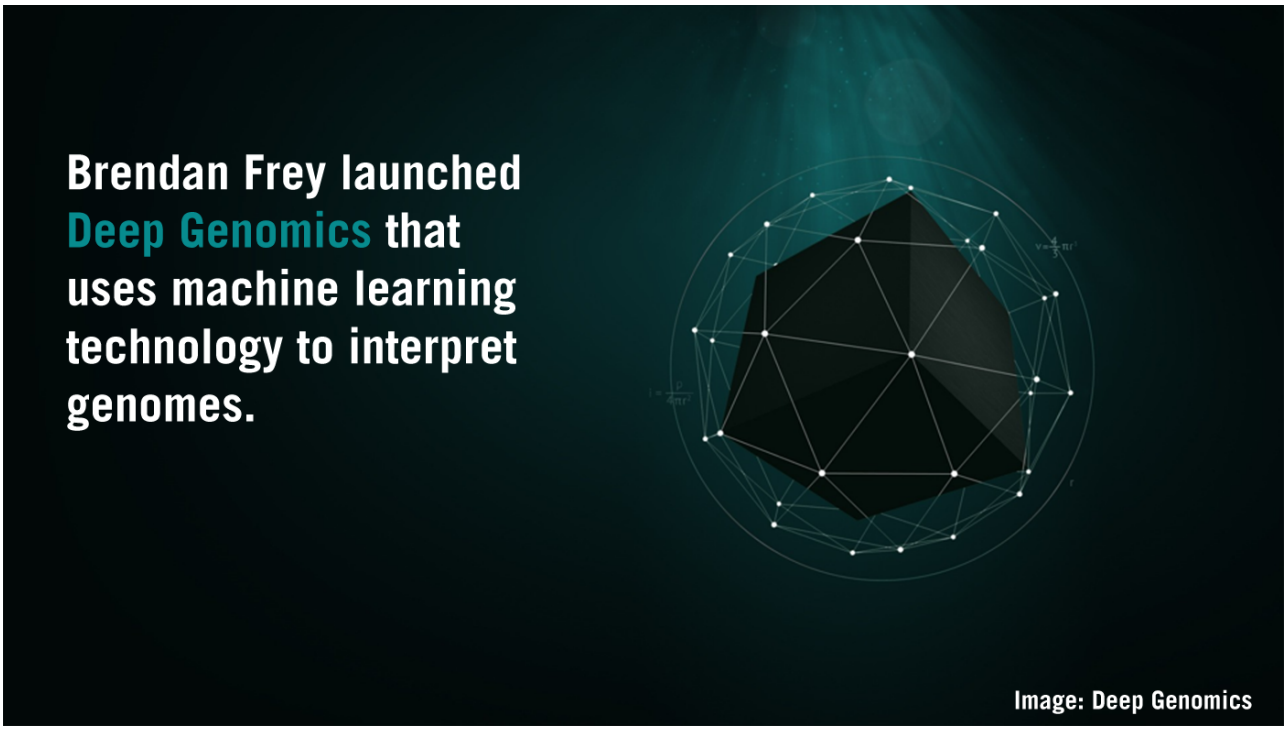
At the heart of the device's workings are protein-based "nanopores" – microscopically small tubular structures at the centre of a protein shell. An electrical current is passed through the hollow protein tubes. When DNA strands are then threaded through the electrified channels, their composite molecules – four pairing bases – each cause signature disturbances in the current.

These telltale disturbances identify the composition of the genetic material being scanned. Depending on which DNA strand the app is concerned with, the desired DNA strands – typically genes – can be separated from the rest of their home chromosome using standard lab equipment.

"They are working on a version of it where you can put blood straight onto it," Ammar says. "That's a couple of years away."

The device is usually covered with a thin cooling shell that gives it the look of an old iPod music player. As opposed to its $750,000 neighbours, which can process the entire genome in about a week at a cost of several thousand dollars, the MinION can produce readings on smaller segments of DNA in hours, for a fraction of those costs, Ammar says.

"You can actually in theory go from taking the sample from a person, getting the DNA and having it run on this (MinION) and within three hours getting data out."



Deep Genomics Startup Uses AI to Read Genomes

By Marit Mitchell, U of T Engineering

It's the first startup in the world to combine more than a decade of world-leading expertise in the fields of both deep learning and genome biology.

Its goal: to transform the way genetic diseases are diagnosed and treated.

Launched July 22, **Deep Genomics** was spun out of research at the University of Toronto and its founders say it will transform genetic testing, pharmaceutical development and personalized medicine. The company is already grabbing headlines around the world, including in *The Washington Post*, *The Globe and Mail* and *Vice|Motherboard.*

"**We're inventing a new generation of deep learning technologies that can tell us what will happen within a cell when DNA is altered by natural mutations, therapies or even by deliberate gene editing**," said Dr. **Brendan Frey**. The company's president and CEO, Frey is also a professor in both The Donnelly Centre and The Department of Electrical & Computer Engineering at U of T and a senior fellow of the Canadian Institute for Advanced Research.

Scientists have discovered how to read and write the DNA code in a living body, using hand-held genome sequencers and gene-editing systems. But knowing how to write is different from knowing what to write. To diagnose and treat genetic diseases, scientists

must predict the biological consequences of both existing mutations and those they plan to introduce.

"Companies like Google, Facebook and DeepMind have used deep learning to hugely improve image search, speech recognition and text processing. We're doing something very different. The mission of Deep Genomics is to save lives and improve health," said Frey.

Deep Genomics is also releasing its first product, called SPIDEX, which provides information about how hundreds of millions of DNA mutations may alter splicing in the cell, a process that is crucial for normal development. Because errant splicing is behind many diseases and disorders, including cancers and autism spectrum disorder, SPIDEX has immediate and practical importance for genetic testing and pharmaceutical development. The science validating the SPIDEX tool was described in the January 9, 2015 issue of the journal *Science.*

"The genome contains a catalogue of genetic variation that is our DNA blueprint for health and disease," said Professor Stephen Scherer, director of The Centre for Applied Genomics at SickKids and the McLaughlin Centre at U of T, a CIFAR Senior Fellow, and an advisor to Deep Genomics.

Until now, geneticists have spent decades experimentally identifying and examining mutations within specific genes that can be clearly connected to disease, such as the BRCA-1 and BRCA-2 genes for breast cancer. However, the number of mutations that could lead to disease is vast and most have not been observed before, let alone studied.

These mystery mutations pose an enormous challenge for current genomic diagnosis. Labs send the mutations they've collected to Deep Genomics, and the company uses their proprietary deep learning system, which includes SPIDEX, to 'read' the genome and assess how likely the mutation is to cause a problem. It can also connect the dots between a variant of unknown significance and a variant that has been linked to disease.

"Faced with a new mutation that's never been seen before, our system can determine whether it impacts cellular biochemistry in the same way as some other highly dangerous mutation," said Frey.

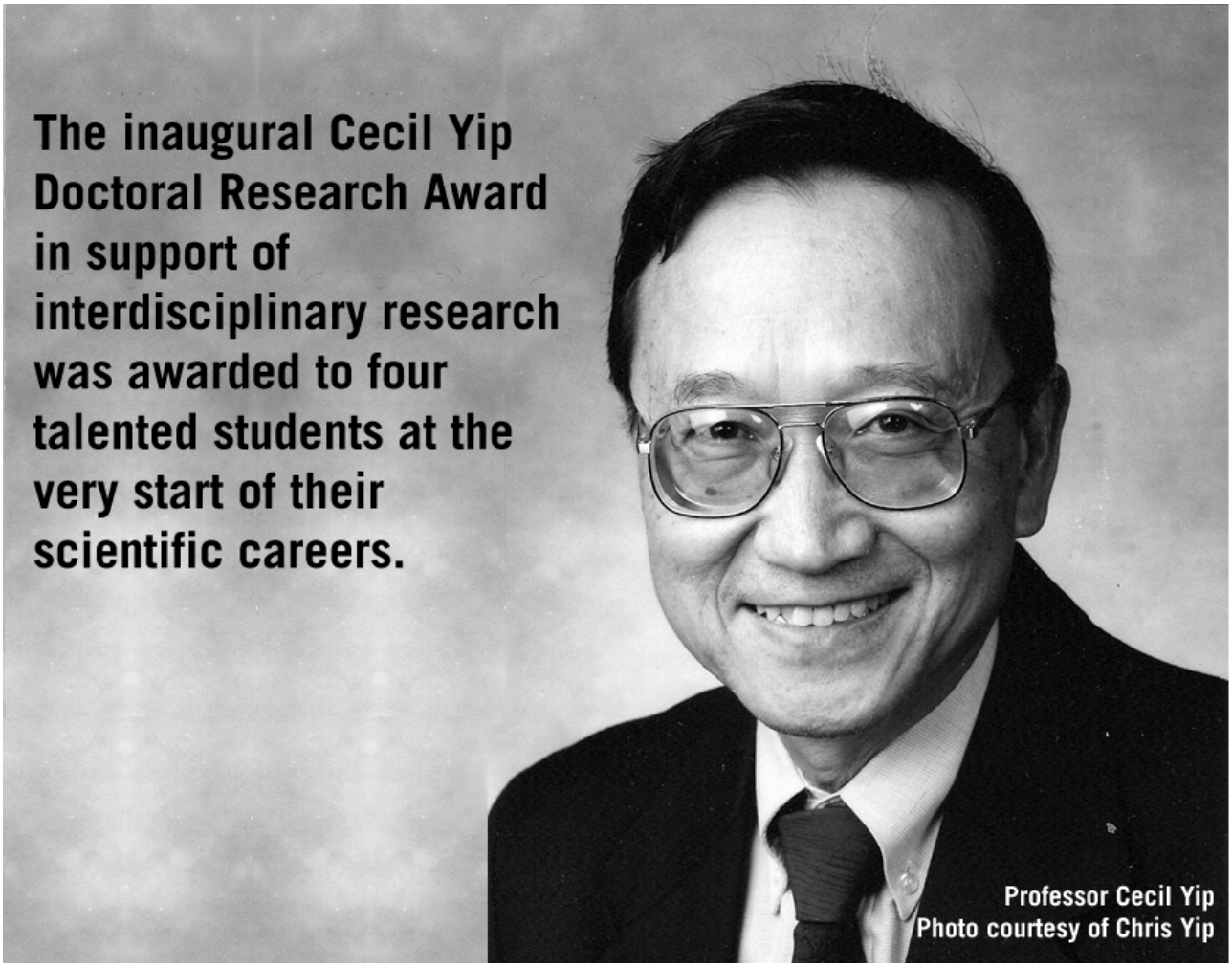
Deep Genomics is committed to supporting publicly funded efforts to improve human health. "Soon after our Science paper was published, medical researchers, diagnosticians and genome biologists asked us to create a database to support academic research," says Frey. "The first thing we're doing with the company is releasing this database—that's very important to us."

"Soon, you'll be able to have your genome sequenced cheaply and easily with a device that plugs into your laptop. The technology already exists," Frey said. "When genomic data is easily accessible to everyone, the big questions are going to be about interpreting the data and providing people with smart options. That's where we come in."

Deep Genomics envisions a future where computers are trusted to predict the outcome of experiments and treatments, long before anyone picks up a test tube. To realize that vision, the company plans to grow its team of data scientists and computational biologists. Deep Genomics will continue to invent new deep learning technologies and work with diagnosticians and biologists to understand the many complex ways that cells interpret DNA, from transcription and splicing to polyadenylation and translation. Building a thorough understanding of these processes has massive implications for genetic testing, pharmaceutical research and development, personalized medicine and improving human longevity.

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

WE CONTINUE TO ATTRACT THE BEST STUDENTS AND FELLOWS



Meet the Recipients of the Inaugural Cecil Yip Doctoral Research Award

By Jovana Drinjakovic

From targeting glioblastoma to improving nanoparticle traffic in the body to charting protein diversity in the brain, the recipients of the inaugural Cecil Yip Doctoral Research Award — Amy Arnold, Amy Hu, Wilson Poon and Jonathan Roth — are diving into their PhDs by tackling some of the biggest questions in biomedicine.

The award was established as a tribute to Professor **Cecil Yip**, who co-founded the Donnelly Centre. It recognizes outstanding candidates, in their first year of graduate studies, whose

proposed research crosses disciplinary boundaries. The Award Committee is chaired by Professor Chris Yip and its members are: Professors Charlie Boone, Warren Chan, Andy Fraser, Quaid Morris and Will Ryu.

Meet the 2015's award recipients:

Amy Arnold became fascinated with the idea of using polymers as drug vehicles as a summer research student, midway through her undergraduate degree in chemistry at University of Prince Edward Island. Having decided to pursue a PhD in polymer design and drug delivery in the Department of Chemistry, Arnold joined the Shoichet lab.

"**I chose the Shoichet lab for my PhD because I believe the lab is working at the frontier of both polymer chemistry and biomedical applications for innovative applications**," says **Arnold**.

During her PhD, Arnold will investigate if tiny polymer-based capsules, called nanomicelles, can be used to deliver drugs to glioblastoma – the deadliest form of brain cancer. "**Even with aggressive surgery and chemotherapy, patients only survive for a few months**," says **Arnold**. Arnold will target the glioblastoma stem cells, from which the tumour spreads, with siRNAs that turn down the genes responsible for tumor invasion and drug resistance.

Arnold is collaborating with other labs to achieve her goals. With the help of **Sidhu** and **Moffat** labs, Arnold has already coupled the nannomicelles to specific antibodies that will help deliver the siRNA to the brain tumor. Arnold's collaborations extend beyond **Toronto** – Drs. Kevin Petrecca and Masad Damha from McGill University will provide siRNA and glioblastoma samples, respectively.

Amy Hu's project is also looking for ways to attack glioblastoma but her approach is different to Arnold's. Co-supervised by **Sidhu** and **Moffat** in the Department of Molecular Genetics, Hu will carry out a comprehensive analysis of proteins known as the Ephrin receptors, which are hypothesized to play a role in glioblastoma stem cells and drive tumor growth and resistance.

"**I feel that applying the Sidhu lab's technology of synthetic antibody development to the Moffat lab's study of cancer is extremely promising. The ultimate goal is to provide new hope for glioblastoma patients**," says **Hu**.

To better understand the causes behind tumour growth, Hu is using the synthetic antibody production platform to help develop and apply antibodies that specifically recognize different Ephrin receptors. This will allow Hu to analyze the dynamic changes in Ephrin receptors at the level of individual cancer stem cells in an effort to find potential drug targets.

Hu had previously worked as a researcher at the University of Ottawa's Institute of Mental Health Research and then at Pfizer Canada. Once she earns her PhD, Hu wants to return to drug development in a senior role.

A U of T engineering graduate, **Wilson Poon** first delved into an interdisciplinary biomedical research as a masters student at McGill in Montreal, where he investigated the use of nanoparticles in medicine. Poon will continue to pursue these interests as a PhD student in Dr. **Warren Chan's** lab, jointly affiliated between the Donnelly Centre and the Institute of Biomaterials and Biomedical Engineering.

The goal of Poon's project is to find a way to make the drug-delivery by nanoparticles more effective. Nanoparticles all too often accumulate in the liver, which causes chronic inflammation and limits their therapeutic potential. By removing the liver macrophages, the cells that engulf the tiny particles and accumulate them in the liver, Poon has been able to improve the nanoparticles' ability to reach disease sites.

Straddling engineering and biology, Poon will collaborate both with Donnelly researchers, such as **Andrew Emili** to analyze the proteins involved in nanoparticle-blood interaction, as these proteins may dictate their transport inside the body, and with external researchers such as Dr. **Ian McGilvray** at the UHN, who is a specialist in liver disease.

Jonathan Roth graduated in Molecular Genetics at U of T before joining its graduate program, where he is pursuing a PhD under co-supervision of Drs. **Ben Blencowe**, at the Donnelly Centre and **Anne-Claude Gingras**, at Mount Sinai's Lunenfeld Tanenbaum Research Institute (LTRI).

Roth is investigating how alternative splicing – a process key to generating protein diversity in the cell — influences interactions between proteins that drive brain development and disease.

A project of this scope would be hard to carry out in a single research group. To analyze effects of alternative splicing on neural protein-protein interactions, Roth will use a robotic platform in collaboration with Drs. **Mikko Taipale** (Donnelly) and **Jeff Wrana** (LTRI) and also advanced mass spectrometry methods recently developed in Dr. Gingras' lab. Roth will also employ the latest computational methods to analyze a vast amount of data that these experiments will produce.

"**I think that the Donnelly Centre is a excellent place for my work, which involves the combination of different transcriptomic and proteomic approaches, the integration of which is only possible through the multidisciplinary and collaborative nature of the Donnelly Centre**," says **Roth**.

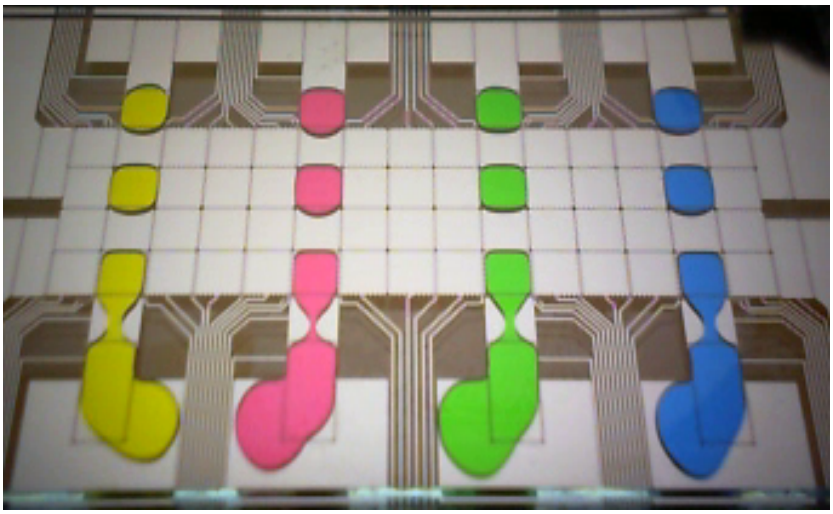
Alphonsus Ng Won the Donnelly Centre's Thesis Prize

By Jovana Drinjakovic

In the true collaborative spirit of the Donnelly Centre, **Alphonsus Ng** brought his skills as an engineer to solve some of biology's difficult questions. He was awarded the highest student accolade - the 2015 Donnelly Thesis Prize - for his work on developing **microfluidics-based technologies** for use in clinical diagnostics and biological research. This work was supervised by Dr. **Aaron Wheeler**, a professor at the Donnelly Centre and Department of Chemistry.

The award committee, chaired by Professor **Christopher Yip**, also of the Donnelly Centre, announced their decision on May 27, 2015. "**The Donnelly Thesis Prize Committee was impressed with not only the exceptional interdisciplinary and collaborative nature of Alphonsus' work, but also its clear translational potential**," says **Yip**.

The goal of Ng's research was to miniaturize laboratory processes, such as clinical diagnostics, onto chips no bigger than a credit card. The reading of the chip, and data analysis, are done by another custom-built instrument. Such instruments are smaller and faster than the cumbersome robotic liquid handlers that are currently used for sample analyses in central facilities.



A microfluidics chip with colored liquid split into droplets

Microfluidics chips engineered in the Wheeler lab are special in that liquid is moved around as individual droplets rather than as a stream. This is made possible by tiny electrodes that form a checkerboard pattern on the chip. By applying voltage to these electrodes, electric fields can be generated that split liquid with biologically relevant materials into many separate droplets, which can be individually manipulated. This allows experiments to be done in batches where each droplet corresponds to a single test tube in a standard laboratory experiment.

During his doctorate, Ng developed two distinct applications for the microfluidic device, to be used for clinical diagnostics and biological research.

Last year, Ng and his colleagues won a Grand Challenges Canada grant of $112,000 to test how well their device detects rubella and measles in a population in Vietnam, where infection rates are high. The researchers will use the grant to prepare the device and instrument for use in the field. "I want to make it smaller, lighter and cheaper," says Ng, who hopes to apply his technology in the field later next year.

Another application of Ng's research will help scientists get a better grasp of dynamic signaling events in a cell, such as protein phosphorylation, which play out rapidly and are often missed by traditional, slower methods. Using microfluidics chips, Ng, along with Dr. Dean Chamberlain, a former postdoc (now research associate) in Professor Michael Sefton's group at the Donnelly Centre, have been able to observe these events closer to real time. Their work will be published later this month.

Ng's love of engineering started when he was in high-school. "I was playing a lot of video games back then," says Ng. This led to an interest in graphics card design and an

undergraduate degree in engineering science at the University of Toronto. In his final year, Ng "tested the waters" in the Wheeler lab and never looked back.

"The Donnelly Centre is truly like a home to me," says Ng, who collaborates extensively with other labs in the building. "The environment is really amazing. There are three other groups on my floor and I talk to them very often and come up with joint projects. I don't think that would have been possible if it was not for the shared environment," says Ng.

Wheeler said he had never met a student like Ng. "Alphonsus brings an almost unbelievable combination of intellect, hard work, persistence, kindness, and a nose for what is 'important' to his work as a scientist. I am grateful for the opportunity to have worked with him over these past few years," says Wheeler, who is also a professor in the Department of Chemistry and the Institute of Biomaterials and Biomedical Engineering.

Ng's future plans include a postdoctoral position in the west coast of U.S., where he wants to continue to engineer small and powerful biomedical instruments.

"Eventually I hope to be a prof one day. I want to develop some really cool technology in the U.S. and bring it back to Canada," says Ng. Would he like to come back to the Donnelly Centre? "I'll try my best," Ng says with a broad smile.

Donnelly Thesis Prize was established in 2006 and its previous recipients have gone on to take postdoctoral and faculty positions in world-leading research institutions, including Harvard, MIT and Princeton.

Marjan Barazandeh Won the Charles H. Best Postdoctoral Fellowship

By Jovana Drinjakovic

Dr. Brenda Andrews and The Charles H. Best Fellowship Committee were pleased to announce that **Dr. Marjan Barazandeh** was awarded the 2015 Best Fellowship. The Committee members were particularly impressed by Marjan's evolutionary background and her desire to switch gears for her postdoctoral work in Dr. **Timothy Hughes'** group.

Marjan earned her PhD from the University of Alberta where she studied barnacle mating behavior and population genetics. Using molecular biology tools, Marjan was able to show that isolated barnacles mate by transferring sperm in the water. Her work settled an old dispute in the field of marine biology.

In her postdoc, Marjan will study the complex relationship between transcription factors (TFs), proteins that bind DNA, and transposons, or the "selfish-DNA", that move around the genome and change gene function in a way that can lead to diseases such as cancer. Marjan will focus on the C2H2 ZF family of TF, which can halt this "selfish DNA". C2H2 ZFs are fast-evolving, and Marjan will investigate if their high rate of change is driven by the rapid movement of the transposons they are trying to silence. Her postdoc will likely bring new discoveries on genome evolution and how diseases occur.

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

BRINGING OUR SCIENCE TO THE NEXT GENERATION OF RESEARCHERS

From primary school kids to high school students and parents, our outreach efforts this year touched a broad audience.

High School Outreach

We hosted a day of fun science for students from Bnei Akiva and Dunbarton high schools in Toronto.

Each visit kicked off with an inspirational science talk from one of Donnelly investigators. With the help of volunteering Donnelly graduate students, our visitors then got first-hand experience of basic methods in molecular biology and genetics. The students also toured the building and had an opportunity to see the robotic equipment for large scale yeast genetics, retinal stem cells growing in a dish and transgenic organisms such as fluorescing yeast and worms.

At the end of the day, the Donnelly volunteers and outreach organizers held a Q&A addressing any questions students might have about further education and careers in science.

Dunbarton high school students looking at different worm mutants in a dish

Bring Our Children to Work Day

BOCW is a whole day event, organized every year by the University of Toronto, when university employees can show their kids in grades 4-7 what mom or dad (or both) do all day when they go to work.

20 children and eight parents participated in the event organized by Dr. Christine Misquitta with the help from amazing Donnelly graduate students. The day started with Misquitta's presentation on the DNA and different ways in which Donnelly researchers tackle some of the biggest questions in genetics. The children then got to extract from their mouth their DNA which they took home in specially made necklace pendants.

Misheel Chuluunbaatar isolating her own DNA

Science Rendezvous

Science Rendezvous is a nation-wide day event that brings wonders of science to everyone. In Toronto, kids of all ages, and their parents, are invited to visit stalls set up by different U of T departments to learn about diverse research that occurs across the campus.

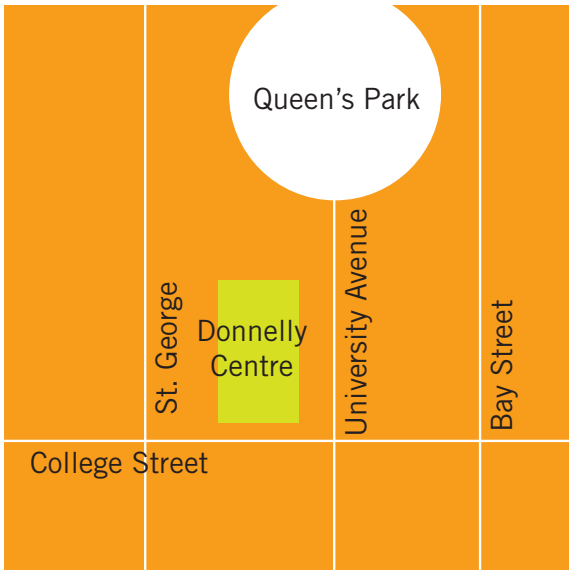
The Donnelly Centre stall attracted more than 200 people and included microscopes through which visitors could see live animals, such as worms and fish – all are model organisms used at the Centre to study basic biology as well as human disease. We also had a station for loading DNA gels CSI-style and for decoding a secret message written in the DNA language.

YOUR SUPPORT WILL HELP US HAVE AN EVEN GREATER IMPACT IN 2016

THANKS EVERYONE FOR A FANTASTIC 2015!

Please visit our website:

www.thedonnellycentre.utoronto.ca



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