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Minister of Health



Ministre de la Santé

Ottawa, Canada K1A 0K9

**Message from the Minister of Health
Organization for the Study of Sex Differences
11th Annual Meeting
Sex Differences across the Lifespan
May 15-18, 2017
Montreal, Quebec**

It is a pleasure to welcome you to Montreal for the 11th annual meeting of the Organization for the Study of Sex Differences. We are pleased to be hosting this international conference in Canada for the first time.

This meeting is a wonderful opportunity to bring together researchers and members of the global scientific community, health professionals, students and others. Momentum is building in Canada and around the world to ensure that our health research, policies and services incorporate the most cutting edge evidence on biological sex and sociocultural gender. Each of you plays a significant role in advancing our understanding of how sex and gender differences influence and affect our overall health.

I congratulate the Organization for the Study of Sex Differences for their leadership in catalyzing the community to take action on sex and gender differences at all levels. The work you do is immensely valuable. I extend my best wishes to all participants and your hosts for a successful and productive meeting.

A handwritten signature in blue ink that reads "Jane Philpott".

The Honourable Jane Philpott, P.C., M.P.

Canada

THANK YOU TO OUR SPONSORS



ELSEVIER



MESSAGE FROM THE PRESIDENT

Welcome to OSSD 2017, the 11th annual meeting of the Organization for the Study of Sex Differences

There has never been a more important and exciting time to promote excellence in the science of sex differences. New policies at major research funding agencies in the US, Canada and Europe are shining a bright light on the importance of understanding sex as a biological variable in preclinical, epidemiological, translational and clinical research. We, the members of the OSSD, are at the forefront of this pivotal effort and it is both our privilege and our responsibility to insure that all research addressing the importance of sex and/or gender is of the highest rigor, reproducibility and impact. That we are committed to that goal is self-evident in the record number of exceptionally strong proposals for symposia and poster presentations submitted for this meeting. The work we do is essential and will affect the lives of boys and girls, men and women in the immediate future and for the long term. I congratulate each of you for your dedication to this most fundamental of science questions.

The OSSD is a collective of volunteers and would not be able to function without the dedication and tireless effort of so many. The Program Committee was chaired by Dr. Anne Murphy and was tasked with evaluating and ranking a record number of high quality proposals. They have created a broad and balanced program that is sure to provide topics of interest to all attendees throughout the meeting. Our local hosts, Drs. Jeffrey Mogil and Julie Côté, have worked on every detail of the meeting, from selecting our venue to sign placement to AV to the menu. Thank them for how seamlessly the meeting is running and know that it is because they thought of every little thing in advance no matter how small, despite the many other demands on their time and attention. Joëlle Dorais was their able assistant and we owe both her and Dr. Cara Tannenbaum a debt of gratitude.

Which brings me to the Canadian Institute of Health Research and the Institute of Gender Health under the directorship of Dr. Tannenbaum. Her enthusiastic support in both intellectual guidance and tangible resources are a foundational underpinning of the entire meeting. The inclusion of the banquet as part of the registration fee is one the many ways in which the meeting is enhanced by the IGH and the leadership of Dr. Tannenbaum and her team. Rachel MacNeill and Dr. Sherri Lee Jones created our program booklet and Brittany Osborne collated and organized all the abstracts. Dr. Melissa Holmes chaired the Awards Committee and assured that a fair and transparent process was used in the selection of nine travel awardees, four Elizabeth Young Investigators and two Florence Haseltine Poster Awardees. Be sure to attend the poster sessions and vote for your favorite on Tuesday and Wednesday and don't miss the Young Investigators Symposium on Tuesday afternoon. We also thank the many students and postdocs from McGill and surrounding universities who provide invaluable assistance at the registration desk and beyond. Lastly, it is impossible to exaggerate the invaluable contribution of Dr. Jackie Schwarz who serves as the OSSD's institutional memory, webmaster, grant writer, former secretary and essential ingredient that keeps the gears turning in this complex machine.

This years meeting is further enhanced by the participation and support of the Society for Women's Health Research, the Office of Research on Women's Health of the NIH, the Federal Drug Administration of the US, Biomed Central which publishes our official journal, *Biology of Sex Differences*, and donations from Morgan and Claypool, Elsevier, Stoelting, Merck and Ferring Pharmaceuticals.

Finally, I thank all of you for attending and making the 2017 OSSD Annual Meeting an exciting and rewarding experience for all.

Margaret M McCarthy, PhD
President – OSSD

Professor and Chair
Department of Pharmacology
University of Maryland School of Medicine
Baltimore MD USA

GENERAL INFORMATION

LOCATION

Hyatt Regency Montreal
1255 Jeanne Mance St. (Rue Jeanne-Mance)
Montreal, QC H5B 1E5
(514) 982-1234
<https://montreal.regency.hyatt.com>

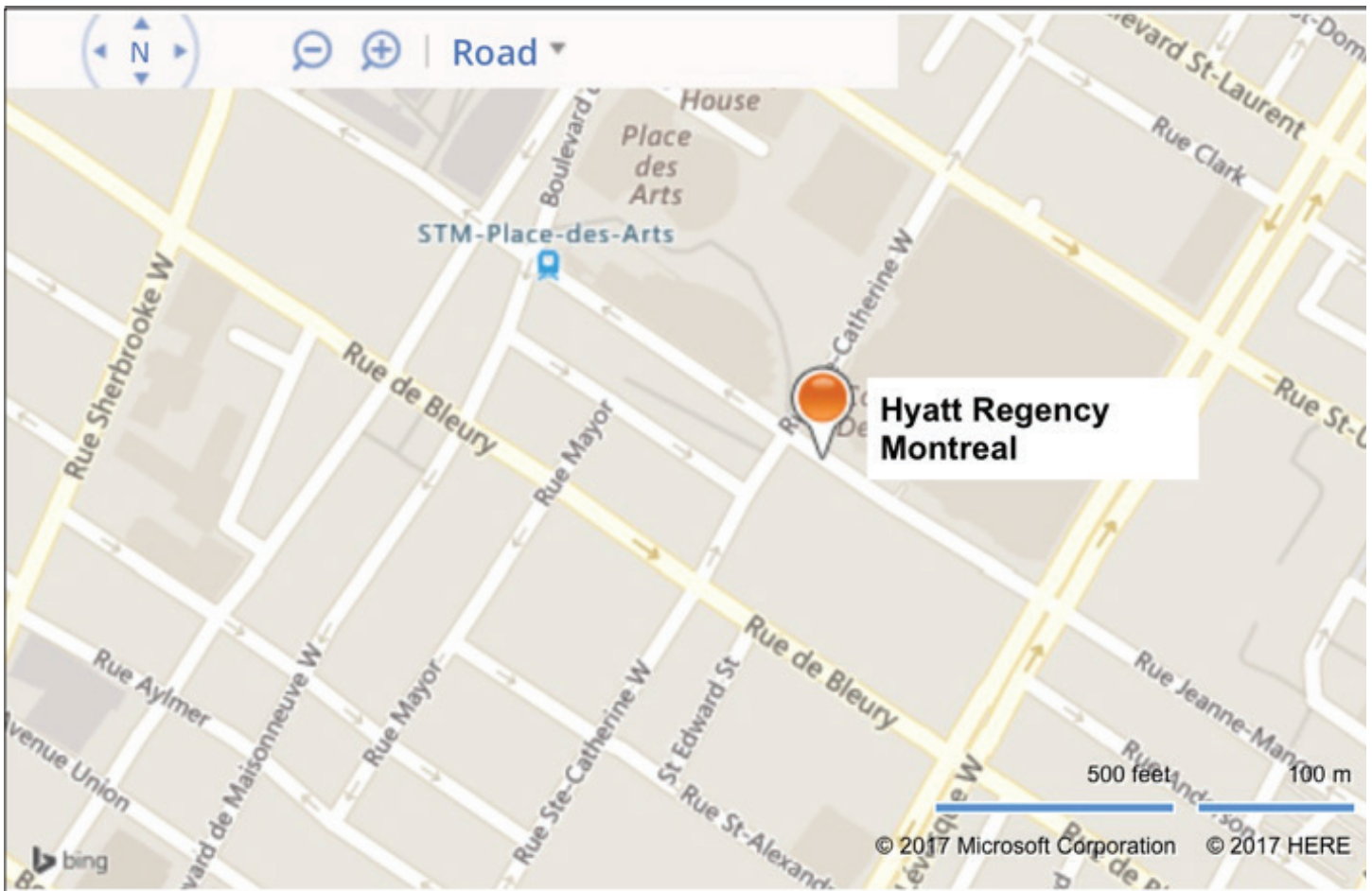
PARKING

Hyatt Regency Montreal is connected to the largest underground parking garage in the city, which also includes several “plug-in spots” for electric cars.

Complex Desjardins Parking: \$21/day
(entrances on Jeanne-Mance St. and St. Urbain St.)

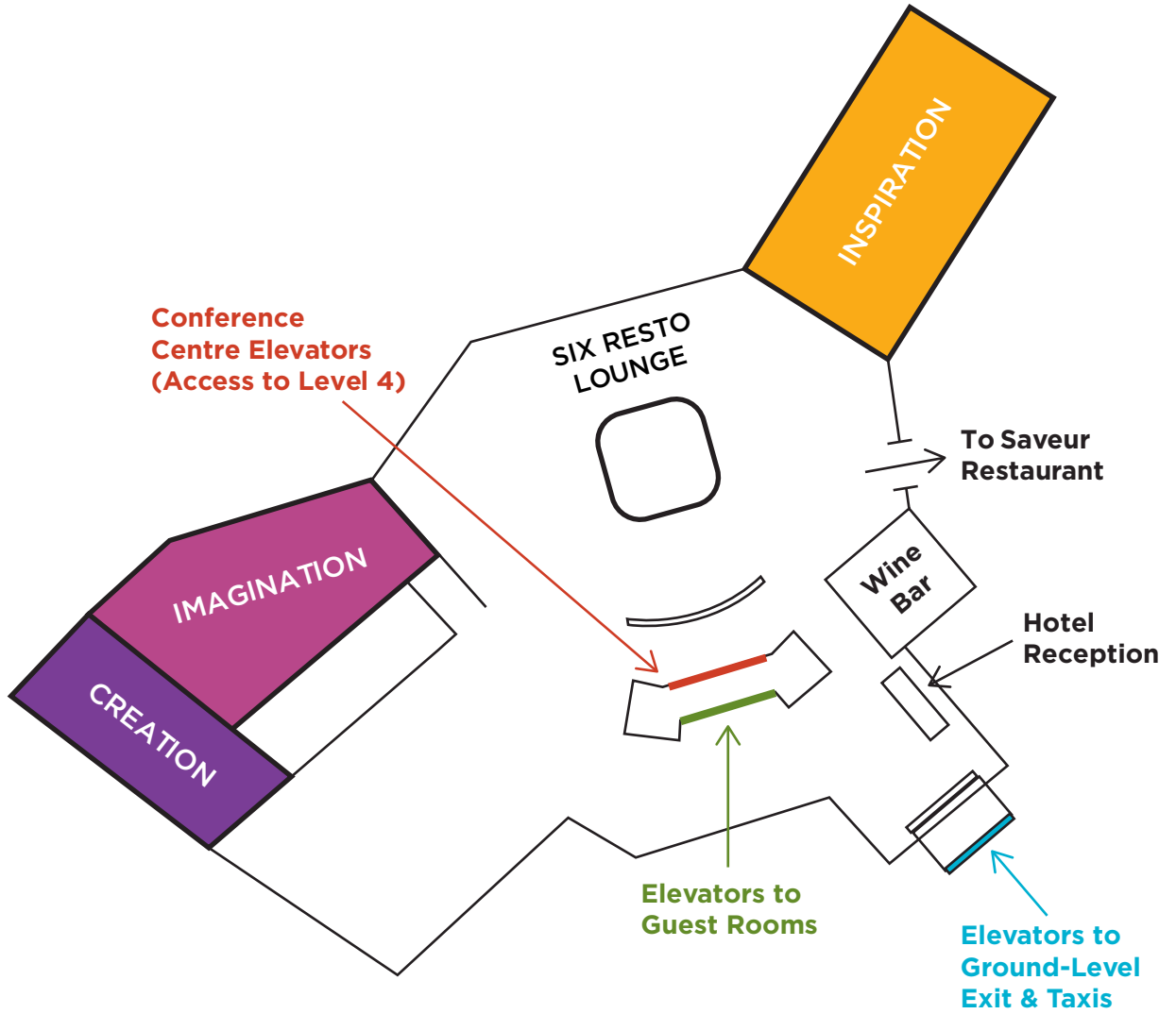
Overnight Valet: \$32/day
(includes in and out privileges, places are limited)

Please note that the Complexe Desjardins offers indoor parking services to hotel guests.

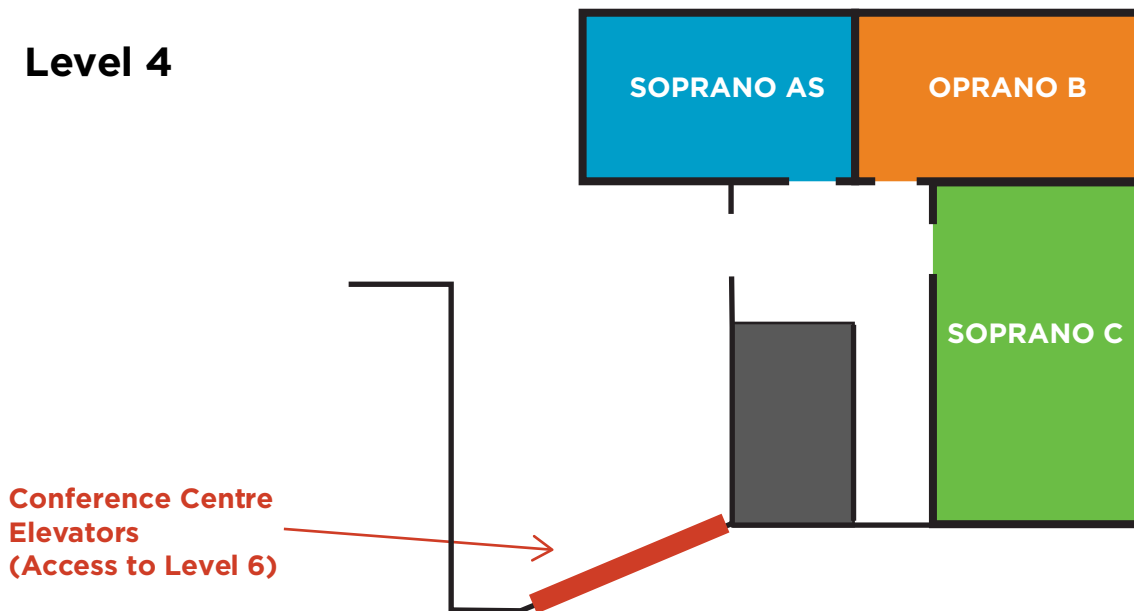


HOTEL FLOOR PLAN (EVENTS OCCUR IN HIGHLIGHTED ROOMS)

Level 6



Level 4



OSSD OFFICERS

President

Margaret M. McCarthy, Ph.D.
University of Maryland School of Medicine

President-Elect

Sabra L. Klein, Ph.D.
Johns Hopkins University

Immediate Past-President

Louise D. McCullough, M.D.
University of Texas Health Science Center, Houston

Secretary

Gretchen Neigh, Ph.D.
Virginia Commonwealth University

Treasurer

Arbi Nazarian, Ph.D.
Western University of Health Sciences

Councilors

Arthur P. Arnold, Ph.D. (BSD Editor-in-Chief)
Christine Disteche, Ph.D.
C. Neill Epperson, M.D.
Liisa Galea, Ph.D.
Melissa M. Holmes, Ph.D.
Judith Lichtman, Ph.D.
Kristen Pleil, PhD (Young Investigator Councilor)
Vera Regitz-Zagrosek, M.D., Ph.D.
Rebecca Shansky, Ph.D.
John Stallone, Ph.D.
Marcia L. Stefanick, M.D.
Jennifer A. Tremmel, M.D.

OSSD COMMITTEES

Scientific Program Committee

Anne Z. Murphy, Ph.D. Chair
Julie Côté, Ph.D.
Montserrat Anguera, Ph.D.
Jayne Danska, Ph.D.
Brittany Osborne, M.S.
Doug Portman, Ph.D.
David Rubinow, M.D.
Farida Sojrabji, Ph.D.
Rohnda Voskuhl, Ph.D.

Local Organizing Committee

Jeffrey S. Mogil, Ph.D.
Julie Côté, Ph.D.
Christopher Bailey, M.Sc.
Jason Bouffard, O.T., Ph.D.
Boram Ham, Ph.D.
Sarah Rosen, B.S.
Sherri Lee Jones, Ph.D.
Annamaria Otto, B.Sc.

Institute of Gender and Health Committee

Cara Tannenbaum, MD, MSc.
Krystle van Hoof, M.A.
Joëlle Dorais, B.A.
Rachel MacNeill, M.A.

ELIZABETH YOUNG NEW INVESTIGATORS

Mandakh Bekhbat	Emory University
Karina Gasbarrino	Research Institute of McGill University Health Centrecom
Emily Mackey	Michigan State University
Jordan Marrocco	The Rockefeller University

TRAVEL AWARDS

Cameron Wasson	University of Guelph
Jonathan VanRyzin	University of Maryland School of Medicine
Lionel Tastet	Universite Laval
Sara Stockman	University of Maryland School of Medicine
Andrea Hanson	Texas A&M University College of Veterinary Medicine
Maen Obeidat	University of British Columbia
Nadia Maarouf	University of Calgary
Erika Bongen	Stanford University
Henricks, Angela	Geisel School of Medicine at Dartmouth
Hui, Chin Wai	Centre de Recherche du CHU de Québec, Université Laval

KEYNOTE SPEAKER



Dr. Jeffrey S. Mogil, Ph.D. is currently the E.P. Taylor Professor of Pain Studies and the Canada Research Chair in the Genetics of Pain (Tier 1) at McGill University, and the Director of the Alan Edwards Centre for the Study of Pain. Dr. Mogil has made seminal contributions to the field of pain genetics and is the author of many major reviews of the subject, including an edited book, *The Genetics of Pain* (IASP Press, 2004). He is also a recognized authority in the fields of sex differences in pain and analgesia, and pain testing methods in the laboratory mouse. Dr. Mogil is the author of over 200 journal articles and book chapters since 1992, and has given over 280 invited lectures in that same period. He is the recipient of numerous awards, including the Neal E. Miller New Investigator award from the Academy of Behavioral Medicine Research, the John C. Liebeskind Early Career Scholar Award from the American Pain Society, the Patrick D. Wall Young Investigator Award from the International Association for the Study of Pain, the Early Career Award from the Canadian Pain Society, the SGV Award from the Swiss Laboratory Animal Science Association, and the Frederick W.L. Kerr Basic Science Research Award from the American Pain Society. He currently serves as a Councilor at IASP, and was the chair of the Scientific Program Committee of the 13th World Congress on Pain.

CAPSTONE SPEAKER



Alyson J. McGregor, M.D., M.A., F.A.C.E.P. is a women's health pioneer who has brought the concept of sex and gender differences in the delivery of acute medical care to the national stage. She is an Associate Professor of Emergency Medicine at the Warren Alpert Medical School of Brown University, the Co-Founder and Director for the Division of Sex and Gender in Emergency Medicine (SGEM) at Brown University's Department of Emergency Medicine. Dr. McGregor is also a Co-Founder and Vice Chair for the national organization Sex and Gender Women's Health Collaborative. Dr. McGregor's research focus is on the effects that sex and gender have on emergent conditions and has been an advocate for this model nationally through talks such as "Why Medicine Often has Dangerous Side Effects for Women" on TED.com.

PROGRAM AT A GLANCE: MONDAY, MAY 15

9:00AM - 8:30PM	REGISTRATION		<i>Hotel reception, Level 6</i>
9:30AM - 12:00PM	IGH Catalyst Grant Recipients Only REPORT FROM THE TRENCHES ON SEX DIFFERENCES RESEARCH		<i>Imagination, Level 6</i>
12:00PM - 1:15PM	LUNCH		<i>Six Resto Lounge, Level 6</i>
1:15PM - 3:00PM	<i>Soprano A, Level 4</i> SESSION 1 Developmental neuro-imaging of the sexually dimorphic brain across species, <i>sponsored by Biomed Central</i> <i>Chair: Raznahan</i>	<i>Soprano B, Level 4</i> SESSION 2 Sex differences in cardiovascular aging: common mechanisms in different clinical syndromes <i>Chairs: Regitz-Zagrosek & Miller</i>	<i>Soprano C, Level 4</i> PANEL Troubleshooting problems while studying sex differences <i>Chair: Tannenbaum</i>
3:00PM - 3:15PM	COFFEE BREAK		<i>Foyer, Level 4</i>
3:15PM - 5:00PM	<i>Soprano A, Level 4</i> SESSION 3 Sex differences in the interactions between the microbiome and stress/immune system across the lifespan, <i>sponsored by Elsevier</i> <i>Chairs: Ismail & Kentner</i>	<i>Soprano B, Level 4</i> SESSION 4 Sex differences in transplantation: from stem cells to the whole organ <i>Chairs: Mahnke & West</i>	<i>Soprano C, Level 4</i> WORKSHOP (ends 4:15pm) Encouraging journals to get serious about sex influences <i>Chair: Cahill</i>
5:10PM - 5:30PM	WELCOMING REMARKS		<i>Soprano AB, Level 4</i>
5:30PM - 6:30PM	PRESIDENTIAL LECTURE Sex differences in pain from both sides of the syringe <i>Jeffrey Mogil, McGill University</i>		<i>Soprano AB, Level 4</i>
6:30PM - 8:30PM	OPENING RECEPTION		<i>Inspiration, Level 6</i>

PROGRAM AT A GLANCE: TUESDAY, MAY 16

7:30AM - 5:00PM	REGISTRATION		<i>Foyer, Level 4</i>
7:30AM - 8:45AM	BREAKFAST		<i>Six Resto Lounge, Level 6</i>
8:45AM - 10:30AM	<p><i>Soprano A, Level 4</i> SESSION 5</p> <p>Neuroimmune interactions in health and disease: sex differences across the lifespan <i>Chair: Reyes</i></p>	<p><i>Soprano B, Level 4</i> SESSION 6</p> <p>Sex chromosomes and sex differences in health and disease <i>Chairs: Lau & Charchar</i></p>	<p><i>Soprano C, Level 4</i> SESSION 7</p> <p>Sex differences with aging in human motor performance from the frail to the elite athlete <i>Chair: Jakobi</i></p>
10:30AM - 10:45AM	COFFEE BREAK		<i>Foyer, Level 4</i>
10:45AM - 12:30PM	<p><i>Soprano A, Level 4</i> SESSION 8</p> <p>Age and sex interact in schizophrenia: Clinical perspectives and animal models <i>Chair: Biegon</i></p>	<p><i>Soprano B, Level 4</i> SESSION 9</p> <p>Effects of sex hormonal change on vision and age-related eye disease <i>Chairs: Eisner & Einstein</i></p>	<p><i>Soprano C, Level 4</i> SESSION 10</p> <p>The gender gap in workers' mental health: What have we learned from the Salveo study? <i>Chairs: Marchand & Durand</i></p>
12:30PM - 1:45PM	WORKING LUNCH (served in Foyer, Level 4) Adaptive clinical trial designs: Opportunities to identify sex- and gender-specific outcomes <i>Chair: Jenkins</i>		<i>Soprano AB, Level 4</i>
2:00PM - 3:45PM	<p><i>Soprano A, Level 4</i> SESSION 11</p> <p>Prenatal stress in relation to sex differences: from birth to adolescence <i>Chairs: Barrett & King</i></p>	<p><i>Soprano B, Level 4</i> SESSION 12</p> <p>Young at heart: Sex and the aging heart <i>Chair: Pyle</i></p>	<p><i>Soprano C, Level 4</i> SESSION 13</p> <p>Aging & care: Taking sex, gender and health into consideration <i>Chair: Daly</i></p>
3:45PM - 4:00PM	COFFEE BREAK		<i>Foyer, Level 4</i>
4:00PM - 5:30PM	ELIZABETH YOUNG NEW INVESTIGATORS SYMPOSIUM		<i>Soprano AB, Level 4</i>
5:30PM - 7:15PM	POSTER SESSION 1		<i>Inspiration, Level 6</i>
7:30PM	TRAINEE SOCIAL		<i>NYKS Bistro Pub 1250 Rue Bleury</i>

PROGRAM AT A GLANCE: WEDNESDAY, MAY 17

7:30AM - 5:00PM	REGISTRATION			<i>Foyer, Level 4</i>
7:30AM - 8:45AM	BREAKFAST			<i>Six Resto Lounge, Level 6</i>
8:45AM - 10:30AM	<p><i>Soprano A, Level 4</i> SESSION 14</p> <p>Sex differences in neuroactive steroid actions <i>Chairs: Melcangi & Garcia Segura</i></p>	<p><i>Soprano B, Level 4</i> SESSION 15</p> <p>Sex differences in cardio-metabolic disease across the life-course: from epidemiology to epigenetics <i>Chair: O'Keefe</i></p>	<p><i>Soprano C, Level 4</i> SESSION 16</p> <p>Sex, gender and musculoskeletal disorders in the aging worker <i>Chair: MacDermid for CIHR MSD</i></p>	
10:30AM - 10:45AM	COFFEE BREAK			<i>Foyer, Level 4</i>
10:45AM - 12:30PM	<p><i>Soprano A, Level 4</i> SESSION 17</p> <p>Sex differences in mechanisms of stress and anxiety: Human and animal perspectives across development <i>Chairs: Moser & Shansky</i></p>	<p><i>Soprano B, Level 4</i> SESSION 18</p> <p>Sex-specific targeting of kidney function in children, adults, and the elderly: From genes to policy, sponsored by Ferring Pharmaceuticals <i>Chairs: de Vries & Nørgaard</i></p>	<p><i>Soprano C, Level 4</i> SESSION 19</p> <p>Sex-specific mechanisms of upper limb musculoskeletal disorders <i>Chair: Hunter</i></p>	
12:30PM - 1:45PM	<p><i>Soprano AB, Level 4</i> WORKING LUNCH (served in Foyer, Level 4) Addressing the 'Data Gap' across the life-span: Experiences with integrating sex and gender <i>Chair: Mason</i></p>	<p><i>Imagination, Level 6</i> Biology of Sex Differences Editorial Board Meeting</p>		
2:00PM - 3:45PM	<p><i>Soprano A, Level 4</i> SESSION 20</p> <p>Sex differences in neonatal brain injury: role of sex steroids and their receptors, sponsored by Morgan Claypool <i>Chairs: Cengiz</i></p>	<p><i>Soprano B, Level 4</i> SESSION 21</p> <p>Sex differences in cerebral ischemia across the lifespan <i>Chairs: Liu & Selvamani</i></p>	<p><i>Soprano C, Level 4</i> SESSION 22</p> <p>Adverse experiences in sex-based differences in cardio-respiratory function <i>Chair: Kinkead</i></p>	
3:45PM - 4:00PM	COFFEE BREAK			<i>Foyer, Level 4</i>
4:00PM - 4:30PM	<p><i>Soprano AB, Level 4</i> BUSINESS MEETING</p>		<p><i>Imagination, Level 6</i> SEX AND GENDER TRAINEE NETWORK LAUNCH</p>	
4:30PM - 6:15PM	POSTER SESSION 2			<i>Inspiration, Level 6</i>
6:45PM - 7:30PM	COCKTAIL RECEPTION			<i>Creation, Level 6</i>
7:30PM	BANQUET			<i>Soprano ABC, Level 4</i>

PROGRAM AT A GLANCE: THURSDAY, MAY 18

7:30AM - 9:00AM	BREAKFAST		<i>Six Resto Lounge, Level 6</i>
9:00AM -10:45AM	<p><i>Soprano A, Level 4</i> SESSION 23</p> <p>Sex differences in the hippocampus and related structures: Implications for cognition and stress reactivity throughout the lifespan <i>Chair: Frick</i></p>	<p><i>Soprano B, Level 4</i> SESSION 24</p> <p>Sex differences in cardiovascular disease with aging: Getting beyond the classic roles of sex hormones <i>Chair: Stafford</i></p>	
10:45AM - 11:00AM	COFFEE BREAK		<i>Foyer, Level 4</i>
11:00AM - 12:00PM	<p>CAPSTONE LECTURE</p> <p>How the evolution of sex- and gender-based research impacts the practice of medicine <i>Alyson McGregor, Brown University</i></p>		<i>Soprano AB, Level 4</i>
END OF MEETING			
12:30PM - 3:00PM	OSSD 2017 COUNCIL MEETING <i>(lunch provided)</i>		<i>Imagination, Level 6</i>

DETAILED PROGRAM: MONDAY, MAY 15

9:00AM - 8:30PM	REGISTRATION	<i>Hotel reception, Level 6</i>
9:30AM - 12:00PM	IGH Catalyst Grant Recipients Only REPORT FROM THE TRENCHES ON SEX DIFFERENCES RESEARCH	<i>Imagination, Level 6</i>
12:00PM - 1:15PM	LUNCH	<i>Six Resto Lounge, Level 6</i>
1:15PM - 3:00PM: PANEL, SESSIONS 1 & 2		
<p><i>Soprano A, Level 4</i> SESSION 1: Developmental neuro-imaging of the sexually dimorphic brain across species, sponsored by Biomed Central <i>Chair: Armin Raznahan, M.D., Ph.D. National Institute of Mental Health</i> 1:15pm - 1:25pm: Overview <i>Armin Raznahan, M.D., Ph.D. National Institute of Mental Health</i> 1:25 PM - 1:45 PM: Imaging the development of sexual dimorphisms in the brains of mice <i>Jason P. Lerch, Ph.D. University of Toronto</i> 1:45 PM - 2:05 PM: Sexually Dimorphic Brain Development in Nonhuman Primates and Human Infants. <i>Rebecca C. Knickmeyer, Ph.D. University of North Carolina at Chapel Hill</i> 2:05 PM - 2:25 PM: Sex differences in human brain development from childhood to adulthood <i>Armin Raznahan, M.D. Ph.D., National Institute of Mental Health</i> <i>Questions and discussion</i></p>		
<p><i>Soprano B, Level 4</i> SESSION 2: Sex differences in cardiovascular aging: common mechanisms in different clinical syndromes <i>Chair: Vera Regitz-Zagrosek, M.D. Charité University medicine</i> <i>Co-chair: Virginia Miller, Ph.D. Mayo Clinic</i> 1:15 PM - 1:25 PM: Overview <i>Vera Regitz-Zagrosek, M.D. Charité University medicine</i> 1:25 PM - 1:45 PM: Cardiac genes that escape X inactivation: implications of epigenetic modifications in aging <i>Christine M. Disteche, Ph.D. University of Washington</i> 1:45 PM - 2:05 PM: Loss of Y chromosome in blood is associated with major cardiovascular events during follow-up in men after carotid endarterectomy <i>Hester M. den Ruijter, Ph.D. University Medical Center Utrecht</i> 2:05 PM - 2:25 PM: Postmenopausal decrease in sex hormones - a trigger for cardiovascular disease? <i>Vera Regitz-Zagrosek, M.D. Charité University medicine</i> 2:25 PM - 2:45 PM: Coronary microvascular dysfunction and heart failure with preserved ejection fraction: Hormone or age dependent <i>C. Noel Bairey Merz, M.D. Cedars-Sinai Heart Institute</i> <i>Questions and discussion</i></p>		
<p><i>Soprano C, Level 4</i> PANEL: Troubleshooting problems while studying sex differences <i>Chair: Cara Tannenbaum, M.D. CIHR Institute of Gender and Health</i> 1:15pm - 1:25pm: Overview <i>Cara Tannenbaum, M.D. CIHR Institute of Gender and Health</i> 1:25pm - 1:45pm: Sex Influences on Drug Action: An Issue Whose Time Has Come <i>Larry Cahill, Ph.D. University of California, Irvine</i> 1:45pm - 2:05pm: Rodent issues <i>Arthur P. Arnold, Ph.D. University of California, Los Angeles</i> 2:05pm - 2:25pm: Species differences <i>Gillian Einstein, Ph.D. University of Toronto</i> 2:25pm - 2:45pm: Statistical pitfalls <i>Lea Davis, Ph.D. Vanderbilt University</i> <i>Questions and discussion</i></p>		

3:00PM - 3:15PM	COFFEE BREAK	Foyer, Level 4
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3:15PM - 5:00PM: Sessions 3 & 4

<p><i>Soprano A, Level 4</i> SESSION 3: Sex differences in the interactions between the microbiome and stress/immune system across the lifespan, sponsored by Elsevier</p> <p><i>Chair: Nafissa Ismail, Ph.D. University of Ottawa Co-chair: Amanda Kentner, Ph.D. Massachusetts College of Pharmacy & Health Sciences</i></p> <p>3:15 PM - 3:25 PM: Overview <i>Nafissa Ismail, Ph.D. University of Ottawa</i></p> <p>3:25 PM - 3:45 PM: Causal role of the maternal vaginal microbiome in programming offspring brain and immune development <i>Eldin Jasarevic, Ph.D. University of Pennsylvania</i></p> <p>3:45 PM - 4:05 PM: Do gut reactions lead to sex differences in social preference following a neonatal inflammatory challenge? <i>Amanda Kentner, Ph.D. Massachusetts College of Pharmacy & Health Sciences</i></p> <p>4:05 PM - 4:25 PM: Sex differences in response to probiotic treatment and pubertal stress <i>Nafissa Ismail, Ph.D. University of Ottawa</i></p> <p>4:25 PM - 4:45 PM: Sex and gender differences in the outcomes of vaccination over the life course <i>Sabra Klein, Ph.D. Johns Hopkins Bloomberg School of Public Health</i></p> <p><i>Questions and discussion</i></p>	<p><i>Soprano B, Level 4</i> SESSION 4: Sex differences in transplantation: from stem cells to the whole organ</p> <p><i>Chair: Amanda Mahnke, Ph.D. Texas A&M University Co-chair: Lori West, M.D., D.Phil. University of Alberta</i></p> <p>3:15 PM - 3:25 PM: Overview <i>Amanda Mahnke, Ph.D. Texas A&M University</i></p> <p>3:25 PM - 3:45 PM: Sex really matters when working with human pluripotent stem cells <i>Montserrat Anguera, Ph.D. University of Pennsylvania</i></p> <p>3:45 PM - 4:05 PM: Sex differences in kidney graft failure risk differ by age <i>Bethany J. Foster, M.D. McGill University Faculty of Medicine</i></p> <p>4:05 PM - 4:25 PM: Sex and age differences impact organ transplantation <i>Lori West, M.D., D.Phil. University of Alberta</i></p> <p><i>Questions and discussion</i></p>	<p><i>Soprano C, Level 4</i> WORKSHOP: Encouraging journals to get serious about sex influences (ends 4:15pm)</p> <p><i>Chair: Larry Cahill, Ph.D. University of California, Irvine</i></p>
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5:10PM - 5:30PM	WELCOMING REMARKS	Soprano AB, Level 4
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5:30PM - 6:30PM	PRESIDENTIAL LECTURE Sex differences in pain from both sides of the syringe <i>Jeffrey Mogil, Ph.D.</i> <i>McGill University</i>	<i>Soprano AB, Level 4</i>
6:30PM - 8:30PM	OPENING RECEPTION	<i>Inspiration, Level 6</i>

DETAILED PROGRAM: TUESDAY, MAY 16

7:30AM - 5:00PM	REGISTRATION	<i>Foyer, Level 4</i>
7:30AM - 8:45AM	BREAKFAST	<i>Six Resto Lounge, Level 6</i>

8:45AM - 10:30AM: SESSIONS 5, 6 & 7

<p><i>Soprano A, Level 4</i> SESSION 5: Neuroimmune interactions in health and disease: sex differences across the lifespan</p> <p><i>Chair: Teresa M. Reyes, Ph.D.</i> <i>University of Cincinnati</i></p> <p>8:45am - 8:55am: Overview <i>Teresa M. Reyes, Ph.D.</i> <i>University of Cincinnati</i></p> <p>8:55am - 9:15am: Brain-resident immune cells are crucial regulators of sex differences in the development of motivated behaviors <i>Kathryn M. Lenz, Ph.D.</i> <i>Ohio State University</i></p> <p>9:15am - 9:35am: Female resiliency to intrauterine inflammation during pregnancy <i>Teresa M. Reyes, Ph.D.</i> <i>University of Cincinnati</i></p> <p>9:35am – 9:55am: Stress challenges during early adolescence yield divergent outcomes in adulthood for males and females <i>Terrence Deak, Ph.D.</i> <i>Binghamton University-SUNY</i></p> <p>9:55am – 10:15am: Sex differences in human experimental inflammatory models <i>Bianka Karshikoff, Ph.D.</i> <i>Karolinska Institutet</i></p> <p><i>Questions and discussion</i></p>	<p><i>Soprano B, Level 4</i> SESSION 6: Sex chromosomes and sex differences in health and disease</p> <p><i>Chair: Chris Lau, Ph.D.</i> <i>University of California</i> <i>Co-chair: Fadi J. Charchar, Ph.D.</i> <i>Federation University Australia</i></p> <p>8:45am - 8:55am: Overview <i>Chris Lau, Ph.D.</i> <i>University of California</i></p> <p>8:55am - 9:15am: Y Chromosome and Sex Differences in Cardiovascular Disease <i>Fadi J. Charchar, Ph.D.</i> <i>Federation University Australia</i></p> <p>9:15am - 9:35am: SRY and male sex bias in Parkinson’s disease <i>Vincent R. Harley, Ph.D.</i> <i>Monash University</i></p> <p>9:35am – 9:55am: The human sex-determining gene expression in early embryo of transgenic mice induces postnatal growth retardation and lethality <i>Chris Lau, Ph.D.</i> <i>University of California</i></p> <p>9:55am – 10:15am: Sex chromosomes and sex differences in genome regulation <i>Adrianna K. San Roman, Ph.D.</i> <i>Whitehead Institute for Biomedical Research</i></p> <p><i>Questions and discussion</i></p>	<p><i>Soprano C, Level 4</i> SESSION 7: Sex differences with aging in human motor performance from the frail to the elite athlete</p> <p><i>Chair: Jennifer M. Jakobi, Ph.D.</i> <i>UBC Okanagan</i></p> <p>8:45am - 8:55am: Overview <i>Sandra K. Hunter, Ph.D.</i> <i>Marquette University</i></p> <p>8:55am - 9:15am: Sex differences in balance, gait and functional mobility and their relationship with hand-grip strength in healthy elderly <i>Massimiliano Pau, Ph.D.</i> <i>University of Cagliari</i></p> <p>9:15am - 9:35am: Sex and frailty: Important variables when considering exercise interventions for older adults <i>Jennifer M. Jakobi, Ph.D.</i> <i>University of British Columbia Okanagan</i></p> <p>9:35am – 9:55am: Sex Differences with Aging among Elite Athletes: The Roles of Physiology and Participation <i>Jonathon W. Senefeld, B.S.</i> <i>Marquette University</i></p> <p><i>Questions and discussion</i></p>
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10:45AM - 12:30PM: SESSIONS 8, 9 & 10

Soprano A, Level 4
SESSION 8: Age and sex interact in schizophrenia: Clinical perspectives and animal models

*Chair: Anat Biegon, Ph.D.
Stony Brook University*

10:45am – 10:55am: Overview
*Anat Biegon, Ph.D.
Stony Brook University*

10:55am - 11:15am: Sex differences in psychotic disorders: Fresh observations
*Ashok Malla, M.D.
McGill University*

11:15am – 11:35am: Neural and behavioral sex-dependent developmental trajectories in a maternal immune activation model of schizophrenia in the rat
*Michal Arad, Ph.D.
University of Maryland*

11:35am – 11:55am: Age- and sex-specific effects of maternal immune activation on neuroinflammation and dopamine receptors revealed by quantitative autoradiography in rat brain
*Anat Biegon, Ph.D.
Stony Brook University*

Questions and discussion

Soprano B, Level 4
SESSION 9: Effects of sex hormonal change on vision and age-related eye disease

*Chair: Alvin Eisner, Ph.D.
Portland State University
Co-chair: Gillian Einstein, Ph.D.
University of Toronto*

10:45am – 10:55am: Overview
*Alvin Eisner, Ph.D.
Portland State University
Gillian Einstein, Ph.D.
University of Toronto*

10:55am - 11:15am: Dry eye and sex/gender-dependent eye care differences
*Janine Austin Clayton, M.D.
Office of Research on Women's Health, National Institutes of Health*

11:15am – 11:35am: Sex differences in neuro-ophthalmologic disorders
*John Chen, M.D., Ph.D.
Mayo Clinic*

11:35am – 11:55am: Sex differences in the pathophysiology and treatment of glaucoma
*Shandiz Tehrani, M.D., Ph.D.
Oregon Health & Science University*

11:55am – 12:15pm: Estrogen activity and visual response mediated via short-wavelength-sensitive (SWS) cones
*Alvin Eisner, Ph.D.
Portland State University*

Questions and discussion

Soprano C, Level 4
SESSION 10: The gender gap in workers' mental health: What have we learned from the Salveo study?

*Chair: Alain Marchand, Ph.D.
University of Montreal
Co-chair: Pierre Durand, Ph.D.
University of Montreal*

10:45am – 10:55am: Overview
*Alain Marchand, Ph.D.
University of Montreal*

10:55am - 11:15am: The gendered mechanisms leading to psychological distress among working women and men
*Jaunathan Bilodeau, B.Sc.
University of Montreal*

11:15am – 11:35am: Men and Women gap in depressive symptoms: Vulnerability or exposure to work and family stressors?
*Alain Marchand, Ph.D.
University of Montreal*

11:35am – 11:55am: Examining gender differences in the work and non-work determinants of burnout: Results from the SALVEO Study
*Nancy Beaugard, Ph.D.
University of Montreal*

11:55am – 12:15pm: Gender and work-family conflict: A differential exposition explanation
*Victor Y. Haines III, Ph.D.
University of Montreal*

Questions and discussion

<p>12:30PM - 1:45PM</p>	<p>WORKING LUNCH <i>Soprano AB, Level 4</i></p> <p>Adaptive clinical trial designs: Opportunities to identify sex- and gender-specific outcomes</p> <p><i>Chair: Marjorie Jenkins, M.D., M.Ed.H.P. Office of Women's Health, Office of the Commissioner, U.S. Food and Drug Administration (FDA)</i></p> <p>12:30pm - 12:40pm: Overview <i>Marjorie Jenkins, M.D., M.Ed.H.P. Office of Women's Health, Office of the Commissioner, U.S. Food and Drug Administration (FDA)</i></p> <p>Subpopulation analysis and adaptive clinical trial designs: New frontiers for sex and gender-specific medicine <i>Che Smith, Ph.D. Center for Drug Evaluation and Research, FDA John Scott, Ph.D. Center for Biologics Evaluation and Research, FDA</i></p>
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2:00PM - 3:45PM: SESSIONS 11, 12 & 13

<p><i>Soprano A, Level 4</i></p> <p>SESSION 11: Prenatal stress in relation to sex differences: from birth to adolescence</p> <p><i>Chair: Emily S. Barrett, Ph.D. Rutgers School of Public Health Co-chair: Suzanne King, Ph.D. McGill University</i></p> <p>2:00pm – 2:10pm: Overview <i>Emily S. Barrett, Ph.D. Rutgers School of Public Health</i></p> <p>2:10pm – 2:30pm: Prenatal stress exposures and sex-dependent development in early childhood: an adaptive perspective <i>Emily S. Barrett, Ph.D. Rutgers School of Public Health</i></p> <p>2:30pm – 2:50pm: Placental H3K27me3 promotes female resilience to prenatal stress <i>Bridget M. Nugent, Ph.D. University of Pennsylvania</i></p> <p><i>(Continued on next page)</i></p>	<p><i>Soprano B, Level 4</i></p> <p>SESSION 12: Young at heart: Sex and the aging heart</p> <p><i>Chair: W. Glen Pyle, Ph.D. University of Guelph</i></p> <p>2:00pm – 2:10pm: Overview <i>W. Glen Pyle, Ph.D. University of Guelph</i></p> <p>2:10pm – 2:30pm: Impact of age, sex hormones and frailty on cardiac function: why studies in young male animals may not be enough <i>Susan E. Howlett, Ph.D. Dalhousie University</i></p> <p>2:30pm – 2:50pm: Menopausal mice are hypersensitive to cardiovascular disease <i>John P. Konhilas, Ph.D. University of Arizona</i></p> <p><i>(Continued on next page)</i></p>	<p><i>Soprano C, Level 4</i></p> <p>SESSION 13: Aging & care: Taking sex, gender and health into consideration</p> <p><i>Chair: Tamara Daly, Ph.D. York University</i></p> <p>2:00pm – 2:10pm: Overview <i>Tamara Daly, Ph.D. York University</i></p> <p>2:10pm – 2:30pm: The importance of a sex/gender based analysis of the healthcare workforce <i>Ivy Lynn Bourgeault, Ph.D. University of Ottawa</i></p> <p>2:30pm – 2:50pm: Aging and care: Sex, gender considerations relevant to traumatic brain injury <i>Angela Colantonio, Ph.D. University of Toronto</i></p> <p><i>(Continued on next page)</i></p>
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<p>2:50pm – 3:10pm: Prenatal maternal stress from a natural disaster disrupts sexual dimorphisms in childhood and adolescence: The SPIRAL studies <i>Suzanne King, Ph.D.</i> <i>McGill University</i></p> <p><i>Questions and discussion</i></p>	<p>2:50pm – 3:10pm: Taking it to heart: Do naturally occurring changes in CapZ offer sex-dependent protection against ageing? <i>W. Glen Pyle, Ph.D.</i> <i>University of Guelph</i></p> <p>3:10pm – 3:30pm: Influence of sex, androgens and age on atrial fibrillation <i>Céline Fiset, Ph.D.</i> <i>Université de Montréal</i></p> <p><i>Questions and discussion</i></p>	<p>2:50pm – 3:10pm: Gender differences of caregiver-Employees: What's different about how men and women navigate informal care & full-time employment <i>Allison M. Williams, Ph.D.</i> <i>McMaster University</i></p> <p>3:10pm – 3:30pm: Care gaps and gendered care work in long-term care facilities <i>Tamara Daly, Ph.D.</i> <i>York University</i></p> <p><i>Questions and discussion</i></p>
<p>3:45PM - 4:00PM</p>	<p>COFFEE BREAK <i>Foyer, Level 4</i></p>	
<p>4:00PM - 5:30PM</p>	<p>ELIZABETH YOUNG NEW INVESTIGATORS SYMPOSIUM <i>Soprano AB, Level 4</i></p> <p>4:00pm - 4:20pm: Chronic adolescent stress leads to neuroimmune alterations and transcriptomic remodeling in the rat hippocampus in a sex-specific manner <i>Mandakh Bekhbat</i> <i>Emory University</i></p> <p>4:20pm - 4:40pm: Sex differences in the adipokine, lipid, and immune profiles of men and women with severe carotid atherosclerosis <i>Karina Gasbarrino</i> <i>McGill University Health Centre</i></p> <p>4:40pm - 5:00pm: Dysfunctional androgen receptor feminizes the mast cell phenotype <i>Emily Mackey</i> <i>Michigan State University</i></p> <p>5:00pm - 5:20pm: A sexually dimorphic “pre-stressed” translational signature in CA3 pyramidal neurons of BDNF Val66Met mice <i>Jordan Marrocco, Ph.D.</i> <i>The Rockefeller University</i></p> <p><i>Questions and discussion</i></p>	
<p>5:30PM - 7:15PM</p>	<p>POSTER SESSION 1 <i>Inspiration, Level 6</i></p>	
<p>7:30PM</p>	<p>TRAINEE SOCIAL <i>NYKS Bistro Pub, 1250 Rue Bleury</i></p>	

DETAILED PROGRAM: WEDNESDAY, MAY 17

7:30AM - 5:00PM	REGISTRATION	Foyer, Level 4
7:30AM - 8:45AM	BREAKFAST	Six Resto Lounge, Level 6
8:45AM - 10:30AM: SESSION 14, 15 & 16		
<p><i>Soprano A, Level 4</i> SESSION 14: Sex differences in neuroactive steroid actions</p> <p><i>Chair: Roberto Cosimo Melcangi, Ph.D. Università degli Studi di Milano Co-chair: Luis M. Garcia-Segura, Ph.D. Instituto Cajal, CSIC and CIBERFES</i></p> <p>8:45am – 8:55am: Overview <i>Roberto Cosimo Melcangi, Ph.D. Università degli Studi di Milano</i></p> <p>8:55am – 9:15am: Sex difference in the Levels of neuroactive steroids <i>Roberto Cosimo Melcangi, Ph.D. Università degli Studi di Milano</i></p> <p>9:15am – 9:35am: Rapid brain estrogen signaling in male and female songbirds <i>Luke Remage-Healey, Ph.D. University of Massachusetts Amherst</i></p> <p>9:35am – 9:55am: Sex differences in Regulation of Neurogenesis in the Hippocampus <i>Liisa A.M. Galea, Ph.D. University of British Columbia</i></p> <p>9:55am – 10:15am: Effects of sex and estradiol on neuritogenesis <i>Luis M. Garcia-Segura, Ph.D. Instituto Cajal, CSIC and CIBERFES</i></p> <p><i>Questions and discussion</i></p>	<p><i>Soprano B, Level 4</i> SESSION 15: Sex differences in cardio-metabolic disease across the life-course: from epidemiology to epigenetics</p> <p><i>Chair: Linda M O’Keeffe, Ph.D. University of Bristol</i></p> <p>8:45am – 8:55am: Overview <i>Linda M O’Keeffe, Ph.D. University of Bristol</i></p> <p>8:55am – 9:15am: Diabetes and the female disadvantage <i>Sanne A.E. Peters, Ph.D. University of Oxford</i></p> <p>9:15am – 9:35am: Sex differences in cardio-metabolic risk factors during childhood and adolescence <i>Linda M O’Keeffe, Ph.D. University of Bristol</i></p> <p>9:35am – 9:55am: Biology of sex differences in cardio-metabolic disease: DNA methylation and sex hormones <i>Matthew Suderman, Ph.D. University of Bristol</i></p> <p><i>Questions and discussion</i></p>	<p><i>Soprano C, Level 4</i> SESSION 16: Sex, gender and musculoskeletal disorders in the aging worker</p> <p><i>Chair: Joy MacDermid, Ph.D. Western University, for CIHR MSD</i></p> <p>8:45am – 8:55am: Overview <i>Joy MacDermid, Ph.D. Western University, for CIHR MSD</i></p> <p>8:55am – 9:15am: Sex and age differences in disability duration for work-related musculoskeletal injuries <i>Mieke Koehoorn, Ph.D. University of British Columbia</i></p> <p>9:15am – 9:35am: Male/female differences in return to work. What is the contribution of gendered labour and non-labour market factors? <i>Peter Smith, Ph.D. Institute for Work & Health</i></p> <p>9:35am – 9:55am: Epigenetics and precision health: sex and epigenome tailored approaches for the development of precision medicine tools <i>Olga Kovalchuk, Ph.D. University of Lethbridge</i></p> <p><i>Questions and discussion</i></p>
10:30AM - 10:45AM	COFFEE BREAK	Foyer, Level 4

10:45AM - 12:30PM: SESSIONS 17, 18 & 19

Soprano A, Level 4

SESSION 17: Sex differences in mechanisms of stress and anxiety: Human and animal perspectives across development

Chair: Jason Moser, Ph.D.

Michigan State University

*Co-chair: Rebecca M. Shansky, Ph.D.
Northeastern University*

10:45am – 10:55am: Overview

Jason Moser, Ph.D.

Michigan State University

10:55am – 11:15am: Sex-specific determinants of active vs. passive coping strategies in rodents

Rebecca M. Shansky, Ph.D.

Northeastern University

11:15am – 11:35am: Sex differences in stress response: the role of estrogens, monoamines and brain circuits

Christina Dalla, Ph.D.

National & Kapodistrian University of Athens

11:35am – 11:55am: Error monitoring brain activity as a marker of sex differences in anxiety-related cognitive dysfunction: moderation by developmental stage and ovarian hormones

Jason Moser, Ph.D.

Michigan State University

11:55am – 12:15pm: Sex differences in amygdala perfusion among children and adolescents with trait anxiety

Antonia N. Kaczurkin, Ph.D. University of Pennsylvania

Questions and discussion

Soprano B, Level 4

SESSION 18: Sex-specific targeting of kidney function in children, adults, and the elderly: From genes to policy, sponsored by Ferring Pharmaceuticals

Chair: Geert J. de Vries, Ph.D.

Georgia State University

Co-chair: Jens Peters Nørgaard, M.D., DMSc

Ferring Pharmaceuticals

10:45am – 10:55am: Overview

Chair: Geert J. de Vries, Ph.D.

Georgia State University

10:55am – 11:15am: Structure and expression of genes that escape X inactivation in kidney and kidney-derived cells

Christine M. Disteche, Ph.D.

University of Washington

11:15am – 11:35am: Sex differences in vasopressin V2 receptor expression: Implications for pathophysiology and treatment of disorders of urine concentrating ability

Joseph G. Verbalis, M.D.

Georgetown University

11:35am – 11:55am: Sex differences in enuresis and nocturia across lifespan

Kristian V. Juul, Ph.D.

Ferring Pharmaceuticals

Questions and discussion

Soprano C, Level 4

SESSION 19: Sex-specific mechanisms of upper limb musculoskeletal disorders

Chair: Sandra K. Hunter, Ph.D.

Marquette University

10:45am – 10:55am: Overview

Sandra K. Hunter, Ph.D.

Marquette University

10:55am – 11:15am: Sex-Specific Mechanisms of Fatigue

Sandra K. Hunter, Ph.D.

Marquette University

11:15am – 11:35am: Sex-specific sEMG normalization procedures and their effects on indicators of shoulder muscle activity

Ana Beatriz Oliveira, PT Ph.D.

Federal University of São Carlos

11:35am – 11:55am: Sex-specific mechanisms of acute to chronic neck-shoulder pain

Pascal Madeleine, Ph.D.

Aalborg University

11:55am – 12:15pm: Sex-specific mechanisms incorporated into rehabilitation and prevention approaches

Karen Sjøgaard, Ph.D.

University of Southern Denmark

Questions and discussion

12:30PM - 1:45PM: WORKING LUNCH & BIOLOGY OF SEX DIFFERENCES EDITORIAL BOARD MEETING

Soprano AB, Level 4

WORKING LUNCH: Addressing the 'Data Gap' across the life-span: Experiences with integrating sex and gender

*Chair: Robin Mason, Ph.D.
Women's College Hospital*

12:35pm – 12:45pm: Overview

*Robin Mason, Ph.D.
Women's College Hospital*

12:45pm – 12:55pm: Development of research support in the integration of sex and gender in health

*Robin Mason, Ph.D.
Women's College Hospital*

12:55pm – 1:05pm: Sex and gender considerations in youth suicide prevention: implications for observational and interventional research

*Daphne Korczak, M.D., MSc, FRCPC (peds), FRCPC (psych)
Hospital for Sick Children, University of Toronto*

1:05pm – 1:15pm: Diabetes Action Canada: Acknowledging the challenges of integrating sex and gender into patient-oriented research

*Bruce A. Perkins, M.D., MPH, FRCPC
University of Toronto*

1:15pm – 1:25pm: Contextualizing the self-management of heart pain in women: An evidence map

*Monica Parry, Ph.D., Med, MSc, NP-Adult, CCNC
University of Toronto*

Questions and discussion

Imagination, Level 6

Biology of Sex Differences Editorial Board Meeting

2:00PM - 3:45PM: SESSIONS 20, 21 & 22

Soprano A, Level 4

SESSION 20: Sex differences in neonatal brain injury: role of sex steroids and their receptors, sponsored by Morgan Claypool

*Chair: Pelin Cengiz, M.D.
University of Wisconsin*

(Continued on next page)

Soprano B, Level 4

SESSION 21: Sex differences in cerebral ischemia across the lifespan

*Chair: Fudong Liu, M.D.
University of Texas Health Science Center McGovern Medical School
Co-chair: Amutha Selvamani, Ph.D.
Texas A&M University*

(Continued on next page)

Soprano C, Level 4

SESSION 22: Adverse experiences in sex-based differences in cardio-respiratory function

*Chair: Richard Kinkead, Ph.D.
Université Laval*

(Continued on next page)

<p>2:00pm – 2:10pm: Overview <i>Pelin Cengiz, M.D.</i> <i>University of Wisconsin</i></p> <p>2:10pm – 2:30pm: Mediators of a female advantage in behavioral outcome following late-preterm HI injury in a rodent model <i>R. Holly Fitch, Ph.D.</i> <i>University of Connecticut</i></p> <p>2:30pm – 2:50pm: Sex differences and effects of estradiol treatment on hypoxia-ischemia induced hippocampal damage in neonatal rats <i>Margaret M. McCarthy, Ph.D.</i> <i>University of Maryland School of Medicine</i></p> <p>2:50pm – 3:10pm: Sex difference in the role of ER-mediated neuroprotection following neonatal brain injury <i>Pelin Cengiz, M.D.</i> <i>University of Wisconsin</i></p> <p><i>Questions and discussion</i></p>	<p>2:00pm – 2:10pm: Overview <i>Amutha Selvamani, Ph.D.</i> <i>Texas A&M University</i></p> <p>2:10pm – 2:30pm: Sex differences in immune responses to cerebral ischemia in neonatal and aged mice <i>Fudong Liu, M.D.</i> <i>University of Texas Health Science Center McGovern Medical School</i></p> <p>2:30pm – 2:50pm: Age- and sex-related characteristics of the atherosclerotic plaque <i>Hester M den Ruijter, Ph.D.</i> <i>University Medical Center Utrecht</i></p> <p>2:50pm – 3:10pm: Sex differences in cerebral ischemia at menopause/ reproductive senescence: declining levels of estrogen and Insulin-like growth factor (IGF)-1 <i>Farida Sohrabji, Ph.D.</i> <i>Texas A&M Health Science Center College of Medicine</i></p> <p>3:10pm – 3:45pm: Sexual dimorphism in inflammasome activation: Possible cause of exacerbated ischemic brain damage in reproductively senescent (RS) female rats <i>Ami P. Raval, Ph.D.</i> <i>University of Miami</i></p> <p><i>Questions and discussion</i></p>	<p>2:00pm – 2:10pm: Overview <i>Richard Kinkead, Ph.D.</i> <i>Université Laval</i></p> <p>2:10pm – 2:30pm: Sex differences in the developmental programming of blood pressure across the lifespan <i>Barbara T. Alexander, Ph.D.</i> <i>University of Mississippi Medical Center</i></p> <p>2:30pm – 2:50pm: Sex differences in T cell-dependent hypertension: Role of menopause in disease onset <i>Heddwen L. Brooks, Ph.D.</i> <i>University of Arizona</i></p> <p>2:50pm – 3:10pm: Neonatal stress and sex-based differences in respiratory manifestations of panic disorders <i>Richard Kinkead, Ph.D.</i> <i>Université Laval</i></p> <p><i>Questions and discussion</i></p>
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3:45PM - 4:00PM **COFFEE BREAK** *Foyer, Level 4*

4:00PM - 4:30PM: BUSINESS MEETING AND LAUNCH OF THE SEX AND GENDER TRAINEE NETWORK

<p><i>Soprano AB, Level 4</i> BUSINESS MEETING</p>	<p><i>Imagination, Level 6</i> SEX AND GENDER TRAINEE NETWORK LAUNCH</p> <p><i>Trainees are invited to participate in the launch of a Sex and Gender National Trainee Network aimed at 1) promoting the integration of sex and gender into health research; 2) fostering collaboration among trainees; and 3) advancing the science and dissemination of knowledge about sex and gender in health research.</i></p>
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4:30PM - 6:15PM	POSTER SESSION 2	<i>Inspiration, Level 6</i>
6:45PM - 7:30	COCKTAIL RECEPTION	<i>Creation, Level 6</i>
7:30PM	BANQUET	<i>Soprano AB, Level 4</i>

DETAILED PROGRAM: THURSDAY, MAY 18

7:30AM - 9:00AM	BREAKFAST	<i>Six Resto Lounge, Level 6</i>
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9:00AM - 10:45AM: SESSIONS 23 & 24

Soprano A, Level 4

SESSION 23: Sex differences in the hippocampus and related structures: Implications for cognition and stress reactivity throughout the lifespan

*Chair: Karyn M. Frick, Ph.D.
University of Wisconsin-Milwaukee*

9:00am – 9:10am: Overview

*Karyn M. Frick, Ph.D.
University of Wisconsin-Milwaukee*

9:10am – 9:30am: Estrogenic regulation of memory in males and females: Molecular mechanisms and implications for aging

*Karyn M. Frick, Ph.D.
University of Wisconsin-Milwaukee*

9:30am – 9:50am: Hormonal factors in male and female social behavior in rodents

*Elena Choleris, Ph.D.
University of Guelph*

9:50am – 10:10am: Sex differences in stress reactivity and neurogenesis during development and adolescence

*Liisa A.M. Galea, Ph.D.
University of British Columbia*

Questions and discussion

Soprano B, Level 4

SESSION 24: Sex differences in cardiovascular disease with aging: Getting beyond the classic roles of sex hormones

*Chair: John M. Stafford, M.D., Ph.D.
Vanderbilt University Medical Center*

9:00am – 9:10am: Overview

*John M. Stafford, M.D., Ph.D.
Vanderbilt University Medical Center*

9:10am – 9:30am: Targeted estrogen delivery to delay diabetes in women

*Franck Mauvais-Jarvis, M.D., Ph.D.
Tulane University*

9:30am – 9:50am: The roles of the G protein-coupled estrogen receptor GPER in physiology and disease

*Eric R. Prossnitz, Ph.D.
University of New Mexico*

9:50am – 10:10am: Role of sex chromosomes in obesity and metabolic co-morbidities

*Karen Reue, Ph.D.
University of California, Los Angeles*

10:10am – 10:30am: The role of cholesteryl ester transfer protein in mediating sex-differences in cardiovascular risk with obesity and aging

*John M. Stafford, M.D., Ph.D.
Vanderbilt University Medical Center*

Questions and discussion

10:45AM - 11:00AM	COFFEE BREAK	<i>Foyer, Level 4</i>
11:00AM - 12:00PM	CAPSTONE LECTURE How the evolution of sex- and gender-based research impacts the practice of medicine <i>Alyson McGregor, M.D.</i> <i>Brown University</i>	<i>Soprano AB, Level 4</i>
END OF MEETING		
12:30PM - 3:00PM	OSSD 2017 COUNCIL MEETING (<i>lunch provided</i>)	<i>Imagination, Level 6</i>

SPEAKERS' ABSTRACTS: MONDAY, MAY 15

1:15pm - 3:00pm: SESSION 1

Developmental neuroimaging of the sexually dimorphic brain across species

Sponsored by Biomed Central

Chair: Armin Raznahan, M.D. Ph.D., National Institute of Mental Health

Male and females show behavioral sex-differences throughout the animal kingdom, which may relate to sex-differences in brain development over the lifespan. In vivo neuroimaging provides a powerful tool for the study of sexually dimorphic brain development, and neuroimaging research methodologies have undergone dramatic advances in recent years – yielding new insights about the spatiotemporal patterning of sex-differences in brain structure and function. Moreover, integration of this neuroimaging data with genomic and behavioral assays is offering new ways of examine the causes and consequences of sexually-dimorphic brain development. This proposed panel would bring together the latest work of laboratories that have been applying cutting edge methods for in vivo structural neuroimaging to generate detailed 4D maps of sexually dimorphic brain development in humans, non-human primate and mice. Neuroimaging studies of brain development will be integrated with closely aligned transcriptomic datasets to provide molecular insights into sex-specific biological influences in brain development.

Imaging the development of sexual dimorphisms in the brains of mice

Jason P. Lerch, Ph.D. Mouse Imaging Centre, The Hospital for Sick Children, and Department of Medical Biophysics, University of Toronto

Sex differences exist in behaviours, disease and neuropsychiatric disorders. Sexual dimorphisms, however, have yet to be studied across the whole brain and across a comprehensive time course of postnatal development. Here, we used manganese enhanced magnetic resonance imaging (MEMRI) to longitudinally image male and female C57BL/6J mice across 9 postnatal time points, beginning at postnatal day 3. We recapitulated findings on canonically sexually dimorphic areas, demonstrating the ability of MEMRI to study neuroanatomical sex differences. We discover, upon correcting for whole-brain volume, that neuroanatomical regions larger in males develop early in life, while regions larger in females develop in post-pubertal life. Furthermore, we found groups of areas that shared coordinated sexually dimorphic development and also underlie behavioural and functional networks. We then assessed the relative contribution of sex chromosomes and sex steroids by comparing the developmental data to adult-imaged four-core genotype mice.

Sexually Dimorphic Brain Development in Nonhuman Primates and Human Infants.

Rebecca C. Knickmeyer, Ph.D. University of North Carolina at Chapel Hill

Sex differences in adult brain are often hypothesized to originate in prenatal development, when gonadal steroids masculinize the reproductive system, or in adolescence, when endocrinological changes lead to emergence of secondary sex characteristics. This talk will present results from two complementary lines of research on developmental origins of sex differences in brain structure, one focused on nonhuman primates and the other on human infants. In the first study we will present, MRI scans were obtained on 37 rhesus monkeys (20M, 17F) between 10 and 64 months of age. Males and females showed similar maturational patterns, but males had larger total brain volumes, females had proportionately larger caudates, putamens and hippocampi, and males had absolute and relatively larger corpus callosa. Subsequently, we examined longitudinal change in global and regional brain volumes in monkeys which had either been gonadectomized or sham operated prior to puberty. Results suggest gonadal hormones have minimal effects on structural brain development in male rhesus macaques during puberty, with the potential exception of prefrontal gray matter. The latter half of the talk will focus on characterization of sex differences in an extraordinary cohort of over 800 typically developing neonates. An initial tensor-based morphometry study showed that males had larger volumes in medial temporal cortex and rolandic operculum, and females had larger volumes in dorsolateral prefrontal, motor, and visual cortex. A later study showed females also have relatively larger gray matter volumes around the temporal-parietal junction, a key region in attentional and social processes. Current studies are

revealing sex differences in cortical thickness and surface area change across the first two years of life. Overall, our research shows sex differences in cortical structure vary in a complex and highly dynamic way across development, even in periods when the gonads are relatively quiescent.

Sex differences in human brain development from childhood to adulthood

Armin Raznahan, M.D. Ph.D. National Institute of Mental Health

Epidemiological studies show robust sex-difference in the prevalence of adolescent-emergent affective (females>males) and externalizing (males>females) disorders. The temporal proximity of these behavioral sex-differences to puberty, and their stability across cultural/historical settings, suggests a potential role for sex-biased brain development in adolescence. This talk will present results from a series of structural neuroimaging studies that detail spatio-temporal patterning of male-female differences in human brain development using a longitudinal dataset of ~1500 structural magnetic resonance imaging brain scans gathered from ~700 typically-developing males and females ages 5-30 years. Morphometric indices of interests were extracted from each scan using well-validated and fully automated image analysis tools for measurement of volume and shape in the cortex ("CIVET") and subcortex ("MAGeT Brain"). In keeping with the ~10% sex-difference in total brain volume, all regional brain volumes examined were significantly larger in males than females throughout development. However, analysis of anatomical sex-differences at higher spatiotemporal resolution identifies rostral prefrontal, ventral striatal and medial thalamic "hotspots" of dynamic male-female divergence over adolescence, which may represent biological substrates for developmentally-emergent behavioral sex differences in adolescence. In a complementarity series of cross-sectional studies, we show how non-linear anatomical scaling in the human brain can distort analysis of regional sex-differences given male-female differences in total brain size. Statistical methods that account for brain allometry provide an entirely new view of male-female differences in cortical, subcortical and cerebellar organization. Taken together, these studies help to pinpoint male-female differences in regional brain anatomy for further analysis as potential substrates for sex-biased domains of behavior and cognition.

1:15pm - 3:00pm: SESSION 2

Sex differences in cardiovascular aging - common mechanisms in different clinical syndromes

Chair: Vera Regitz-Zagrosek, M.D. Charité University medicine

Co-chair: Virginia Miller, Ph.D. Mayo Clinic

Aging and changes in sex hormone Levels contribute to impaired cardiovascular (CV) function in elderly women and men. At present, the interaction of aging and hormonal changes is not clear. In women, decline in estrogen Levels during menopause predisposes to different forms of HF, including diastolic HF and stress-induced cardiomyopathy. Y-chromosome loss, which occurs frequently at aging, may lead to deleterious CV phenotypes in men, including atherosclerosis. We want to demonstrate in 4 typical clinical CV syndromes that aging and changes in sex hormone Levels interact in their impact on the CV system in women and men and lead to progression of CV disease phenotypes. We will identify common pathophysiological mechanisms between the different disease phenotypes.

Cardiac genes that escape X inactivation: implications of epigenetic modifications in aging

Christine M. Disteche, Ph.D. University of Washington

Among the genes that show sex bias in heart and vascular systems are many genes located on the sex chromosomes, especially genes that escape X chromosome inactivation and have higher expression in females. Based on analyses of RNA-seq datasets we find that there is a significant female bias in X-linked gene expression in heart. The role of these genes in cardiac disorders due to aging is not well defined. However, epigenetic alterations and loss of the X or Y chromosome are associated with aging. Examples of genes potentially implicated in sex differences in the aging heart include the escape gene Kdm6a, a histone demethylase that removes H3K27me3. Its role in development is highlighted in knockout cells and animal models in which reduced expression of Kdm6a is mid-gestation lethal due to heart malformations and neural tube closure defects. Moreover, Turner females with haploinsufficiency of KDM6A exhibit a number of congenital abnormalities including heart defects, which are also reported in Klinefelter individuals with increased KDM6A expression, suggesting that dosage of this gene is critical. Kdm6a ablation by CRISPR-Cas9, which we induced in mouse ES cells, results in downregulation of a number of genes, including Pitx2 and Myl7, both implicated in heart development and function. Thus, Kdm6a dosage may

play a role in cardiac disorders due to aging, in which sex-specific demethylation of H3K27me3 may cause aberrant gene expression. In addition to alterations in histone marks other types of age-related epigenetic anomalies may occur, for example due to loss of chromatin organizers such as CTCF. We investigated the Car5b gene that encodes for carbonic anhydrase and has higher expression in female heart. We found that loss of CTCF causes aberrant gene expression, suggesting that CTCF is implicated in the maintenance of escape from X inactivation.

Loss of Y chromosome in blood is associated with major cardiovascular events during follow-up in men after carotid endarterectomy

Hester M. den Ruijter Ph.D.

University Medical Center Utrecht

Recent studies found an immune-regulatory role for Y, and a relation between loss of Y (LOY) in blood cells and a higher risk of cancer and mortality. Given the involvement of immune cells in atherosclerosis, we hypothesized that LOY is associated with the severity of atherosclerotic plaque characteristics and outcome in men undergoing carotid endarterectomy (CEA). LOY was quantified in blood and plaque from raw intensity genotyping data in men within the Athero-Express biobank study. Plaques were dissected, and the culprit lesions were used for histology and the measurement of inflammatory proteins. We tested LOY for association with (inflammatory) atherosclerotic plaque phenotypes and cytokines and assessed the association of LOY with secondary events during 3-year follow-up. Out of 366 CEA patients, 61 exhibited some degree of LOY in blood. LOY was also present in atherosclerotic plaque lesions (n = 8/242, 3%). LOY in blood was negatively associated with age (beta=-0.03/10yr, r²=0.07, p=1.6*10⁻⁷), but not with cardiovascular disease severity at baseline. LOY in blood was associated with a larger atheroma size (OR 2.15, 95% CI: 1.06-4.76, p= 0.04) however this association was not significant after correction for multiple-testing. LOY was independently associated with secondary major cardiovascular events (HR = 2.28, 95% CI: 1.11-4.67, p=0.02) in blood when corrected for confounders. In this hypothesis-generating study, LOY in blood is independently associated with secondary major cardiovascular events in a severely atherosclerotic population. Our data could indicate that LOY affects secondary outcome via other mechanisms than inflammation in the atherosclerotic plaque.

Postmenopausal decrease in sex hormones - a trigger for cardiovascular disease?

Vera Regitz-Zagrosek, M.D. Charité University medicine

Women have less coronary artery disease (CAD), hypertension, diabetes, heart failure and sudden cardiac death than men below 60 years. In contrast, after 60 there is a steeper increase in many syndromes and women even outran men in numbers of hypertensives, strokes, or develop specific age related forms of cardiovascular disease (CVD), such as stress induced or tako tsubo cardiomyopathy, diastolic heart failure, diabetes complications. The so called Hormone replacement therapy failed to keep numbers of CVD in women after menopause low but this does not exclude that the decrease in sex hormones is pathophysiologically linked to changes of disease incidence in women. To understand the link between a decrease in sex hormones and CVD, epidemiological studies have been undertaken, such as Gutenberg health and BEFRI. In 5000 individuals of the population-based Gutenberg Health Study, we found sex-specific associations of classical CVD risk factors with markers for vascular and cardiac dysfunction. These markers were related to CVD such as coronary artery disease, heart failure, stroke, myocardial infarction or lower extremity artery disease. Men had more risk markers and more CVD, only HF was more prevalent in women. Almost linear changes toward less beneficial values with age were observed in both sexes, however, no interactions with menopausal status were found. Thus, we observed sex differences in risk factors and in a broad range of intermediate phenotypes but no obvious link to menopause and hormonal decrease. A similar age related decrease of vascular stiffness and diastolic function without clear link to menopause associated changes was found in the Berlin women risk evaluation study, BEFRI. These results favor age related cause in contrast to hormone induced changes. In contrast, the frequent appearance of Tako Tsubo CMP shortly after menopause suggest a link to a decrease in estrogen levels. At molecular level, few data are available. Among others, our proteomic studies suggest age related and sex related changes in the proteomic patterns in the human heart. Fibrosis related proteins, energy metabolism and free radical scavengers are mainly concerned. However a clear link of these changes to sex hormones is missing. A number of observations in animal models clearly show the role of sex hormones in the CV system. However the complex changes in menopause and the drastic changes induced by surgical gonadectomy may differ. Thus more data are needed to differentiate age related changes from hormone related changes.

Coronary microvascular dysfunction and heart failure with preserved ejection fraction: Hormone or age dependent

C. Noel Bairey Merz, M.D.

Cedars-Sinai Heart Institute

The WISE, a cohort study of over 1000 women, has made many contributions to our understanding of cardiovascular disease. A milestone acknowledged in the 2011 AHA Herrick Lecture is the role of Coronary Microvascular Dysfunction (CMD) in women with symptoms/signs of ischemia without obstructive coronary artery disease (CAD). While in 1996, CMD was considered “an imaging artifact”, in 2013 it is widely accepted as a pathophysiologic process requiring systematic cohesive scientific pursuit. We have determined that CMD is prevalent, associated with adverse clinical outcomes, poor quality of life and healthcare costs rivaling obstructive CAD. There are 2-3 million US women with CMD, and 100,000 new cases projected annually placing CMD prevalence, morbidity and costs higher than all female reproductive cancers combined. Among women with ischemia, preserved ejection fraction and no obstructive CAD, we have observed relatively more new onset HF hospitalizations than nonfatal myocardial infarction (MI). We hypothesize that CMD contributes to LV diastolic dysfunction and subsequent heart failure with preserved ejection fraction (HFpEF). Our preliminary data suggests that left ventricular (LV) diastolic dysfunction is linked to CMD via a mechanism of augmentation and/or perpetuation by cardiomyocyte fat accumulation. HFpEF is prevalent in women and older men, but poorly understood. Mechanistic understanding is critical to HFpEF intervention and guideline development. The role of aging, risk variables and hormones will be discussed.

3:15pm - 5:00pm: SESSION 3

Sex differences in the interactions between the microbiome and stress/immune system across the lifespan

Sponsored by Elsevier

Chair: Nafissa Ismail, Ph.D. University of Ottawa

Co-chair: Amanda Kentner, Ph.D. Massachusetts College of Pharmacy & Health Sciences

Despite the growing body of literature illustrating sex differences in stress and immune responses, the mechanisms underlying these effects remain unknown. This symposium connects researchers at both the basic and clinical levels highlighting the translational role of the microbiome at the crossroads between stress, immunity and health across the lifespan. Eldin Jasarevic will present his work on sex-specific prenatal reprogramming of the gut-brain immune axis and lasting alterations to host-microbiome interactions. Amanda Kentner will discuss her work on gut changes in pain processing and social preference impairments in male and female animals following neonatal inflammatory challenge. Nafissa Ismail will present her work on the protective effects of probiotic treatment on anxiety-like behavior following pubertal stress. Finally, Sabra Klein will discuss her work on sex differences in immune responses to both self and foreign antigens in adults with a specific focus on interactions between the microbiome and immunity. Together this symposium will underscore sex differences across the lifespan while bridging the gap between the microbiome and stress/immune system.

Causal role of the maternal vaginal microbiome in programming offspring brain and immune development

Eldin Jasarevic, Ph.D. University of Pennsylvania

Prenatal stress is associated with an increased risk for gastrointestinal neurodevelopmental disorders, such as autism spectrum disorders and mood disorders. Mounting evidence points to a likely influence of maternal stress experience on reprogramming of the gut-brain axis, especially involving the hypothalamus. Using our mouse model of early prenatal stress (EPS), we established that stress alters the vaginal microbiota transmitted to offspring during birth, and changes in the gut microbiome were associated with lasting effects on offspring metabolism and neurodevelopment. However, evidence of a causal role for the microbiome in such studies is lacking. Using cesarean delivery and oral gavage with vaginal inoculant, we demonstrate a causal role of the maternal vaginal microbiome in promoting sex-specific recapitulation of aspects of our EPS phenotype. As the mucosal immune system impacts postnatal gut-brain axis function, we tested the hypothesis that EPS disrupts the transcriptional and immune profiles of the fetal gut. Early prenatal stress exposure reprogrammed fetal intestinal transcriptional profiles in a sex-specific manner prior to birth, including disruption of genes encoding innate immunity pathways in EPS male offspring. Further, EPS increased trafficking of inflammatory monocytes into the male fetal gut and brain, revealing a proinflammatory phenotype along the gut-brain axis in EPS males. As adults, EPS males exhibit exaggerated

stress-induced defects in intestinal barrier integrity, increased proinflammatory cytokine production, and gut microbiota alterations, demonstrating that EPS exposure markedly exacerbates gut-brain axis dysfunction in response to stress in adulthood. Together, these studies support a causal role of the maternal vaginal microbiome in sex-specific programming of the developing gut-brain axis that may underlie lifetime sex differences in stress and immune disease risk.

Do gut reactions lead to sex differences in social preference following a neonatal inflammatory challenge?

Amanda Kentner, Ph.D. Massachusetts College of Pharmacy & Health Sciences

Inflammatory challenges in early life are associated with several behavioral and cognitive deficits that manifest in a sex-dependent manner across development. Using a rodent model of infection, we report that neonatal lipopolysaccharide (nLPS) challenge at 3 and 5 days of age reduced overall social contact time in male adolescent rats. This was primarily mediated by the low amount of contact they received from their healthy novel conspecifics compared to neonatal (n)saline animals. Females were immune to this 'social rejection' unless exposed to a second LPS challenge in adolescence. Given that there are important sensory, motor, and motivational components that underlie social interactions, we sought to identify the mechanism(s) responsible for the reduced social contact directed towards nLPS rats. Overall, there were no differences in ultrasonic vocalizations across neonatal treatments. Moreover, basal levels of plasma corticosterone were not elevated in nLPS males or females, nor did they display anxiety-like behavior. Administering diazepam to adolescent nLPS rats did not eliminate the social preference bias for nsaline animals. Using an intranasal perfusion procedure, we induced a ZnSO₄ lesion in a subset of novel conspecifics, effectively disrupting their olfactory processing. Notably, this procedure equalized the amount of social contact they directed towards nLPS compared to nsaline rats. Moreover, treating nLPS rats with antibiotics also increased the amount of social investigation they received. Together, this indicates that neither vocalized motor pathways or anxiety cues, mediated by auditory communication, are involved in the social deficits following nLPS. Instead, our data suggest that olfactory signals, likely mediated through the microbiota, as opposed to fear pheromones, underlie the reductions in social contact that follow nLPS. We are currently following this line of investigation in our laboratory by evaluating the microbiota directly.

Sex differences in response to probiotic treatment and pubertal stress

Nafissa Ismail, Ph.D. University of Ottawa

Puberty is a critical period of development during which sexual maturity is reached. It is also an important period during which the brain is remodelled and reorganized, making it a sensitive and vulnerable period to environmental stress. Pubertal exposure to an immune challenge results in an enduring decrease in behavioral responsiveness to estradiol as measured both in reproductive and non-reproductive behaviors. The objective of this presentation is to discuss age and sex differences in immune response and the impact of the gut-brain axis on this response. To date, our results show that exposure to an immune challenge induces important age and sex differences in immune response, thermoregulation, cytokine mRNA, c-Fos and TH expression. Exposure to probiotics during puberty alters immune response differently in males and females and appears to prevent enduring changes in behavior, especially in the males. These findings propose potential mechanisms through which exposure to an immune challenge can cause enduring alterations in reproductive and non-reproductive behaviors and possible preventative measures.

Sex and gender differences in the outcomes of vaccination over the life course

Sabra Klein, Ph.D. Johns Hopkins Bloomberg School of Public Health

Both sex and gender impact vaccine acceptance, responses, and outcomes. Clinical data illustrate that among children, young adults, and aged individuals, males and females differ in vaccine-induced immune responses, adverse events, and protection. Although males are more likely to receive vaccines, following vaccination, females typically develop higher antibody responses and report more adverse effects of vaccination than males. Using data from animal models of malaria and influenza vaccines, the immunological, hormonal, and environmental factors that differ between males and females across the life course and contribute to sex- and gender-specific vaccine responses and outcomes will be discussed. Herein, I will address the impact of sex and gender variables in juveniles, adults, and aged individuals that should be considered in preclinical and clinical studies of vaccines.

3:15pm - 5:00pm: SESSION 4

Sex differences in transplantation: from stem cells to the whole organ

Chair: Amanda Mahnke, Ph.D. Texas A&M University

Co-chair: Lori West, M.D., D. Phil. University of Alberta

From the stem cells to the whole organ, studies have shown that sex may be an important determinant of recovery and outcome after transplantation. At the cellular level, both endogenous and induced stem cells can display sex differences in treatment efficacy and complication risk. Whole organ transplants can have poorer survival if there is a sex mismatch of donor and recipient. This symposium proposes to discuss the sex differences that arise in transplantation of both cells and whole organs, examining both embryonic and adult induced stem cells as well as from pediatric age into adulthood.

Sex really matters when working with human pluripotent stem cells

Montserrat Anguera, Ph.D. University of Pennsylvania

Human pluripotent stem cells are a powerful tool for regenerative medicine and also for modeling the early events of the human embryo. These female cells, unlike male cell lines, exhibit epigenetic instability during routine culture, which affects global gene expression, including expression from the inactive X-chromosome. Female mammals use X-chromosome Inactivation (XCI) for dosage compensation of X-linked genes, where expression of the long noncoding RNA XIST initiates and maintains XCI. Nearly all of the NIH-approved female human embryonic stem cell (hESC) lines have undergone XCI, and most hESC and induced pluripotent stem cell (iPSC) lines display abnormal epigenetic features on the inactive X. I will present evidence of perturbed silencing from the inactive X in female hESCs and iPSCs, and phenotypic consequences from abnormal XCI. In addition, we are investigating the sex-specific gene expression differences during placental development, using directed differentiation of hESC lines. Our results demonstrate that sex-biased expression observed in full-term placentas originates in trophoblast progenitor cells.

Sex differences in kidney graft failure risk differ by age

Bethany J. Foster, M.D. McGill University Faculty of Medicine

Prior studies of sex differences in kidney graft survival showed conflicting results. We hypothesized that the association between recipient sex and kidney graft failure risk differs by recipient age and by donor sex. We evaluated 159,417 patients recorded in the Scientific Registry of Transplant Recipients database who received a first deceased donor kidney transplant between 1995 and 2013. We used time-varying Cox models to estimate the association between recipient sex and death-censored graft failure. Models, stratified on donor sex and adjusted for potential confounders, included a recipient sex by current age (0 to 14, 15 to 24, 25 to 44, or ≥ 45 years) interaction term. Among recipients of male donors, females of all ages had significantly higher graft failure risks than males (adjusted hazard ratios 0-14 years: 1.51 (95% confidence intervals 1.19, 1.90); 15-24 years: 1.37 (1.18, 1.59); 25-44 years: 1.14 (1.03, 1.26); 45 years 1.05 (1.01, 1.09)). When the donor was female, only female recipients 15-24 years had significantly higher risks of graft failure than males (adjusted hazard ratio 1.28 (1.06, 1.53)). Female recipients 45 years had significantly lower graft failure risks than males of the same age when the donor was female (adjusted hazard ratio 0.95 (0.91, 0.99)). The combined influence of several factors likely explain these observations, including recognition of sexually-determined minor histocompatibility antigens, influence of sex hormones on immune activation, sex and age differences in medication adherence, and sex-related differences in body size. Additional studies are needed to determine whether sex- and age-specific immunosuppression strategies are warranted.

Sex and age differences impact organ transplantation

Lori West, M.D., D.Phil. University of Alberta

Emerging evidence suggests important differences exist both in access to and clinical outcomes after solid organ transplantation between female and male recipients, as well as between recipients of organs from male vs female donors. Differences in outcomes are likely to be influenced by additional age-related factors including immune development and medication metabolism, particularly in infants and young children. These and related factors from recent studies, particularly related to non-renal organ transplants, will be addressed in this presentation.

5:30pm - 6:30pm: PRESIDENTIAL LECTURE

Sex differences in pain from both sides of the syringe

Jeffrey S. Mogil, Ph.D. McGill University

Pain researchers have now come to some consensus regarding the existence of small quantitative sex differences in the sensitivity to and tolerance of pain in humans. However, broad conclusions regarding the existence and direction of such sex differences are complicated by emerging evidence from laboratory animals that sex differences interact with genetic background; even the direction of sex differences may depend on genetic factors. In addition to these quantitative sex differences, evidence is rapidly emerging that the sexes may differ qualitatively in their neural mediation of pain and analgesia. That is, different neural circuits, transmitters, receptors and genes may be relevant to pain processing in males and females. I will present new data from our laboratory demonstrating that the specific cellular and neurochemical mediation of chronic pain processing in the spinal cord in male and female mice are radically different. In addition, we have recently uncovered evidence that another kind of sex difference can affect the pain of rodents: the sex of the experimenter. Olfactory signals associated with isolated males produce stress, and stress-induced analgesia, in rats and mice. This previously unappreciated phenomenon may represent a major confound of existing behavioural studies using laboratory animals.

SPEAKERS' ABSTRACTS: TUESDAY, MAY 16

8:45am - 10:30am: SESSION 5

Neuroimmune interactions in health and disease: sex differences across the lifespan

Chair: Teresa M. Reyes, Ph.D. University of Cincinnati

Interactions between the immune system and the brain are a key determinant in the pathways to either health or disease, and these interactions play out throughout the lifespan. Importantly, sex differences in neuroimmunological responses have been robustly observed. The goal of this symposium will be to (1) introduce and define sex differences in neuroimmunological responses and (2) highlight the link between these responses and eventual health or disease. The speakers will include data encompassing a range of time periods, including pregnancy and early life, adolescence, adulthood, and aging, as well as inclusion of both animal models and human imaging data. This symposium should be of interest to the broad range of scientists that attend OSSD, as neuroimmunological processes contribute to a wide variety of disease states, from mental health disorders and pain, through obesity and cardiovascular disease, metabolic syndrome to cancer. The symposium speakers represent all stages of career development (postdoc through full professor).

Brain-resident immune cells are crucial regulators of sex differences in the development of motivated behaviors

Kathryn M. Lenz, Ph.D. Ohio State University

Innate immune cells colonize the brain prenatally and are known to regulate many processes of brain development, including cell genesis, cell death, migration, and synaptic patterning. We have recently been investigating the role of innate immune cells, such as microglia and mast cells, as regulators of sex differences in the development of the rodent brain and related motivated behaviors. Both microglia and mast cells are sexually dimorphic in the developing rat brain, and their inflammatory signaling is hormone sensitive. We have found prominent sex differences in microglia in the developing hippocampus, notably a female-biased sex difference in the rate of phagocytosis of progenitor cells and the expression of genes associated with phagocytosis. Furthermore, using liposomal clodronate to temporarily ablate microglia from the developing rat brain, we have found that microglial loss impacts hippocampal neurogenesis more profoundly in males than in females. Following microglial loss in early life, adult females in particular show decreases in anxiety-like and depressive-like behavior, a decreased acute stress response and decreased immediate early gene activation in the prefrontal cortex. Conversely, in response to two perinatal inflammatory challenges, juvenile males show alterations in social play behavior, with females showing resilience. In response to early life inflammatory experiences, males and females show differing patterns of immune cell number and activation in limbic regions of the brain. The female brain also shows higher levels of anti-inflammatory cytokines as well as the neurotransmitter, histamine, that we hypothesize may be protective against inflammation induced disruptions in sociality. Together, these studies suggest that males and females show significant differences in immune cell function in the developing brain that impact both normal development as well as the brain's response to early life perturbations.

Female resiliency to intrauterine inflammation during pregnancy

Teresa M. Reyes, Ph.D. University of Cincinnati

Exposure to inflammation during pregnancy has been linked to adverse neurodevelopmental consequences for the offspring. Using a mouse model of chorioamnionitis (intrauterine (IUI) lipopolysaccharide (LPS), 50 µg at E15), we assessed placental and fetal brain inflammatory responses, white matter integrity, anxiety-related behaviors (elevated zero maze, light dark box, open field), microglia numbers, and the CNS cytokine response to an acute injection of LPS in both males and females. For many of the endpoints, male IUI offspring were uniquely affected, while female IUI offspring did not differ from controls. Interestingly, for white matter damage and behavioral changes, both male and female offspring were equally affected by the prenatal exposure to inflammation. This presentation will discuss how the present data may inform observed sex differences in neurodevelopmental disorders.

Stress challenges during early adolescence yield divergent outcomes in adulthood for males and females

Terrence Deak, Ph.D. Binghamton University-SUNY

Adolescence is a time of profound neural and behavioral change during which developing organisms transition to adult-like functioning. Importantly, adolescents are exposed frequently to major life stressors, and initiate alcohol consumption. Thus, in a series of studies using pre-clinical models, we exposed male and female Sprague Dawley rats to intermittent alcohol from PND30-50 and then assessed stress reactivity and evoked cytokine responses later in adulthood (P75-85). Interestingly, the longitudinal effects of adolescent alcohol exposure were sex-specific, with males demonstrating severely blunted cytokine reactivity when challenged by restraint or LPS exposure as adults, whereas female cytokine reactivity was unaffected. In contrast, females with a history of adolescent alcohol exposure evinced sensitization of the hypothalamic-pituitary-adrenal (HPA) axis, whereas males displayed normal stress responses. Subsequent studies tested whether these sex-specific outcomes were unique to adolescent alcohol exposure or represented a more general response to adolescent perturbations by exposing adolescent rats (PND29-32) to a single session of intermittent footshock (80 shocks, 5 sec each, 1.0 mA, 90 sec variable ITI). Once again, adult females with a history of adolescent stress exposure evinced a significant sensitization of the HPA axis response to a subsequent stress challenge (restraint) in adulthood, an effect that was completely absent in male comparators. Instead, males (but not females) displayed enhanced behavioral signs of anxiety in the light-dark box. Neither sex demonstrated any long-term changes in social interaction, forced swim behavior, or locomotor activity. Together, these findings suggest that HPA axis dysregulation may be a common outcome of developmental perturbations uniquely for females, and may have implications for the development of sex-specific interventions for health-related problems that emerge during adulthood.

Sex differences in human experimental inflammatory models

Bianka Karshikoff, Ph.D. Karolinska Institutet

Models of experimentally induced sickness (EIS) reveal mechanisms of immune-brain interactions with implications for diseases with an inflammatory component. Several EIS models are available for humans, and one of the most studied inflammatory model is injections of low-dose lipopolysaccharides (LPS), a bacterial endotoxin. This model elicits an acute inflammatory response and induces characteristic behavioral changes, such as increased fatigue, depressed mood and increased pain sensitivity. Specific brain activity changes driven by inflammation that accompany these behavioral effects have also been described. Immune responses to infectious agents are known to differ between men and women. Furthermore, many of the diseases that are in focus of this line of research are more prevalent in women, such as depression and chronic pain. EIS models in animals and humans have revealed sex differences that may be of importance for e.g. chronic pain. In this talk, I will present the current knowledge on sex differences in the behavioral response to inflammation as revealed by EIS, with a focus on pain mechanisms.

8:45am - 10:30am: SESSION 6

Sex chromosomes and sex differences in health and disease

Chair: Chris Lau, Ph.D. University of California

Co-chair: Fadi J. Charchar Ph.D. Federation University Australia

The Y chromosome is the male-specific portion of the human genome. Traditionally, it has been considered to only serve the critical functions in determining and maintaining the male sex, i.e. the determination, differentiation, and physiology of the male sex organ, the testis. Yet, recent advances in the field have demonstrated that genes on the Y chromosome, particularly those at the male-specific region (MSR), could participate in numerous additional developmental and physiological functions in a multitude of organs and cell types, thereby exerting significant male-specific influences in these biological processes. The proposed session will examine the specific roles of this male-specific chromosome in a variety of quantitative traits associated with both normal development and diseases, including early onset ones, such as autism, mid-life ones, such as schizophrenia, and late onset ones such as neurodegenerative diseases, and cardiovascular abnormalities throughout life. The session will start with an overview of the genes on this chromosome, and follow with individual discussions on their contributions to cardiovascular disease, neurological diseases, and experimental assessment of a Y-located gene in human diseases.

Y Chromosome and Sex Differences in Cardiovascular Disease

Fadi J. Charchar Ph.D. Federation University Australia

Cardiovascular disease (CVD) is a major cause of death in the world. Men are more prone to CVD throughout their lives but it is not known whether women are more protected, or men are at a higher risk. An obvious molecular contrast between the sexes is the sex chromosomes. Studies from our group and others have revealed that the Y chromosome influences cardiovascular risk factors such as hypertension and cholesterol. Intriguingly, evidence suggests the influence of the Y chromosome alters responses to infection (adaptive immunity) rather than innate immunity, exaggerating inflammatory response in the macrophage - a cell type with an established role in atherosclerotic plaque initiation and progression. The study of biologically unrelated men from three large studies (the cross-sectional British Heart Foundation Family Heart Study, the prospective West of Scotland Coronary Prevention Study, and the Cardiogenics Study) showed that Y chromosome genetic variations in Caucasian men carrying a type of Y chromosome called haplogroup-I increase the risk of coronary artery disease by 50%. In the macrophages of haplogroup-I carriers, 30 gene pathways were differentially expressed compared to those derived from non-carriers. Our other findings also revealed sex-specific associations with coronary artery disease with the pseudoautosomal region shared by the X and Y chromosomes. In a search for causative genes, we found a novel Y-linked long non-coding RNA (lncRNA) called lnc-KDM5D-4 to be underexpressed in diseased human vessels. lnc-KDM5D-4 knockdown resulted in an upregulation of anti-apoptosis and lipid metabolism-related genes. In this context, we are interested in determining the Y-specific molecular factors that contribute to CVD including long non-coding RNAs (lncRNAs), a new class of regulatory RNA molecules. Our study provides the first evidence of a Y-specific gene and a new lncRNA in a possible modulating role for the imbalance of CVD between the sexes.

SRY and male sex bias in Parkinson's disease

Vincent R. Harley Ph.D. Monash University

Parkinson's disease (PD) results from the selective loss of dopaminergic neurons from the substantia nigra compacta (SNc). Whilst the cause of dopamine cell loss in Parkinson's disease (PD) is unknown, it is clear that the male-sex is a strong risk factor. The incidence and prevalence of PD is 2-fold higher and disease progression more rapid in males than females. Growing evidence suggests that sex-specific genes contribute to this male-bias in PD. We previously showed that the male-sex determining gene encoded by the Y chromosome and therefore only found in males, SRY, co-localises with male dopamine neurons, where it regulates dopamine biosynthesis and motor function (1,2). Here, we investigated the regulation and function of nigral SRY in normal and 6-hydroxydopamine (6-OHDA) or rotenone lesioned hemiparkinsonian rats. Results of experiments designed to assess the effect of manipulating SRY levels in the rat substantia nigra upon motor and dopaminergic function will be discussed.

The human sex-determining gene expression in early embryo of transgenic mice induces postnatal growth retardation and lethality

Chris Lau, Ph.D. University of California

Sexual dimorphisms are prevalent in humans. The contributions of genes on the male-specific region of the Y chromosome (MSY) in these processes are uncertain. The MSY-encoded sex-determining SRY is the founder of a family of cell fate-determining transcription factors harboring an SRY-box (SOX). SRY and SOXs could bind to the promoters of common targets and differentially regulate their expression. We hypothesize that ectopic expression of SRY in non-gonadal tissues could modulate the gene regulatory programs of the resident SOX(s)/other transcription factors, thereby exerting a male-specific effect(s) on the development and physiology. Low levels of SRY expression could result in sexual dimorphisms normally observed between the sexes. At high/pathological levels, it could exert severe effects on pathogenesis, resulting in human diseases with higher male incidence and penetrance. To test this hypothesis, we have established a Cre-LoxP transgene activation system, and activated the human SRY gene in the single-cell embryos of the mouse. Pups with SRY activated (SRYON) are born of equal sizes as those of non-activated controls. However, they retard significantly in postnatal growth and development and all die of multi-organ failure in two weeks. Pathological and molecular analyses indicate that SRYON pups lack innate suckling activities, and develop fatty liver disease, arrested alveologenesis in the lung, impaired neurogenesis in the brain and occasional myocardial fibrosis. Transcriptome analysis shows that, in addition to those unique to the respective organs, various cell growth and survival pathways and functions

are differentially affected in the transgenic mice. These observations suggest that ectopic activation of a MSY-located SRY gene could exert male-specific effects in development and physiology of multiple organs, thereby contributing to sexual dimorphisms in normal biological functions and disease processes in affected individuals.

Sex chromosomes and sex differences in genome regulation

Adrianna K. San Roman, Ph.D. Whitehead Institute for Biomedical Research

Males and females exhibit striking differences in health and disease, but the underlying mechanisms remain poorly understood. At the genetic level, different sex chromosome constitutions, XX in females and XY in males, result in differential expression of sex chromosome genes. Autosomal genes are also differentially expressed between the sexes due to epigenetic differences that may be driven by cell-intrinsic or extrinsic factors, such as sex chromosomes, sex hormones, or environmental exposures, the relative contributions of which are difficult to tease apart. Nevertheless, the sex chromosomes encode transcription factors and chromatin modifiers, which could contribute to sexually dimorphic expression across the genome if they have different expression levels and/or activities in males and females. To test this hypothesis, we modeled the effects of sex chromosome dosage on gene expression by performing RNA-sequencing on lymphoblastoid cell lines from males and females varying in their sex chromosome complement (X,XX, XY, XXY, XYY, XXXXY, and XYYYY). Using this approach, we identified hundreds of genes throughout the genome that vary with X or Y chromosome dosage, and are sex-biased in a large independent dataset. This work increases our mechanistic understanding of differences between the sexes, and motivates future research on syndromes associated with sex chromosome aneuploidy and sex-biased diseases.

8:45am - 10:30am: SESSION 7

Sex differences with aging in human motor performance from the frail to the elite athlete

Chair: Jennifer M. Jakobi, Ph.D. University of British Columbia Okanagan

Physiological sex differences underlay the abilities between men and women to execute basic functional tasks of daily life through to elite sport performance. The influence of these differences between men and women on performance increases with age, is likely exacerbated by disease and needs to be considered in the context of engagement in sport and application to exercise interventions. This symposium presents how sex differences in old adults influences the spectrum of abilities ranging from the frail old adult to the elite athlete. The first speaker will identify how sex-differences in basic motor abilities; inclusive of gait speed, step length and dynamic balance influence the risk of falls in older adults. This knowledge will be applied to the second talk describing how males and females experience and progress differentially across frailty phenotypes (robust, prefrail, frail) and the necessity in designing sex-specific exercise interventions. The session will end with a focus on the sex differences in performance and participation among highly functioning old adults, elite athletes. This symposium will highlight how sex-specific physiological differences are a potent contributor to differing mobility and elite sport performances between men and women. Illustrating how sampling bias and sweeping sport assessments and exercise interventions can hamper robust aging for women.

Sex differences in balance, gait and functional mobility and their relationship with hand-grip strength in healthy elderly

Massimiliano Pau Ph.D. University of Cagliari

In the present study, we aimed to assess the existence of differences between men and women in balance, spatial-temporal and kinematic features of gait and Timed-Up-and-Go (TUG) in a cohort of healthy elderly aged over 65, using quantitative techniques for human motion analysis. In particular, we employed a motion capture system for gait analysis, force platforms for postural sway and inertial sensors for TUG tests. Also, hand-grip strength (HGS) was measured using a digital dynamometer. Participants were recruited for the study among individuals enrolled at the University of the Third Age of Quartu S. Elena (Italy). Balance was assessed through postural sway analysis calculated on the basis of center-of-pressure (COP) time series acquired using a pressure platform. Gait analysis was performed using a motion capture system composed by 8 infrared cameras set at 120 Hz frequency. Spatial-temporal parameters (i.e. speed, cadence, step length and width, stance, swing and double support phase) and kinematic

variables in the sagittal plane at hip, knee and ankle joints were calculated. Instrumented TUG was carried out by placing an inertial sensor at lower back's participant. The results show that men exhibit worse postural control than women both in eyes open (increased COP displacements in ML and increased COP velocity in AP direction) and eyes closed condition (increased path length and COP velocity in AP direction). Also, men are characterized by larger step width during gait. No significant differences between men and women were found for any of the TUG parameters. In women, HGS correlates with a largenumber of gait parameters and with higher Pearson's coefficients with respect to men. In contrast, HGS is not correlated with balance and TUG parameters in both sexes. Such findings suggest the existence of different patterns of balance and mobility deterioration with aging that should be considered when physical activity or rehabilitation programs are planned.

Sex and frailty: Important variables when considering exercise interventions for older adults

Jennifer M. Jakobi, Ph.D. University of British Columbia Okanagan

There is a marked discrepancy between the functional health and survival of the sexes. Despite health advantages contributing to longer life expectancy, females experience greater Levels of disability, acquire more co-morbidities, and report poorer self-perceived health. This sex paradox between survival and function is evident in accelerated and earlier onset of muscle strength decline in females and contributes to ~1.5x reduced ability to control force relative to males. We have also shown that muscles of females burst fewer times but ~3x longer in duration compared to males to execute daily tasks. These sex-differences are intensified with frailty. Frailty is a clinical geriatric syndrome associated with the accumulation of physiological deficits across multiple systems. In frail females, the number of muscle bursts is ~28% fewer and the duration ~26% longer compared with non-frail controls. Despite these, and other well-documented physiological differences between sexes and across frailty phenotypes, interventions continue to be generalized across sex and states of frailty. Our recent work identifies that exercise is a potent therapy to reduce the sex-difference gap and reverse frailty. The type and dose of exercise should be modified to target the specific challenges experienced by females as they transition toward frailty. For example, frail should exercise 3x per week for 30-45 minutes but the multi-component exercise program should focus on aerobic training. Pre-frail females (transitioning to frailty) should undertake a multi-component exercise program 2-3x a week, for 45-60 minutes emphasizing resistance and balance exercises. Following 12-weeks of resistance training pre-frail females balanced longer and lifted ~60% more weight. Exercise interventions accounting for frailty progression in females increases strength, positively alters muscle activity and reduces the physiological gap that influence functional independence between males and females.

Sex Differences with Aging among Elite Athletes: The Roles of Physiology and Participation

Jonathon W. Senefeld, B.S. Marquette University

Greater understanding of sex differences across the lifespan in human performance can be gained by examining elite athletes where differences in motivation are minimal. Despite this, sex differences in elite athletic performance are larger than expected due to physiological and anatomical factors alone, and this sex difference widens with advanced age. We hypothesized that large sex differences in elite athletic performance would be associated lower participation rates of females compared with males. Data were collected from the top performances in World leading events in running (marathon and ultramarathon), Olympic-distance swimming, and rowing (2000m). Sex differences in performance, the number of male and female participants, the ratio of participation (number of male:female participants), and the decline in performance across finishing place (% 1st place) were collected from online databases. A larger sex difference in performance was associated a lower participation ratio (male:female) for the marathon ($r^2=0.34$, $p<0.001$) and ultramarathon (50, 80, 100 and 160km distances, $p<0.001$). Females had a greater drop-off in performance across finishing place for the marathon (~5% sex difference, $p<0.001$), ultramarathon (~5%, $p<0.001$) and freestyle swimming (~2.5%, $p<0.001$), indicating less depth within the females relative to males. In contrast, females had a lesser drop-off in performance across finishing place in elite, collegiate rowing (~1.5% better performance in women, $p<0.001$), where there are ~3 times as many female participants than males. These data support the sociocultural hypothesis that sex-related differences in opportunity and participation can impact sex-differences in elite athletic performance especially with aging where participation is even less among the older women. The implications are that biomedical research findings and therefore the true sex differences due to physiology alone can be masked with inclusion of less females compared with males.

10:45am - 12:30pm: SESSION 8

Age and sex interact in schizophrenia: Clinical perspectives and animal models

Chair: Anat Biegon, Ph.D. Stony Brook University

Schizophrenia is a debilitating and chronic psychotic illness affecting about 1% of the population worldwide. Gender differences in schizophrenia have been noted since the disease was first defined, though the most replicated findings actually reflect an age X sex interaction. Thus, Differences in age of onset are found in all studies into gender differences in schizophrenia. Men usually develop the illness at age 18–25, while in women, the mean age of onset is 25–35. Furthermore, Women with schizophrenia have a more favorable course of illness than men during the reproductive years, characterized lower symptom severity and better response to antipsychotic treatment. However, increased symptom severity and reduced response to treatment are seen after menopause, and there is a second onset peak unique to postmenopausal women. The sex X age interaction in symptom onset was recently replicated in a neurodevelopmental animal model of schizophrenia entailing maternal immune activation. Male and female offspring differ not only in age of onset of schizophrenia-like symptoms, but also in the maturational trajectories of brain structures as studied by MRI, and brain markers of neuroinflammation and neurotransmitter receptors implicated in schizophrenia. The findings from animal models may help explain the sex and age differences observed with the clinical disease and point to novel sex and age specific treatment targets.

Sex differences in psychotic disorders: Fresh observations

Ashok Malla, M.D. McGill University

Psychiatry text books have generally reported an equal incidence of schizophrenia and related disorders in men and women along with better outcomes in women. These reports may need to be challenged in light of new evidence. In this presentation, data on incidence rates, and similarities and differences between previously untreated male and female individuals with a first episode of psychosis will be presented. Based on administrative data from a defined catchment area, the incidence of schizophrenia spectrum psychotic disorders in a population of 14-25 year old was 82.9 per 100,000 for males and 32.2 per 100,000 for females. In a sample of 500 patients (14-30 years) treated for FEP in an early intervention service treated incidence rates were higher in males than females (7:3). There were significant differences at the time of treatment initiation between male and female patients on pre-morbid adjustment, duration of untreated psychosis, Level of negative symptoms, diagnosis of substance abuse and Level of social and occupational functioning, all favouring females. However, one and two years of treatment in a specialized early intervention service, there were no differences in outcome on symptoms or social and occupational functioning. In a smaller sample of FEP, an examination of stress response using salivary cortisol awakening response and response to a stress induction test revealed female patients to be responding similar to healthy controls while male patients showed a lack of normal healthy response. Similar results were obtained from a sample of individuals defined as in a state of ultra-high risk for psychosis. The differences in patient characteristics observed at entry to treatment between male and female patients may be partly explained by differences in stress response and a higher incidence of substance abuse. However, specialized treatment comprising multiple psychosocial interventions may account for lack of differences following treatment.

Neural and behavioral sex-dependent developmental trajectories in a maternal immune activation model of schizophrenia in the rat

Michal Arad, Ph.D. University of Maryland

Prenatal exposure to infection has been implicated by epidemiological studies as a risk factor for schizophrenia. This association has been supported by numerous demonstrations of a direct link between prenatal infection and postnatal schizophrenia-like neural and behavioral abnormalities in animal studies. However, in most studies the biological sex of the offspring was not studied as a factor or sex differences were not identified. We traced the developmental trajectories of brain structure and behavioral abnormalities from adolescence to adulthood in rats born to mothers that were exposed to the viral mimic polyriboinosinic-polyribocytidylic acid (poly:IC; 4mg/kg) on gestational day 15. Volumes of lateral ventricles, hippocampus, striatum and prefrontal cortex in male and female offspring were assessed longitudinally on postnatal days 35, 46, 56, 70 and 90 using in-vivo MRI. On equivalent days, their littermates underwent behavioral testing (latent inhibition [LI], and amphetamine-induced activity, [AIA]) and MRI (cross-sectional assessment). While poly:IC offspring of both sexes had smaller volumes of all measured areas, in females the structural pathology was observed at a later age. Delayed onset in poly:IC females was also observed in the assessed behavioral deficits, disrupted LI and excessive AIA. Assessment of early interventions

with antipsychotic drugs (APDs), within the above timeline, successfully alleviated the neural and behavioral deficits. However, therapeutic potential was age- and sex- dependent as treatment was more effective the earlier the intervention took place and had a superior effect in females. We concluded that although gestational poly I:C lead to schizophrenia-like neural and behavioral deficits in both sexes, the onset of these deficits, similarly to humans, is delayed in females. This in turn might contribute to their superior response to early pharmacological interventions.

Age- and sex- specific effects of maternal immune activation on neuroinflammation and dopamine receptors revealed by quantitative autoradiography in rat brain

Anat Biegon, Ph.D. Stony Brook University

Infections during pregnancy are known to increase the risk of schizophrenia in offspring. Consequently, maternal immune activation is used as a neurodevelopmental animal model of schizophrenia. Both Dopamine receptors and neuroinflammation are implicated in this disorder. We hypothesized that maternal immune activation in rats affects dopamine receptor density and neuroinflammation in an age, sex and region dependent manner. Pregnant rats were injected on gestational day 15 with saline or the viral mimic polyriboinosinic-polyribocytidylic acid (poly I:C). Brains of male and female offspring (N=5/sex/age/treatment) killed on postnatal days 34, 48 or 95 were cryosectioned and processed for quantitative autoradiography with radioligands sensitive to neuroinflammation ([³H] PK11195) and dopamine D1 ([³H]SCH23390) receptors. In adult male offspring, prenatal poly-I:C was associated with significant elevations in [³H]PK11195 binding in the dorsal hippocampus (64%), frontal (23%) and occipital (33%) cortex and striatum (37%). In adult females, smaller though statistically significant increases were restricted to ventral hippocampus (47%) and occipital cortex (19%). Younger (pre-symptomatic) animals did not differ from controls. D1 receptors density was decreased in adult males (substantia nigra and peri-rhinal cortex) but not females. There was also no effect of poly I:C on younger animals, however a large and statistically significant sex difference was observed in prepubertal rats, with 2 fold higher D1 receptor density in male hippocampus relative to females. These results demonstrate a sex-dependent developmental trajectory for dopamine D1 receptors and a sexually divergent response to maternal immune activation, which may explain, at least in part, the sex differences in brain structure and behavior observed in this animal model and in schizophrenia.

10:45am - 12:30pm: SESSION 9

Effects of sex hormonal change on vision and age-related eye disease

Chair: Alvin Eisner, Ph.D. Portland State University

Co-chair: Gillian Einstein, Ph.D. University of Toronto

In the field of sex differences research, sensory systems and their corresponding primary sense organs are considered relatively infrequently. Of all the senses, the eye and visual system are most amenable to study, even subtle visual change can impact a person's well-being, and not-so-subtle visual change can be life-altering. For some ophthalmological conditions, definite causal relations exist between the condition and a patient's hormonal activity or hormonal history, while for other conditions the relation is less certain or more difficult to separate from other contributing causes. The February 2015 issue of *Current Eye Research* contained 13 review articles discussing various Male/Female Distinctions in Ophthalmic Disorders, and several of the areas covered will provide the focus for this symposium. In particular, this symposium will address gender differences (or sex hormone effects) important for dry eye, glaucoma, neuro-ophthalmology, visual function, and for eye care generally. Dry eye involves the ocular surface and can accompany menopause-related changes in hormonal balance. Glaucoma is an optic neuropathy depending on physiologic and anatomic vulnerabilities that can differ between men and women and/or involve differences in estrogenic activity (e.g., affecting intraocular pressure). The domain of neuro-ophthalmology extends from the eye into the brain, and it encompasses a wide range of conditions, many of which (e.g., multiple sclerosis) occur much more often for women of certain ages than for men. Visual function mediated via Short-Wavelength-Sensitive [SWS] cones can be effectively isolated, and the neural response timing appears to be measurably altered by reductions of estrogenic activity (e.g., as caused by use of adjuvant endocrine therapy for breast cancer). And superimposed on ophthalmic conditions generally are sex differences that impact eye care access and utilization.

Dry eye and sex/gender-dependent eye care differences

Janine Austin Clayton, M.D. Office of Research on Women's Health, National Institutes of Health

Sex differences exist in ocular diseases. Dry eye disease (DED) is an example of an ocular surface disease for which there is a clear sex difference, as more women experience DED than men. DED occurs when the eye does not produce enough tears, or when the tears are not of the right consistency and therefore evaporate too quickly. DED

is associated with symptoms such as ocular pain, irritation, and burning sensation, and signs like blurred vision. Compared to men, women with DED typically report more problems with reading, watching television, working on a computer, and driving at night. DED has adverse effects on overall quality of life, visual function, daily activities, social and physical functioning, computer use, driving, television viewing, and work productivity. Animal studies suggest linkages between sex differences in biology and DED. Differences may arise from genetic effects linked to sex chromosomes, sex-specific autosomal factors, or even epigenetics. DED is sometimes associated with gonadal hormone fluctuations, such as menopause-related changes. Ocular health and disease in general are also affected by gender-related factors; such as socially derived differences between men and women that influence health care access and utilization. Gender dynamics between the eye care provider and patient can be an important factor, as well. Eye health is a particularly critical matter for women, as two thirds of those visually impaired or blind worldwide — including in the United States — are women. This talk will explore the linkages between sex, gender, and eye health and disease in the context of DED.

Sex differences in neuro-ophthalmologic disorders

John Chen, M.D., Ph.D. Mayo Clinic

There are many neuro-ophthalmic diseases that have a clear sex predilection, which mostly show a female predominance. Recognizing this sex predilection is not only important in making a diagnosis based on risk stratification, but also plays a large role in understanding the pathogenesis of the disease. The sex differences are presumably due to a combination of endogenous sex hormones, genetic differences conferred by the X and Y chromosomes, and exogenous environmental factors that differ between females and males. Interestingly, many of these diseases are seen in equal incidence in pre-pubertal children and the elderly, but have a distinct female preponderance in the intervening years, which suggests that gonadal hormones modulate these diseases. In addition, many of these diseases come to medical attention during pregnancy and the postpartum period, suggesting a hormonal influence. Lastly, exogenous hormones and treatments, such as oral contraceptives and post-menopausal hormone therapy, are likely to influence some of these diseases. We will discuss the more common neuro-ophthalmic diseases with a female predilection, including idiopathic intracranial hypertension, cerebral venous sinus thrombosis, multiple sclerosis and neuromyelitis optica, meningioma, giant cell arteritis, migraine, breast-cancer associated neuro-ophthalmic manifestations, and pregnancy-related neuro-ophthalmic disorders. In addition, the male predominance in the clinical manifestation of Leber's Hereditary Optic Neuropathy will be discussed. Lastly, the etiology of the sex discrepancies for each disease will be explored.

Sex differences in the pathophysiology and treatment of glaucoma

Shandiz Tehrani, M.D., Ph.D. Oregon Health & Science University

Glaucoma is the leading cause of irreversible blindness in the world, and the second leading cause of blindness in the United States. Glaucoma results in optic nerve axon degeneration and corresponding vision loss. Intraocular pressure (IOP) is the only known modifiable risk factor in glaucoma. Non-modifiable risk factors for glaucoma include age, ethnicity, central corneal thickness, and family history. While our understanding of the role of sex as a risk factor in glaucoma continues to develop, multiple observations have shown sex differences in the incidence and prevalence of glaucoma. Hormone therapy, oral contraceptive use, and menopausal status have also been associated with glaucoma. Lastly, pregnancy leads to changes in IOP, and the treatment of glaucoma must be tailored during pregnancy and breast feeding.

Estrogen activity and visual response mediated via short-wavelength-sensitive (SWS) cones

Alvin Eisner, Ph.D. Portland State University

Historically, little attention has been paid to effects of hormonal change on visual function. This absence stems from various factors. Some reflect the formidable difficulties conducting interdisciplinary research, while others stem from implicit assumptions concerning extrapolation of results to populations not typically tested. Although human photopic vision is widely known to depend on the responses of 3 types of cone photoreceptors, it is less widely known that the responses of 1 of these cone types (the SWS cones) signal to the visual cortex via a restricted set of dedicated neural pathways. Moreover, stimulus conditions can be arranged allowing SWS-cone-mediated response to be functionally isolated and readily assessed. Thus, if SWS-cone-mediated response were found to depend meaningfully on changes in estrogenic activity, it may be possible to biomark functional changes of reduced estrogenic activity on other CNS areas, important clinically but inherently difficult to assess. In fact, psychophysical techniques applied to various human subject populations have shown that SWS-cone-mediated response can

depend meaningfully on changes in estrogenic activity. The following are some of the results found: (1) For about 1/3 of postmenopausal women, the reported color appearance of stimuli detected via SWS cones under certain conditions differs qualitatively from that reported by men (and implicitly assumed for everyone), and moreover, the altered color appearance for the women is associated with adaptation effects indicative of an overly sluggish visual response. (2) For postmenopausal women using the SERM tamoxifen, almost all long-term (>2 years) users experience the same altered color appearance. (3) For women using the aromatase-inhibitor anastrozole, this altered appearance is more common among younger users. (4) Visual adaptation within SWS cone pathways varies cyclically for some young women (with PMS?) and can be altered by oral contraceptive use.

10:45am - 12:30pm: SESSION 10

The gender gap in workers' mental health: What have we learned from the Salveo study?

Chair: Alain Marchand, Ph.D. University of Montreal

Co-chair: Pierre Durand, Ph.D. University of Montreal

Mental health problems related to psychological distress, depression, and burnout have assumed major proportions among the workforce. Epidemiological studies suggest that more women than men are affected by these problems. However, clear explanations of this gender gap in mental health are still lacking. Contributors to this symposium will present and discuss results obtained by the Salveo study carried out over 63 private organisations and 2162 men and women workers. Three specific pathways will be under review to explain differences between the genders: (1) the differential exposure to stressors arising from disparities in the way workers are integrated in their work and family environment; (2) the differential gender vulnerability to work and family stressors; (3) the mediating role of work-to-family conflict and family-to-work conflict. This symposium will help shedding light on the social etiology of mental health problems among men and women, and on possible public and company policies that could be taken.

The gendered mechanisms leading to psychological distress among working women and men

Jaunathan Bilodeau, B.Sc. University of Montreal

Psychological distress is significantly higher among women than among men. The aim of this study is to explore how work and family stressors as well psychosocial resources operate as gendered determinants of the psychological distress gap between working women and men. More specifically, we test the hypotheses that this inequality is caused by differences in the exposure and the vulnerability to work and family stressors and psychosocial resources. We also propose a model in which work-to-family conflict (WFC) and family-to-work conflict (FWC) intervene as gendered mediators of these relationships. Data come from the SALVEO study conducted on a sample of 2028 Canadians workers from 63 establishments. A multiLevel path analysis was performed to test the exposition hypothesis and the model was stratified by sex categories to test the vulnerability hypothesis. The results support both hypotheses. Women have less skills utilization, they are more single parents and are more exposed to WFC, contributing to increasing their psychological distress. On the other hand, women work fewer hours per week, work less at night, have fewer irregular hours and more support offside work, which indirectly contribute to lowering their Level of psychological distress through a decrease Level of WFC. Regarding the vulnerability hypothesis, while WFC is a mediator between some of the work's stressors and the personal resources for men and women, the FWC acts as mediators between some work and family's stressors, psychosocial resources and psychological distress for women only. However, only three of these relationships are significantly different between the sexual categories. Concretely, number of hours worked, problems with children and self-esteem are indirectly associated with psychological distress through the FWC for women. These results have important policy implications, at the national Level and at the company Level, to reduce inequality in mental health between men and women.

Men and Women gap in depressive symptoms: Vulnerability or exposure to work and family stressors?

Alain Marchand, Ph.D. University of Montreal

Research has shown that employed women are more prone to depression than men, but the pathways linking gender to depression remain poorly understood. The aim of this study was to examine how work and family conditions operated as potentially gendered antecedents of depression. It evaluated more specifically how differences in depressive symptoms in women and men could be explained by their differential vulnerability and exposure to work and family conditions, as well as by the mediating role of work-to-family conflict (WFC) and family-to-work conflict

(FWC). Data were collected in 2009–2012 as a part of the Salveo Study. It contained a sample of 1,935 employees (48.9% women) from 63 workplaces in the province of Quebec (Canada). Data were analyzed with multiLevel path analysis models. Results supported both hypothesized, but only WFC played a mediating role between work-family stressors and depression. WFC was more strongly associated with women depressive symptoms, and the magnitude of the association between family income and WFC was stronger for women. The differential exposure hypothesis, however, seemed to reach a greater empirical support. After accounting for work and family stressors as well as WFC, differences in depressive symptoms in women and men were no longer significant. WFC associated with higher depressive symptoms and skill utilization with lower depressive symptoms. WFC related to higher working hours and irregular work schedule. Compared to men, women reported higher WFC, but lower working hours, less irregular work schedule and lower skill utilization at work. Overall, this study shows that women have a higher rate of depression is intrinsically linked to their different social experiences as shaped by a gendered social structure and gendered organizations.

Examining gender differences in the work and non-work determinants of burnout: Results from the SALVEO Study

Nancy Beauregard, Ph.D. University of Montreal

The integration of work and non-work domains has retained a growing attention from organizational research and practice. Negative consequences from conflicts between the work and non-work domains are numerous, affecting workers (e.g., mental and physical health), their family (poor family life satisfaction), and their workplace (e.g., absenteeism). Yet, little is known about the specific role gender plays in the patterning of work and non-work determinants and associated health outcomes among workers. The aim of this study is to investigate the presence of gender differences in work and non-work stressors in association with burnout, and further assess whether work-family conflict (WFC) mediate these associations. Data are derived from the SALVEO study, a cross-sectional study of N=2,026 workers from 63 workplaces from the province of Quebec (Canada). Data were analyzed using multiLevel path analyses. Women compared to men were distinctively exposed to work (e.g., lower Levels of decision latitude) and non-work (e.g., higher Levels of child-related strains) stressors. In turn, work and non-work stressors, as well as WFC, were directly associated with burnout. WFC mediated the associations between working hours and burnout, as well as the associations between irregular work schedules and burnout, to the disadvantage of men. In sum, our results suggest that gender distinctively shapes the associations between work and non-work determinants and burnout. Accordingly, healthy public policies (organizational, societal) striving for better mental health outcomes among the workforce should look more closely at gender differences in work and non-work domains integration.

11:55am – 12:15pm: Gender and work-family conflict: A differential exposition explanation

Victor Y. Haines III, Ph.D. University of Montreal

This study tested a differential exposition explanation of the association between demographic gender and work-family conflict. It addresses the question of why men and women may experience similar or dissimilar Levels of work-family conflict and tests whether differences are due to their different gendered demands and resources. Drawing from a sample of 1,751 employed adults from 63 workplaces, the results suggest that women spend less time in paid employment than do men; a gendered response that is associated with lower work-to-family conflict, but higher family-to-work conflict. Women were also found to be less involved in irregular work schedules, which would appear to be associated with lower work-to-family conflict. The differential exposure explanation was also supported by indirect effects involving commute time, family income, and social support outside work.

12:30pm - 1:45pm: WORKING LUNCH

Adaptive clinical trial designs: Opportunities to identify sex- and gender-specific outcomes

Chair: Marjorie Jenkins, M.D., M.Ed.H.P. Office of Women's Health, Office of the Commissioner, U.S. Food and Drug Administration (FDA)

The analysis and reporting of clinical trial results by sex is important for the discovery of clinically relevant sex and gender differences. However, reliance upon underpowered or poorly planned sex subgroup analyses in decision-making can have dangerous consequences. Therefore, there is a need for application of rigorous statistical techniques to sex subgroup analysis in clinical trials. The U.S. FDA Office of Women's Health recognizes the poten-

tial of adaptive clinical trial designs to contribute to sex and gender-specific medicine through adaptive enrichment and subgroup analysis. For example, pre-planned interim analyses could include sample size reassessment to allow for separate hypotheses by sex subgroup if there is reason to believe that data should not be pooled across sexes.^{2\} Alternatively, if interim analyses indicate a less favorable risk/benefit profile among patients of one sex compared to the other, the inclusion/exclusion criteria and population indication could be updated to be sex-specific, thereby sparing future trial participants and patients from the risk of adverse events. As women may be more likely than men to experience adverse events from drugs, the utilization of sex subgroup analysis holds great promise for improving patient protection. This proposed panel discussion will focus on potential applications of adaptive clinical trials designs toward advancing women's health through subgroup analysis. The speakers of the proposed panel are experts in adaptive clinical trial design, biostatistics, and the science of sex and gender differences.

Subpopulation analysis and adaptive clinical trial designs: New frontiers for sex and gender-specific medicine

Che Smith, Ph.D. Center for Drug Evaluation and Research, FDA

John Scott, Ph.D. Center for Biologics Evaluation and Research, FDA

The analysis and reporting of clinical trial results by sex is important for the discovery of clinically relevant sex and gender differences. However, reliance upon underpowered or inadequately-planned sex subgroup analyses in decision-making can have deleterious consequences. Therefore, there is a need for thoughtful application of statistical techniques to the analysis of sex and gender-specific outcomes in clinical trials. In this panel discussion, FDA experts will provide a regulatory perspective on the current and potential future applications of statistical methodology, study design, and data dissemination to the advancement of sex and gender-specific medicine. Dr. Che Smith will present "The State of Subgroups: A Statistical and Regulatory Perspective." In this presentation, Dr. Smith will discuss opportunities in the regulatory review process for the consideration of subgroups. Current practices in the regulatory setting pertaining to subgroup analysis and the dissemination of demographic data will be discussed. Dr. John Scott will present "Adaptive Clinical Trial Design: Implications and Opportunities for Sex and Gender-Specific Medicine." Dr. Scott will provide an overview of adaptive clinical trial designs and their potential application to the study of sex and gender-specific outcomes. Motivating examples of adaptive trial designs in the context of sex and gender-specific women's health will be discussed. The panel discussion will be led by Dr. Marjorie Jenkins and end with a moderated question and answer session to allow for interaction between the panelists and the audience.

2:00pm - 3:45pm: SESSION 11

Prenatal stress in relation to sex differences: from birth to adolescence

Chair: Emily S. Barrett, Ph.D. Rutgers School of Public Health

Co-chair: Suzanne King, Ph.D. McGill University

Sex differences in human health and disease are well-documented and are often evident early in life. Recent animal studies suggest that many such sex differences may have prenatal origins. As a result, manipulation of the prenatal environment may alter typical sex differences. In murine models exposing the pregnant dam to a stressor (e.g., restraint) alters the sex-typical prenatal hormonal milieu and in guinea pig models, exposure to prenatal social stress masculinizes behavior and alters neuroendocrine function in female offspring. Extending these findings and translating them to better understand the early origins of sex differences in human health are research priorities. This symposium will highlight diverse, complementary lines of research focused on prenatal stress and the development of subsequent sex differences in animal models and humans. Our first speaker will adopt an adaptive perspective as to why we might expect the sexes to respond differently to prenatal stressors, drawing upon physiological and behavioral evidence from epidemiological studies of pregnant women and their resulting children. The next speaker will delve into molecular mechanisms, examining sex differences in murine neurodevelopment following prenatal stress and demonstrating that male vulnerability and female resilience may be mediated by placental activity. Our third speaker will further consider neuroendocrine and behavioral sex differences in a guinea pig model, discussing how prenatal stressors may reverse downstream sex-typical development throughout the lifespan. Finally, our last speaker will consider similar issues in humans, discussing sex-dependent endpoints from birth to adolescence, as measured in a unique cohort who experienced acute, in utero exposure to a natural disaster. After this symposium, attendees will have a better understanding of: (1) how stress in early life may contribute to and alter sex differences in animal models and humans; and (2) the possible underlying mechanisms.

Prenatal stress exposures and sex-dependent development in early childhood: an adaptive perspective

Emily S. Barrett, Ph.D. Rutgers School of Public Health

The Developmental Origins of Health and Disease (DOHaD) model has become a leading way to conceptualize how health develops across the life course. This perspective emphasizes how prenatal exposures can alter fetal development leading to changes in physiology, and ultimately, disease risk. In some cases, this altered development is clear evidence of pathology or dysfunction (such as folic acid deficiencies and neural tube defects). However in other cases, altered fetal development may represent a trade-off to “make the best of a bad situation” or even an optimization to better prepare the organism for the postnatal environment. These alternatives are relevant to understanding the relationship between prenatal stress and child development and may offer insight regarding early sex differences in response to prenatal stress. Evidence from animal models and humans consistently demonstrates male vulnerability to a variety of prenatal stressors. For example, following natural disasters (e.g. famine, earthquake), the ratio of male to female infant births typically drops, suggesting greater male fetal loss. One hypothesis is that compared to females, male fetuses are less responsive to maternal cues, leading to discordance between the developmental trajectory and the quality of the postnatal environment. The female fetus, on the other hand, is hypothesized to be responsive to a changing prenatal environment, altering the course of development to better face adverse postnatal conditions. For example, growth of the female (but not the male) placenta is adaptive to changes in maternal glucocorticoids. Girls who experience high in uterostress, moreover, show differences in early reproductive and neurodevelopmental outcomes that could confer adaptive advantages in stressful environments. We will present an overview of research on prenatal stress and children’s development, focusing on how an adaptive perspective may inform our understanding of sex differences.

Placental H3K27me3 promotes female resilience to prenatal stress

Bridget M. Nugent, Ph.D. University of Pennsylvania

Prenatal stress is a risk factor for male-biased neurodevelopmental disorders. Our mouse model of early prenatal stress (EPS) imparts long-term HPA stress axis, metabolic and cognitive deficits to male offspring. The placenta, a fetally-derived tissue reflecting fetal sex chromosome complement, provides necessary factors for brain development. Thus, sex differences in placental function can radically influence sex biases in neurodevelopmental vulnerability to prenatal insults. We previously identified the X-linked, stress sensitive, nutrient sensor OGT as a mediator of the EPS phenotype. OGT escapes X-inactivation in the placenta, providing females with two copies and males with one. OGT modifies several epigenetic regulators including the H3K27me2/3 methyltransferase, EZH2. We hypothesized that sex differences in OGT mediate sex differences in placental histone methylation and promote sex-specific programs of gene expression. In mouse placentas with trophoblast-specific OGT reduction, we found that OGT determines genome-wide sex differences in H3K27me3 and gene expression. RNA-Seq of the embryonic hypothalamus revealed that reducing OGT in the female placenta masculinized the expression of key genes associated with hypothalamic development, suggesting that placental OGT contributes to sex differences in brain development. We next hypothesized that female-biased epigenetic repression (H3K27me3) protects females from prenatal insults. To test this hypothesis, we reduced H3K27me3 in female placentas using trophoblast-specific deletions of EZH2 and then exposed these animals to EPS. Decreasing placental EZH2, and H3K27me3, rendered females vulnerable to the effects of EPS, sensitizing their HPA axis reactivity and causing long-term changes in body weight. These studies, aimed at elucidating the basic biological differences between male and female developmental programs, bring us closer to fully understanding the etiology of sex-biased neurodevelopmental disorders.

Prenatal maternal stress from a natural disaster disrupts sexual dimorphisms in childhood and adolescence: The SPIRAL studies

Suzanne King, Ph.D. McGill University

Prenatal maternal stress (PNMS) can be randomly assigned to laboratory animals in order to draw causal conclusions about the effects on development in the offspring, including effects on sexual dimorphisms. Pure, randomized experiments are not available when studying PNMS in humans, but Mother Nature often assigns stress to pregnant women in quasi-random fashion. SPIRAL is an ensemble of three studies of pregnant women going through natural disasters. Our goal is to determine the effects of different aspects of PNMS on their unborn children’s development. Project Ice Storm was begun in 1998 following severe winter storms in Quebec, Canada that knocked out electricity for 3 million people for as long as 45 days; the Iowa Flood Study began following 50-year flooding in the summer of 2008; and the QF2011Queensland Flood Study began following disastrous flooding in the Australian state of Queensland. In all three studies, we assessed three aspects of PNMS soon after the disaster: the objective severity

of the mothers' hardship from the disaster (threat, loss, scope, change); their cognitive appraisal of the disaster as a positive, neutral or negative experience; and their Levels of subjective distress from the disaster. We then monitored pregnancy outcomes, and the children's behavioral, motor, physical and cognitive development. Results demonstrate differential effects of PNMS on a number of outcomes by sex, including expression of some genes in the placenta, and fetal growth. PNMS also results in the loss of some of the usual sexual dimorphisms in cognitive, behavioral, physical and motor development, and HPA axis reactivity. 2D:4D finger length ratios and cortical thickness from brain MRIs in Project Ice Storm suggest that greater PNMS masculinizes girls in the study. We will present an overview of results that reflect different effects of PNMS on child development by child sex, and those that result in reversed sexual dimorphisms.

2:00pm - 3:45pm: SESSION 12

Young at heart: Sex and the aging heart

Chair: W. Glen Pyle, Ph.D. University of Guelph

Ageing populations are a worldwide trend: by 2030 the number of people over 65 years of age will double (Jahangir et al. 2007). Ageing demographics have a profound impact on the utilization of increasingly scarce health resources (Mozaffarian et al. 2014) as older populations have significantly higher rates of diseases including atherosclerosis, hypertension, diabetes, and heart failure. Age itself is the primary risk factor for cardiovascular disease with a 22% increase in risk every 5 years after age 65 (de Giuli et al. 2005). In North America nearly 75% of individuals aged 75 or older have cardiovascular disease (Hunter & Korzick 2005). Despite the known link between age and cardiovascular disease, studies investigating altered heart function and the underlying mechanisms in aged animals are scarce (Rozenberg et al. 2006; Mellor et al. 2014). The effects of age on myocardial disease are dependent on sex as older male animals have a greater susceptibility than age-matched females (Fares et al. 2013; Feridooni et al. 2015). There is emerging experimental evidence that male-female disparities in the ageing heart are estrogen-dependent (Parks & Howlett 2013) but the intracellular and molecular changes underlying these differences are poorly understood. In fact, no published study has examined sex-dependent differences in ageing heart function (Feridooni et al. 2015). Determining the differences between ageing male and female hearts is vital for establishing how sex contributes to different disease susceptibilities and outcomes, and to design therapies that target the specific problems associated with each sex. This symposium will bring together scientists from several areas of cardiovascular research to present their most recent findings about the roles of ageing and sex in the regulation of cardiac function and the susceptibility to cardiovascular disease. Dr. Glen Pyle will present his laboratory's discovery concerning age- and sex-dependent changes in the cardiac Z-disc protein 'CapZ' that may contribute to the cardiovascular protection seen in females, and the therapeutic potential in targeting this protein to reduce cardiac dysfunction in ageing animals. Dr. Susan Howlett will speak of her research group's long-standing interest in the relationship between sex and frailty on heart function in ageing animals. Dr. Céline Fiset is an internationally recognized expert in cardiac rhythms and electrophysiology who will present her work on the influence of sex hormones on atrial fibrillation. Finally, Dr. John Konhilas will talk about his laboratory's research concerning the increased risk of cardiovascular disease in a mouse model of menopause. In total these speakers will provide coverage of several areas of cardiovascular research from the molecular basis by which sex and ageing increase risk of cardiovascular disease to novel therapeutic strategies, while covering cardiovascular conditions from arrhythmias to heart failure.

Impact of age, sex hormones and frailty on cardiac function: why studies in young male animals may not be enough

Susan E. Howlett, Ph.D. Dalhousie University

Pre-menopausal women are less likely to suffer from cardiovascular disease (CVD) than are men, but this female advantage disappears with age. As estrogen receptors are present in individual ventricular myocytes, we explored male-female differences in intracellular Ca²⁺ handling with voltage clamp techniques to simultaneously measure Ca²⁺ currents, Ca²⁺ concentrations (fura-2) and contractions in cells from adult (3-6 mos) and aged (~24 mos) rodents of both sexes. In adult animals, we found smaller Ca²⁺ transients and contractions in cells from females, although peak Ca²⁺ current densities were similar. Sarcoplasmic reticulum (SR) Ca²⁺ content did not differ, but subcellular SR Ca²⁺ release events (Ca²⁺ sparks) were smaller in cells from females. These sex differences were due to changes in the cAMP/protein kinase A pathway that regulates Ca²⁺ release. cAMP Levels were lower in females compared to males, as a consequence of increased expression of phosphodiesterase type 4B, an enzyme that breaks down cAMP. To mimic menopausal changes, we removed the ovaries from female mice to reduce their estrogen Levels. This caused intracellular Ca²⁺ Levels and SR Ca²⁺ content to rise dramatically, similar to the increases we

have seen in cells from aged female mice. This demonstrates that low estrogen states, such as aging and ovariectomy, disrupt the ability of myocytes to regulate internal Ca²⁺ Levels. Our exciting new data suggest that it is actually overall health (quantified with a frailty index), rather than simply age alone, that modifies cardiac Ca²⁺ handling in both sexes. The idea that sex hormones and overall health regulate intracellular Ca²⁺ in myocytes is important. Ca²⁺ is required to activate cardiac contraction, but too much or too little can promote CVD. Loss of protective effects of estrogen on intracellular Ca²⁺ homeostasis may help explain the higher incidence of CVD in post-menopausal women, in particular in those who are frail.

Menopausal mice are hypersensitive to cardiovascular disease

John P. Konhilas, Ph.D. University of Arizona

Women are protected against cardiovascular disease (CVD) compared to age-matched men; this protection is lost in menopausal women. The critical barrier impeding translational progress is the lack of appropriate rodent models to study menopause. Most studies have used surgical removal of ovaries (ovariectomy) as a model of menopause; yet this technique poorly recapitulates the natural, physiological transition to menopause that 90% of women experience. Using the chemical 4-vinylcyclohexene diepoxide (VCD), we can mirror progressive ovarian failure and preserve the critical "perimenopause" transitional period, and androgen secreting capacity of residual ovarian tissue, similar to humans. Using the VCD model of menopause, we demonstrate that perimenopausal and cycling females are protected from pathological angiotensin II (Ang II)-induced cardiac remodeling, and menopausal female mice lose this protection. Protection is restored following estrogen replacement. Our novel finding that perimenopausal females remain protected, despite the disruption of cyclicity (prior to complete loss of estrogen), underscores the importance of studying the role of estrogen in CVD disease, across the transition from perimenopause to menopause. Yet, the cellular and molecular mechanisms underlying the transition from CVD-resistance (perimenopause) to CVD-susceptibility (postmenopause) in women is unknown and remains the focus of our laboratory.

Taking it to heart: Do naturally occurring changes in CapZ offer sex-dependent protection against ageing?

W. Glen Pyle, Ph.D. University of Guelph

Females have lower rates of heart failure compared to age-matched males throughout most of their life. However, after menopause the risk for heart failure in women rises until the sex differences disappears by age 80. Ageing itself is an independent risk factor for heart failure and with populations throughout the world seeing significant increases in older demographics it is expected that the rates of heart failure will rise dramatically. It has been speculated that estrogens contribute to the protection against heart failure, but the intracellular and molecular mechanisms that mediate this effect remain unidentified. We have shown that hearts from aged (18 months) male mice exhibit significant increases in the level of an actin binding protein called 'CapZ'. This decrease corresponds with a reduction in heart function. Interestingly, age-matched female mice show a natural reduction in CapZ protein in the heart along with normal function. Mice of both sexes engineered to have reduced levels of CapZ in the heart show no decline in heart function with ageing. In cardiac myocytes beta-adrenergic activation declines with age, potentially underlying the age-dependent decline in heart function eventually seen in both sexes. We have previously shown that modest reductions in cardiac CapZ alter the ability of beta-adrenergic signaling to control the contractile apparatus of the cell. To determine if decreased cardiac CapZ levels abrogate impaired beta-adrenergic signaling with age we treated Langendorff perfused CapZ-deficient transgenic mouse hearts with isoproterenol. The decline in cardiac CapZ levels corresponded with an intact response to beta-adrenergic receptor activation. This research advances our understanding of the influence sex mediates over heart function, identifies a molecular model that may explain sex-dependent cardiac dysfunction in ageing mice, and establishes the therapeutic potential of reducing CapZ to block cardiac decline.

Influence of sex, androgens and age on atrial fibrillation

Céline Fiset, Ph.D. Université de Montréal

Atrial fibrillation (AF) is the most common arrhythmia. Its prevalence is around 2-3% in the general population and increases to 10% in elderly individuals. After adjusting for age and other predisposing conditions, male sex is associated with a 2-fold risk of developing AF and despite its importance, the mechanisms responsible for this sex difference are still unknown. The objectives of this study were to identify electrophysiological substrates implicated in the male prevalence of AF and to explore the contribution of androgens in these sex differences. Electrical programmed stimulation studies were performed to compare AF susceptibility between male and female mice.

Using voltage-clamp techniques, the major atrial ionic currents (Na⁺, Ca²⁺ and K⁺) were recorded in atrial myocytes from both sexes. qPCR was used to compare atrial mRNA expression of the underlying ion channels as well as of connexin40 (Cx40), the major gap junction in atria. To examine the role of androgens orchietomized (ORC) male mice were also examined. The incidence of AF was significantly higher in males (52%, n=21) compared to females (25%, n=24). Sex differences in ionic currents and channels could not explain the male prevalence of AF. However, the expression of Cx40 that was 40% lower in atrial tissues (n=5/group) from males is consistent with delayed atrial conduction and AF development. Finally, AF incidence in ORC mice was lower (38%, n=16) than in intact males and their Cx40 mRNA expression was augmented to Levels similar to those of female mice. Our findings show that similar to humans, the incidence of AF is higher in male than female mice and this difference is associated with a lower expression of Cx40 in males. Moreover, these sex differences were abolished in ORC animals, supporting an important role for androgens in AF pathophysiology. Ultimately, awareness of sex differences in electrical activity of the heart may help develop a sex-specific approach for the management of AF.

2:00pm - 3:45pm: SESSION 13

Aging & care: Taking sex, gender and health into consideration

Chair: Tamara Daly, Ph.D. York University

Drawing from the CIHR Research Chairs in Gender, Work and Health Program, this session will draw together chairholders to discuss their programs of research, particularly focused on sex and gender differences across the lifespan. Paying particular attention to aging and paid and unpaid work, papers will address the following: What complement of health and care workers are needed to adequately provide care for older adults? What are the needs of health care workers? What are the needs of workers who provide unpaid care? How is the gap between paid and unpaid care addressed? In addition, how do women and men access resources such as inpatient rehabilitation following brain injury, particularly when returning to paid work compared with unpaid domestic labour? Chairholders will discuss the aging of the care workforce, how many aging workers are simultaneously managing paid employment with family eldercare demands, and outcomes including putting their own health and quality of life at risk. The unpaid care of family, friends and formal paid care providers, in addition to workplace accommodations will be discussed.

The importance of a sex/gender based analysis of the healthcare workforce

Ivy Lynn Bourgeault, Ph.D. University of Ottawa

The tenets of a sex/gender analysis are to be cognisant of how sex and gender are two of the most fundamental source of differentiation we make of people; to be critical— that is, challenge assumptions and ideas of gender neutrality; be systematic— by applying this lens consistently and thoroughly and be transparent. When one applies a sex/gender based analysis to the health workforce in Canada (and elsewhere), one realizes how the healthcare division of labour is structured by gender and is permeated with complex gender dynamics. It is well established that social-cultural gender arrangements shape the structural location of men and women in the health workforce as well as the classification of caring and curing, formal and informal work, and skilled and unskilled work. The gendered arrangement of health labour occurs both between professions as well as within professions. The dominance of the medical profession within the health care division of labour was achieved in part through the historic exclusion of women. Medicine is still very much a male dominated profession in spite of the recent and rapid expansion of a number of women into its ranks. Female health professions, such as midwifery and nursing, have a circumscribed scope distinguished typically through the use of gendered ideology of women's societal role as 'carers'. This also involves an under-valuing of the skills possessed by these largely female health professionals, reflective of the broader societal undervaluing of women's work. That is, gender play a critical role in the value of work and how tasks are shifted from 'higher skilled' and paid to 'lower skilled' and unpaid workers, the latter group being predominantly female. Indeed, the WHO (2011) suggests task shifting as one of four key areas where gender equality needs to be assessed. Female health professionals are also more likely to experience a caring dilemma, first proposed by Reverby to denote the tension caused between the obligation to provide care in a context that does not enable the right to determine how that care is to be provided. A series of illustrative examples will be presented and discussed with a particular focus on care for an aging population.

Aging and care: Sex, gender considerations relevant to traumatic brain injury

Angela Colantonio, Ph.D. University of Toronto

Traumatic Brain Injury is a leading cause of death and disability globally, however, there is a paucity of research

addressing sex and gender with respect to this condition. The aim of this presentation is to present highlights of program of research primarily funded by a CIHR Research Chair in Gender Work and Health that focuses on traumatic brain injury in relation to the theme of "Aging & Care: Taking Sex, Gender and Health into Consideration". This presentation aims to provide an overview of demographic and clinical factors associated with traumatic brain injury (TBI) based on population based epidemiological data that includes comorbidities by age and sex that have not been previously reported in the literature. Population based data on up to 30,000 TBI cases are generated from the National Ambulatory Care Reporting System, the Discharge Abstract Data and the National Rehabilitation Reporting System from the province of Ontario where there is mandatory reporting. Using Data from Emergency Room and Acute Care records the profile of TBI is one that is characterized by predominantly males in younger ages however more older females with advancing age. Using data from the National Rehabilitation Reporting System, our findings reveal many common comorbidities such as conditions related to the circulatory system by sex but also distinct differences. Musculoskeletal comorbidity was more common females, for instance in older adults. The implications of these sex differences in relation to an aging patient population for care providers are discussed.

Gender differences of caregiver-Employees: What's different about how men and women navigate informal care & full-time employment

Allison M. Williams, Ph.D. McMaster University

More than 1/3 of all informal caregivers in Canada are also juggling paid employment. Given aging demographics, the need for informal caregivers is expected to increase. Data suggest that men are now nearly as likely as women to become caregivers, but little is known about the lived experience of male caregiver-employees, particularly given the normative gendered expectations of the caregiving role. Using available literature via a scoping review, as well as an ethnographic approach to field data, this paper will use a comparative framework in examining caregiver characteristics across men and women caregiver-employees, paying particular attention to: caregiver characteristics, effects of caregiving, and support and coping strategies. Clear gendered differences in the process of managing paid work and informal caregiving are found, as are the strategies used for coping.

Care gaps and gendered care work in long-term care facilities

Tamara Daly, Ph.D. York University

Focusing on examples from long-term care for seniors, this paper explores the relational and organizational complexities of the unpaid care work of families, volunteers and students and the privately contracted care work of paid companions. This focus is particularly important because familial, voluntary and companion health and social care in these settings is under-explored and highly gendered work. This paper focuses on the following questions: What is it that families, volunteers, companions and students do in voluntary and residential care settings for older adults in relation to staff? How does reliance on these forms of care relieve and create precarity in the system, its organizations and for individuals? What promising and challenging practices accompany reliance on these forms of care for those performing it, for staff and for organizations? This CIHR funded study explored the relationship between paid and unpaid care work in residential long-term care facilities (LTCF). A main study objective was to better understand the extent and nature of the unpaid care work of families and volunteers as well as the privately contracted care work of paid companions, especially considering the impacts on residents and staff. We conducted week-long rapid ethnography observations from 7 am until about midnight and 203 key informant interviews in each of 7 long-term care facilities in the Greater Toronto Area, as well as a survey of LTCF executive directors / directors of care in Alberta and Ontario (n=393). One quarter or more of survey respondents reported that without families, volunteers or paid companions their facility lacked sufficient staff resources to provide good quality care, especially because families, companions, and volunteers supported social and dining care. In addition, paid companions often performed the same body care as paid staff, though employees of the families and not of the facilities. There were challenges coordinating volunteers such as matching skills, interests and opportunities; and creating mutually meaningful and convenient positions. In addition, families', companions' and volunteers' schedules were often unpredictable, leading to conflict with staff and resident routines. Students schedules were predictable but not consistent. Finally, students and companions often added to staff workload. Arlie Hochschild (2003) argues that a gap exists between fragmented and sometimes fragile familial care systems, the limits of governments' care funding, and private care provision by voluntary organizations and for-profits. Indeed, health systems increasingly fill care gaps by relying on families, volunteers and students to augment, supplement and even replace publicly funded care for older adults. Increasingly, in residential settings, families are privately contracting with paid companions to provide one-on-one care to residents. Despite this reliance, sustaining family, volunteer paid companion and student

care work is challenging for organizations, in part because paid care staff may not be afforded the time to properly engage with them. Due to the reportedly insufficient staffing Levels in LTRC, unpaid and contracted care work can fill the care gaps that exists in LTCF settings and serve to extend the paid care available. It can increase residents' individual attention and the overall atmosphere, though it can also be unpredictable. Over-reliance on this care as a substitute for staff reduces the need for governments to collectively bear the costs of increasing staffing Levels to match staffing norms from other countries.

4:00pm - 5:30pm: ELIZABETH YOUNG NEW INVESTIGATORS SYMPOSIUM

Chronic adolescent stress leads to neuroimmune alterations and transcriptomic remodeling in the rat hippocampus in a sex-specific manner

Mandakh Bekhbat, Emory University

Chronic stress during development is a prominent risk factor for mood disorders, and causes neuroimmune alterations that contribute to the etiology of these conditions. We have previously shown that chronic adolescent stress (CAS) primes the hippocampal inflammatory response in adult male, but not female, rats. However, the mechanism underlying CAS-induced neuroinflammatory priming, and associated sex differences are currently unknown. Here we hypothesized that a history of CAS would exaggerate the hippocampal induction of the pro-inflammatory NFkB signaling pathway in adult male rats only. Male and female adolescent rats underwent a mixed-modality CAS paradigm or received no stress. Five weeks following the last stressor all rats, now adults, received a single, systemic injection of either a low dose of lipopolysaccharide (LPS), a potent immune stimulant, or vehicle to unmask possible priming effects of CAS. Total RNA from the hippocampus was used to perform RNA-Seq (Illumina HiSeq), and enriched transcriptional pathways were identified using gene set enrichment analysis. Upon LPS stimulation, both male and female rats that underwent CAS displayed an enhanced enrichment of the NFkB pathway in the hippocampus compared to non-stressed, same-sex controls. Targeted qPCR experiments further confirmed that CAS equally primed the expression of the NFkB complex in males and females. Interestingly, CAS also led to an enhanced enrichment of the glucocorticoid receptor (GR) signaling pathway in females. As GR signaling is the primary mechanism of NFkB suppression, our results suggest sex differences in the impact of CAS on NFkB regulation via an altered balance between GR and NFkB signaling. Collectively, our results indicate that chronic stress experienced during adolescence leads to long-lasting changes to the hippocampal genomic profile, and that CAS alters the balance between the stress and immune pathways in female rats.

Sex differences in the adipokine, lipid, and immune profiles of men and women with severe carotid atherosclerosis

Karina Gasbarrino, McGill University Health Centre

Men develop more unstable plaques than women. Yet, stroke kills more women than men. Despite this, no sex-specific guidelines for carotid disease management exist. Thus, circulating markers that reflect sex-specific features in the plaque should be explored for better prediction of stroke risk. We investigated differences in the adipokine, lipid, and immune profiles of men and women with severe carotid atherosclerosis. Subjects with $\geq 50\%$ carotid stenosis scheduled for a carotid endarterectomy (CEA) were recruited from McGill-affiliated hospitals. Pre-operative plasma/sera samples were collected. Plaque stability was assessed by two gold standard histological classifications. In our database (n=342) there were twice as many men who underwent a CEA compared to women (68 vs. 32%). Men had more unstable plaques than women ($P < 0.001$), exhibiting greater plaque hemorrhage ($P = 0.014$), less fibrous tissue ($P < 0.001$), larger lipid core size ($P < 0.001$), greater number of foam cells ($P = 0.020$) and inflammatory cells ($P < 0.001$), and greater cap infiltration ($P < 0.001$). Women had more severe (80-99%) plaque stenosis than men (75.8 vs. 69.1%) but shared a similar percentage of ruptured plaques ($P > 0.05$). More men suffered a stroke than women (41.1 vs. 32.5%), while more women suffered a transient ischemic attack (48.8 vs. 41.1%). Total and globular adiponectin, and leptin Levels were higher in women than men. Increasing adiponectin Levels were correlated with increased total cholesterol, high-density lipoprotein cholesterol, and ApoA1 Levels ($P < 0.01$), which were also higher in women than men ($P < 0.001$). In contrast, men had higher Levels of pro-inflammatory cytokines and chemokines, IL-6 ($P = 0.039$), TNF- α ($P = 0.005$), MIP1- α ($P = 0.009$), and sVCAM-1 ($P = 0.031$), and a greater percentage of monocyte to white blood cell counts. Women exhibit more favorable adipokine, lipid, and immune profiles compared to men, which may explain the lower instability grade in their carotid atherosclerotic plaques.

Dysfunctional androgen receptor feminizes the mast cell phenotype

Emily Mackey, Michigan State University

Biological sex is an important risk factor for mast cell (MC)-associated immune diseases including allergy/anaphylaxis, irritable bowel syndrome, and chronic pain disorders, with females at increased risk. The mechanisms underlying sex differences in MC disorders remain poorly understood. Our previously published studies showed that compared with male mice, females exhibited more severe pathophysiology in IgE-mediated anaphylaxis and psychological restraint stress. Further studies revealed that female MCs stored and released greater amounts of immune mediators than male MCs, likely contributing to sex-specific differences in disease. The objective of the present study was to determine the components of sex that may be involved in the development of the sexually dimorphic MC. Our hypothesis is that the androgen receptor (AR) plays a key role in masculinizing the MC phenotype. To study this, we utilized XY male rats carrying the testicular feminization mutation (Tfm), characterized by non-functional ARs and therefore insensitive to their own androgens. Peritoneal MCs (pMCs) were isolated from such rats and wildtype (WT) sibling controls and histamine content was evaluated. As expected, pMCs from female rats exhibited higher histamine contents than pMCs from WT male rats while pMCs from Tfm males had intermediate histamine contents, significantly different from both WT males and females (mean \pm SEM: 46,080 \pm 1070 (WT male) vs. 55,252 \pm 2762 (Tfm male) vs. 63,879 \pm 2429 (female) ng/106cells). This finding demonstrates that the AR has a significant influence on MC histamine content which could be protective for males in MC diseases. Also, the current findings in Tfm male MCs suggest that non-AR-dependent sex differences, perhaps mediated via estrogen receptors, also play a role in the sexual differentiation of MCs. Understanding how AR influence MC phenotype and MC-associated disease could reveal novel therapeutic targets for MC-associated diseases.

A sexually dimorphic “pre-stressed” translational signature in CA3 pyramidal neurons of BDNF Val66Met mice

Jordan Marrocco, Ph.D. The Rockefeller University

Males and females use distinct brain mechanisms to cope with similar environmental stimuli, such as stress. The effects of stressors on discrete brain regions, along with high-risk inherited genetic factors, may induce an increased likelihood of developing psychiatric illness, with women suffering of mood disorders at twice the rate of men. The hippocampus, a brain region that regulates memory and emotions, is a crucial target of stress, sex hormones, and allostatic load, because of its neuroanatomical connectivity and because of its expression of steroid hormone receptors. We hypothesized that transcriptional regulation in CA3 pyramidal neurons, a hippocampal subfield displaying sex-dimorphic remodeling in response to stress, was affected in a sex-by-stress-by-genotype manner. Using CA3-specific mRNA purification by translating ribosome affinity purification (TRAP), we studied gene expression with RNA sequencing. Female mice displayed greater gene expression activation after acute stress than males. The effect of acute stress was recapitulated in unstressed heterozygous BDNF Val66Met mice, a model of genetic susceptibility to stress, which displayed a “pre-stressed” translational phenotype, i.e. genes, except immediate early genes, were altered in the absence of acute stress. Unstressed BDNF Val66Met mice and stressed wild-type mice showed similar alterations in both the glutamatergic and glucocorticoid pathways. Behaviorally, only heterozygous BDNF Val66Met females exhibited spatial memory impairment, regardless of acute stress. This effect was not observed in males of either genotype, which instead showed impaired memory only after stress. This work sheds light on ways that genes, environment and sex interact to program the transcriptome, furthering our understanding of different strategies that men and women use to manage stressful experiences.

SPEAKERS' ABSTRACTS: WEDNESDAY, MAY 17

8:45am - 10:30am: SESSION 14

Sex differences in neuroactive steroid actions

Chair: Roberto Cosimo Melcangi, Ph.D. Università degli Studi di Milano

Co-chair: Luis M. Garcia-Segura, Ph.D. Instituto Cajal, CSIC and CIBERFES

The term neuroactive steroids includes molecules that are synthesized in the nervous system by neurons and glial cells (i.e., neurosteroids) and molecules synthesized in peripheral glands, such as the testis, the ovary and the adrenal glands (i.e., steroid hormones). Neuroactive steroids are important physiological regulators of neural function. In addition, some neuroactive steroids exert neuroprotective actions. As recently emerged, Levels and actions of these molecules exert sex dimorphic effects in the nervous system. Indeed, as will be reported by R.C. Melcangi (Italy) the Levels of neuroactive steroids in the nervous system are differently affected by ovariectomy and orchidectomy, suggesting that neural tissue regulates steroid synthesis and metabolism in adaptation to peripheral steroid changes. However, the changes in brain steroid Levels do not parallel the changes in peripheral steroid Levels and in some cases are in the opposite direction. In addition, the Levels of neuroactive steroids in the nervous system are affected by pathology with regional specificity and in a different way in males and females, also indicating that the possible therapeutic interventions based on neuroactive steroid should consider the brain region affected and the sex of the patient.

Sex difference in the Levels of neuroactive steroids

Roberto Cosimo Melcangi, Ph.D. Università degli Studi di Milano

Neuroactive steroids are important physiological regulators of nervous function (Melcangi et al., *Cell Mol Life Sci.* 65:777-797, 2008). This family includes molecules that are synthesized in the nervous system by neurons and glial cells (i.e., neurosteroids) and molecules synthesized in peripheral glands, such as the testis, the ovary and the adrenal glands (i.e., steroid hormones). In the nervous system, the Levels of these molecules are differently affected by ovariectomy and orchidectomy, suggesting that nervous tissue regulates steroid synthesis and metabolism in adaptation to peripheral steroid changes. Moreover, the Levels of neuroactive steroids in non pathological animals are different: a) between peripheral and central nervous system (CNS), b) among CNS areas, c) between plasma, cerebrospinal fluid and nervous system and d) between the two sexes (Caruso et al., *Psychoneuroendocrinology* 38:2278-90, 2013). Neurodegenerative and psychiatric disorders, such as Parkinson's disease, Alzheimer's disease, Huntington's disease, multiple sclerosis, traumatic brain injury, stroke, autism, schizophrenia, depression, anxiety disorders, eating disorders and peripheral neuropathy, show sex differences in their incidence, symptomatology and/or neurodegenerative outcome. In agreement, as demonstrated in different experimental models of neurodegenerative and psychiatric disorders, Levels of neuroactive steroids are affected by the pathology and the sex (Melcangi et al., *Neurosci Biobehav Rev.* 2016 67:25-40, 2016). These observations might provide the basis to design sex-specific neuroprotective therapies based on neuroactive steroids.

Rapid brain estrogen signaling in male and female songbirds

Luke Ramage-Healey, Ph.D. University of Massachusetts Amherst

Sex differences in brain structure first came to prominence four decades ago due to pioneering observations in songbirds. The motor circuits involved in song learning and production are larger in males, and are strikingly visible in thin brain sections without magnification. By contrast, the forebrain circuits involved in auditory processing of song are largely similar in size and cytoarchitecture in adult male and female songbirds. A defining feature of the songbird auditory forebrain is the local production of estrogens, via the enzyme aromatase. Similar to the auditory cortex of humans, the abundance and distribution of aromatase is largely similar in male and female songbirds. In this talk, I will highlight the sex-dependent similarities and differences that have arisen in our recent work on estrogen production and action in the songbird brain. We have accumulated evidence for similar neuromodulatory actions of estrogens in male and female auditory circuits, with some important sex differences in local estrogen synthesis and mechanism-of-action. Using a combination of approaches including in vivo microdialysis, extracellular

and intracellular electrophysiology, and immunocytochemistry we have determined that estrogen signaling in the auditory forebrain of songbirds shares many aspects between males and females, with some notable differences that may reflect compensation as well as divergent life-history profiles.

Sex differences in Regulation of Neurogenesis in the Hippocampus

Liisa A.M. Galea, Ph.D. University of British Columbia

Men and women differ in their vulnerability to develop neurodegenerative and psychiatric diseases, many of which are also associated with sex differences in the severity of cognitive disruptions and neural manifestations of the disease. For example, women are more likely to be diagnosed with Alzheimer's disease (AD) and suffer from greater cognitive deterioration with AD compared to men. The hippocampus produces new neurons throughout the lifespan in rodents and humans and adult neurogenesis plays a crucial role for pattern separation and for spatial long-term memory. However, it is important to establish how neurogenesis in the hippocampus may be involved in hippocampus-dependent cognition in both males and females given the sex differences in cognitive disruptions following diseases that impact the hippocampus. Work in my laboratory has shown that there are sex differences, favoring males, in spatial navigation and pattern separation. We found that male spatial strategy users outperformed female spatial strategy users only when separating similar, but not distinct, patterns and typically males travel shorter distances to reach a hidden platform than females. Furthermore, male spatial strategy users had greater neurogenesis in response to pattern separation training than all other groups consistent with findings in the Morris Water Maze showing that spatial training increased neurogenesis in males but not in females. Despite this, neurogenesis was positively correlated with performance females but not in males in both cognitive tasks. These results suggest that the survival of new neurons may play an important positive role for pattern separation of similar patterns in females. These findings emphasize the importance of studying biological sex on hippocampal function and neural plasticity and have implications for neurodegenerative and psychiatric disorders that target the hippocampus and affect cognition differentially in women versus men.

Effects of sex and estradiol on neuritogenesis

Luis M. Garcia-Segura, Ph.D. Instituto Cajal, CSIC and CIBERFES

In embryonic day 17 (E17) unsexed primary hippocampal neurons, estradiol promotes neuritogenesis by a mechanism mediated by G-protein coupled estrogen receptor 1 (GPER), the activation of PI3K signaling and the repression of HES1, a Notch-regulated gene that negatively controls the expression of the neuritogenic factor neurogenin 3 (Ngn3). When neurons from both sexes are cultivated separately, female neurons have higher expression of Ngn3 and enhanced neuritogenesis than males. Exogenous estradiol increases Ngn3 expression and neuritogenesis in male neurons, but not in female neurons, while aromatase inhibition abolishes the sex differences. These data suggest that gonadal-independent estradiol synthesis by female neurons participates in the generation of sex differences in hippocampal neuritogenesis. Sex differences in neuritogenesis have been also detected in primary neuronal hypothalamic cultures prepared from male and female E14 mouse embryos, before the fetal peak of testosterone. In these cultures, female neurons show enhanced neuritogenesis and higher expression of Ngn3 than male neurons. The silencing of Ngn3 abolishes sex differences in neuritogenesis, decreasing the differentiation of female neurons. Interestingly, the sex difference in Ngn3 expression is determined by sex chromosomes, as demonstrated using the four core genotypes mouse model, in which a spontaneous deletion of the testis-determining gene Sry from the Y chromosome was combined with the insertion of the Sry gene onto an autosome. In addition, as observed for hippocampal neurons, the expression of Ngn3 is increased in the cultures treated with estradiol, but only in those from male embryos. These findings indicate that Ngn3 mediates both cell-autonomous actions of sex chromosomes and hormonal effects to generate sex differences in neuritogenesis.

8:45am - 10:30am: SESSION 15

Sex differences in cardio-metabolic disease across the life-course: from epidemiology to epigenetics

Chair: Linda M O'Keeffe, Ph.D. University of Bristol

Cardiovascular disease (CVD) is the leading cause of death worldwide. However, men and women do not experience CM diseases equally. Up until old age, CVD incidence and mortality is lower in women than men (1). However, this advantage is lost following diabetes onset: risk of coronary heart disease and stroke are up to 50% higher in women compared to men with diabetes (2, 3). Sex differences in CM diseases are not fully explained by differences

in traditional risk factors for disease and remain poorly understood. Epidemiological studies have rarely drawn from across the life-course to increase aetiological understanding of sex differences in CM disease, despite compelling evidence that these differences have their origin in early life. In addition, studies of sex differences in CM disease have often ignored epigenetic and genetic differences between the sexes that may explain sex differences in CM disease. We will use a life-course perspective on sex differences in CM diseases, drawing from conventional epidemiological studies, routinely collected health records, and data from more advanced “omics” including data on sex differences in DNA methylation. Taken together, our symposium will provide important multi-faceted insights into the sex-specific aetiology of CM diseases by combining a life-course perspective with triangulation of evidence from observational studies, health services data, and epigenetic epidemiology.

Diabetes and the female disadvantage

Sanne A.E. Peters, Ph.D. University of Oxford

Diabetes is a major epidemic and a risk factor for several major vascular conditions, dementia, certain cancers, respiratory disease, and infectious diseases. Cardiovascular disease (CVD) is the most common adverse outcome of diabetes. On average, people with diabetes have about twice the risk of CVD compared to those without diabetes. However, not everyone with diabetes has the same degree of excess risk. In large-scale meta-analyses, summarising all the evidence available to date, we have provided compelling evidence that diabetes confers a 44% greater excess risk of coronary heart disease (CHD) and a 27% greater excess risk of stroke in women than in men, independent of sex differences in other major risk factors. Most cases included in these meta-analyses had type 2 diabetes. However, type 1 diabetes was a much stronger risk factor for premature death among women than men, which was primarily driven by sex differences in relative risks of vascular events. Moreover, we recently found a 19% greater relative risk of vascular dementia among women than men with diabetes, suggesting that the sex differences in the consequences of diabetes reach further than macrovascular disease alone. The mechanisms underlying the sex differences in the relative effects of diabetes on the risk of CVD remain unknown. However, three main factors will be discussed in this talk. First, women’s greater excess risk could be a mathematical artefact caused by the relatively low background rate for CVD among women, compared with men. Second, women could be receiving poorer health care than men for the prevention, management, and treatment of diabetes. Third, certain genetic and biological differences between women and men, such as differences in the distribution of body fat or a sexual dimorphism in genetic loci, could explain this female disadvantage.

Sex differences in cardio-metabolic risk factors during childhood and adolescence

Linda M O’Keeffe, Ph.D. University of Bristol

Women and men do not experience cardio-metabolic diseases equally. Cardio-metabolic disease risk emerges in childhood and adolescence, yet sex-specific changes in cardio-metabolic risk factors during early life are poorly understood. In this talk, I will discuss sex differences in trajectories of nine repeatedly measured cardio-metabolic risk factors in a contemporary prospective birth cohort study in England (N for different outcomes: 5,172-14,574). These include triglycerides, high density lipoprotein (HDL-c), non-HDL-c and insulin measured from birth to 17 years and body mass index (BMI), fat mass, lean mass, systolic blood pressure, pulse rate and glucose, measured from one to 17 years. We will show that sex differences in most conventional cardio-metabolic risk factors are already evident at birth or in early childhood with some sex differences widening or changing direction over time and others remaining stable. Linking sex differences in cardio-metabolic risk factors in early life to adult sex differences in cardio-metabolic risk, we will also discuss how the study of sex differences in cardio-metabolic risk factors during childhood and adolescence can increase understanding about the mechanisms underlying sex differences in cardio-metabolic risk across the life course.

Biology of sex differences in cardio-metabolic disease: DNA methylation and sex hormones

Matthew Suderman, Ph.D. University of Bristol

DNA methylation is known to contribute to sex discordance through well-established mechanisms including X-inactivation in females, imprinting and parent-of-origin effects. In this talk we will describe sex-specific DNA methylation throughout childhood in a sample of 700 individuals from the Avon Longitudinal Study of Parents and Children (ALSPAC). We will show that autosomal sex-discordant methylation is widespread throughout the genome and stable; most of the differences are maintained from birth to adolescence, and a large proportion are discordant in both the fetal and adult brain cortices. Only about 15% of differences change from birth to late adolescence, nearly all between birth and age seven. Stable methylation differences are enriched in genomic loci

containing androgen but not estrogen targets and in genes involved in tissue development but not housekeeping functions. A methylation-derived sex score capturing the variance within and between the sexes and was found to be highly correlated over time. This score is nominally associated with sex hormone Levels in childhood as well as some phenotypes previously linked to sex hormone Levels. These findings suggest that sex-discordant DNA methylation is widespread throughout the genome, likely due to the first androgen exposures in utero. It is then stably maintained from birth to late adolescence. Variation of DNA methylation at sex-discordant genomic loci likely reflects androgen exposure and is therefore likely relevant to CM disease as a biomarker and possibly also as a mediator.

8:45am - 10:30am: SESSION 16

Sex, gender and musculoskeletal disorders in the aging worker

Chair: Joy MacDermid, Ph.D. Western University, for CIHR MSD

This symposium brings together half of the holders of the Gender, Work and Health Chairs program of the Canadian Institutes for Health Research who have common interest and expertise in research on how sex, gender and age affects the musculoskeletal health of Canadian workers. Chairholders will present their original research findings that relate to the symposium theme and will also discuss the impact of the Chairholders' program on their careers.

Sex and age differences in disability duration for work-related musculoskeletal injuries

Mieke Koehoorn, Ph.D. University of British Columbia

The Canadian Institutes for Health Research Chairs program in Gender, Work and Health was the impetus for a program of research to investigate differences in workers' compensation outcomes in Canadian jurisdictions. Using secondary analysis of workers' compensation and health data from British Columbia, longer disability durations were observed for women compared to men for the same work-related musculoskeletal injury (back strains, fractures, connective tissue injuries). The observed disability differences by gender persisted in quantile regression models adjusted for sociodemographic, economic, injury and occupation characteristics at all points of the disability duration distribution (25th, 50th and 75th percentiles). In an investigation of age interaction effects, disability duration increased with age regardless of gender or injury type, but the greatest increases by age within the same gender were observed for fractures, followed by connective tissue injuries and then back strains. For example, women aged 50 to 64 years had 30 days longer disability duration for a fracture compared to women aged 20 to 29 year, versus 20 days longer for men for the same age comparison, at the 75th percentile of the distribution. Differences by gender within the same age groups were greatest for connective tissue injuries, followed by back injuries, and with small differences observed for fractures. For example, there was an approximate 20- to 30-day longer disability duration for women compared to men within the same 10-year age grouping for connective tissue injuries, at the 75th percentile of the distribution. Additional workplace supports are required to accommodate and retain older/aging workers with musculoskeletal injuries in the workforce and to reduce disability durations. Some of these workplace supports need to consider gender as part of work disability and recovery processes.

Male/female differences in return to work. What is the contribution of gendered labour and non-labour market factors?

Peter Smith, Ph.D. Institute for Work & Health

Research on return to work (RTW) following a work-related injury has consistently documented that women tend to take longer to RTW and have greater duration of wage replacement than men, even when examining the same types of injuries. Despite this, most analyses examining RTW adjust for age, rather than exploring the biological and social factors that may explain this male/female difference. In this presentation we will provide two examples of how researchers can make male/female differences the focus of their analyses when examining RTW and recovery following injury. These examples will utilize two RTW cohorts from Ontario of workers' compensation claimants with musculoskeletal conditions; and a more recent cohort study from Victoria, Australia of workers' compensation claimants with musculoskeletal and psychological injuries. All cohorts follow claimants with multiple surveys over a 12-month period. The first example involves a path modeling approach, where male/female is the primary variable of interest and the goal of the analyses is to explore pathways that explain male/female inequalities in RTW and recovery outcomes. The second example will illustrate an approach to develop a "gender index", focusing on male/female differences in labour market and non-labour market roles. Each of these approaches help to focus on, and estimate, the relative contribution of gender (social) differences in explaining inequalities in RTW and recovery outcomes between men and women.

Epigenetics and precision health: sex and epigenome tailored approaches for the development of precision medicine tools

Olga Kovalchuk, Ph.D. University of Lethbridge

Our genome and epigenome are vulnerable to a wide array of physical, chemical and social environmental factors and stressors. Epigenetic changes govern faithful gene expression patterns and therefore underlie the healthy development and functioning of cells and organisms. We have shown that a well-known genotoxic agent, ionizing radiation, profoundly affects the epigenome and causes changes in DNA methylation, histone modifications, and small RNA patterns. Radiation-induced epigenetic and gene expression changes are sex specific. Sex and tissue-specific epigenetic changes occur upon exposure to environmental chemicals and chemotherapy agents as well as to physiological stress by circadian deregulation. Aging processes are also characterized by sex- and tissue-specific epigenetic changes. Sex-specific epigenetic alterations may play a causative role in various diseases, including cancer, and underlie susceptibility to therapies. Over the past decade, we started to identify the nature, sex specificity, and biological consequences of epigenetic changes under normal conditions, exposure conditions, and disease conditions (with a focus on cancer and cancer treatment responses), have developed novel epigenetic biomarkers of exposures and cancer, and started the precision medicine initiative. Through excellence in epigenomics, knowledge management, and bioinformatics as well as our relentless pursuit for exposure, epigenomics, and clinical outcomes data, we work towards further expanding precision medicine approaches. I will discuss the roles of epigenetic changes in health and disease, focusing on cancer and age-related diseases, and radiation responses through the sex and gender lens. The analysis of health and disease as a function of sex and gender constitutes the key step towards approaches to precision healthcare tailored to an individual patient.

10:45am - 12:30pm: SESSION 17

Sex differences in mechanisms of stress and anxiety: Human and animal perspectives across development

Chair: Jason Moser, Ph.D. Michigan State University

Co-chair: Rebecca M. Shansky, Ph.D. Northeastern University

Stress- and anxiety-related problems are nearly twice as likely to affect women than men. Moreover, such problems have a greater adverse impact on women's health and well-being. Yet, little is known about the mechanisms involved in sex differences in anxiety and its unique impact on women. This symposium aims to illuminate such mechanisms by bringing together four researchers utilizing multiple methods across animal and human studies. Shansky and Dalla will present findings in animals speaking to sex differences in stress response and associated coping strategies. Kaczurkin and Moser will follow with findings in humans pointing to developmentally sensitive sex differences in subcortical and cortical mechanisms involved in anxiety. Together, the findings reviewed in this symposium intend to stimulate translational thinking regarding mechanisms involved in sex differences in anxiety across development.

Sex-specific determinants of active vs. passive coping strategies in rodents

Rebecca M. Shansky, Ph.D. Northeastern University

Behavioral strategies to cope with potentially threatening or aversive stimuli tend to cluster into two forms: active, escape-driven behaviors, or passive responses that may conserve energy or prevent detection by a predator. Since an individual's coping strategy is closely linked to long-term clinical outcomes after trauma exposure, a better understanding of the neurobiological basis of coping responses could greatly impact public health for both men and women. We have recently found that in classical fear conditioning paradigms, some female rats (but not males) engage in an active "darting" behavior in response to the conditioned stimulus. We are now investigating whether darting is predictive of active responses in other stress coping paradigms (specifically, forced swim), and whether active vs. passive responses are characterized by distinct patterns of neural activity in males and females. Here we report sex-by-strain interactions in the FST that correspond to differential activity in the medial prefrontal cortex.

Sex differences in stress response: the role of estrogens, monoamines and brain circuits

Christina Dalla, Ph.D. National & Kapodistrian University of Athens

Women are more prone than men to depression and certain stress-related disorders. In this respect, we have studied sex differences in models of depression and antidepressant activity, as well as stress mod-

els for more than a decade. We have shown that female rats exhibit higher immobility than males in the Forced Swim Test (FST) and gonadectomy further enhances this “depressive-like” behavioral index in both sexes. Marked sex differences were also observed in the behavior of head swinging in the FST, with females exhibiting lower counts than males. This behavioral index is not influenced by corticosterone, but is correlated with testosterone and is decreased in ovariectomized, adult, female rats treated with an aromatase inhibitor, suggesting a role for extra-gonadal estrogens in the expression of this behavior. Moreover, following FST and chronic mild stress, female rats exhibit decreased serotonergic activity in the hippocampus, whereas dopaminergic changes in the prefrontal cortex (PFC) are also sex-differentiated. Estrogen withdrawal with letrozole treatment, also decreases noradrenaline levels and dopaminergic ratio in the hippocampus and PFC of male and female rats. Moreover, letrozole treatment enhances the serotonergic ratio in the hippocampus of males and females. Recently, we have also shown that the integrity of the circuit hippocampus - prefrontal cortex is necessary for the stress response and the expression of “depressive” behaviors in both sexes. This was shown with behavioral models, neuroplasticity changes following chronic mild stress, as well as with the use of the dexamethasone suppression test in male rats. Overall, our studies highlight the importance of inclusion of both male and female animals in preclinical research for stress and depression.

Error monitoring brain activity as a marker of sex differences in anxiety-related cognitive dysfunction: moderation by developmental stage and ovarian hormones

Jason Moser, Ph.D. Michigan State University

Stress- and anxiety-related problems are nearly twice as likely to affect women than men. Moreover, such problems have a greater adverse impact on women’s health and well-being. Yet, little is known about the mechanisms involved in sex differences in anxiety and its unique impact on women. My talk will discuss findings in humans pointing to developmentally sensitive sex differences in subcortical and cortical mechanisms involved in anxiety. Together, the findings reviewed in this symposium intend to stimulate translational thinking regarding mechanisms involved in sex differences in anxiety across development.

Sex differences in amygdala perfusion among children and adolescents with trait anxiety

Antonia N. Kaczurkin, Ph.D. University of Pennsylvania

Adolescence is a critical period for emotional maturation and is a time when clinically significant symptoms of anxiety and depression increase, particularly in females. However, few studies relate developmental differences in symptoms of anxiety and depression to brain development. Cerebral blood flow (CBF) is one brain phenotype that is known to have marked developmental sex differences and may contribute to observed sex differences in anxiety and depression. We hypothesized that the relationship between greater anxiety symptoms in females would be mediated by CBF in affective regions, such as the amygdala. To test our hypothesis, we capitalized upon a large sample of 875 youths who completed cross-sectional imaging as part of the Philadelphia Neurodevelopmental Cohort. Perfusion was quantified on a voxelwise basis using arterial spin labeled MRI at 3T. Perfusion images were related to trait and state anxiety using a general additive model with penalized splines, while controlling for gray matter density on a voxelwise basis. Clusters found to be related to anxiety were evaluated for interactions with age, sex, and puberty. Trait anxiety was associated with elevated perfusion in a network of regions including the amygdala, anterior insula, and fusiform cortex, even after accounting for pre-scanner state anxiety. Notably, these relationships strengthened with age and the transition through puberty. Moreover, higher trait anxiety in post-pubertal females was mediated by elevated perfusion of the left amygdala. Taken together, these results demonstrate that differences in the evolution of cerebral perfusion during the adolescent period may be a critical element of the affective neurobiology underlying sex differences in anxiety and mood symptoms.

10:45am - 12:30pm: SESSION 18

Sex-specific targeting of kidney function in children, adults, and the elderly: From genes to policy

Sponsored by Ferring Pharmaceuticals

Chair: Geert J. de Vries, Ph.D. Georgia State University

Co-chair: Jens Peters Nørgaard, M.D., DMSc. Ferring Pharmaceuticals

The central theme of this symposium will be sex differences in the expression of the X-linked V2 receptor in the kidney. This gene likely escapes X inactivation and is expressed in double dosage in females. This has important clinical

consequences affecting multiple body systems, including the brain. For example, the popular drug desmopressin, used to treat bedwetting in children and nocturia in adults among other things, is twice as effective in females than in males, in rats as well as humans. This symposium will take a multifaceted look at this issue and should therefore have broad appeal. The first viewpoint will be genetics: Christine Disteche will discuss the mechanism by which genes escape inactivation on the X chromosomes and its consequences for the AVP2 gene (which codes for the V2 receptor). The second will be physiological: Joe Verbalis will discuss molecular, cellular, and physiological consequences of sex differences in V2 expression as well as compensatory mechanisms that prevent this difference from causing overt differences in kidney function. The third will be clinical: Kristian Juul will demonstrate that sex differences in V2 receptor action as well as in vasopressin secretion relate to incidence as well as treatment options in voiding problems in children, adults, and elderly. The fourth will be regulatory: Jens Peter Norgaard will discuss the development of desmopressin as a drug to treat multiple disorders, the importance of stratifying its dosage by sex, and road blocks in getting regulatory agencies to approve this stratification. In addition to being of interest to basic and clinical researchers, this symposium should appeal to participants from regulatory agencies from Canada and the USA, like the CIHR, NIH, and FDA, who will be present at this meeting. Furthermore, this symposium will have support from Ferring, a pioneer among pharmaceutical companies focusing on peptidergic drugs and one of the very few that publicly acknowledge the importance of stratifying drug dosage by sex.

Structure and expression of genes that escape X inactivation in kidney and kidney-derived cells

Christine M. Disteche, Ph.D. University of Washington

Sexual dimorphisms are due to hormonal effects and to differences in sex-linked genes. In particular, genes that escape X inactivation have higher expression in females than males. To investigate the structure of genes that escape X inactivation we used a cell line derived from embryonic kidney of an F1 mouse (resulting from a cross between an inbred mouse and a wild-derived *Mus spretus*) in which X inactivation was skewed. The 3D structure of the inactive X chromosome was determined using Hi-C, which showed that the inactive X chromosome forms a bipartite structure, with the escape genes located at the outside of the condensed structure. Topologically associated domains (TADs) are attenuated on the inactive X compared to the active X chromosome. However, TADs are present around genes that escape X inactivation even on the inactive X chromosome. CRISPR-Cas9 induced deletion of the region located between the superdomains of condensation of the inactive X leads to unraveling of the condensed structure and to reactivation of some genes on the inactive X, suggesting that condensation helps prevent aberrant escape from X inactivation. In human, the AVPR2 gene is included in a large domain of variable escape, suggesting that the gene escapes X inactivation in some cells types (Balaton, Cotton and Brown, 2015). Comparisons of gene expression Levels between human male and female kidney show a female sex bias, but this has not been clearly demonstrated for AVPR2.

Sex differences in vasopressin V2 receptor expression: Implications for pathophysiology and treatment of disorders of urine concentrating ability

Joseph G. Verbalis, M.D. Georgetown University

The renal vasopressin V2 receptor subtype (V2R) plays a critical role in the physiological and pathophysiological processes associated with arginine vasopressin (AVP)-induced antidiuresis. Because clinical data suggests that females may be more prone to hyponatremia from AVP-mediated antidiuresis, we investigated whether there are sex differences in the expression and function of the renal V2R. In normal rat kidneys, V2R mRNA (measured by real-time PCR) and protein (measured by Western blotting) expression was 2.6- and 1.7-fold higher, respectively, in females compared to males. To investigate the potential physiological implications of this sex difference, we studied changes in urine osmolality induced by the AVP V2R agonist desmopressin. In response to different doses of desmopressin, there was a graded increase in urine osmolality and decrease in urine volume during a 24-hr infusion. We also studied renal escape from antidiuresis produced by water loading in rats infused with desmopressin (5.0 ng/hr). After 5 days of water loading, we found the urine osmolality of both female and male rats escaped to the same degree physiologically, but V2R mRNA and protein in females kidneys was reduced to a greater degree (-63% and -73%, respectively) than in males (-32% and -48%, respectively). Our results therefore demonstrate that female rats express more V2R mRNA and protein in their kidneys than males, and that this results physiologically in a greater sensitivity to V2R agonist administration. Because the V2R gene is located on the X chromosome and has a high probability of escaping X-inactivation, these results may be due to a failure of complete X-inactivation. The potential pathophysiological implications of our findings are that females may be more susceptible to the development of dilutional hyponatremia because of a greater sensitivity to lower Levels of endogenously secreted AVP or exogenously administered V2R agonists.

Sex differences in enuresis and nocturia across lifespan

Kristian V. Juul, Ph.D. Ferring Pharmaceuticals

Our understanding of urinary concentrating mechanisms has taken great strides in recent decades with, for example, the discovery of aquaporin (AQP2) water channels, and the identification of the pivotal role of arginine vasopressin (AVP) and the V2 receptor (V2R) in these processes. A key evolving area of new findings is that of sex differences in V2R function, which are suggested by several emerging lines of evidence. This presentation will explore the data amassing from basic research as well as clinical studies in enuresis and nocturia to support this hypothesis. A number of studies have suggested a sex difference in renal sensitivity to AVP in human subjects. Other studies have failed to find such a difference in adults, and published paediatric studies to date suggest no sex differences in renal AVP sensitivity during childhood; findings reported in a recent PhD thesis from the University of Aarhus challenge this, however, with a greater renal sensitivity to desmopressin infusion observed in girls compared with boys. Basic research suggesting a sex difference in antidiuresis, be it through genetic or hormonal regulation of V2R expression, renal sensitivity or osmoregulatory processes, is supported by recent clinical data. One of the earliest indications that there may be a clinically significant difference in renal sensitivity to V2 agonists came with the first studies of low-dose desmopressin orally disintegrating tablet (ODT) in nocturia patients. Follow-up studies of gender-specific dosing in adults with nocturia confirmed that a lower dose of 25 µg desmopressin ODT was effective in women, while men required 50 µg to achieve adequate efficacy. The incidence of hyponatraemia increased with increasing dose. At the highest dose (100 µg), serum sodium decreases seen in women ≥ 50 years of age were approximately double those seen in men. The gender difference in efficacy in favour of females with desmopressin ODT 25µg persisted in long-term trials (up to 56 weeks). In summary, tailoring the dose according to gender provides an improved therapeutic window, with the benefits of a decreased risk of hyponatraemia without compromising efficacy. It also allows older patients, who are most at risk of nocturia but also of hyponatraemia, to receive therapy for the condition with an acceptable safety profile.

10:45am - 12:30pm: SESSION 19

Sex-specific mechanisms of upper limb musculoskeletal disorders

The goal of this symposium is to present original experimental findings from 4 world-leading labs that have been making significant grounds towards the understanding of the physiological mechanisms underlying the development of musculoskeletal injuries, whether in sports or work contexts. The experts use experimental animal and human models to study the impact of well-known injury risk factors: posture, force, repetition, fatigue, and neuromuscular control in how they affect the pain response and may lead to musculoskeletal injury. Considerations of the basic effects of aging and of the aging worker and athlete will be incorporated into the talks.

Sex-Specific Mechanisms of Fatigue

Sandra K. Hunter, Ph.D. Marquette University

Performance fatigability is characterized as an acute decline in motor performance due to an exercise-induced reduction in force or power of the involved muscles. Multiple mechanisms contribute to performance fatigability and originate from neural and muscular processes, with the task demands dictating the mechanisms for both men and women. There are large sex differences in performance fatigability for several upper limb muscles including the elbow flexor and finger flexor muscles (handgrip). When males are stronger than females, the elbow flexor muscles of young females are usually less fatigable than young males for similar intensity sustained and intermittent isometric (static) contractions. First, this presentation highlights the dominant mechanisms for the sex difference in fatigability of upper limb muscles. The primary mechanisms involve a difference between males and females in skeletal muscle physiology, metabolism and muscle perfusion, usually with minimal evidence for neural mechanisms. Second, data will be presented that demonstrates the sex difference in fatigability of the elbows flexor muscles is altered for fatiguing tasks; (1) with different velocity dynamic contractions; (2) when a cognitive challenge is imposed during a fatiguing contraction, and (3) with advanced age. Data will be presented showing that the sex difference in fatigability is diminished as the contraction velocity increases, and is also diminished when a difficult cognitive challenge is performed during as sustained contraction in young and old adults. Examining the underlying mechanisms of sex-based differences in performance fatigability across different task conditions and older populations can shed light on the benefits and limitations that fatigability can exert in both males and females during daily activities, ergonomic tasks, exercise performance, training and rehabilitation.

Sex-specific sEMG normalization procedures and their effects on indicators of shoulder muscle activity

Ana Beatriz Oliveira, PT Ph.D. Federal University of São Carlos

Sex/gender differences have been a central issue in the study of work-related musculoskeletal disorders (WRMD). Recent literature has pointed out that difference on muscle activity patterns between genders is an important factor to explain the higher prevalence of WRMD in women. Those results are based on the application of surface electromyography (sEMG). An important challenge related to sEMG is amplitude normalization, an important procedure applied to reduce intrinsic and extrinsic interferences to the magnitude of the signals. Amplitude normalization has important consequences since, for instance, previous studies applying sEMG to investigate sex/gender differences on muscle activation found differences in the sEMG signal normalized, while no gender difference was found in raw RMS values. Therefore, this presentation will focus on the discussion of sex-specific sEMG normalization procedures, based on a recent study that seek to investigate if gender differences in muscular activation vary according to the method applied to normalize sEMG recorded during an experimental task. Seventeen healthy women and 19 healthy men participated. sEMG was recorded from four portions of the trapezius and the serratus anterior muscles. Four different normalization methods involving maximal and submaximal contractions were applied on sEMG signal recorded during a repetitive task. Amplitude Probability Distribution Function (APDF) analysis was applied to obtain the 10th, 50th, and 90th percentiles. In general, there was gender difference when the sEMG signal was normalized through submaximal contraction at 25% of maximal force exertion. Men and women had the same amount of electrical activity during maximal contractions but men produced at least 50% more force than women for all muscles. Results support the conclusion that normalization methods based on maximal exertions may be the most adequate in the evaluation of gender differences in healthy participants.

Sex-specific mechanisms of acute to chronic neck-shoulder pain

Pascal Madeleine, Ph.D. Aalborg University

There is a higher predominance of musculoskeletal disorders in the neck-shoulder region in females compared with males. These sex differences can be attributed to many biological factors and complex inter-linked relations. Biological factors encompass for instance different sex-related hormonal influences, resting blood pressure, genetic influences, fatigability, motor variability, muscular activation, mechano-sensitivity, and descending inhibitory pain control. One of the main factors is pain as it is an essential constituent of musculoskeletal disorders. There exists similarities in somatosensory changes between experimentally induced and chronic pain. The present presentation will focus on pain modulation mechanisms at different pain stages and explore current knowledge that can contribute to explain the links between acute, sub-acute and chronic in females. Sex differences in pain characteristics (frequency, intensity and spreading) and modulation (descending inhibition, pain habituation) are among the known biological pain-related mechanisms. Imbalance in pain characteristics and modulation has been reported to lead to a long-lasting pain process and to play an important role in the chronification of musculoskeletal disorders. Sex differences in pain characteristics and modulation underline the predominance of neck shoulder pain reported in females compared with males.

Sex-specific mechanisms incorporated into rehabilitation and prevention approaches

Karen Søgaard, Ph.D. University of Southern Denmark

For the work related upper extremity pain, the risk factors causing pain can be identified as physical activity that involves peak loads, static loads and high repetitions as well as long duration. In contrast physical activity training that can cure muscle and joint pain relies on tailoring regarding intensity, duration, repetitions and doses based on evidence from work physiology. My research group has over the last 10 years developed the concept Intelligent Physical Exercise Training as an attempt to standardize a comprehensive individual tailoring of health enhancing physical activity. This incorporates also sex, age, capacity, work exposure, region with pain as well as individual motivation and barriers. More than 15 randomized controlled trials (RCT) with this concept have been conducted at Danish workplaces within different job sectors covering a range of work exposures and including more than 3500 employees. In Denmark the labor market is highly gender segregated and therefore it is not possible to compare the effect between men and women within the same RCT. Only office workers, dental teams and musicians offered mixed populations, while military helicopter pilots, F16 fighter pilots, construction workers were male jobs and cleaning personal, health care workers and laboratory technicians were female jobs. Even in similar jobs the tasks performed by males and females were different and comparison must be performed with care. Clinical trials among patient with upper extremity disorders offer more mixed populations, however then the work exposure is different. An overview will be given of the differences in effect on upper extremity pain, the participants motivation and

the needs assessment between the male and female populations in the RCT and clinical trials. Focus will be on the future perspectives intailoring health enhancing physical activity to the sex differences in capacity, work exposure and motivation.

12:35pm - 1:45pm: WORKING LUNCH

Addressing the 'Data Gap' across the lifespan: Experiences with integrating sex and gender

Chair: Robin Mason, Ph.D. Women's College Hospital

The integration of both and sex and gender considerations in health research are now widely acknowledged as essential to closing the 'data gap' and improving the quality and utility of health research evidence, ensuring appropriate treatments, care, and policies for both men and women. Funders, such as the Canadian Institutes of Health Research and the National Institutes of Health in the U.S. now require researchers to address sex and gender in proposal submissions. However, to date there has been limited understanding or knowledge of how best to do so. In this symposium we consider the integration of sex and gender from the perspective of different disciplines, practices and health problems. Presenters will discuss what they have learned about sex and gender within their field and why this lens is important to their research.

Development of research support in the integration of sex and gender in health

Robin Mason, Ph.D. Women's College Hospital

Sex describes the biologic characteristics of male and female bodies while gender describes the socially constructed roles, behaviours, activities and attributes ascribed to men and women. The integration of both and sex and gender considerations in health research are now widely acknowledged as essential to closing the 'data gap' and improving the quality and utility of health research evidence, ensuring appropriate treatments, care, and policies for both men and women. Yet, many researchers who want to integrate a sex and gender lens into their studies do not always know how to effectively do so. With support from Ontario's Ministry of Health and Long-Term Care and the Ontario Strategy for Patient-Oriented Research SUPPORT (Support for People and Patient-Oriented Research and Trials) Unit, Women's Xchange, a women's health research knowledge translation and exchange centre based at Women's College Hospital in Toronto, began responding to researchers' requests for assistance with integrating a sex and gender lens in their study proposals. From this beginning, a formalized Sex and Gender Research Support Service was developed to enhance research outcomes for both men and women. During this interdisciplinary symposium, four panelists present on 1) the development of Women's Xchange's Sex and Gender Research Support Service; and the ways in which sex and gender are being integrated into studies of 2) patient oriented research on diabetes; 3) the development of a smartphone and web-based app for managing heart pain and, 4) youth focused suicide prevention strategies.

Sex and gender considerations in youth suicide prevention: implications for observational and interventional research

Daphne Korczak, M.D., MSc, FRCPC (peds), FRCPC (psych). Hospital for Sick Children, University of Toronto

Suicide is the leading cause of non-accidental death among children in Canada. While both boys and girls have experienced an increase in the medical severity of their emergency department presentations for suicide-related behaviour, notable sex differences in rates of death by suicide persist. Increased understanding of potential sex- and gender-specific pathways to suicidal behaviour and response to intervention is critical to developing effective youth suicide prevention programs. This presentation will provide a broad overview of current knowledge regarding sex- and gender- considerations in (i) the epidemiology of youth suicide; (ii) the help-seeking behaviour of suicidal youth; and (iii) empirical data regarding the effectiveness of specific youth suicide prevention interventions. Implications for future observational research and intervention studies will be discussed.

Diabetes Action Canada: Acknowledging the challenges of integrating sex and gender into patient-oriented research

Bruce A. Perkins, M.D., MPH, FRCPC, University of Toronto

Diabetes Action Canada is a new national patient-oriented research network, one of the five funded through the Canadian Institutes of Health Research's Strategies for Patient-Oriented Research, established to transform the health outcomes for individuals with diabetes and its related complications. Diabetes Action Canada is the first and

only nation-wide collaborative network of clinicians, researchers, public diabetes foundations, industry partners - in direct partnership with Canadians living with diabetes - that is focused on the ultimate goal of prevention of diabetes complications. To this end, Diabetes Action Canada will facilitate important and meaningful connections between patients, their primary healthcare providers, and specialists to improve health care and significant cost savings within the health system. It aims to accomplish this by way of directed Goal Groups focused on Retinopathy Screening Programs, Medical Informatics platforms, Knowledge Translation, Patient Engagement, Indigenous and Vulnerable Populations, Training and Mentoring, Health Policy, Sex and Gender Research, and a goal group dedicated to the efficient conduct of high-impact Clinical Trials. This presentation will focus on the context and strategies for the implementation and integration of the sex and gender lens into a patient-oriented clinical trials network.

Contextualizing the self-management of heart pain in women: An evidence map

Monica Parry, Ph.D., Med, MSc, NP-Adult, CCNC, University of Toronto

Heart pain disproportionately burdens more women than men, and women have a varied pattern and distribution of chest- and non-chest-related pain symptoms associated with obstructive and non-obstructive coronary artery disease (CAD). Women also have a higher prevalence of heart pain after percutaneous coronary interventions (PCI) and cardiac surgery. To describe the current evidence related to the self-management of heart pain in women using the process and methodology of evidence mapping. The main purpose of evidence mapping is to provide an overview of a broad range of research and identify evidence gaps and future research needs. The evidence map construction followed six steps: 1) identify the scope, 2) define the key variables, 3) establish a search strategy, 4) identify inclusion and exclusion criteria, 5) systematically retrieve, screen and classify the evidence, and 6) report the findings in an evidence map. In total, 6,582 eligible citations were identified. After exclusions, 288 unique articles were included in the evidence map: 24% (n=68) reviews, 17% (n=49) intervention studies, and 59% (n=168) non-intervention studies. Seventy percent (n=200) of the citations represented obstructive CAD, 5% (n=14) non-obstructive CAD, and 14% (n=41) post-procedural pain. The median sample size across the primary research studies was 90 and the mean age was 63 years. Our evidence map suggests that while much is known about the differing presentations of obstructive heart pain in middle-aged women, little research has focused on young and old women, non-obstructive heart pain, or self-management interventions to assist women to manage heart pain.

2:00pm - 3:45pm: SESSION 20

Sex differences in neonatal brain injury: role of sex steroids and their receptors

Sponsored by Morgan Claypool

Chair: Pelin Cengiz, M.D. University of Wisconsin

Neonatal brain injury leads to severe, life-long morbidities in thousands of neonates and children born in the world and US each year. The physical, emotional, and economic toll taken by these adverse early childhood events is incalculable. Unfortunately, few therapies are available to mitigate the injury and improve outcomes following neonatal brain injury. Interestingly, clinical studies indicate that male neonate brains are more susceptible resulting in greater long-term cognitive deficits as compared to females with comparable brain injury. The relative resistance of the female neonatal brain suggests that some sex-specific mechanisms afford females greater neuroprotection and/or facilitates recovery. Therefore, it is important to understand the cellular basis of sex differences in the pathological consequences of brain injury, in order to find novel therapeutic strategies to help neonates of both sexes grow into maximally functioning adults. Unlike neonatal brains, the role of sex steroids and their receptors have been extensively studied in adult animal brain injury models. However, neonatal brain is sexually differentiated during development and following brain injury. There is increasing evidence that sex steroids and their receptors can play a role in the sex differences seen in neonatal brains following injury.

Mediators of a female advantage in behavioral outcome following late-preterm HI injury in a rodent model

R. Holly Fitch, Ph.D. University of Connecticut

A sex discrepancy favoring females is seen for a variety of perinatal complications and neurodevelopmental disorders that affect males more frequently. Female neonates also show better recovery from perinatal brain insults relative to matched males. Although a robust adult female stroke advantage has been attributed at least in part to estrogen, the factor(s) protecting female neonates remain unknown. We performed a series of studies using a rat model of induced hypoxic-ischemic (HI) injury (Rice-Vannucci) on postnatal day 7 (P7). This unilateral HI injury simulates insults in near-term/term infants with birth complications, as well as preterm populations with hemorrhagic

intra-periventricular events, ischemic injury, and chronic hypoxia. Results showed superior outcomes for HI females on a variety of behavioral tasks (particularly maze tasks) as compared to male HI rats. Interestingly, sex effects were seen despite comparable neuropathologic indices (tissue loss) in the injured hemisphere. Additional results showed that perinatal treatment with an aromatizable androgen (testosterone propionate) led female rats to express more robust behavioral deficits, similar to those seen in HI males. We also report evidence that some female protection may arise from sex differences in the apoptotic cascade, including an X-linked inhibitor of apoptosis (XIAP). Combined results suggest multiple variables contribute to the observed female advantage, including deleterious effects of perinatal androgens, and X-linked variables moderating apoptotic events. Finally, intriguing new results showed increased laminar thickness in the contralateral hippocampus following unilateral HI injury in P7 female rats, as compared to contralateral tissue loss in males. This could reflect more optimal compensatory reorganization in the female neonatal brain, and could help explain post-injury behavioral enhancement that is observed despite comparable pathology in the affected hemisphere.

Sex differences and effects of estradiol treatment on hypoxia-ischemia induced hippocampal damage in neonatal rats

Margaret M. McCarthy, Ph.D. University of Maryland School of Medicine

Hypoxia-ischemia (HI) of the brain in near-term and term infants is a leading cause of infant mortality and lifelong disability and occurs in 1-4/1000 live births, yet current therapeutic approaches remain limited. Males consistently display greater vulnerability to the deleterious consequences of HI in both humans and animal models. Using the laboratory rat we determined that rates of neurogenesis are high in the hippocampus during the perinatal period and increase still further after neonatal HI, but survival of these new neurons is low. Uninjured males make more new neurons than their female siblings and many of these endure into young adulthood. Harnessing this capacity offers a potential therapeutic target for recovery after HI. The steroid hormone estradiol is found at very low concentrations in the developing hippocampus but potently up regulates cell genesis and survival in both sexes during a neonatal sensitive period. Estradiol has been extensively explored as a neuroprotectant in adult models of stroke in female rodents and women but with mixed results. Less consideration has been afforded to this naturally occurring agent in the developing brain, which has unique challenges from the adult. Using a model of term HI in the rat we explored the impact of this insult on cell genesis in the hippocampus of males and females and the ability of estradiol treatment immediately after insult to restore function. Both short-term (3 days) and long-term (7 days) post-injury were assessed and revealed that only females had markedly increased cell genesis on the short-term but both sexes were increased long-term. In juvenile and young adult animals a battery of behavioral tests revealed motor impairment and compromised episodic memory in males while both sexes were modestly impaired in spatial memory. Juvenile social play was also depressed in both sexes after HI. Estradiol therapy improved behavioral performance in both sexes but did not reverse a deficit in hippocampal volume ipsilateral to the insult. Thus the effects of estradiol do not appear to be via cell death or proliferation but rather involve other components of neural functioning.

Sex difference in the role of ER-mediated neuroprotection following neonatal brain injury

Pelin Cengiz, M.D. University of Wisconsin

Female newborns are two times more resistant to the effects of hypoxia ischemia (HI) related brain injury, a phenomenon that is poorly understood. Our recent studies have demonstrated a similar female bias in neuroprotection following neonatal HI in mice, and have clearly implicated estrogen receptor alpha (ER) in conferring this sex-specific neuroprotective mechanism. We demonstrated that ER may confer neuroprotection in female neonatal hippocampus through cross-talk with the neurotrophin receptor, tyrosine kinase B (TrkB), which has been shown to play an important role in neuroprotection and improving long-term functional recovery following HI by increasing neuronal survival. Administration of 7,8-dihydroxyflavone (7,8-DHF; potent and selective TrkB agonist) increases TrkB phosphorylation and hippocampal neuronal survival following HI in female, but not in male newborn mice, and these female specific effects are absent in ER null mutant mice. Consistent with these in-vivo results, we have used sexed hippocampal neuronal cells in culture, to demonstrate that hippocampal neuronal cell survival following in-vitro ischemia recovers to normoxic values with 7,8-DHF treatment only in female neurons. This sexually differentiated neuroprotection is ablated in neurons derived from ER null mutant mice. Our findings thus reveal that female-specific upregulation of ER expression after HI, and resultant increase in ER crosstalk with TrkB receptors, mediate the female-specific neuroprotection after neonatal HI. Mechanisms that underlie increased ER expression in the neonatal female vs. male hippocampus remain unknown. Exciting preliminary results from our ongoing studies implicate that epigenetic modifications may result in female-specific ER gene expression following HI. An

improved understanding of the cellular basis of sex differences in brain injury is essential in order to find novel therapeutic strategies to help neonates grow into maximally functioning adults.

2:00pm - 3:45pm: SESSION 21

Sex differences in cerebral ischemia across the lifespan

Chair: Fudong Liu, M.D. University of Texas Health Science Center McGovern Medical School

Co-chair: Amutha Selvamani, Ph.D. Texas A&M University

Clinically cerebral ischemia is a sexually dimorphic disease throughout the lifespan. In neonates, male infants are not only more vulnerable to ischemic insult; they also suffer more long-term cognitive deficits as compared to females with comparable injury. It is less likely that circulating gonadal hormones contribute to the sex differences as neonates of both sexes have equivalently low circulating hormone levels. Estrogen's neuroprotective role may account for the "male sensitive" stroke phenotype seen in young adult stroke patients; however, with the diminishing level of estrogen after menopause, the incidence of stroke in women does not climb until well after natural menopause, suggesting there are hormone independent effects on ischemic sensitivity. Despite the higher overall lifetime incidence of stroke in men, aged women have more severe strokes, poorer recovery and greater long-term disability compared to age-matched men. The epidemiology of sex differences in stroke across the lifespan has aroused increasing research interest of scientists, and it has been recognized that mechanistic studies into this ischemic sexual dimorphism may lead to development of novel and effective therapeutic strategies. Emerging data have clearly shown that hormones, immune responses, chromosomes, etc. are important interacting factors in the sexual dimorphism of stroke. We propose a symposium on "Sex differences in cerebral ischemia across the lifespan" for OSSD 2017, and have confirmed that at least three scientists with different expertise in this field would like to address the sex difference in neonatal, young, menopausal, and aged population.

Sex differences in immune responses to cerebral ischemia in neonatal and aged mice

Fudong Liu, M.D. University of Texas Health Science Center McGovern Medical School

Cerebral ischemia is a sexually dimorphic disease where immune response is a fundamental pathophysiological procedure. We hypothesized that at both ends of the age spectrum when effects of circulating hormones are minimal, the inflammatory response plays an important role in mediating the sex-specific ischemic injury and outcomes. To induce the ischemic injury, Rice-Vannucci Model (RVM) and middle cerebral artery occlusion (MCAO) model were used in neonatal and aged C57BL6 mice respectively. Stroke outcomes including infarct size and behavior deficits were measured at 1d and 3d after ischemia. Flow cytometry was performed on ischemic brain samples to examine the infiltration of immune cells; Multiplex and Elisa were used to examine inflammatory cytokine levels in the blood. In neonatal mice, no sex difference in outcomes was seen at day 1 of stroke; however, males had significantly larger infarct volumes and higher neurological deficit scores 3 days after ischemia than females. Consistently, males had significantly higher serum IL-1 β and TNF- α levels than females. There were more infiltrating lymphocytes and MHCII+ microglia in male vs. female neonatal stroke brains. In aged mice, females had worse stroke outcomes compared to males 3 days after stroke. Neuronal NF κ B and microglial MHCII expression was higher in aged female vs. male group. More infiltrating monocytes, neutrophils and lymphocytes were seen in female vs. male ischemic brains. Aged females also had significantly higher circulating IL-1B, IL-6, TNF- α and MCP-1 levels than males. We conclude that sex differences in ischemic injury exhibit an opposite pattern in neonatal and aged mice, and that the inflammatory response to cerebral ischemia may mediate the sexual dimorphism. Future studies are warranted to investigate the causal relationship between the sex-specific immune response and ischemic injury, and to "fine-tune" the post-stroke inflammation in hopes of developing effective therapeutic strategies.

Age- and sex-related characteristics of the atherosclerotic plaque

Hester M den Ruijter, Ph.D. University Medical Center Utrecht

Sex differences in cardiovascular disease are evident. Women are approximately ten years older when experiencing a first cardiac event as compared to men. The underlying pathology, the atherosclerotic plaque, is also different in women as compared to men. In the hearts of sudden death victims, plaque erosion is more commonly found in women as compared to men. Men more often display plaque rupture as the substrate for the acute cardiac event. Little is known on sex differences in the composition of the atherosclerotic plaque and its association with sex hormones. Within the Athero-Express biobank, we included patients with stroke, transient ischemic attack, amaurosis fugax and asymptomatic carotid stenosis who underwent carotid surgery. During surgery the atherosclerotic plaques are harvested and used for histological assessment. Plaque specimens were stained using CD68 (macro-

phages), -actin (smooth muscle cells), picro-sirius red (collagen) and CD34 (microvessels). Furthermore the presence of plaque thrombosis was determined, using a combination of luminal thrombi, intraplaque haemorrhage, hematoxylin-eosin staining and Mallory's phosphotungstic acid-hematoxylin staining (fibrin). Either luminal thrombus, intraplaque haemorrhage or both were considered presence of plaque thrombosis. Computerized analyses quantitatively assessed macrophages and smooth muscle cells as percentage of plaque area. Microvessels were identified morphologically and counted in three hotspots and subsequently averaged per slide. Collagen and calcifications were scored semi-quantitatively into no (1), minor (2), moderate (3) or heavy (4) staining at 40x magnification. These categories were grouped into bins (no/minor and moderate/heavy) for the present analyses. The size of the lipid core was assessed using polarized light and cut off at an area of 10% and 40% of the plaque. All histological slides were assessed by the same dedicated technician. Blood was drawn at the time of surgery. Cardiac biomarkers and sex hormone Levels were determined. Sex differences were observed for the majority of the atherosclerotic plaque features. Women more often displayed plaques with more stable features such as collagen as compared to male plaques, independent of the clinical diagnosis. In addition, sex hormones were strong predictors of plaque composition in both men and women. The clinical implications of these sex differences in severe atherosclerotic disease warrant further investigation.

Sex differences in cerebral ischemia at menopause/reproductive senescence: declining Levels of estrogen and Insulin-like growth factor (IGF)-1

Farida Sohrabji, Ph.D. Texas A&M Health Science Center College of Medicine

The incidence of cerebral ischemia is uniquely influenced by age and sex, such that young males are more susceptible to stroke than young females, while stroke prevalence is greater and stroke severity is worse in older females compared to men. Stroke prevalence is significantly elevated in women at ages 45-54 (Towfighi et al., 2007) and between 55-64 years, stroke prevalence is similar in both sexes (Reeves et al., 2008), supporting the idea that loss of estrogen at menopause contributes to greater stroke risk in older women. In preclinical studies, young male rats (and mice) routinely show larger stroke-induced infarction and greater sensory motor dysfunction as compared to young, normally (estrous) cycling females. This sex difference is abolished by ovariectomy and reinstated by estrogen treatment, indicating that estrogen is neuroprotective in young females. In contrast, middle-aged, acyclic (estrogen-deficient) female rats (10-12 months) show large infarct volumes and greater stroke-induced motor disability as compared to young females and are no different from age-matched males. Paradoxically, estrogen treatment to middle aged females is not neuroprotective, and increases stroke induced infarction. The loss of estrogen in middle-aged females is paralleled by a decline in another trophic factor, insulin like growth factor (IGF)-1, in several sources including plasma, brain homogenates and specifically in astrocytes. Our studies show that IGF-1 treatment administered after stroke improves stroke outcomes in middle-aged female rats treated with estrogen as well as in estrogen-deficient middle-aged females. Furthermore, IGF-1 gene transfer to astrocytes in middle aged females is sufficient to improve sensory motor performance after stroke and reduce-stroke induced neuroinflammation. Thus, while the beneficial effects of estrogen treatment is age-delimited, IGF-1 treatment modulates ischemic injury irrespective of age.

Sexual dimorphism in inflammasome activation: Possible cause of exacerbated ischemic brain damage in reproductively senescent (RS) female rats

Ami P. Raval, Ph.D. University of Miami

A woman's risk of a stroke increases exponentially following the onset of menopause, and underlying mechanisms remains unknown. The current study tests the hypotheses that: (1) inflammasome activation is significantly higher in the brain of RS females as compared to their young counterparts and senescent male rats, (2) RS triggers an innate immune inflammatory response in the ovaries that spreads to the brain, making the brain more susceptible to ischemic damage. We tested our hypotheses using Sprague-Dawley rats of both sexes (6-7 and 9-12 months). The estrous cycles of female rats were monitored for 14-20 days prior to experimentation by daily examination of vaginal smears. Rats that remain in constant diestrus were considered RS. Rats (n= 4-7) of both sexes and ages were sacrificed and hippocampus, gonads, serum and cerebrospinal fluid (CSF) were collected. Additionally, cerebrospinal fluid (CSF) of women (<40 and >50 age) was obtained. Extracellular vesicles (EV) were isolated from serum and CSF using an Invitrogen kit. Inflammasome proteins caspase-1, apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) and IL-1 β significantly increased in the hippocampus, serum, and ovaries of RSF as compared to YF (p<0.05). This was not observed in the hippocampus or gonads of age-matched males. Importantly, EV obtained from RSF contains significantly higher Levels of the inflammasome proteins as compared to YF

($p < 0.05$). EV containing inflammasome proteins originates in the ovaries of RSF and then are carried to the brain via blood. The observed increase in ovary-derived EV containing inflammasome proteins in the brain contributes to the inflammation present in the brain of RSF, and it might exacerbate ischemic brain damage. Future studies investigating the role of ovarian EV in post-ischemic inflammation are underway to understand how modulating EV trafficking can reduce the incidence and impact of cerebral ischemia in post-menopausal women.

2:00pm - 3:45pm: SESSION 22

Adverse experiences in sex-based differences in cardio-respiratory function

Chair: Richard Kinkead, Ph.D. Université Laval

Although there is growing appreciation and description of sex-based differences in cardio-respiratory physiology, mechanistic insight into the pathophysiology remains limited. Perinatal secretion of sex hormones is essential to sexual differentiation and “programming” of various brain circuits including those regulating cardio-respiratory function. Since decrease in gonadal function can be associated with the emergence of disease, these hormones may also contribute to the maintenance of the cardio-respiratory health. It is not surprising therefore that sex also plays an important role in the aging process of cardio-respiratory function. Because early life exposure to adverse conditions interferes with this neuroendocrine process, studies addressing the impact of perinatal stress on cardio-respiratory development provide a unique opportunity to further understand the origins of sex-specific manifestations of cardio-respiratory dysfunction. With that in mind, the primary objective of this symposium is to gain new insights into the neuro-humoral mechanisms underlying sex-based differences in cardio-respiratory disorders. To do so, speakers will highlight recent advances in sex-based differences in the pathophysiology of renal/ cardio-respiratory disorders in animal models. Specifically, Dr. Alexander’s presentation will discuss how exposure to an insult during early life can disrupt the long-term regulation of blood pressure control leading to sex- and age-specific developmental programming of cardiovascular risk. Dr. Brooks will then highlight how changes in hormonal status associated with ageing can lead to inflammation and the emergence of hypertension in women. Dr. Kinkead will close the session by discussing how neonatal stress contributes to the sexual dimorphism of respiratory manifestations panic attacks. Each speaker will be encouraged to share their views on future directions and challenges for their specific areas. This session will offer its audience the possibility to learn basic concepts in a somewhat distant yet related fields of physiology. Given the degree of complementarity between the topics being covered, this session aims to stimulate discussions and interactions necessary to explore new research avenues and collaborations.

Sex differences in the developmental programming of blood pressure across the lifespan

Barbara T. Alexander, Ph.D. University of Mississippi Medical Center

It is well-established that hypertension is less common in women relative to men prior to menopause; yet, the prevalence of hypertension is augmented after menopause. Numerous epidemiological studies demonstrate that birth weight is inversely associated with blood pressure in men and women. Few studies directly address the effect of sex on blood pressure in low birth weight individuals. However, the prevalence of hypertension is significantly increased in low birth weight women by age 60 relative to age-matched normal birth weight counterparts. Thus, these studies indicate that factors that slow fetal growth increase blood pressure and cardiovascular risk in a manner that is exacerbated with age in low birth weight women. Experimental studies indicate that the inverse association between birth weight and blood pressure is greater in males versus females in young adulthood but this protection is lost with age. Low birth weight is also associated with an increased risk for early age at menopause. Whether the transition into early reproductive senescence is secondary to, or contributes to, enhanced blood pressure and cardiovascular risk in low birth weight females is not clear. Estradiol Levels decrease in women after menopause; testosterone is positively associated with blood pressure in women after menopause. Although sex steroids can modulate blood pressure through multiple pathways, the beneficial effect of estradiol or testosterone on blood pressure in women after menopause is controversial. The pathogenesis of age-dependent increases in blood pressure in low birth weight females is unknown. Thus, the objective of this presentation will be to discuss the changes in the hormonal milieu and the neural-humoral mechanisms that contribute to the increase in blood pressure that develops with age in low birth weight females.

Sex differences in T cell-dependent hypertension: Role of menopause in disease onset

Heddwyn L. Brooks, Ph.D. University of Arizona

Cardiovascular disease is the number one killer of women in the U.S., and hypertension is a primary contributing factor. Prior to menopause, women are protected against hypertension and its associated cardiovascular complications compared to men, however its incidence and progression are rapidly accelerated in postmenopausal women. Postmenopausal women with hypertension do not respond well to current anti-hypertensive medications; 64% of postmenopausal women with hypertension do not have their blood pressure under control. The VCD mouse model of menopause (ovarian failure in rodents) is a follicle-deplete, ovary-intact animal that closely approximates the natural human progression through perimenopause and into the postmenopausal stage of life. Our lab has utilized this model to demonstrate that VCD-treated postmenopausal female mice become hyper-responsive to Ang II infusion, displaying a robust increase in blood pressure and cardiovascular dysfunction. The mechanism underlying this shift in blood pressure regulation and disease onset in postmenopausal women is unknown and impairs our ability to adequately treat the progression and severity of hypertension. T cells, an important component of the adaptive immune system, play a critical role in the development of hypertension and cardiovascular disease in males. However, we recently demonstrated that premenopausal females are protected against T cell mediated hypertension. We have now demonstrated that the protection against T cell mediated hypertension is lost following menopause. Using the VCD model of menopause in T cell deficient mice (Rag1^{-/-}) we show that T cell mediated hypertension progresses rapidly in the absence of ovarian hormones. We will also present data to demonstrate that premenopause, female protection against Ang II induced hypertension is mediated via T-regulatory cells. Translational potential of our studies are high: by studying the onset of T cell-mediated hypertension in postmenopausal females, the pathogenic mechanisms uncovered may lead to novel treatments in decreasing hypertension-related complications in postmenopausal females.

Neonatal stress and sex-based differences in respiratory manifestations of panic disorders

Richard Kinkead, Ph.D. Université Laval

The prevalence of panic disorder (PD) is about twice as high in women compared to men. Clinical manifestations are diverse and can include respiratory symptoms with hyper-responsiveness to CO₂ stimulation. Neonatal maternal separation (NMS) is a form of early life stress that causes persistent and sex-specific disruption of the respiratory control network. At adulthood, rats previously subjected to NMS display several features reported in PD patients including a significant augmentation of the ventilatory response to CO₂ inhalation (hypercapnia; 5% CO₂) in females but not male. Using NMS as a model, we explored the pathophysiology of PD and its sex-specific manifestations by testing the hypothesis that neonatal stress alters natural (cyclic) hormonal influence on the ventilatory response to CO₂. In control rats, the responsiveness to CO₂ did not change across the estrus cycle whereas the response of NMS females was phase-dependent with the greatest hyperventilation observed during proestrus. Because orexin neurons (ORX) have CO₂ chemo-sensing properties and have been associated to PD, we then hypothesized that neonatal stress augments ORX modulation of the CO₂ response. Comparison of ORX Levels in hypothalamic extracts of NMS versus control rats using ELISA showed that ORXA Level is 51% greater in NMS rats than control. Administration of the ORX1 antagonist SB334867 (15mg/kg; i.p) had no effect on ventilatory response of control but abolished the phase-dependent hyper-responsiveness to CO₂ normally observed in NMS females. This work points to neuroendocrine disruption of ORX neurons as a key mechanism in respiratory manifestations of PD.

SPEAKERS' ABSTRACTS: THURSDAY, MAY 18

9:00am - 10:45am: SESSION 23

Sex differences in the hippocampus and related structures: Implications for cognition and stress reactivity throughout the lifespan

Chair: Karyn M. Frick, Ph.D. University of Wisconsin-Milwaukee

Although sex differences in cognitive function among humans and non-human animals have been reported for well over two decades, the nature and magnitude of these differences have been subject to considerable debate. This issue is particularly important for mental health, given the existence of sex differences in the prevalence and symptomatology of disorders such as autism, depression, substance abuse, and Alzheimer's disease. Thus, considerably more research at multiple levels of analysis is needed to better understand sex differences in cognition and in the function of brain regions that regulate cognition. This proposed symposium will focus on sex differences in memory, social behavior, stress reactivity, neurogenesis in the hippocampus, and recovery from stroke using examples from early development, adolescence through to aging, with an emphasis on identifying neural mechanisms underlying sex differences in these phenomena. As such, this symposium will touch upon numerous aspects of human mental health, as well as hormonal regulation of brain and behavioral function in rodent models. The proposed speakers, two of whom are from Canadian institutions and two from U.S. institutions, address this topic using a variety of model systems. Dr. Frick will open the symposium with an overview of the molecular mechanisms through which estrogens regulate memory consolidation in male and female mice. Her work suggests that the mechanisms used by estrogens to enhance memory differs between the sexes, which could have significant implications for sex differences in neurodegenerative disorders like Alzheimer's disease. Dr. Elena Choleris will discuss the effects of estrogen treatments on social behaviors in male and female rodents, and describe differences in neural function that underlie these effects. Dr. Liisa Galea will outline how maternal exposure to corticosterone or exposure to stress during adolescence results in sex differences in hippocampal neuroplasticity and stress reactivity throughout the adult lifespan. Finally, Dr. Farida Sohrabji will discuss sex differences in the effects of estrogens on neuroprotection in rodent models of ischemic stroke, with special attention paid to the differential effects of estrogens on the molecular mechanisms underlying recovery from stroke in youth and old age. We believe that this symposium will provide OSSD attendees with valuable insights about the role of sex differences in cognition and neural function throughout the lifespan, as findings from these labs have provided essential foundational knowledge about hormonal regulation of cognitive function that should advance the understanding of the etiology of, and further new treatments for, cognitive dysfunction in men and women.

Estrogenic regulation of memory in males and females: Molecular mechanisms and implications for aging

Karyn M. Frick, Ph.D. University of Wisconsin-Milwaukee

Women bear a significantly greater risk of age-related memory loss and dementia women than men, likely due to estrogen loss at menopause. However, the beneficial effects of conventional estrogen therapies on cognition are limited to younger menopausal women and increase the risk of deleterious side effects including cancer and stroke. Reaping the beneficial effects of estrogens on memory without these side effects will require a more precise understanding of the molecular mechanisms through which estrogens regulate memory formation. This talk will first summarize our laboratory's work in adult female mice identifying cell signaling and receptor mechanisms in the dorsal hippocampus necessary for estradiol to enhance memory consolidation and/or increase hippocampal and prefrontal dendritic spine density in females. Next, our recent work examining how estradiol regulates memory consolidation in gonadally-intact and castrated male mice will be discussed, including data suggesting sex differences in the cell-signaling mechanisms underlying estradiol-induced memory enhancement. Finally, implications of these nascent biochemical sex differences for age-related memory loss will be discussed.

Hormonal factors in male and female social behavior in rodents

Elena Choleris, Ph.D. University of Guelph

Hormone-regulated sex differences in social behavior are common. A frequent sex difference is in agonistic behavior, often more severe and violent in males than females. In addition, social species typically possess adaptive social cognitive skills, including social recognition, the ability to distinguish between conspecifics, and social learning the ability to learn from others. We investigated the involvement of estrogens and their main receptors, ER, ER and the G protein-coupled ER (GPER1) and found that ER promotes sex-typical agonistic behaviors: attacks in males and dominance behaviors in females, whereas ER enhances dominance behavior in both sexes. ER, ER and GPER also regulate social recognition. ER "knockout" (KO) mice are impaired, and 17-estradiol (E2) and ER, and GPER agonists enhance social recognition minutes after administration, suggesting rapid non-genomic mechanisms of action. Dorsal hippocampal E2, ER, GPER and cell membrane impermeable BSA-E2 similarly facilitated social recognition, suggesting membrane mediated rapid effects. Infusion of E2 facilitated social recognition even in the Hypothalamic Paraventricular Nucleus and Medial Amygdala. In the latter, all 3 ER agonists facilitated social recognition suggesting varying role for ER in different brain regions. E2, ER, ER and GPER also affect social learning. With rapid and delayed effects of treatment, E2 facilitated social learning whereas an ER agonist blocked it. Conversely, a GPER agonist rapidly facilitated social learning. An ER agonist instead prolonged a socially acquired food preference via delayed effects, whereas it shortened it via rapid non-genomic mechanisms. Intriguingly, we are finding that dopaminergic regulation of social learning in the dorsal hippocampus is different in males and females suggesting a possible downstream effector of estrogens' effects. Overall, we are identifying a network of brain regions involved in estrogenic regulation of social behaviors.

Sex differences in stress reactivity and neurogenesis during development and adolescence

Liisa A.M. Galea, Ph.D. University of British Columbia

Sex differences exist in the incidence and timeline of manifestation of psychiatric disease. For example, men are more likely to develop schizophrenia earlier in life, while women are more likely to develop depression later in life (particularly during the perinatal period). Interestingly stress exposure can affect neuroplasticity and behavior in males and females differentially depending on when during the lifespan stress exposure occurs. While both sexes are vulnerable to stress, developing males are more vulnerable to stress during the perinatal period while females may be more vulnerable to stress during adolescence or adulthood. In a series of studies, we have explored the influence of high corticosterone (CORT) administered to the dams (during gestation and/or postpartum as an animal model of perinatal depression) on both the dams and her male and female offspring. CORT treatment increased depressive-like behavior, suppressed neurogenesis, reduced dendritic complexity in pyramidal cells in the hippocampus, and disrupted maternal care in the dams. Male adolescent and adult offspring were more likely to show anxiety-like behavior in response to exposure to maternal postpartum CORT or fluoxetine, respectively. Maternal postpartum CORT enhanced hypothalamic-pituitary-adrenal (HPA) negative feedback in the dexamethasone-suppression test in adult male and female offspring. Only adult female offspring showed reduced neurogenesis in response to maternal postpartum CORT. In a separate study, exposure to restraint stress across adolescence reduced hippocampal neurogenesis and increased basal CORT Levels in adult female, but not male, rats. Together these studies show that perturbations during different developmental periods (in utero, postpartum, adolescence, adulthood) lead to sex differences in endophenotypes that may explain sex differences in vulnerability to psychiatric diseases during different points of across the lifespan in men and women.

9:00am - 10:45am: SESSION 24

Sex differences in cardiovascular disease with aging: Getting beyond the classic roles of sex hormones

Chair: John M. Stafford, M.D., Ph.D. Vanderbilt University Medical Center

There are large sex-differences in cardiovascular disease with aging. This symposium explores non-conventional aspects of sex-differences research with regard to cardiometabolic disease. There is recent evidence in humans and in rodents that estrogen signaling has important roles in glucose metabolism, lipid metabolism and body composition in males, not just females. Additionally there are chromosomal contributions to sex-differences in metabolic disease that are unrelated to prevailing estrogen and androgen levels. The session will be chaired by Dr. John Stafford whose lab focuses on mechanisms for sex-differences in lipoprotein metabolism, and on the sex-specific changes in cardiovascular risk encountered for women after menopause. Dr. Stafford will speak on novel effects of a lipid

transfer protein Cholesteryl Ester Transfer Protein (CETP) in mediating estrogen and androgen actions with regard to glucose and lipid metabolism. Dr. Karen Reue will speak on the role of sex-chromosomes in energy metabolism and obesity. Dr. Franck Mauvais-Jarvis will speak on targeted estrogen delivery to liver and beta cells to treat diabetes. Dr. Joel Finkelstein will speak on the contribution of estrogens made by aromatization of testosterone toward metabolism in males.

Targeted estrogen delivery to delay diabetes in women

Franck Mauvais-Jarvis, M.D., Ph.D. Tulane University

Menopausal estrogens therapy decreases the incidence of diabetes in women. However, the use of general estrogen therapy to delay diabetes in postmenopausal women is not indicated because of reproductive adverse effects. This presentation will discuss novel and alternative ways to direct estrogen action to metabolic tissues, without activation of estrogen action in reproductive tissue.

The roles of the G protein-coupled estrogen receptor GPER in physiology and disease

Eric R. Prossnitz, Ph.D. University of New Mexico

Estrogen is involved in regulating the function of almost every system in the human body. Although its actions have traditionally been thought to be mediated solely by the classical nuclear estrogen receptors (ER and ER), principally through gene regulation, it is now clear that many of estrogen's actions occur through non-genomic or rapid cell signaling events, initiated to a significant extent by the novel G protein-coupled estrogen receptor GPR30/GPER. GPER is a member of the 7-transmembrane G protein-coupled receptor (GPCR) superfamily and was first identified as an orphan GPCR 20 years ago. Our work has focused on understanding the roles of GPER in normal physiology and multiple disease states. To accomplish this, we have developed and characterized highly selective agonists and antagonists for GPER, that lack binding to ER and ER, and employed GPER knockout mice. These complementary approaches have revealed that GPER plays important and sometimes unexpected roles in cancer, cardiovascular function and metabolism, including obesity and diabetes, through multiple rapid and genomic signaling pathways. These results suggest that selective modulators of GPER function could represent novel therapeutic agents in the treatment of numerous diseases.

Role of sex chromosomes in obesity and metabolic co-morbidities

Karen Reue, Ph.D. University of California, Los Angeles

Males and females differ in risk, development, and manifestations of obesity-related conditions such as diabetes and cardiovascular disease. To identify factors that underlie sex differences in obesity and co-morbidities, we have used mouse models in which the sex chromosome complement and number is varied independently from gonads. In addition to the effects of gonadal hormones, we determined that XX mice and XY mice experience metabolic disease in a remarkably different fashion. Following gonadectomy as adults, XX mice have greater body fat, hyperinsulinemia, and hyperlipidemia than XY mice regardless of original gonadal type. With intact gonads, XX mice gain more weight and fat than XY mice when fed a high fat diet. We demonstrated that the increased obesity in XX mice is dependent on the presence of two X chromosomes, rather than the absence of the Y chromosome. We hypothesize that the metabolic effects of the XX chromosome complement are imparted by X chromosome genes that escape inactivation and are therefore expressed at higher levels in XX compared to XY cells. Consistent with this, analysis of mice with altered levels of specific X chromosome escapee genes has identified genes that contribute to the obesity effect. The characterization of the action of these genes in metabolism may reveal novel mechanisms that contribute to sex differences in obesity.

The role of cholesteryl ester transfer protein in mediating sex-differences in cardiovascular risk with obesity and aging

John M. Stafford, M.D., Ph.D. Vanderbilt University Medical Center

Obesity-associated coronary heart disease (CHD) increases with age and is related to the decline in estrogen for women and testosterone for men. Estrogen treatment in women and testosterone treatment in men promote healthy glucose metabolism, yet both worsen dyslipidemia and increase CHD risk, limiting their clinical use to improve metabolic and cardiovascular outcomes in women and men. We found a pathway mediated by cholesteryl ester transfer protein (CETP) that contributes to both the beneficial and harmful effects of sex-hormones with regard to CHD risk in obesity. CETP, a lipid transfer protein, has been mostly studied for its lipid effects on VLDL and HDL. Mice naturally lack CETP expression. By introducing CETP into mice, we discovered several novel metabolic roles for

CETP: 1) it improves insulin sensitivity in obese females in an estrogen-dependent manner, 2) it is necessary for the deleterious increase in serum triglycerides with estrogen treatment, 3) it creates gain-of-function signaling in the liver, specifically with many genes uniquely regulated by estrogen, 4) it augments androgen action in the liver in males, resulting in dyslipidemia. These results suggest that CETP plays a key role in sex-differences in glucose and lipid biology with obesity.

11:00am - 12:00pm: CAPSTONE LECTURE

How the evolution of sex- and gender-based research impacts the practice of medicine

Alyson McGregor, M.D. Brown University

With the increasing recognition of the significant role sex and gender have in research design, outcome, and reproducibility, so increases the evidence that will change the clinical practice of medicine. The importance of sex related pharmacologic differences in drug pharmacokinetics and pharmacodynamics is now indisputable but not before Zolpidem-induced impaired driving reports incited a sex specific labeling revision. As a practicing emergency medicine physician, the impact of sex and gender based differences in health and disease is known to be broad and significant. Translation of this new knowledge to the bedside requires bridging the gap between sex and gender based research and personalized patient care. In this address, the expanding influence sex and gender have on disease presentation, performance of diagnostic testing, treatment responses and outcomes will be reviewed utilizing examples with high public health significance such as cardiovascular disease, pharmacologic toxicity and resuscitation. For example, as research that includes sex as a biological variable continues, more sex-specific thresholds for biomarkers and laboratory value references will become increasingly available. Additionally, health care provider behavior, health care utilization and disparities in delivery of medical care have also been demonstrated to have effects linked to patient sex and gender and will be discussed. Patients' biological sex and gender identity are becoming increasingly important components for health care providers to identify and subsequently utilize in risk assessment, choice in diagnostic testing, interpretation of results and tailored treatment. Incorporating sex and gender based medicine into clinical care has immediate implications for safe, effective and tailored therapeutic regimens that can provide life saving measures and improve medical care for both women and men.

POSTER SESSION 1

- 1. Sex Differences in T cell Immune Responses and Outcome after Stroke in Aged Mice**
Hilda Ahnstedt, Ph.D., Anthony Patrizz, B.A., Javiera Bravo Alegria, Ph.D., Monica Spychala, B.A., Meaghan Roy-O'Reilly, M.S., Anjali Chauhan, Ph.D., Louise D McCullough, MD, Ph.D.
- 2. Sex-based differences in the aortic function of a novel (UC Davis) rat model of Type 2 Diabetes Mellitus (UCD-T2DM)**
Farjana Akther, Sonali Shaligram, Mujibullah D. Karimi, James L. Graham, Kimber L. Stanhope, Peter J. Havel, and Roshanak Rahimian
- 3. Sex and the blood-brain barrier: assessing physiological differences and response to stroke injury in vitro using patient-derived stem cells**
Shyanne Page B.S., Ronak Patel M.S., & Abraham Al-Ahmad, Ph.D.
- 4. Basal differences in cue-triggered motivation are modulated by the ovarian cycle only in obesity-prone but not in obesity-resistant rats**
Yanaira Alonso-Caraballo, Carrie R Ferrario
- 5. Knockout of Neurexin 1 differentially alters male and female juvenile rat social behaviors**
Kathryn J. Argue, Ph.D. and Margaret M McCarthy, Ph.D.
- 6. Incident smoking trajectories among novice adolescent smokers**
Lauzon B. M.Sc., Sylvestre MP, Ph.D., O'Loughlin J, Ph.D.
- 7. Sex-specific effects of exercise on cognition: Evidence from clinical and epidemiological data**
Cindy K. Barha, Ph.D., John R. Best, Ph.D., Caterina Rosano, MD, MPH, Anne B. Newman, MD, MPH, Hilsa N. Ayonayon, Ph.D., Susan M. Rubin, MPH, Janet M. Catov, Ph.D., Liisa A. Galea, Ph.D., Teresa Liu-Ambrose, Ph.D., PT.
- 8. Sex-specific cognitive deficits following early-life stress: A role for parvalbumin in the orbitofrontal cortex**
Kevin G. Bath, Ph.D., Gabriela Manzano-Nieves; Shirley Lin; Haley Goodwill.
- 9. Cardiovascular risk after prophylactic salpingo-oophorectomy in patients with genetic risk of cancer**
Zarah Batulan Ph.D., Matthew Clarkson M.Sc., Chunhua Shi Ph.D., Liane Belland M.D., & Edward O'Brien M.D.
- 10. Sex differences in children's provision of help**
Joyce F. Benenson, Ph.D., Henry Markovits, Ph.D., & Evelyne Gauthier, M.A.
- 11. Estrogen Signals through PPAR γ coactivator 1 α to Reduce Oxidative Damage Associated with Diet-induced Fatty Liver Disease**
Aurèle Besse-Patin, M.Sc, Mélissa Léveillé, Daniel Oropeza, Ph.D.^{1,3}, Bich N. Nguyen, M.D., Ph.D.^{4,5}, Annick Prat, Ph.D. and Jennifer L. Estall, Ph.D.
- 12. Sex differences in self-reported work stress and physiological measures of autonomic regulation in 911 communicators**
Arija Birze, M.A., Jessica Scott, Vicki Leblanc, Ph.D., Cheryl Regehr, PhD, Elise Paradis, Ph.D., & Gillian Einstein Ph.D.
- 13. Profiling immune system sex differences in the healthy human transcriptome**
Erika L. Bongen, P.J. Utz, & Purvesh Khatri

14. **Progesterone receptors expressed in central nervous system contribute to breathing stability of 10 days old rats**
Ryma Boukari, Ms; Aida Bairam, M.D., Ph.D; Vincent Joseph, Ph.D.
15. **The interplay of sex and gender in women and men's health**
Andreea Brabete, Ph.D., Bilkis Vissandjée, Ph.D; & Ruchika Handa MSc
16. **Maternal inflammation at midgestation produces male-selective impairments in fetal neurodevelopment**
Amy Braun, B.A., Pamela Carpentier, Ph.D., Theo Palmer Ph.D.
17. **Studying genes that escape from human X-chromosome inactivation to identify DNA elements regulating the process**
Carolyn J Brown, Ph.D., Samantha B. Peeters, B.Sc., Bradley P. Balaton, B.Sc., Andrea J. Korecki, B.Sc., Elizabeth M. Simpson, Ph.D. & Wyeth W. Wasserman, Ph.D.
18. **Incorporating sex and gender into the medical school curriculum: Osteoporosis**
Robert Casanova, M.D., Marjorie Jenkins, M.D.
19. **Chronic letrozole influences hippocampal neurogenesis but not depressive-like behaviour in middle-aged, female mice**
Jessica A. Chaiton, B.Sc., Rand Mahmoud, B.Sc., Stephanie E Lieblich, B.Sc., Liisa A.M. Galea, Ph.D.
20. **Role of female sex hormones in modulating the severe pulmonary arterial hypertension phenotype induced by VEGFR2 inhibition in a 'hyper-responsive' colony of Sprague Dawley rats**
Ketul R. Chaudhary, Ph.D., Yupu Deng, M.D., Kurt Tyson, B.Sc., Duncan J. Stewart, M.D.
21. **Sex difference in the muscle activity pattern, functional connectivity and muscular fatigue of trapezius and serratus anterior muscles during performing a repetitive task**
Marina M. Cid, Leticia B. Januario, Roberta F. C. M. Padovez, Ph.D., Julie Côté, Ph.D., Pascal Madeleine, Ph.D., Ana Beatriz Oliveira, Ph.D.
22. **Sex differences in aortic stenosis: Insight from dyslipidemic and diabetic mouse model**
Marine Clisson B.Sc., Mohammed-Salah Annabi, M.D., Maxime Hervault, M.Sc., Mylène Shen, M.Sc., Anne-Julie Boilard, Maxime Perron, Lionel Tastet, M.Sc., Marie-Annick Clavel, DMV, Ph. D.
23. **Sex differences in total PYY and GLP-1 after moderate-intensity continuous and sprint interval cycling exercise**
Jennifer L. Copeland, Logan K. Townsend, Jillian Hallworth, Jon Doan and Tom J. Hazell.
24. **Sex-specific circuit regulating anxiety in situation of chronic stress in mice**
Laurence Coutellier, Ph.D.
25. **Association between the probability of autism spectrum disorder and normative sex-related phenotypic diversity in brain structure**
Christine Ecker, Ph.D., Derek S. Andrews, M.Sc., Christina M. Gudbrandsen, M.Sc., Andre F. Marquand, Ph.D., Cedric E. Ginestet, Ph.D., Eileen M. Daly, Ph.D., Clodagh M. Murphy, Ph.D., Meng-Chuan Lai, Ph.D., Michael V. Lombardo, Ph.D., Amber N. V. Ruigrok, Ph.D., Edward T. Bullmore, Ph.D., FRCPsych., John Suckling, Ph.D., Steven C. R. Williams, Ph.D., Simon Baron-Cohen, Ph.D., Declan G. M. Murphy, FRCPsych, and Michael C. Craig, Ph.D., FRCPsych.
26. **Mechanisms of gender-specific hepatic cancer induction by the organochlorine contaminant, hexachlorobenzene**
Daniel G. Cyr and Isabelle Plante.

- 27. Iron deficiency and maternal depression at mid to late pregnancy**
Manish Dama, B.Sc., Ryan Van Lieshout, M.D., Ph.D., FRCP(C), Meir Steiner, M.D., Ph.D., FRCP(C).
- 28. Gender differences in predictors for counselling seeking in infertility patients**
Shrinkhala Dawadi B.A. & Sc., Phyllis Zelkowitz Ed.D.
- 29. Sex-specific effects of chronic administration of relaxin-3 on food intake, body weight and the hypothalamic-pituitary-gonadal axis in rats**
Camila de Ávila, M,Sc, Juliane Calvez, Ph.D., Geneviève Guèvremont, Elena Timofeeva, Ph.D.
- 30. The role of X chromosome inactivation in ovarian cancer**
Stacey J. Winham, Ph.D., Nicholas B. Larson, Ph.D., Zachary Fogarty, MS., Melissa C. Larson, MS, Sebastian M. Armasu, MS, Kimberly R. Kalli, Ph.D., Kate Lawrenson, Ph.D., Simon Gayther, Ph.D., Brooke L. Fridley, Ph.D., Ellen L. Goode, Ph.D.
- 31. Implementing a sex and gender medicine curriculum at Cedars-Sinai Medical Center**
Shivani Dhawan, M.S., Lorie Younger B.A., Michael Elliott B.A., Sarah J. Kilpatrick M.D., Ph.D., C. Noel Bairey Merz, M.D.
- 32. Oxytocin regulation of social behaviour and neurogenesis in adult rats: comparing two delivery methods in males and females**
Paula Duarte-Guterman, Ph.D., Wansu Qiu, B.Sc., Kim Go, B.Sc., Stephanie E. Lieblich, B.Sc., Laura Casanueva, & Liisa A.M. Galea, Ph.D.
- 33. Hippocampal Integrity in women with Bilateral Salpingo-Oophorectomy Prior to Natural Menopause: preliminary findings**
Annie Duchesne, Ph.D., April Au, Nicole J. Gervais, Ph.D., Cheryl Grady, Ph.D., Wendy Meschino, M.D., and Gillian Einstein, Ph.D.
- 34. Photoperiod length influences cocaine-induced behavioral sensitization in Japanese quail**
Shannon E. Eaton, B.A. & Chana K. Akins, Ph.D.
35. Philip Enyan. University of Ghana
36. Philip Enyan. University of Ghana
37. Philip Enyan. University of Ghana
- 38. Considering sex and gender at the research protocol development and review Stages**
Anne Freeman, Patrick Stanko, Lily Berkowitz, Neanta Parnell, Anastasia Zuppe, Tracy L. Bale, Tracy Ziolk, C. Neill Epperson.
- 39. Maternal early life stress (ELS) impact on offspring hypothalamic pituitary adrenal (HPA) axis: Differential effects in male versus female fetal adrenal volume**
Liisa Hantsoo, Ph.D., Mary D. Sammel, Sc.D., Eileen Wang, M.D., Grace Ewing, B.A., C. Neill Epperson, M.D.
- 40. Neuroendocrine control of socially-mediated puberty occurs in a sex-specific manner**
Mariela Faykoo-Martinez, HBSc, Maxwell Barranti, M.A., D. Ashley Monks, Ph.D., Iva Zovkic, Ph.D., Melissa M. Holmes, Ph.D.
- 41. Effects of gut-derived endotoxin on anxiety-like and repetitive behaviors in male and female mice**
Christopher T. Fields, Benoit Chassaing Ph.D., & Geert J. de Vries, Ph.D.

- 42. Can transcriptomic profiles be used to predict sex-associated drug-induced adverse events?**
James C. Fuscoe, Ph.D., Qiang Shi, Ph.D., Lijun Ren, M.D., Jun Zhang, Ph.D., Joseph Hanig, Ph.D., Richard D. Beger, Ph.D., Lisa M. Pence, Ph.D., Laura K. Schnackenberg, Ph.D., Jinchun Sun, Ph.D., Thomas C. Schmitt, B.S., Tao Han, Ph.D., Varsha G. Desai, Ph.D., Carrie L. Moland, A.A.S., and Vikrant Vijay, Ph.D.
- 43. Sex-specific effects on TNF- α derived changes in GluA2-containing AMPARs after early life stress**
Prabarna Ganguly, M.A., Jennifer A. Honeycutt, Ph.D., June H. Rowe-Hill, Camila Demaestri, Heather C. Brenhouse, Ph.D.
- 44. Human experimenter gender modulates mouse behavioral responses to stress and to the antidepressant ketamine**
Polymnia Georgiou, Ph.D., Panos Zanos, Ph.D., Carleigh Jenne, BS, Jackie Highland, BS, Danielle Gerhard, MS, Ronald Duman, Ph.D., Todd D. Gould, M.D.
- 45. Considering sex and gender in the design of a mobile health application for interstitial cystitis/painful bladder syndrome management**
Janessa Griffith, M.Sc.
- 46. Cytotoxic T cells induce pain hypersensitivity in female but not male mice after nerve injury in an interferon- γ -receptor-dependent manner**
Boram Ham, Ph.D., Sarah Rosen, B.Sc., Nadia Boachie, Jean-Sebastien Austin, and Jeffrey Mogil, Ph.D.
- 47. Sex differences in psychiatric comorbidity among patients receiving methadone maintenance treatment**
Tea Rosic, M.D., Leen Naji, B.H.Sc., Monica Bawor, Ph.D., Brittany B. Dennis, Ph.D., Carolyn Plater, MSW, David C. Marsh, M.D., Lehana Thabane, Ph.D., Zainab Samaan, Ph.D.
- 48. A unified approach of maximizing the partial likelihood for the X-chromosome association studies**
Meiling Hao, Ph.D., Wei Xu, Ph.D.
- 49. The human transcriptome of endothelial cells points to histone demethylase differences between the sexes throughout life**
Robin J.G. Hartman, M.Sc., Saskia Haitjema, M.D., Mete Civelek, Ph.D., Mireille N. Bekker, M.D., Ph.D., Rolf T. Urbanus, M.D., Ph.D., Gerard Pasterkamp, M.D., Ph.D. & Hester M. den Ruijter, Ph.D.
- 50. Sex differences in alcohol withdrawal-induced negative affect and corticoamygdalar endocannabinoids**
Angela M. Henricks, Ph.D., Anthony L. Berger, M.S., Janelle M. Lugo, B.S., Lydia N. Baxter-Potter, B.S., Kennedy V. Bieniasz, B.S., Rebecca M. Craft, Ph.D., Matthew N. Hill, Ph.D., Ryan J. McLaughlin, Ph.D.
- 51. Sex-related differences in aortic stenosis lesions are present in bicuspid and tricuspid aortic valves**
Maxime Hervault M.Sc., Mylène Shen M.Sc., Maxime Perron B.Sc., Marine Clisson B.Sc., Marie-Chloe Boulanger Ph.D., Patrick Mathieu MD, Marie-Annick Clavel DVM, Ph.D.
- 52. Women interviewing men: Ten questions raised**
Carla T. Hilario, Genevieve Creighton, Ph.D., & Maya Lefkowich.
- 53. Sex differences in the effects of dietary emulsifiers on the gut-brain axis in mice**
Mary K. Holder, Ph.D., Benoit Chassaing, Ph.D., Nicole V. Peters, Jack J. Whylings, Andrew T. Gewirtz, Ph. D. & Geert J. de Vries, Ph.D.
- 54. Sex differences in a schizophrenia model with exposure to prenatal immune challenges: comparison at the behavioral, molecular, and microglial levels**
Chin Wai Hui, Hassan El Hajj, Marie-Eve Tremblay.

- 55. Lipid metabolism during fasting and refeeding in male and female mice**
Mika Jikumaru, M.D., Ph.D., Kouji Azuma M.S., Hirohisa Miyashita, M.S., Eisuke F. Sato Ph.D., Keiichi Hiramoto, Ph.D., Emiko Kasahara, Ph.D., Masayasu Inoue, M.D., Ph.D., and Etsuro Matsubara M.D., Ph.D.
- 56. Increased impulsivity, autistic traits, and sleep complaints in younger through older adults reporting preterm birth**
Kendall C. John, Ashley Yaughner, M.A., Gerianne M. Alexander Ph.D.
- 57. Studying sex differences with structural magnetic resonance imaging (sMRI): Status of a manual sMRI protocol of the hypothalamic-pituitary-gonadal axis**
Sherri L. Jones, Ph.D., Chloe Anastassiadis, Jamie Near, Ph.D., David P. Laplante, Ph.D., Suzanne King, Ph.D. & Jens Pruessner, Ph.D.
- 58. Preliminary Evidence Supporting Neck Mass and Sore Throat**
Emmanuel Zuzer Josiah, Solomon Oduro Nyamekye, Eugenia Kwakye.
- 59. Age of onset of obsessive-compulsive disorder predicts behavioural symptom severity in women during the perinatal period**
Gabriella F. Mattina, B.Sc., Lauren Mak, M.Sc., Geoffrey Hall, M.Sc., Ph.D., Meir Steiner, M.D., M.Sc., Ph.D., FRCPC.
- 60. Sex differences in vascular function: The effect of race**
Rebecca M. Kappus, Ph.D., Jacob M. Haus, Ph.D., Tracy Baynard, Ph.D., Shane A. Phillips, Ph.D., Michael D. Brown, Ph.D., Bo Fernhall, Ph.D.
- 61. Sex-stratified analysis of obsessive-compulsive disorder reveals differences in genetic architecture**
Ekaterina A Khramtsova, Ph.D., Barbara E Stranger, Ph.D., Lea K Davis, Ph.D.
- 62. Prenatal depression in sequential pregnancies and school readiness in siblings.**
Marta Karpinski, Gabriella Francesca Mattina, B.Sc., Roberto Sassi, M.D., Ph.D., Alison Fleming, Ph.D., & Meir Steiner, M.D., Ph.D., FRCPC.
- 63. Somatosensory-insula connectivity gradients in healthy men and women**
Lisa A Kilpatrick, Ph.D., Kirsten Tillisch, M.D., Emeran A. Mayer, M.D., Jennifer S. Labus, Ph.D.
- 64. Sex differences in depression studies: what can we learn from preclinical research?**
Nikolaos Kokras, Ph.D. & Christina Dalla, Ph.D.
- 65. The role of adult sex hormones in pubertal LPS-induced effects on adult hippocampal neurogenesis and cellular proliferation**
Daria Kolmogorova, B.S.c., Zein Ahmed Mohamed, Elizabeth Houlding, Nicholas LeBel, Mohamed Serhan, & Nafissa Ismail, Ph.D.
- 66. Sex-Immune of reovirus-assisted cancer immunotherapy: Discovery, characterization and therapeutic implications**
Prathyusha Konda, Patrick Murphy, Derek Clements, Youra Kim, Namit Holay, Patrick Lee & Shashi Gujar.
- 67. Data-driven gene signatures and networks underlying sex differences across the human lifespan from hundreds of thousand gene expression profiles**
Arjun Krishnan, Ph.D. & Olga G. Troyanskaya Ph.D.
- 68. The association between pre-eclampsia and end stage renal disease: A nationwide cohort study**
Ali S Khashan, Ph.D., Marius Kublickas, M.D., Ph.D., Louise C Kenny, M.D., Ph.D., Peter Stenvinkel, M.D., Ph.D., Karolina Kublickiene, M.D., Ph.D.

POSTER SESSION 2: WEDNESDAY, MAY 17

- 69. Corticotropin releasing factor regulation of sustained attention in male and female rats**
Debra A. Bangasser, Ph.D., Samantha Eck, Brittany Wicks, Madeleine Salvatore, Sarah Cohen, Nina Duncan, Joy Bergmann, Attilio Ceretti, & Arron Hall.
- 70. Sex-differences in cancer drivers and signatures**
Constance H. Li, Syed Haider, Ph.D., Yu-Jia Shiah, Kevin Thai, Paul C. Boutros, Ph.D.
- 71. Heightened adiposity and metabolic dysfunction in female rats and mice exposed to Early Life Stress**
Analia S. Loria, Ph.D.
- 72. The athero-protective effects of heat shock protein 25 in the absence of ovarian function**
Nadia Maarouf, M.Sc., Vipul Shrivastava, M.Sc., Matthew Clarkson, M.Sc., Zarah Batulan, Ph.D., Edward O'Brien, M.D.
- 73. Transient and persistent effects of maternal experience on the hippocampal neurogenic niche and the inflammatory milieu**
Rand Mahmoud, B.Sc., Jessica A. Chaiton, B.Sc., Stephanie E. Lieblich, B.Sc., & Liisa A.M. Galea, Ph.D.
- 74. Prenatal treatment with testosterone changes expression of ER α and increases autism like behaviour in mice**
M, Marcotte, E. Martin, C. Howes, C. Wasson, H. Katzman, N. MacLusky, E. Choleris.
- 75. Sexually differentiated effects of prenatal testosterone on social learning behaviour in mice**
Emily R. Martin, Colin Howes, M.Sc., Cameron S. Wasson, B.A., Anthony J. Giuga, Marian Castro. M.Sc., Angela N. Tiessen, B.Sc., Michael Marcotte, M.Sc., Neil J. MacLusky, Ph.D. & Elena Choleris, Ph.D.
- 76. Rapid Effects of Hippocampally Synthesized Estrogens on Recognition Learning in Female Mice**
Theresa K. Martin, BAH, Emma Harma & Elena Choleris, Ph.D.
- 77. Involvement of nucleus accumbens dopamine D1-type receptors in social learning of food preferences in male and female mice**
Richard Matta, M.Sc., Madison J. Russell, Danielle J. Tessier, Noah Bass & Elena Choleris, Ph.D.
- 78. Prenatal choline supplementation produces tissue-specific and sex-dependent anti-inflammatory effects in a mouse model of prenatal pollutant exposure**
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