CRRD NEWS

A Newsletter of the McGill Centre for Research in Reproduction and Development

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Papadopoulos & Culty Move to USC

Bernard Robaire

Just under ten years ago, I received a call from a friend I had known for many years asking me about Montreal, McGill, and the MUHC. I had the pleasure of meeting Vassili Papadopoulos and his wife, Martine Culty, at several scientific meetings (American Society of Andrology, North American Testis Workshop, Society for the Study of Reproduction), and we had developed a strong friendship over the previous fifteen years. When he indicated that he was considering moving from Georgetown to head the Research Institute of the MUHC (MUHC-RI), I was thrilled and strongly encouraged him to accept this position, after making sure he was well aware of all the opportunities and challenges associated with that position. For the reproductive biology community at McGill and in Canada, having Vassili and Martine join us was a clear asset, given the major contributions they both had made to this field.

Vassili and Martine

Vassili obtained a pharmacy degree in Greece, followed by a PhD in Health and Life Science from the Université Pierre et Marie Curie in Paris, followed by a postdoctoral fellowship in Australia, where he met Martine (and married her), who was also doing a postdoctoral fellowship there. Martine obtained her doctorate in France and did a first postdoctoral fellowship in Canada (McMaster University) and then moved on to Australia. They moved together to join Georgetown University, where, by 2006, Vassili had gone from Professor to Chair and then Associate Vice President for Research and Director of the Biomedical Graduate Research Organization. Clearly, these two globe-trotters were ideally suited to move to our cosmopolitan city in 2007.

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NOTES FROM THE ROAD

The 8th Canadian Developmental Biology Conference was held at the beautiful Banff Centre in Banff, Alberta March 17th-20th, 2016. The meeting included invited speakers from Canada and the USA in five main plenary sessions: Stem Cells and Regeneration; Gene Expression and Development; Growth, Differentiation and Patterning; Cell Proliferation, Migration and Morphogenesis; and Developmental Models of Disease. We awarded stipends to support the travel of three MSc trainees, two from Dr. Yamanaka's lab and one from Dr. Ryan's lab, to the conference. Below, are some highlights of the work they presented at the meeting.

Enrique Gamero (PhD with Dr. Ryan)

Funding from the CRRD provided me with support to attend and present my research at the 8th Canadian Developmental Biology Conference in Banff, Alberta, where I received a poster presentation prize. The meeting was really interesting and different points of developmental biology were presented. But it wasn't all lectures; we had the chance to meet new people through different activities including a western barbeque in an open top tent where we learned how to line dance! Also, the convention center was located in the middle of snowy mountains, offering impressive views.

Western BBQ

My poster described the tools that I am developing to target specific claudin family members in tight junction barriers. Tight junctions are the most apical interaction between apposing cells, where they work as barriers/pores for the transit of water, ions and other solutes to maintain different environments on either side of epithelial cell layers. There are over 20 claudin family members and the combination of claudins present determines the properties of the tight junction barrier. In collaboration with Makoto Nagano's lab, we are studying the tight junctions between Sertoli cells that form the blood testis barrier (BTB), which is essential to maintain the basolateral germ cell niche and prevent the blood from invading the testis lumen. Patients that are exposed to chemotherapeutic drugs usually develop infertility due to the depletion of the rapidly dividing Spermatogonial Stem Cells (SSC) population. Sperm banking prior to chemotherapy is not an option for prepubertal boys with immature sperm. An alternative approach is to harvest SSCs prior to chemotherapy and transplant them into the testis lumen after treatment. Although SSCs are able to migrate and repopulate the niche, the process is inefficient. The goal of my project is to target claudins to transiently open the BTB to allow transplanted SSCs to enter the germ cell niche and restore fertility in cancer survivors.

In order to achieve this, we are using nutraceuticals which alter claudin expression and post- translational modifications and increase barrier permeability. We are also using C-CPE which is the non-toxic C-terminal domain of the Clostridium perfringens enterotoxin. C-CPE is able to bind and remove Claudin3, -4, -6, -7, -8 and -14 and increase barrier permeability. The Nagano lab has shown that it also improves SSC engraftment in mouse testis. In order to improve the effect obtained by C-CPE, I have designed several C-CPE variants where the claudin binding domain has been replaced with the EL2 amino acid sequence of specific claudin family member, in order to target Claudin11 that is the most highly expressed claudin in the BTB and not targeted by C-CPE. We predict that these C-CPE variants will have increased affinity for individual claudin family members and can be used to specifically target the removal of claudins from the BTB.

As a second year MSc student, I really appreciate the chance CRRD gave me to attend this meeting where I was able to increase my network and expand my knowledge in the field.

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Aaron Kwong (MSc with Dr. Yamanaka)

Attending the 2016 Canadian Developmental Biology Meeting was a powerful reminder of the stellar science Canadians contribute to the field of developmental biology. From the behaviour of stem cells in niche environments to understanding ciliated cells in spinal cords for disease modelling, there were plenty of novel and interesting results to be learned and contemplated with fellow researchers. Presenting my poster on the naïve to prime pluripotency transition in early mouse embryos at the Banff Meeting was an exciting opportunity to share my current research with other scientists and foster discussion about the intricacies on mammalian embryogenesis. Although the intended keynote speaker Dr. David Ginty from Harvard Medical School could not attend the event due to illness, Dr. Freda Miller from the University of Toronto's SickKids Research Institute was able to fill in with a spectacular and engaging lecture on early mammalian nervous system development. This year's meeting was a great success in sharing the latest research in developmental biology, stirring conversation among senior scientists and trainees, and emphasizing the important discoveries Canadian scientists are making to shape their field and the global pursuit of regenerative medicine technologies.

Deepak Saini (MSc with Dr. Yamanaka)

During the first year of my Masters, I had the great opportunity to attend the 8th Canadian Developmental Biology Conference in Banff, Alberta. I had the chance to present my current work during a poster session on cell polarization of the pre-implantation mouse embryo and its regulation on the Hippo signaling pathway. Mammalian development is a very interesting process in which, without embryonic pre-patterning within the fertilized zygote, the 8-cell embryo undergoes three main events of polarization, asymmetric division and regulation of gene expression patterns to produce the first round of lineage specification or cell-fate. Thus, my lab and I are interested in understanding how these totipotent to pluripotent blastomeres produce these first distinct cell populations essential for embryonic development through a genetic and molecular perspective. Along with presenting my own work, I was privileged to be able to interact and discuss novel ideas with other top Canadian and international scientists throughout the field of developmental biology. I would like to thank CRRD's help in support for both my research and the experience to travel and share my work through this successful conference.

A Baumholtz, D Saini, A Kwong, and E Gamero at Lake Louise

Hales Group Approved for CIHR Team Grant

Barbara Hales

Dr. Barbara Hales' new team grant , entitled "Endocrine Disrupting Chemicals: Towards Responsible Replacements", was approved for CIHR funding in the recent "Team Grant: Environments and Health: Intersectoral Prevention Research" competition. The goal of this international, interdisciplinary project is to integrate exposure and hazard assessment studies on emerging flame retardants and plasticizers with research on legal, economic and policy issues. At McGill, team members come from the Faculties of Medicine, Engineering, Agricultural and Environmental Sciences, Management and Law. Within Medicine, team members are from the Departments of Pharmacology and Therapeutics, Epidemiology, Biostatistics and Occupational Health, Pediatrics/Experimental Medicine and Obstetrics and Gynecology.

We are pleased to announce the winners of our Fall 2016 Trainee Fellowship Competition!

Keerthana Harwalkar, MSc with Y. Yamanaka - $5000
Emilie Brûlé, MSc with D. Bernard - $5000
Laleh Abbassi, PhD with H. Clarke - $5000

We will be holding our next Fellowship Competition in April 2017.

Keerthana Harwalkar

Emilie Brûlé

Laleh Abbassi

Thank you!

Determining the recipients of Scholarships involves 3 reviewers for each application. A huge thank you to the following for reviewing applications to our fall competition: Asangla Ao, Aimee Ryan, Barbara Hales, Hope Weiler, Raj Duggavathi, Simon Wing, Indra Gupta, Makoto Nagano, and Vilceu Bordignon.

2016-2017 Travel Stipend Recipients To Date

Keith Siklenka, PhD with S. Kimmins, and **Gauthier Schang**, PhD with D. Bernard
49th Annual Meeting of the Society for the Study of Reproduction
16-20 July 2016

Alex Yu, MSc with C. O'Flaherty
Canadian Fertility and Andrology Society Meeting: "ART in the Era of Personalized Medicine"
22-24 September, 2016

Karina Gutierrez, PhD with V. Bordignon
43rd Annual Conference of the International Embryo Technology Society
14-17 January 2017

Another $8.5K available!

Please note: there are no set deadlines associated with these awards; trainees should apply for travel support upon learning the status of their submitted abstract. Maximum 2 travel stipends per lab per fiscal year.

2016 RQR Symposium Recap

The 9th Symposium of the Réseau Québécois en reproduction took place on November 8 and 9, 2016 at the Espaces Dalhousie in Vieux-Québec and was preceded by a pre-Symposium workshop on Gene editing. According to the participants, both events were a great success!

Guest speakers included Alejandro Chavez from Harvard Medical School (*Cas9-mediated whole-cell engineering)*, Ina Dobrinski from the University of Calgary (*Animal models to study germ line stem cells and spermatogenesis*), Pablo J. Ross from UC Davis (*Epigenetic remodeling during bovine preimplantation development*), and Deborah Sloboda from McMaster University (*Programming obesity: maternal, microbial, and metabolic influences*).

In addition to the talks by guest speakers, participants attended 17 platform presentations and 58 posters. CRRD Members Océane Albert (PDF with Dr. Robaire) and Luisina Ongario (PDF with Dr. Bernard) placed first and third in the Platform Presentations, while Luke Currin (MSc Student with Dr. Bordignon) placed 2nd in the Poster Presentations. Congraulations Océane, Luisina and Luke!!

Platform Presentation Winners:
1. Océane Albert, McGill (300$)
2. Lisa-Marie Legault, UdeM (200$)
3. Luisina Ongaro, McGill (100$)

Poster Presentation Winners:
1. Jenna Haverfield, UdeM (300$)
2. Luke Currin, McGill (200$)
3. Shiva Shafiei, McGill (100$)

At the Symposium, Dr. Bruce Murphy was thanked and honoured for what he has created with the network and for his nine years at the head of the RQR! Bruce will be stepping down from his role as Director of the RQR next spring. With collaboration, a special tribute was given to him, at the Symposium, in the form of a video and a memory book. The book can be seen at http://www.rqr.umontreal.ca/PDF/LIVRE_HommageBDM.pdf. We cannot thank you enough, Bruce, for all you have done!

Bruce accepts gift from Julie Blouin

RQR
Réseau Québécois en reproduction

RQR Pre-Symposium Gene Editing Workshop

Luisina Ongaro

On November 7th, the Réseau Québécois en Reproduction (RQR) organized an excellent workshop about gene editing using the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-technique. The day before the 9th RQR Symposium, we were enlightened by five speakers who gave us an overview of the new applications available through CRISPR-Cas9. The workshop started with Dr. Chavez, from Harvard University, who showed us how to use modified forms of Cas9 to guide activators or repressors modulating the expression of specific genes of interest. We then learned about the use of CRISPR-Cas9 in different animal species and biotechnology systems during the talks of Drs. Doyon and Bordignon. Notably, the workshop not only included technical information, we also heard from Dr. Ravitsky about the ethical challenges involved in the use of genetic editing tools to modify embryonic genomes in different countries. In the last talk, Dr. Yamanaka presented the bioinformatic programs available to design your own CRISPR-projects, along with the success rates of his facility to generate novel mouse models with deletion/insertion or point mutations in their genome. Finally, Dr. Bernard led a round table discussion during which the speakers gave their opinion about the opportunities and threats of the use of CRISPR in industry and to treat human diseases. The workshop was well attended and extremely worthwhile!

IMAGE: DAVIDE BONAZZI/@SALZMANART

Kimmins Team Receives 5 year CIHR Grant Worth $1.5 million!

McGill CRRD researchers Sarah Kimmins (PI), Dan Bernard, Jacquetta Trasler and Romain Lambrot, along with other Canadian and South African researchers, have received $1.5 million from CIHR for a team grant to determine **how environmental factors can alter the preconception health of men.**

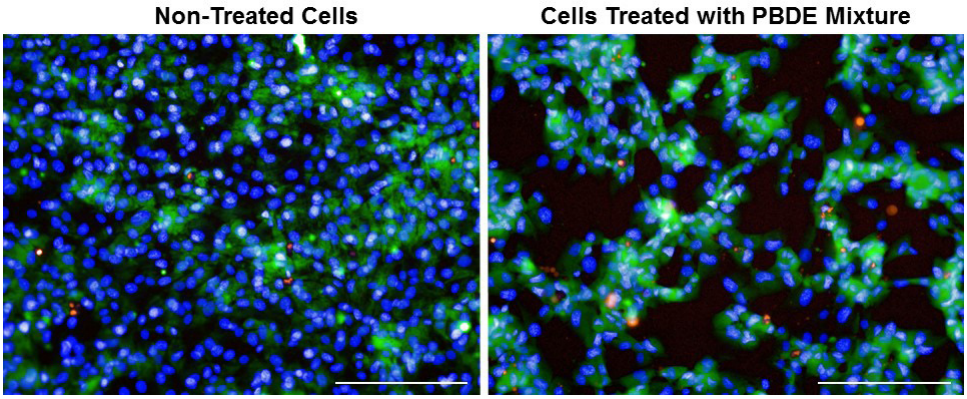
Globally, the prevalence of diabetes, obesity and other chronic diseases is on the rise. These increases have occurred at rates that cannot be due to changes in the genetic structure of the population and are likely caused by environmental factors that modify gene function via epigenetics.

The heritable epigenetic information includes methylation of DNA, post-translational modification of chromatin associated proteins, the histones, and regulatory RNA. **The overarching goal of this research is to understand how environmental exposures alter the heritable epigenetic information during child development and in adult exposures, to impact health across generations.**

With this grant the focus of their research is on determining how a father's exposures to diet and toxicants alter developmental outcomes and to test intervention strategies to lead to more healthy births and children.

Have you ever imagined that laying down on your bed may affect your fertility?

Lefèvre PLC, Wade M, Goodyer C, Hales BF, Robaire B. *A Mixture Reflecting Polybrominated Diphenyl Ether PBDE) Profiles Detected in Human Follicular Fluid Significantly Affects Steroidogenesis and Induces Oxidative Stress in a Female Human Granulosa Cell Line*. Endocrinology. 2016 157(7):2698-711. doi: 10.1210/en.2016-1106.



Non-treated and PBDE - treated KGN cells stained with Calcein (green), Hoechst (blue) and Propidium Iodide (PI). Scale represents 200 µm.

Summary:

Many household products, including pillows and mattresses, contain up to 30% of their weight in flame retardants in order to reduce their flammability. However, these compounds leach out into domestic environments, leading to human contamination. North Americans have the highest body burden of flame retardants worldwide due to our strict flammability regulations. North Americans are also facing major difficulties in conceiving children, with infertility affecting one in seven couples. Polybrominated diphenyl ethers (PBDEs) are a major class of flame retardants. Pregnancy failure has been associated with high levels of PBDEs in human follicular fluid, in direct contact with the ovarian granulosa cells that are essential for oocyte development.

Our recently published study demonstrates that exposure to a mixture of PBDEs reflecting those found in follicular fluid significantly affects critical biological functions in a human ovarian granulosa cell line (KGN cells). Not only do PBDEs trigger oxidative stress, one factor known to be detrimental to ovarian function and to lead to infertility, but also PBDEs clearly disrupt the synthesis of the steroid hormones that are essential for oocyte and early embryo development. With these striking results, we provide evidence for a link between PBDEs and infertility in women.

In the Spotlight

~Continued from page 1, Papadopoulos

Vassili's accomplishments as the Director of the MUHC-RI are attested to by the amazing building and facilities that he had a major hand in developing and getting funded, not only through the biggest CFI grant ever given in Canada but also through many meetings with officials at all levels of government. His success at building the MUHC-RI was not the only thing he did. He kept his lab going at full speed, continued to publish a steady stream of very high quality articles in leading journals and was actively involved with the private sector. Both Martine and Vassili have been a part of Team Grants with several members of our Centre and are well funded by CIHR. Both had appointments in several Departments, including Pharmacology and Therapeutics, where Martine actively participated in teaching at both the undergraduate and graduate levels.

So why would two highly appreciated, tenured Professors leave McGill and Montreal, both of which they truly love, to take on new positions in a new city at a new institution? The drive for building, taking on difficult tasks, and wanting to be challenged by new and different possibilities, is, I believe, what made them decide to move to USC in Los Angeles, where Vassili has taken up the Deanship of the Faculty of Pharmacy and Martine has taken a new appointment in the same Faculty. They have both taken a leave of absence from McGill for a year and will be back occasionally to see us (some of their kids really like Montreal!). We wish them the best of luck with their new jobs and plan on continuing to collaborate scientifically with them over the coming years.

Congratulations Vassili and Martine!

Order CRRD T-Shirts and Sweatshirts Today!!

https://www.mcgill.ca/crrd/files/crrd/crrd_clothing_sales.pdf

Do you have ideas for the next newsletter?

Please send your feedback and suggestions to Charlotte at crrd@mcgill.ca.

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