Molecular Genetics
UNIVERSITY OF TORONTO

MoGeNews

Issue 7 - April 2016

Editor's Message

We hope that you are enjoying a much anticipated start to spring! We are delighted to announce the date for our next Career Development Alumni Symposium, and hope that you will all be able to join us on June 10th from 1-7 pm in Toronto. Our symposium has been widely acclaimed as a model to EDUCATE trainees about career possibilities, EMPOWER trainees to effectively network and identify career opportunities, and ENABLE trainees to develop skills to succeed in diverse careers. It was also an outstanding opportunity to ENGAGE our alumni and build relationships across our vibrant community. Please click here to register!

We would also like to encourage all members of our community to keep us posted on discoveries, awards and achievements. Your input is crucial as we continue to build an engaged community.

We will keep this message short and sweet so that you can focus on the many highlights of community events, alumni trajectories, research discoveries, and faculty and student achievements in this issue of MoGeNews.

Sincerely,

Leah Cowen

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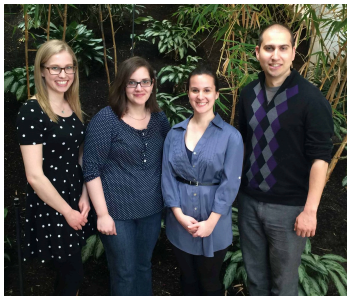
Community Events

MoGen Holiday Party. On December 11, the Department of Molecular Genetics gathered together for its annual Holiday Party. As one of the biggest highlights of the year, almost the entire department puts on their fanciest clothes for a night of socializing, dancing and, lets face it, eating and drinking. Held at the UofT Faculty Club, we saw our biggest crowd ever this year from faculty and students alike. The main attraction was a “selfie booth” featuring a festive backdrop, fun costumes and a selfie stick. As expected, the selfies got goofier and blurrier throughout the night. At the end of the night, people were reluctant to end the fun and had to be escorted out by the faculty club staff. As always, we hope everyone had a great time and look forward to the next year!



2016 GSA Elections. With a new year comes a new team for the MoGen Graduate Student Association! This year, the GSA comprises of over 40 outstanding graduate students, showing just how motivated the students in the department are to provide an exciting and social atmosphere! Sabrina Stanley, from the Davidson lab, will be leading the charge this year. When asked about her thoughts on her new position as the President of the GSA, she very diplomatically says, “I look forward to working with the new Department Chair in making sure our students get the very best graduate experience, and this year will be the best!”. She also wants to tell the students to look forward to lots of exciting pub nights, board games, ice cream, BBQs, and much more! We would like to thank all members of the previous year’s GSA, especially outgoing president Kenneth Grisé, for their hard work in keeping the students and faculty engaged. Photo (left to right): Elizabeth Polvi (VP External), Sabrina Stanley (President), Amanda Veri (VP Internal), Eric Chapman (VP Student Life).

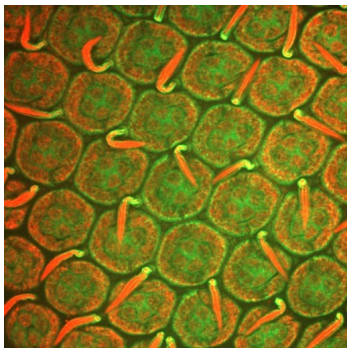
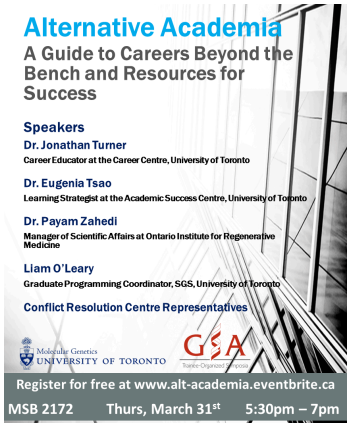


Image from Lauren Del Bel and Julie Brill. Wild-type Drosophila pupal eye stained for actin (red) and armadillo (green).

Collaborative Program in Developmental Biology Mini-Symposium. The Collaborative Program in Developmental Biology (CPDB) brings together researchers from six different departments at the University of Toronto under the unifying theme of developmental biology. The CPDB held its Winter Symposium on February 19th, featuring talks from senior graduate students in the program spanning from planarian brain regeneration to breast cancer to vesicle trafficking. This year, four of the presentations were by Molecular Genetics students: Chikin Kuok (McNeill lab), David Brown (Pearson lab), Nandini Raghuram (Egan lab), and Monica Wu (Claycomb lab), who also had the honour of taking home the second place prize ($200) for her talk. As always, the Symposium was an inspiring day highlighting the importance of fostering collaborations and the amazing research at our University. Many thanks to the CPDB steering committee, especially Julie Brill and Cindy Todoroff, for all of their hard work coordinating the program and organizing the Symposium!

MoGen Career Development Workshop on "Using Your Degree as a Stepping Stone." The MoGen Career Development Initiatives have continued full steam ahead in 2016, with even more amazing invited speakers and a broad range of topics that appeal to everyone. In January, the first workshop entitled "Using Your Degree as a Stepping Stone", was geared towards Masters students and helped to highlight some of the unique careers and continuing education options that are available to them after graduation. The panelists included Meghan O'Brien, MBiotech (Healthcare and Life Sciences Account Executive), Grace Chan, MSc (Clinical Research Coordinator) and Nick Watkins, MSc (Genetic Counsellor). One reoccurring theme from all panelists was how a Masters degree was a valuable investment and the problem solving skills acquired are highly transferable to many career options outside of the lab.

MoGen Career Development Workshop on "Exploring "Industry": Where Do You Fit In?" The February Career Development workshop was co-organized with the Department of Laboratory Medicine and Pathobiology. The Career Ambassadors really went above and beyond for this workshop. They implemented a "Mock Industry Job Interviews" component, which started with students submitting their CVs for four different job postings and then attending an interview with an expert in that field. This option was immensely popular. It provided extremely valuable feedback to students on how they should apply for jobs and practice for how to conduct interviews, which are opportunities that are hard to come by in graduate school. The panel discussion was also very lively and useful. The keynote speaker was John Millholland, PhD (Associate Director at Novartis) and additional panelists included Ronan Rogers, PhD (Medical Liason for Biogen), Jeremy Sivak, PhD (Professor at the University of Toronto & Research Investigator and Project Leader at Novartis), and Eric Lee, MSc (R&D Technical Coordinator at Septodont). All speakers emphasized that industry is a very different atmosphere from academia - it is much more fast-paced, there are usually more meetings and collaborative work, the business lingo takes some getting used to, but there is also the promise of medium-sized barrels of money.



MoGen Career Development Workshop on "Alternative Academia: A Guide to Careers Beyond the Bench and Resources for Success." This workshop educated students on other options in academia besides becoming a principle investigator/professor. Again, standards were held high and the panelists were amazing, including: Jonathan Turner, PhD (Career Educator at the Career Centre), Eugenia Tsao, PhD (Learning Strategist at the Academic Success Centre), Payam Zahedi, PhD (Manager of Scientific Affairs at Ontario Institute for Regenerative Medicine) and Liam O'Leary (Graduate Programming Coordinator). As always, the advice given was broadly applicable and helpful for all graduate students, no matter what stage they were at in their career. A favourite line of the night was "it's not necessarily bad to procrastinate, but procrastinate strategically." Work is already under way for the next set of career development workshops. If you are still unsure as to what career path you would like to pursue or how to get there, be sure to attend as many as you can. There is also plenty of free snacks and coffee!

St. Patrick's Day Pub Night. The annual St. Patrick's Day Pub Night hosted by the GSA was held on March 16th at the Marquis of Granby. Everyone was all decked out in their traditional green attire. Actually, several green MoGen retreat t-shirts could be seen milling around, so it just goes to show how multi-purpose those t-shirts can be! There were some free pitchers of beer and food, although those got finished off fast, but they were certainly not the last pitchers of beer…. After a long day of lab work, it's always great to be able to celebrate like the Irish!

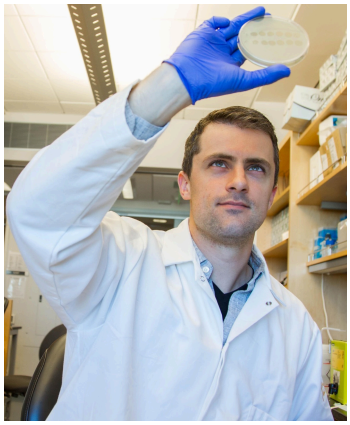
Graduate Information Day. Graduate Information Day was held on April 1st this year and welcomed the largest group of perspective students yet: over 50 attended and a significant portion had already submitted their acceptance letters! Herculean efforts were made by the Graduate Students' Association and the Graduate Recruitment Committee, especially Brian Ciruna, Gary Bader, Ian Scott and Julie Claycomb, for coordinating key aspects of the day and making sure everything ran smoothly. To learn more about highlights of the day, including fascinating faculty talks, navigating the research nodes for faculty interviews, a dynamic poster session, and a vigorous dinner/pub night at Prenup Pub click here.

MoGen Hockey Team Final Game of the Season. The MoGen hockey team, The Fighting Darwins, ended their season this year with an exciting game against the Department of Political Science. The game was intense right from the beginning, with MoGen down one point until halfway though the last period, but team captain, Max Landon, kept spirits high and the game ended as a tie. Both sides looked happy and were satisfied to end the season on a high note. The MoGen hockey team is the only one this season with a good representation of both female and male players. They are always open to new recruits who are interested in getting out of the lab and participating in something active, exciting and semi-competitive (it's more important to have fun than to win, right?).

Alumni Spotlights

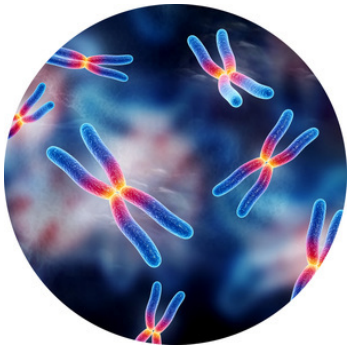
Dr. Zhigang He shares his memories from starting as a medical student in China to his graduate studies in Dr. Jim Ingles' lab to finally becoming a Professor of Neurology at Harvard Medical School. Zhigang discusses his inspiration and work in inducing axon regeneration in the central nervous system in order to develop better neural repair strategies. He also provides advice to students, such as the importance of keeping an open mind and being receptive to the many opportunities around them. Click here to read the full spotlight.

Dr. Cheryl Birmingham completed her PhD in John Brummel's lab and directly started her career in industry through an NSERC-funded industrial post-doc position - she is now the Head of Bacteriology at Sanofi Pasteur. Through her personal experience after working in industry, Cheryl provides sage advice to trainees hoping to break through and land that first position at a company. Cheryl also reminisces about her time as a graduate student in MoGen and all the wonderful friends and connections she made, and the important impact that had on her career trajectory. Click here to read the full spotlight.



Dr. Joseph Bondy-Denomy, Faculty Fellow at UCSF, shares his experiences starting as an accounting major to finding out that working in the lab is his true calling to discovering a whole new component of the CRISPR-Cas system, which he named “anti-CRISPRs”, through his work in Dr. Alan Davidson’s lab. As a recent graduate, Joe offers insight and advice to those who are hoping to pursue a career in academia. Instead of dwelling on the competitiveness and lack of funding, Joe emphasizes the importance of having a polished story and figuring out your own niche in order to obtain a faculty position. Click here to read the full spotlight.

Spotlight on MoGen Research Field: Molecular Medicine and Human Genetics



A new era in medical intervention is on the horizon, enabled by revolutionary advances in genetics and genomics. The Human Genome Project has changed our approach to biology and medicine. As the power of the genome sequence became evident, technologies have also rapidly advanced, allowing sequence data from individuals to be acquired at a phenomenal pace and at increasingly lower costs. Massively parallel sequencing (also known as next generation, or NextGen, sequencing) has ushered in the era of genomic and genetic medicine. Now, equipped with the genome sequence of a patient, scientists can diagnose genetic disease, identify future disease risk, home in on disease modifiers and predict responses to drugs.

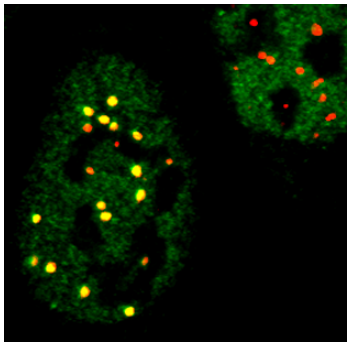
Researchers in the Department of Molecular Genetics have led the world in identification of single genes that, when mutated, cause diseases such as cystic fibrosis, Duchenne muscular dystrophy, myotonic dystrophy, neurofibromatosis, and retinoblastoma. Now, researchers elucidate the more complex genetic basis of many multi-gene major disabling and fatal diseases including autism, muscular dystrophies, heart disease, stroke, diabetes, and several kinds of cancer. The identification of disease-association genes and their products will facilitate a better understanding of their function, as it paves the way towards effective diagnostics, therapeutics and preventative measures.

Identifying the gene is only one step towards understanding how it causes disease. Researchers in the focus area of Molecular Medicine and Human Genetics use cells and organisms as models for human disease to understand how gene mutations affect function, and to find ways to ameliorate the clinical outcome. As the sequencing revolution has changed our approach to science, a genetic revolution is underway with the discovery of the RNA-guided nuclease systems such as CRISPR/Cas9, which allow for the engineering of any type of mutation to be created or corrected in virtually any cell or organism. Therefore, a genetic or genomic analysis of patient samples to study inherited diseases and susceptibility to disease is only the beginning, as new models to understand disease are developed, and used to improve treatments.

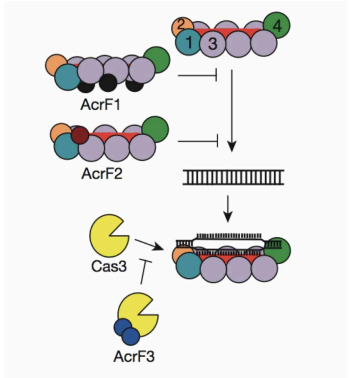
Scientific approaches and disease areas overlap extensively with other Molecular Genetics research focus groups to form an interdisciplinary, cross-institution community that is at the forefront of science nationally and internationally.

We invite you to read the full Field Spotlight for a closer look at some of the exciting research in Molecular Medicine and Human Genetics in MoGen.

Research Highlights

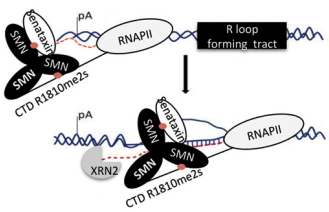


Discovery of how cells control DNA repair that is key to editing human genes as a means to cure disease. (Nature 2015, 528: 422-6). Imagine if we could correct genetic errors inside diseased organs and return them to health? Gene editing, a process by which inherited mutations can be fixed, has become possible, but it only works in cells that are dividing, which are scarce in our bodies. A team led by Dr. Daniel Durocher has discovered a way to perform this kind of precise gene editing in non-dividing, fully differentiated cell types. The key lies in control of homologous recombination, which is the method by which our cells mend mistakes in DNA caused by copying of the genetic material during cell division. Click here to learn more.

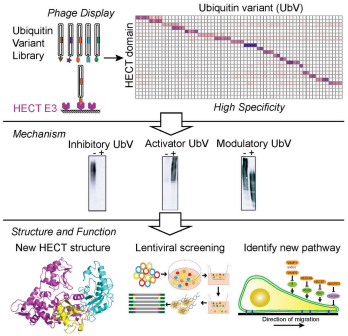


Study reveals new mechanisms by which viral proteins can turn off the CRISPR adaptive immune system of bacteria. (Nature 2015, 526, 136-9). The battle for survival between bacteria and the viruses that infect them has led to the evolution of many bacterial systems to defend against these invaders. CRISPR-Cas, one of the most widespread of these systems, is an adaptive system that that specifically targets viral genomes and stores a memory of previous infections. In prior work, a team led by Dr. Alan Davidson and his then graduate student Joe Bondy-Denomy identified the first examples of proteins produced by bacterial viruses that can inhibit CRISPR–Cas systems. In this paper, they elucidated the mechanisms of action of three of these anti-CRISPR proteins, and found that each functions in a distinct manner. This work provides insight into a completely novel group of proteins and increases our understanding of CRISPR-Cas systems, which have recently been developed into powerful tools for human genome editing.

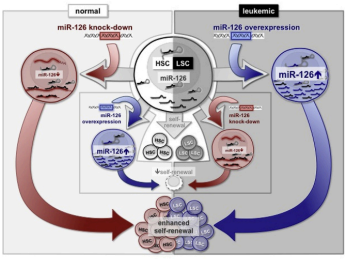
Study pioneers the use of the genome-editing technology to remove a duplicate gene in cells of a patient with muscular dystrophy. (American Journal of Human Genetics 2016, 98: 90-101). Dr. Ronald Cohn's team focused on cells from a young boy suffering from Duchenne muscular dystrophy, an aggressive muscle-wasting disease caused by a genetic mutation, for which there is no treatment and no cure. A duplicated DNA sequence renders his cells unable to make a critical protein called dystrophin. By genome editing, Cohn's team removed the duplication, restoring the gene's function. This work was featured in the Toronto Star. Click here to learn more.



Discovery of a molecular switch that links RNA Polymerase II, a key genome-reading machinery, with neurodegenerative disorders, shedding light on how some of these devastating diseases may begin. (Nature 2016, 529: 48-52). Team led by Dr. Jack Greenblatt found that RNA polymerase II (RNAPII), the key enzyme that puts the RNA together, becomes adorned 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 spinal muscular atrophy, a fatal motor neuron degenerative disease of infancy, and senataxin, which is sometimes mutated in amyotrophic lateral sclerosis, a motor neuron disease that affects speaking, swallowing and eventually breathing. Click here to read more.

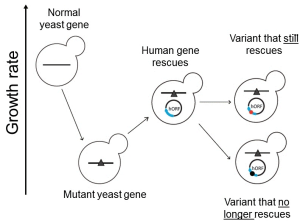


Development of a toolkit of variants of the small protein ubiquitin that modulate function of a core regulator of cellular biology that is misrelated in numerous diseases. (Molecular Cell 2016, 62:121-36). Team led by Dr. Sachdev Sidhu built upon the powerful high throughput synthetic antibody generation pipeline of the TRAC (Toronto Recombinant Antibody Centre), using phage-displayed libraries of small protein variants to generate biologically active modulators of protein function. Postdoctoral fellow Wei Zhang led the effort to characterize ubiquitin variants targeting HECT E3 ubiquitin ligases, which act as both inhibitors and activators of protein function. They established a general strategy for the highly efficient, systematic development of modulators targeting families of signaling proteins.

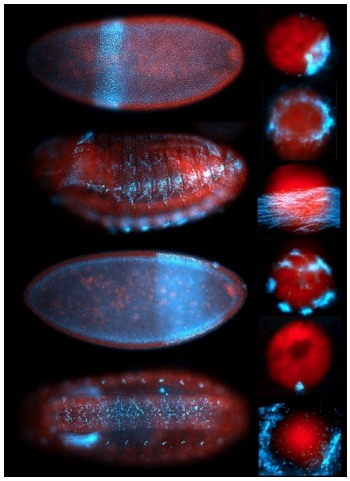


Discovery a mechanism through which a tiny RNA, miR-126, regulates self-renewal in normal and cancer blood stem cells. (Cancer Cell 2016, 29: 214-28). A team lead by Dr. John Dick revealed that this tiny RNA has opposing effects in normal blood stem cells and those associated with the blood cancer acute myeloid leukemia. In cancer stem cells, miR-126 targets core cellular signalling pathways to prevent differentiation and promote resistance to chemotherapy.

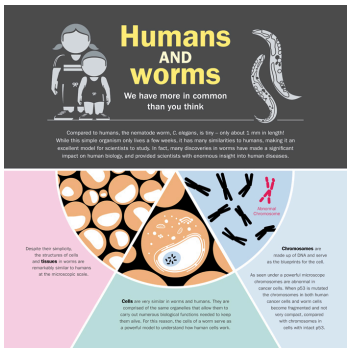
Study uncovers a novel mechanism controlling DNA repair in mammalian cells. (Molecular Cell 2016, 61: 405-18). Team led by Dr. Daniel Durocher uncovered a mechanism that controls how double-strand breaks in DNA are repaired. They discovered that a protein that unwinds DNA, a DNA helicase called HELB, is able to halt the process of chewing back DNA to create single-stranded overhangs that are needed to initiate repair via homologous recombination. This work has broad implications for understanding maintenance of genome integrity, and how this goes awry in cancer.



Study reveals how baker's yeast could improve patient diagnosis. (Genome Research 2016, PMID: 26975778). By testing the effects of human mutations in yeast, Dr. Fritz Roth's research team was able to identify harmful changes in the DNA better than leading algorithms. Roth's team focused on 22 genes, linked to conditions such as autism, mental retardation and heart disease, and whose intact copies were able to replace their yeast counterparts. Based on cell growth data, the researchers were able to identify 62 percent of disease variants as damaging. Click here to read more.



Discovery of distinct RNA neighbourhoods in cells throughout development. (Genes and Development 2016, 30: 594-609). Team led by Dr. Henry Krause builds on their previous discovery that ~70% of protein-coding RNAs are distributed into hundreds of distinct patterns in early fruit fly embryos prior to being translated into proteins. Their current efforts extend to over 8,000 RNA molecules and across different developmental stages. Essentially all examined RNAs, including those that don't code for proteins, existed in distinct spatial distributions in cells at some point during development. This work provides a powerful resource for functional analyses and highlights how mistakes in RNA distribution can lead to disease, including neurological disorders and cancer. Click here to read more.



Discovery of a key role for a tumour suppressor in repair of damaged DNA in a precise and error-free manner. (Current Biology 2016). Team led by Dr. Brent Derry and his MoGen student Abigail Mateo pioneered new insights into how p53 ensures genome stability using the powerful model nematode *C. elegans*. Derry says that "Previous research has primarily focused on how p53 destroys cells, or stops them from dividing, but this new work shines light on how it functions to repair DNA. Our findings are exciting because what we've learned here provides new insights into how p53 ensures genome stability that we can now pursue in human cells." To read more click here.

Faculty Highlights and Awards

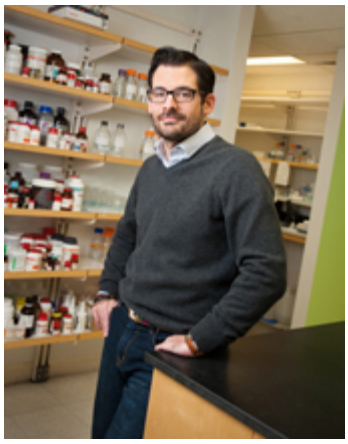
Dr. Brenda Andrews has been appointed as a Companion of the Order of Canada. Dr. Andrews received the highest level of the Order of Canada for her globally significant research in systems biology and for developing and nurturing prominent scientific communities in molecular genetics. Click here to read more.

Dr. Janet Rossant has been awarded the 2016 Henry G. Friesen International Prize in Health Research. The Friesen Prize recognizes Dr. Rossant's exemplary vision and innovation in developmental and stem cell biology. Dr. Rossant will also assume a new role as the President and Scientific Director of the Gairdner Foundation as of May 1, 2016. Click here to read more.

Dr. John Dick has been inducted to the American Association of Cancer Research Academy. The Academy recognizes "scientists whose major scientific contributions have propelled significant innovation and progress against cancer." Click here to read more.

Dr. Ronald Cohn has been appointed to the position of Chief of Paediatrics at The Hospital for Sick Children and Chair of Paediatrics at The University of Toronto. Dr. Cohn was recruited to the Hospital for Sick Children in 2012 to be the Chief of the Division of Clinical and Metabolic Genetics, Co-Director of the Centre for Genetic Medicine and Senior Scientist. He also became the Inaugural Women's Auxiliary Chair in Clinical and Metabolic Genetics in April of 2013, and is an Associate Professor in the Departments of Paediatrics and Molecular Genetics at the University of Toronto. He is the recipient of numerous awards including the David M. Kamsler Award for outstanding compassionate and expert care of pediatric patients, 2004; First Annual Harvard-Partners Center for Genetics and Genomics Award in Medical, 2006; and, the NIH Young Innovator Award, 2008.

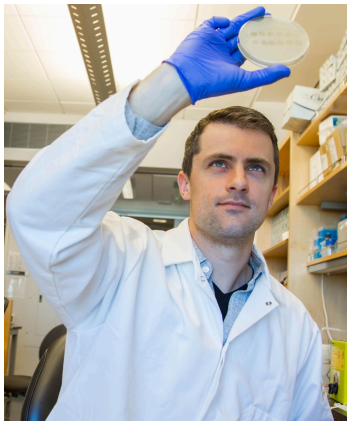
Dr. Helen McNeill has been awarded a Tier 1 Canada Research Chair. Dr. McNeill's research is focused on how cells become organized into tissues, and how growth is controlled during development.



Dr. Daniel Schramek has been awarded a Tier 2 Canada Research Chair. Dr. Schramek's vision is to leverage functional genomics to make major advances in treating human cancers in a personalized and highly specific manner by analyzing the exact molecular underpinnings of why a tumour develops.

Cancer Stem Cell Dream Team is co-led by MoGen Dr. Peter Dirks, with Drs. Gary Bader and Amy Caudy as key investigators. The interdisciplinary team is focused on developing new strategies to fight childhood and adult brain cancers. The team will gather detailed biological profiles on brain cancer stem cells (BCSCs) that drive cancer occurrence. The researchers will catalogue any changes in the cells' genetic code, as well as in epigenetic programming that controls gene activity. Despite advances in cancer care, brain tumours remain the most difficult to treat. The average survival for glioblastoma, the most common form, is entrenched at just 15 months following diagnosis. To gain a deeper understanding of the disease, the researchers will examine cancer stem cells from 70 patients. The team's research is supported by $11.7 million, funded by Stand Up To Cancer Canada, Genome Canada, the Canadian Institutes of Health Research, the Cancer Stem Cell Consortium and the Ontario Institute for Cancer Research (OICR). Photo left to right: Peter Dirks, Amy Caudy, and Gary Bader. Click here to read more.

Trainee Highlights and Awards



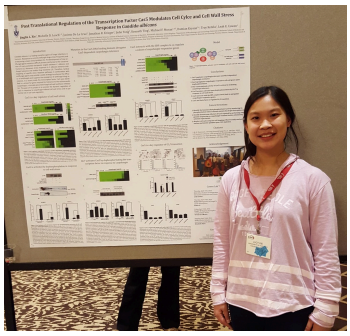
Joe Bondy-Denomy has been recognized with the 6th annual Barbara Vivash Award for most outstanding PhD thesis in the Department of Molecular Genetics for his graduate work in Dr. Alan Davidson's lab entitled "CRISPR meets its match: Bacteriophages inactivate CRISPR function." Joe discovered a new class of proteins that he named "anti-CRISPRs", which allows bacteriophages to turn off the bacterial CRISPR/Cas defense system. This opened up a whole new mechanism in how phages interact with bacteria. His groundbreaking discovery culminated in two first-author publications in Nature. His award ceremony lecture was extremely well attended, and the room was filled with old graduate school friends, all the professors that he interacted with over the years, lab mates, his wife and a proud mentor. Joe clearly had a large impact on many people throughout the Department. Dr. Howard Lipshitz had nothing but praise during his introduction, including commenting on Joe's "natural aptitude for deciphering experiments correctly" and his "independent and strong willed" character. For more insights into Joe's graduate life experience, his career trajectory and his words of wisdom, please check out his Alumni Spotlight, which is also featured in this issue of the newsletter.

Monica Wu from Dr. Julie Claycomb's lab is the recipient of a DeLill Nasser Spring 2016 Award. Ms. Wu has received funding to travel to the Keystone Symposium: Small RNA Silencing: Little Guides, Big Biology. To read more, click here..

Senjuti Saha from Dr. Alan Davidson's lab is one of the top three finalists in the University of Toronto 3-minute thesis (3MT) Competition, with Nathan Schachter from the Sean Egan's lab and Lucy Xie from Leah Cowen's lab also finalists in this intense competition. Click here to read more.

Megha Chandrashekhar from Dr. Jason Moffat's lab is one of the 2016 winners of the Jennifer Dorrington Graduate Research Award. Using the latest gene editing technology, known as CRISPR, Chandrashekhar sifted through the genomes of five different cancer cell lines to find distinct sets of genes that keep each of them alive. These sets of genes also reflect each cancer's unique vulnerability, its Achilles Heel, that could be targeted by specific drugs. Chandrashekhar's pioneering study paves the way for future research that will speed up the discovery of better and more precise treatments. To learn more, click here.

Mathieu Quesnel-Vallières from the laboratories of Drs. Ben Blencowe and Sabine Cordes is one of the 2016 winners of the Jennifer Dorrington Graduate Research Award.



Lucy Xie from Dr. Leah Cowen's lab wins an American Society of Microbiology Poster Presentation Award at the 2016 ASM Conference on *Candida* and Candidiasis.

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