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Molecular Genetics
UNIVERSITY OF TORONTO

MoGeNews

Issue 12 - Nov 2018

Editor's message

Welcome to this issue of MoGeNews! This fall we would like to highlight the **50th anniversary of the Department of Molecular Genetics in 2019**. To celebrate, we are arranging a two-day event: first, a scientific symposium and reception on Friday, May 31, 2019 (see below) followed by lab reunions on Saturday, June 1. We invite all current and former members of Molecular Genetics to visit and attend.

We welcome many new members to Molecular Genetics this fall: our new graduate students who are currently rotating through prospective labs, new MGY undergraduates to our programs, and new faculty and staff highlighted in this newsletter.

Do you have a recent study that we can highlight on the MoGen website as well as this newsletter? Please keep us posted on discoveries, awards and achievements. Your input is crucial as we continue to build an engaged community.

Barbara Funnell

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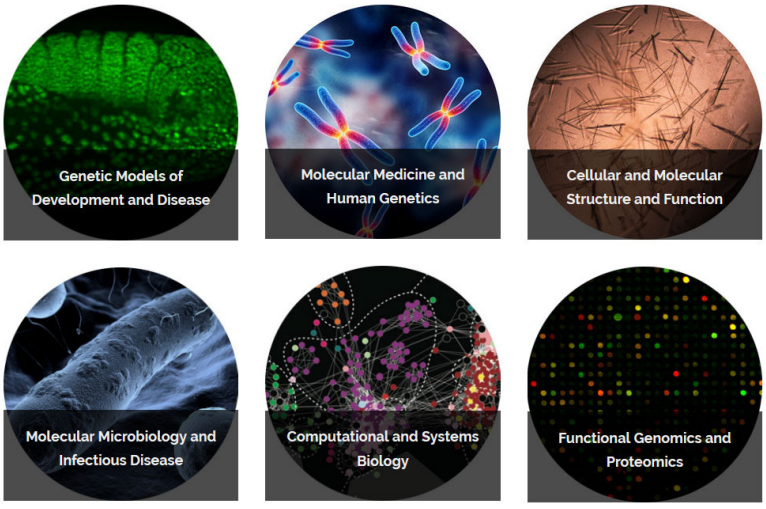
50th Anniversary of Molecular Genetics

Save the date:
May 31, 2019
The Department of Molecular Genetics (including all our previous names and incarnations) will be 50 years young in 2019. Please join us for a scientific symposium on Friday, May 31, 2019,



featuring notable
MoGen Alumni, to
celebrate the history and accomplishments of the Department. All current and former members of Molecular Genetics are invited. Come and visit old friends and make new ones! The event will be held at The Carlu in downtown Toronto. The plans also include lab reunions on the Saturday, so please visit and stay for the weekend! More details and a registration website will be forthcoming in the coming months.

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Community News and Events

4th Annual MoGen Career Development Symposium

The 4th Annual MoGen Career Development Symposium was held on June 4th, 2018 at the Chestnut Conference Centre in downtown Toronto. Our goals are to promote interactions between trainees and our many extraordinary alumni from the Department of Molecular Genetics. It was organized by Dr. Barbara Funnell, Dr. Leah Cowen, and a dedicated group of graduate students, Amanda Veri, Kali Iyer, and Nicole Revie.

The afternoon included round-table discussions between alumni and trainees, networking sessions, and a panel discussion by six distinguished graduates from Molecular Genetics: Dr. Masha Cemma (Policy Advisor, Office of the Chief Science Advisor of Canada), Dr. Blair Gordon (Director of Development, Edesa Biotech), Mr. Douglas Hamilton (President and CEO, MetaStat Inc.), Dr. Pamela Kanellis (Senior Director, Canadian Institute for Advanced Research), Dr. Liz Patton (Professor and MRC Programme Leader Scientist, University of Edinburgh), and Dr. Anthony Vecchiarelli (Assistant Professor, University of Michigan).

We were supported by over a dozen generous sponsors from our friends in biotechnology and the university community. Trainees included graduate and undergraduate students and postdocs from all nodes of MoGen. They networked with alumni and sought advice at the round-tables, coffee break and wine-and-cheese that capped off the afternoon. It was very well attended and was a great success!
For more images of the day, please see our alumni website.

Welcoming Spring at High Park

The GSA organized several events to introduce Toronto to our international students. These students were given first crack at the signup sheet, and then the events were open to all. Our first activity was a stroll through High Park to welcome the annual cherry blossoms

bloom on May 13. Both international and domestic students came out to bid winter's end by enjoying some picnic food kindly provided by the GSA, friendly Frisbee tosses, and the all-around nice weather.

Summer at the Toronto Islands

To end summer with a bang, we headed out to the islands for a potluck session on September 1st. In the midst of the heat wave, MoGen students had their last hurrah by wandering through and getting lost in the William Meany Maze, enjoying the beautiful Toronto skyline, but most of all - each other's company.

Friday Night Live (FNL) at the ROM

Fall was welcomed with 50 students, both international and domestic, exploring the dazzling galleries at the Royal Ontario Museum, accompanied by sumptuous food and drinks. A night full of art, culture and nature remixed, MoGen students hung up their lab coats as they helped launch this season's Friday Night Live, with the GSA providing a generous subsidy for all students who attended.

MoGen Retreat 2018

The retreat was

organized by Dr. Julie Lefebvre, Dr. Daniel Schramek, and Dr. Leah Cowen, with the assistance of Kali Iyer, Amanda Charlesworth, Ellen Langille, and their GSA team. Our Chair, Leah Cowen, organized an excellent scientific program comprising 15 faculty talks that captured the diversity and excellence of the research in MoGen. We also welcomed five new faculty members: Miguel Ramalho-Santos, Neal Sondheimer, Yun Li, Julien Muffat, and Stephanie Protze.

The retreat kicked off on Wednesday evening for first-year students and faculty with Power Hour night. PowerHour is our beloved tradition for student recruitment. Despite a tighter time limit, the faculty were creative and effective in extolling the virtues of their research and lab life in a 2-minute/1 slide pitch. The main retreat began on Thursday morning with 266 attendees, including 44 PIs, 68 rotation students, 136 graduate students, 11 post-docs/staff, and 7 undergraduate MGY specialists. The day began with opening remarks from Leah Cowen, followed by 2 sessions of presentations. In the afternoon, attendees were on the field for the annual trainee-against-faculty soccer match, or transformed their retreat T-shirts with colourful tie dye. Once again, the highlight of the retreat was the poster session, which featured 126 presentations by various members of the community. All available wall space was covered with posters, and rooms were filled with MoGen members presenting their work, and interacting and learning about their peers' research. The research being performed by our trainees is excellent, as highlighted in the eight poster presentations selected for cash awards. We capped off our day with a fantastic line-up of dinner entertainment organized by the GSA. The celebrations went into the night at the fire pits, and with music and dancing in the Barn. We were up and early for the morning session. Thanks to all for a successful retreat! Hope to see you at Geneva Park for our 2019 retreat, which will be held on Wed. Sept. 18th – Fri. 20th, 2019.

Farewell with many, many thanks, Iliana!
Iliana Sztainbok, our MoGen Graduate Program

Administrator, moved this summer to the position of Graduate Programs Administrator in the Faculty of Music. Iliana joined MoGen in 1998, and has kept our graduate program running smoothly for over 20 years. She has been an integral part of our administrative team. Her commitment and dedication played an important role in the success of the graduate program in the Department of Molecular Genetics. The depth of her knowledge is remarkable. We wish Iliana every success in her new role. She will be missed by all of us.

We welcome **Ramadhani (Rama) Ponda** who joins our team as the new Graduate Program Administrator. Rama comes to us from the Department of Laboratory Medicine & Pathobiology at UofT. He brings over 10 years of experience in graduate program administration. You can find him in MSB, Rm 4398, or contact him via email, graduate.coordinator@utoronto.ca.

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Alumni Spotlight

Professor Liz Patton is a MRC Programme Leader Scientist in the MRC Institute of Genetics and Molecular Medicine and Chair of Chemical Genetics at the University of Edinburgh. After completing her PhD in Molecular Genetics at the LTRI with Mike Tyers, Liz moved to Harvard Medical School to work with Len Zon, where she developed some of the first cancer models in zebrafish. Zebrafish followed her to Edinburgh where she

now runs a research group focusing on using zebrafish to study melanocyte development and melanoma.
Click here to read the full spotlight.

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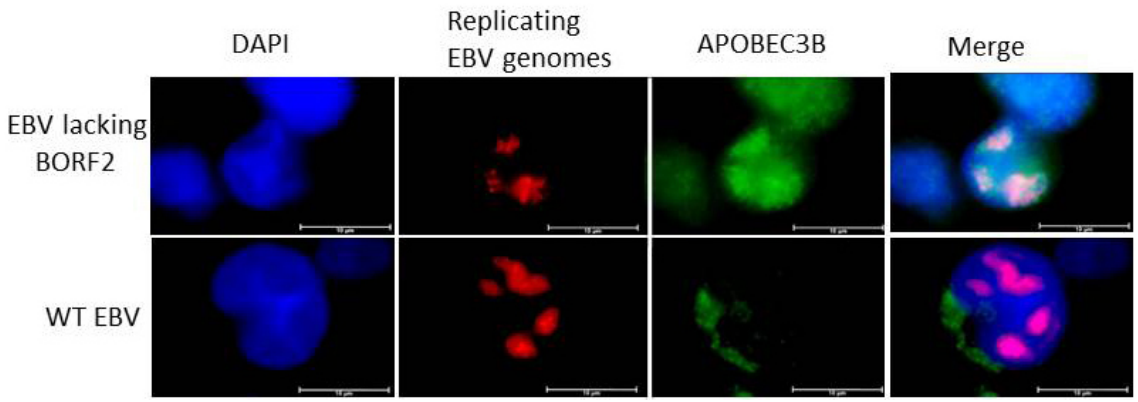
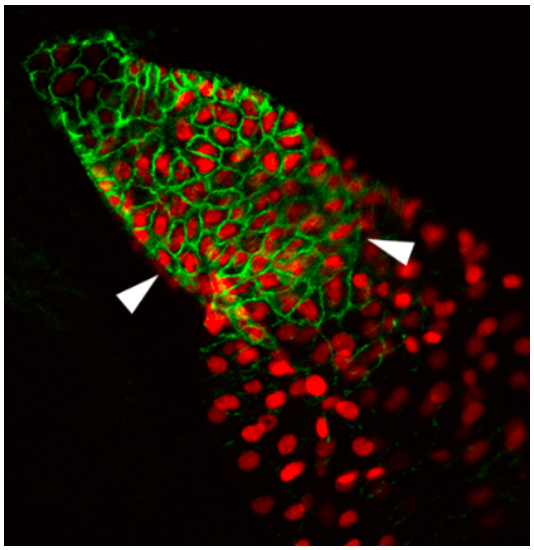
Research Highlights

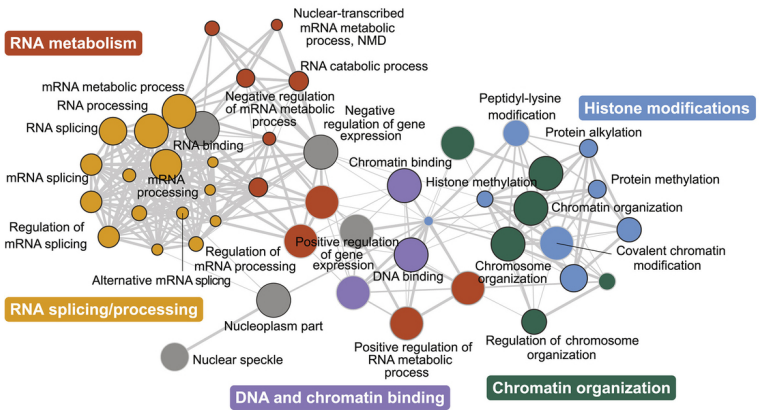


A new mechanism to inhibit Epstein-Barr virus infection, the virus responsible for kissing disease and several types of cancer. Most people are infected with Epstein-Barr virus (EBV), a herpesvirus that establishes a lifetime infection with no current treatments or vaccines. While usually asymptomatic, EBV can cause mononucleosis or "kissing disease" on initial infection, and persistent infection can cause several types of lymphomas and carcinomas. A proteomics experiment in **Dr. Lori Frappier's** lab identified an interaction between an EBV protein (BORF2) and a cellular DNA mutating enzyme called APOBEC3B. In collaboration with Reuben Harris's lab at the University of Minnesota, the team showed that BORF2 inactivates and relocalizes APOBEC3B away from replicating EBV genomes. They further showed that BORF2 was necessary to protect EBV genomes from mutation by APOBEC3B, which impairs the infectivity of the virus. The finding was unexpected, since it was not previously known that herpesviruses are susceptible to genome editing and need a mechanism to protect themselves from cellular editing enzymes. This provides a new opportunity to inhibit EBV infection by interfering with the BORF2-APOBEC3B interaction. It also provides a novel way of inhibiting APOBEC3B, which itself is associated with some human cancers including breast cancer. The study was published in *Nature Microbiology*.
(*Nat Microbiol* 2018, doi:10.1038/s41564-018-0284-6)

Building the right-sized heart. Our heart is built in the embryo from two pools of stem cells that are recruited to add new structures to the growing organ. Maintaining the proper proportion and timing of cell addition is critical for proper patterning and function of the heart, with defects in this process leading to congenital heart disease. However, while genes that direct stem cells to a cardiac

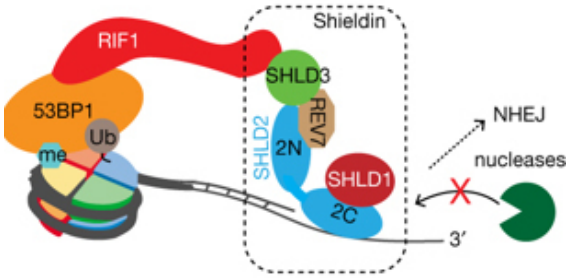


fate are beginning to be well understood, how the size of the cardiac stem cell pools is regulated remains largely unknown. A new study led by **Dr. Ian Scott**, published in *Development*, has found that the transcription factor Hey2 is a key regulator of the size of this stem cell pool. Using the zebrafish embryo model, his group found that loss of *hey2* results in a larger progenitor pool, and subsequent greater addition of cells to the heart. As mutations in *HEY2* cause congenital heart defects in humans, this suggests a novel mechanism through which heart disease can arise. Further, it suggests that Hey2 may be a key brake that can be overcome to allow growth of the heart, suggesting a new avenue for therapeutic approaches to heart disease.
(*Development* 2018: doi: 10.1242/dev.167510)

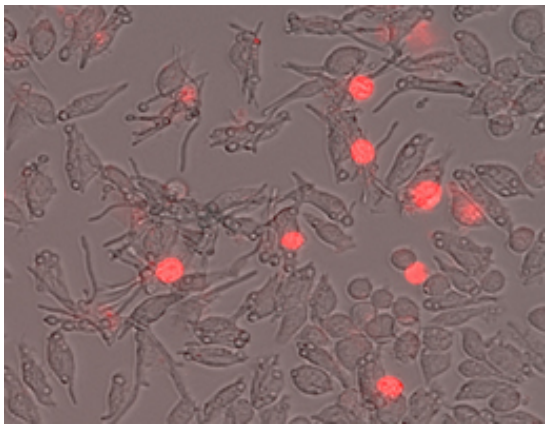


Autism is thought to be caused by mishaps in brain wiring laid down during embryo development. A recent study led by **Dr. Benjamin Blencowe**, and published in *Molecular Cell*, has uncovered a network of more than 200 genes linked to autism. Alternative splicing of small gene fragments, or microexons, has emerged as a rare, unifying concept in the molecular basis of autism after Blencowe's team previously discovered that microexons are disrupted in a large proportion of autistic patients. Microexons affect the ability of proteins to interact with each other during the formation of neural circuits, and are especially critical in the brain, where they are included into the RNA template for protein synthesis during the splicing process. The Blencowe lab developed genome-wide CRISPR-Cas9 screens for detection of alternative splicing regulators and identified over 200 such factors that are often disrupted in autism. The discovery could lead to new therapies for the common neurological disorder.

Click here to read more.
(*Molecular Cell* 2018: doi:10.1016/j.molcel.2018.10.008)

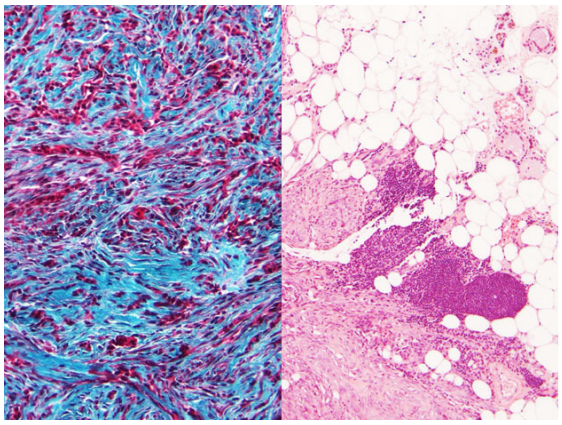


Protecting the ends of broken DNA molecules from degradation is essential during the process that repairs them inside cells. The protein 53BP1 is a chromatin-binding protein that suppresses nucleolytic digestion of DNA ends, but the mechanism of suppression has been elusive. A recent study led by **Dr. Daniel Durocher** and published in *Nature* has identified a novel effector complex called Shieldin, which is recruited to DNA ends by interaction with 53BP1. Shieldin consists of 4 subunits, one of which (SHLD2) binds to single-stranded DNA, supporting the model that Shieldin directly protects DNA ends during 53BP1-mediated DNA repair. Loss of Shieldin leads to defects in non-homologous end joining (NHEJ), and in the gene-rearrangement process necessary for antibody diversity. Notably, in cells and tumours deficient in BRCA1, the loss of Shieldin causes resistance to a powerful class of drugs that target cancer cells, the PARP inhibitors. The results provide a molecular explanation for how some cancer cells develop resistance to these drugs - loss of Shieldin allows cells to use a different repair pathway that is insensitive to the drugs. Understanding how cancer evades these drugs will lead to better diagnosis and treatment of the disease.
(*Nature* 2018: doi: 10.1038/s41586-018-0340-7)
Read the story in UofT News.



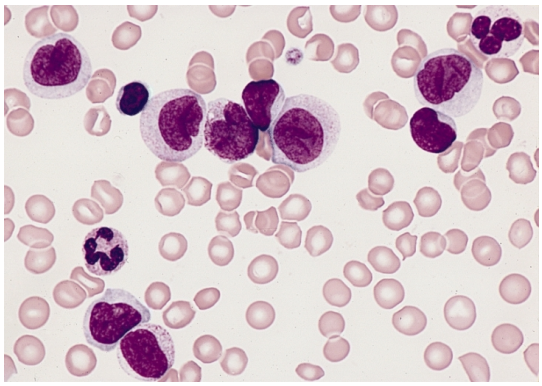
Successful fungal pathogens have evolved sophisticated tactics to interact with and defeat host immune cells. The fungal pathogen *Candida albicans* undergoes a morphogenetic switch from yeast to hyphal growth upon phagocytosis by macrophages. This morphogenesis is coupled with cell wall remodelling that induces an inflammatory cell death program within macrophages, called pyroptosis, which is mediated by activation of the NLRP3 “inflammasome” and caspase-1. Recent work from **Dr. Leah Cowen, Dr. Scott Gray-Owen and**

colleagues, published in *mBio*, investigated *C. albicans* genes and macrophage host factors that promote pyroptosis in response to intracellular fungi. They identified 98 *C. albicans* genes, including determinants of cell wall remodelling and the Hog1 signalling cascade. They observed that macrophages required both Toll-like receptor (TLR) and C-type lectin receptor (CLR) signaling to prime the inflammasome in response to *C. albicans* infection. Understanding how *C. albicans* engages host immune cells may lead to new strategies to modulate the virulence of fungal infections.
(*mBio* 2018, doi: 10.1128/mBio.01581-18)



***CDH1* and *PIK3CA* mutations cooperate to induce Immune-Related Invasive Lobular Carcinoma (IR-IRC) of the breast.** Invasive Lobular Carcinoma, or ILC, is the second most common histological type of breast cancer, accounting for approximately 10% of all cases. Despite having a relatively good 5-year prognosis, ILC patients experience high incidence of local recurrence and a decreased response to chemo- and hormone therapy when compared to the more common breast cancer subtype, Invasive Ductal Carcinoma (IDC). IR-ILC is a subtype of ILC identified through transcriptional profiling, which was defined by gene expression linked to lymphocyte and macrophage infiltration. One of the challenges to developing effective therapeutic interventions for cancers with immune cell involvement, such as IR-ILC, is the lack of an immune-competent model. A new study led by **Dr. Sean Egan** and **Dr. Charles Perou** (University of North Carolina), published in *Cell Reports*, describes a genetically modified mouse model that combines the two most common mutations from human ILC, *CDH1* loss-of-function and *PIK3CA* gain-of-function mutations. The model exhibits properties of immune exhaustion and transcriptional and signaling changes that are conserved in IR-ILC. This model represents an ideal platform for development of combination therapy based on targeting hormone receptors and deregulating signaling pathways, as well as activation of anti-tumor immune surveillance.
(*Cell Reports* 2018: doi:10.1016/j.celrep.2018.09.056)

A team of Canadian and Korean scientists and physicians have



developed the first DNA-based test that allows them to tell which patients will relapse after receiving chemotherapy and a bone marrow transplant, for their acute myeloid leukemia, or AML. Using advanced DNA sequencing technologies along with new computational tools, the team, co-led by **Dr. Zhaolei Zhang**, was able to identify the rare treatment-resistant leukemia cells in the bone marrow. The researchers examined DNA samples at diagnosis and after chemotherapy and bone marrow transplant, and found that treatment eliminated most leukemia cells. However, importantly, some initial mutations were still detected three weeks after the transplant, indicating the presence of treatment-resistant cancer cells. As these same mutations expand in frequency upon relapse, the data suggest that the same cancerous cells that started the leukemia are also responsible for the disease comeback. The nature of mutations reveals further clues about how best to target the disease with drugs.
(*Blood* 2018: doi: 10.1182/blood-2018-04-848028)
Click here to read the full story.

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Faculty Highlights and Awards

Welcome to New Faculty

Dr. Stephanie Protze is a Scientist at the McEwen Stem Cell Institute at the University Health Network, and recently joined the Department as an Assistant Professor. She received her PhD at the University of Dresden, and her postdoctoral training with Gordon Keller at the McEwen Centre for Regenerative Medicine at UHN. Dr. Protze's research focuses on heart development and on advancing new regenerative therapies to treat cardiovascular disease.

Dr. Miguel Ramalho-Santos is a Senior Scientist at the Lunenfeld-Tanenbaum Research Institute and an Associate Professor in Molecular Genetics. He received his PhD at Harvard University, and then a UCSF Fellow at the University of California-San Francisco, where he became an Assistant Professor in 2007. He recently moved to Toronto to become the Canada 150 Research Chair in Developmental Epigenetics at LTRI. His lab studies the epigenetic regulation of stem cell pluripotency using the latest techniques in stem cell biology, embryology, molecular biology, functional genomics and bioinformatics.

Dr. Philipp Maass is a Scientist in the Genetics & Genome Biology program at the Hospital for Sick Children, and has recently joined the Department as an Assistant Professor. He completed his PhD at the Humboldt University Berlin, Max Delbrück Center for Molecular Medicine, and his postdoctoral training at Max Delbrück Center for Molecular Medicine and Harvard University. The Maass lab studies inter-chromosomal interactions and how they regulate gene expression, with particular focus on those of the noncoding genome that impact development and disease mechanisms.

Retirement

On Aug 13, the Department had a celebration to honour **Dr. Andrew Bognar**, who retired on July 1, 2018. Andy has been with the University of Toronto for 33 years, from Microbiology to Medical Genetics & Microbiology to Molecular Genetics. Andy's research interests concerned folate metabolism, the enzymatic mechanisms of folylpolyglutamate synthetase, in bacteria, and one-carbon metabolism in yeast. Andy also served an important role for the University, as the Chair

of the University of Toronto Biosafety committee for over 10 years. We wish him all the best and an extremely restful and happy retirement.

Faculty Honours & Awards

Dr. Jeffrey Wrana has been awarded the *2018 McLaughlin Medal* by the Royal Society of Canada. The medal is awarded for important research of sustained excellence in medical sciences, and is one of just 12 research awards the society granted this year. Jeff was nominated for his seminal discovery of the TGFbeta signal transduction system and its contribution to our understanding of biology, human disease and its treatment.
See the story in UofT News.

Canada Research Chairs
Four faculty from Molecular Genetics are Fall 2018 Recipients of Canada Research Chairs (see the story in U of T News):

Dr. Brian Ciruna - *Tier 1 Canada Research Chair in Developmental Genetics and Disease Modelling*.
Research in the Ciruna lab uses zebrafish as a model to study the molecular and genetic mechanisms that regulate early development, with specific emphasis on the planar cell polarity (PCP) signalling pathway and its role in

embryonic morphogenesis.

Dr. Alan Davidson - *Tier 1 Canada Research Chair in Bacteriophage-Based Technologies*. The Davidson lab studies how bacteriophages assemble and interact with their hosts, with particular focus on anti-CRISPRs (how phage elude the bacterial CRISPR immunity systems) and developing phage-derived bactericidal agents.

Dr. Daniel Durocher - *Tier 1 Canada Research Chair in Molecular Genetics of the DNA Damage Response*. Research in the Durocher lab focuses on mechanisms of genome integrity in eukaryotes: how cells detect, signal and repair DNA damage, how these contribute to cancer, and how the knowledge can by exploited to develop better cancer therapies.

Dr. Mei Zhen - *Tier 1 Canada Research Chair in Neural Circuit Development and Function*. The Zhen lab studies development of the circuitry of the nervous system, using genetics, electrophysiology, and sophisticated imaging approaches in the model nematode *C. elegans*.

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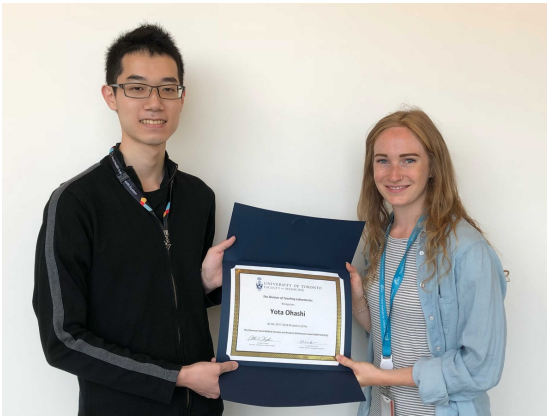
Trainee Highlights and Awards

Yota Ohashi (MGY Specialist) was



awarded the **2018 Clarence Fuerst Award** as the best student in the MGY Genetics lab courses, MGY314 and MGY315. The award comes with a certificate and cheque for $250. It is administered by the Division of Teaching Labs in the Faculty of Medicine, and is given to honour the late Dr. Clarence Fuerst. Clarence was a lambda geneticist, recruited by Lou Siminovitch to the Department, and was responsible for setting up our original lab course experiments in the (then) MGB program. The photo shows Yota's TA, Elyssa Bader, presenting him with the certificate.

Graduate Student Awards 2018

Molecular Genetics has a number of competitive awards and fellowships given annually (and announced at the retreat) to our graduate students. Congratulations to all students!!

L.W. MacPherson Award

Kristina Stzanko (Davidson lab)

Roman Pakula Award

Kento Abe (Gingras lab)

Hannah Farkas-Himsley and Alexander Himsley Memorial Prize

Ellen Langille (Schramek lab)

Norman Bethune Award

Dmitri Segal (Taipale lab)

Eric Hani Fellowship
Amit Weiner (Gray-Owen lab)

MoGen Retreat Poster Awards 2018

Eight students received awards for their posters at the MoGen retreat this year, shown from left to right:

Nicole Lindsay-Moser (Pearson lab)
Katelyn Kozma (Egan lab)
Wendy Cao (Lipshitz lab)
Dayag Sheykhkarimli (Roth lab)
Daniel Schramek
Jessica Lacoste (Tipale lab)
Jaime Yockteng (Frappier lab)
Abilasha Rao (Kim lab)
Chloe Rose (Ciruna lab)

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This newsletter would not be possible without contributions from our community. Thanks to Jonathan Palozzi, Ceryl Tan, Julie Lefebvre, and Julie Claycomb for text and photos for Community Events and the Alumni Spotlight.

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Links to previous editions of MoGeNews

To access previous issues of MoGeNews, please click on the relevant link:

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