SSD

ORGANIZATION FOR THE STUDY OF SEX DIFFERENCES

Founded by the Society for Women's Health Research

2015 Meeting

April 21-23
Stanford, CA

Sponsored by the Stanford WSDM Center and Women's Heart Health at Stanford

OSSD 2015 PRESIDENT'S WELCOME

Welcome to **OSSD 2015**, the 9th annual meeting of the Organization for the Study of Sex Differences!

This is a very exciting time in the field of the study of sex differences. The rate at which we are advancing knowledge has never been greater, and there is increasing recognition of the importance of sex differences. Excellence in biomedical research requires an understanding of these fundamental differences so that medical treatments are appropriate to each sex. The program this year was designed to span many areas of sex differences, from fundamental cellular processes to human physiology and pathology. The Organization for the Study of Sex Differences has developed the 2015 conference under the leadership of Dr. Christine Disteche to provide unique opportunities to meet and network with investigators with wide-ranging research interests and expertise in sex difference research. The local committee under the leadership of Drs. Marcia Stefanick and Jennifer Tremmel, and the Stanford Women and Sex Differences in Medicine (WSDM) Center have been instrumental in organizing and supporting the meeting. In addition, I would like to thank Dr. Jaclyn Schwarz for her help in implementing the program. We hope that you will find that the multi-disciplinary nature of OSSD's community will promote cross-fertilization of ideas among disciplines and honing of 'best practices' in sex and gender medicine within disciplines.

The 2015 program offers exciting opportunities to meet not only with researchers who study interesting aspects of sex differences but also with leaders at both NIH's Office of Research on Women's Health (ORWH) and the Institute of Gender and Health in Canada. On Day 1 we will host a practical Workshop on how to design studies that integrate sex differences. A new "Stakeholder Forum" will be held during lunch with leaders from the NIH and CHIR (RSVP required). This will be followed by the Presidential Symposium that will discuss current policy, advocacy and innovation to help guide the future of sex difference research. The day will finish with an exciting Keynote address on genomics and the first Poster Session. Day two brings opportunities to learn about exciting new research in genomics, vascular disease, immunology and neuroscience. New this year will be a Mentor/mentee luncheon that will provide trainees and investigators new to the field of sex differences research an opportunity to interact with established investigators. A major goal of the OSSD is to inform and attract new researchers to the field, and thus, we have selected new investigators to present in each of the sessions. Day three includes sessions on stress, epigenetics, cognition and aging, developmental disorders and obesity. The program will finish with a Capstone address on sex and gender differences in cardiovascular diseases followed by a second Poster Session. At the banquet the Elizabeth Young new investigators will be recognized and the Florence P. Haseltine award for the best poster presentation by a new investigator in addition to the BSD award for the best research published in the Biology of Sex Differences journal by an OSSD member will be presented.

Finally, I would like to thank the National Institutes of Health, CIHR's Institute of Gender and Health, and Stanford University, for their generous support of this meeting. I would also like to thank the Society for Women's Health Research for its generous financial as well as administrative support in founding the OSSD. Thank you for joining us for this unique event and we hope that you enjoy all the hospitality that sunny California has to offer!

Louise D. McCullough, MD/PhD
President, OSSD
Professor, Departments of Neurology and Neuroscience
UCONN Health and The Stroke Center at Hartford Hospital

OSSD 2015
Program at a Glance

Berg Hall Lobby
Berg Hall A
Berg Hall B
Berg Hall C
Berg Hall B+C

Tuesday, April 21st

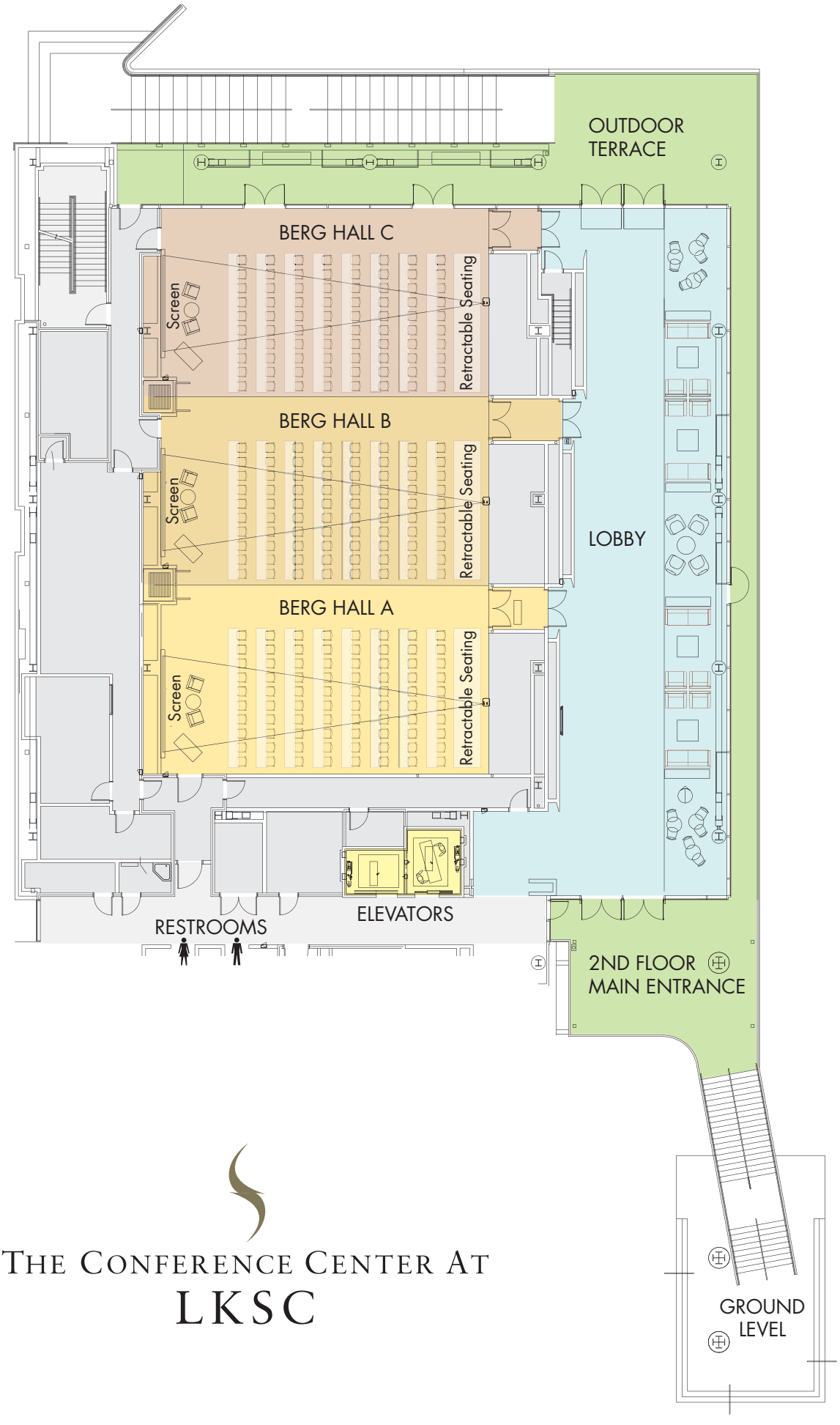
7:30 - 9:00 AM		BREAKFAST
9:00 AM - 12:00 PM		WORKSHOP: "How to study sex differences"
10:30 - 10:45 AM		BREAK
12:00 - 1:30 PM		LUNCH AVAILABLE Stakeholder Forum Lunch: "Introducing Sex as a Variable in Preclinical Research: Metrics and Evaluation" Pre-registration required
1:30 - 3:45 PM		Welcome and Introduction: L. McCullough, C. Disteche PRESIDENTIAL SYMPOSIUM "Policy, advocacy and innovation: the future of sex differences research"
3:45 - 4:15 PM		BREAK
4:15 - 5:15 PM		KEYNOTE ADDRESS: David Page, "Sex and disease: Do males and females read their genomes differently?"
5:30 - 8:00 PM		POSTER SESSION I RECEPTION
Vendor Exhibits Open All Day		
Registration Open 7:30 AM – 1:30 PM		

Wednesday, April 22nd

7:00 - 8:00 AM		BREAKFAST	
8:00 - 9:00 AM		SPECIAL SESSION: J. Tremmel, "Angina in the Absence of Obstructive Coronary Artery Disease: Is There Truly a Sex Difference? "	
9:00 – 9:30 AM		BREAK	
9:30 - 11:15 AM		SESSION I "Sex and vaccines"	SESSION II "Sex differences in brain networks"
11:15 - 11:30 AM		BREAK	
11:30AM - 1:15 PM		SESSION III "Sex effects in early adversity"	SESSION IV "Sex effects in cardiovascular diseases"
1:15 - 2:15 PM		LUNCH AVAILABLE	
		Mentor/Mentee Lunch	
2:15 - 4:00PM		SESSION V "Sleep and sex"	SESSION VI "Sex determination, intersex and transsexualism
4:30 - 5:30 PM		ORGANIZED WALKS	
5:30 PM		FREE TIME	
Vendor Exhibits Open All Day			
Registration Open 7:00 AM – 1:15 PM			

Thursday, April 23rd

7:30 - 8:30 AM		BREAKFAST	
8:30 - 10:15 AM		SESSION VII "Epigenetic dynamics of sexual dimorphisms"	SESSION VIII "Sex differences in sensory perception and cognition"
10:15 - 10:30 AM		BREAK	
10:30AM - 12:15 PM		SESSION IX "Sex differences in neurocognitive aging"	SESSION X "Sex and stress"
12:15 - 1:30 PM		LUNCH AVAILABLE	
		Biology of Sex Difference Editor meeting Lunch LKSC Room 102	
1:30 - 3:15 PM		SESSION XI "Sex, Obesity, and Diabetes"	SESSION XII "The X chromosome in neurodevelopmental disorders"
3:15 - 3:30 PM		BREAK	
3:30 - 4:30 PM		CAPSTONE ADDRESS: Vera Regitz-Zagrosek, "Sex and sex hormones in physiological and pathological cardiovascular stress – implications to management of human disease"	
4:30 - 6:30 PM		POSTER SESSION II	
6:30 - 7:30 PM		General OSSD MEMBERSHIP MEETING LKSC Room 120	
7:30 - 10:00 PM		OSSD AWARDS BANQUET	
Vendor Exhibits Open All Day			
Registration Open 7:30 AM – 12:15 PM			



THE CONFERENCE CENTER AT LKSC

OSSD 2015 PROGRAM TABLE OF CONTENTS

OSSD OFFICERS

OSSD Officers

President

Louise D. McCullough, M.D.

University of Connecticut Health Center

President-Elect

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

Immediate Past President

Geert J. de Vries, Ph.D.,

Georgia State University

Treasurer

Farida Sohrabji, Ph.D.,

Texas A&M Health Science Center

Secretary

Jaclyn M. Schwarz, Ph.D.,

University of Delaware

Councilors

Arthur P. Arnold, Ph.D.

(BSD Editor-in-Chief)

Christine M. Disteche, Ph.D.

(OSSD 2015 Program Chair)

Nancy G. Forger, Ph.D.

Melissa M. Holmes, Ph.D.

Jorge Morales-Montor, Ph.D.

Anne Z. Murphy, Ph.D.

Gretchen N. Neigh, Ph.D.

Vera Regitz-Zagrosek, Ph.D.

Marianne L. Seney, Ph.D.

Rebecca M. Shansky, Ph.D.

John N. Stallone, Ph.D.

Marcia L. Stefanick, Ph.D.

Jennifer A. Tremmel, MD, M.S.

OSSD PROGRAM COMMITTEE

OSSD 2015 Program Committee

Chair: Christine M. Disteche, Ph.D.

Members:

Arthur P. Arnold, Ph.D.

Tracy L. Bale, Ph.D.

Jill B. Becker, Ph.D.

Shannon E. Dunn, Ph.D.

Nancy G. Forger, Ph.D.

Daphna Joel, Ph.D.

Virginia M. Miller, Ph.D.

Gretchen N. Neigh, Ph.D.

Cory Teuscher, Ph.D.

Jun Xu, Ph.D.

LOCAL ORGANIZING COMMITTEE

Marcia L. Stefanick, Ph.D.

Jennifer A. Tremmel, M.D., M.S.

Sonoo Thadaney, M.B.A.

T.O. (Terri) Preising, M.A., J.D.

Laura Becker- Lewke, L.L.B., M.B.A.

OSSD 2015 TRAINEE AWARDS AND HONORS

Elizabeth Young New Investigator Symposium

Jessica L. Bolton, Duke University

Sahin Naqvi, Whitehead Institute, MIT

Sanne A. E. Peters, Oxford University

Kristen E. Pleil, University of North Carolina, Chapel Hill

NIH-Sponsored Travel Award Winners

Caitlin G. Howe, Columbia University

Martin M. Johansson, Uppsala University

Milka Koupenova, University of Massachusetts Medical School

Dimitry N. Kremenstov, University of Vermont

Amutha Selvamani, Texas A&M University, College of Medicine

Maral Tajerian, Stanford University

Amanuel Tesfay, Jimma University

Monan A. Zhang, University of Toronto

KEYNOTE SPEAKER

David C. Page is Director of the Whitehead Institute, Professor of Biology at the Massachusetts Institute of Technology, and Investigator at the Howard Hughes Medical Institute.

His laboratory seeks to understand fundamental differences between males and females in health and disease, both within and beyond the reproductive tract. Most recently, the Page lab discovered that XY and XX sex chromosomes account for subtle differences in the molecular biology of male and female cells and tissues throughout the body. These findings emerged from the lab's comparative genomic and evolutionary studies of the sex chromosomes of humans, other mammals, and birds. In earlier studies, the Page lab reconstructed the evolution of today's X and Y chromosomes from an ancestral pair of chromosomes that existed 300 million years ago. They also discovered and characterized the most common genetic cause of spermatogenic failure in humans: deletion of the *AZFc* region of the Y chromosome. All of these insights were based on technological innovations pioneered by the Page lab to map and sequence Y and X (and Z and W) chromosomes with unprecedented precision and accuracy.

Page's honors include a MacArthur Prize Fellowship, Science magazine's Top Ten Scientific Advances of the Year (in 1992 and again in 2003), and the 2011 March of Dimes Prize in Developmental Biology. He is a Member of the National Academy of Sciences, the Institute of Medicine, and the American Academy of Arts and Sciences.

CAPSTONE SPEAKER

Vera Regitz-Zagrosek (Prof. Dr. Dr. h.c.) is the Founder and Director of the Institute of Gender Medicine (GiM), at the Charité in Berlin. She received her medical degree from Saarland University and did her postdoctoral training at the Max-Planck-Institute for Experimental Cardiology (Prof. Dr. W. Schaper) and at the University of Wisconsin, Madison in the Department of Biochemistry. In addition to the GiM she founded the working group on cardiovascular disease in women at the German cardiac society (DGK), and the German and International Societies for Gender in Medicine (DGesGM and IGM) in 2007. She also coordinates the Berlin site of the "German Centre for Cardiovascular Research (DZHK)" sponsored by the German Federal Ministry of Education and Research (BMBF), as well as three European projects, RADOX, EUGENMED and GENCAD on "Gender in coronary artery disease". She is project leader of the DFG (German Research Foundation) Research Training Group GK 754 and DFG Research Unit FOR 1054 on "Sex-specific mechanisms of myocardial hypertrophy". She is Task Force Leader of the Guidelines "Cardiovascular Diseases in Pregnancy" of the European Society of Cardiology (ESC) and coordinates the pilot project "Gender Medicine" sponsored by the German Federal Ministry of Education and Research (BMBF). She also developed new concepts in teaching Gender medicine for the European ERASMUS project EUGIM (European Curriculum in Gender Medicine).

Vera Regitz-Zagrosek has made important contributions to a better understanding of gender aspects of cardiovascular medicine, research and training. She has developed useful animal and culture models to study sex-specific effects on cardiovascular stress related to disease progression. She has also pioneered efforts to introduce gender medicine in the teaching curriculum.

ORGANIZATION FOR THE STUDY OF SEX DIFFERENCES
Founded by the Society for Women's Health Research

2015 Meeting of the Organization for the Study of Sex Differences
Detailed Program

TUESDAY, APRIL 21

7:30-9:00 **Breakfast – Berg A**

9:00-12:00 **WORKSHOP: "How to study sex differences" - Berg B+C**

Chair: **Virginia Miller**, Mayo Clinic

Art Arnold, University of California, Los Angeles

Kathryn Sandberg, Georgetown University

Jill B. Becker, University of Michigan

Margaret McCarthy, University of Maryland

Gillian Einstein, University of Toronto

Cara Tannenbaum, University of Montréal

Londa Schiebinger, Stanford University

12:00-13:30 **Lunch – Berg A**

Stakeholder Forum hosted by CIHR with participation from NIH-ORWH: *Introducing Sex as a Variable in Preclinical Research: Metrics and Evaluation*. Participants: Cara Tannenbaum, Janine Clayton (**RSVP required**) – **Berg B**

13:30-15:45 **Welcome and Introduction:** Louise McCullough and Christine Disteche **- Berg B+C**

PRESIDENTIAL SYMPOSIUM

Chair: **Louise McCullough**, University of Connecticut

"Policy, Advocacy and Innovation; the Future of Sex Differences Research"

Martha Nolan, Society for Women's Health Research - *The View from Washington: Importance of Advocacy to Biomedical Research*

Londa Schiebinger, Stanford - *Gendered Innovations: How sex and gender interact*

Janine Clayton, Office of Research on Women's Health, NIH - *Sex ~~as~~ IS a Biological Variable*

Panel Discussion and Questions/Answers

15:45-16:15 **Break – Berg A**

16:15-17:15 **KEYNOTE ADDRESS – Berg B+C**

David Page, MIT "*Sex and disease: Do males and females read their genomes differently?*"

17:30-20:00 **POSTER SESSION I – Berg Lobby / Reception – Berg A**

WEDNESDAY, APRIL 22

7:00-8:00 **Breakfast – Berg A**

8:00-9:00 **SPECIAL SESSION sponsored by the Stanford Cardiovascular Institute - Berg B+C**

Jennifer Tremmel Stanford - *Angina in the Absence of Obstructive Coronary Artery Disease: Is There Truly a Sex Difference?*

9:00-9:30 **Break – Berg A**

9:30-11:15 **SESSIONS I AND II**

Session I: "**Sex and Vaccines**"- **Berg B**
Co-Chairs: Mark Davis, Sabra Klein

Sabra Klein Johns Hopkins - *Sex differences and the effects of sex hormones on vaccine efficacy*

Andrew Pekosz Johns Hopkins - *Primary cell cultures as models to identify sex-specific effects on virus replication and host innate immune responses*

Renata Engler University of the Health Sciences - *Sex considerations in vaccine safety and efficacy*

David Furman Stanford - *Testosterone influences humoral immune responses to the influenza vaccine in males*

Session II: "**Sex differences in brain networks**"- **Berg C**

Chair: Ivanka Savic-Berglund

Nirao Shah, UCSF - *Modular genetic and neural control of sexually dimorphic behaviors*

Sarah Burke, VU University - *Sex-typical and sex-atypical white matter microstructure in gender dysphoric children and adolescents – a Diffusion Tensor Imaging study*

Jamie Feusner, UCLA - *Sex differences in functional brain connectivity and relationships to obsessive-compulsive disorder symptoms*

 **Elizabeth Young Award: Kristen Pleil,** University of North Carolina – *Sex-specific effects of chronic voluntary alcohol consumption on limbic neuronal function*

11:15-11:30 **Break – Berg A**

11:30-13:15 **SESSIONS III AND IV**

Session III: "**Sex effects in early adversity**"- **Berg B**
Co-Chairs: Julia Zehr, Tracy Bale

David Lyons, Stanford - *Sex differences in the neurobiology of stress inoculation*

Tanja Jovanovic, Emory - *Genotype and childhood trauma effects on development of sex differences in biomarkers of fear and anxiety*

C. Neill Epperson, University of Pennsylvania - *The role of adverse childhood experiences and lifelong social supports on cognitive aging and risk for depression at menopause*

 **Elizabeth Young Award: Jessica Bolton,** Duke University - *Western Diets during Gestation and Lactation: A Novel Model for Postpartum Depression and Sex-Specific Developmental Programming?*

Session IV: "**Sex effects in cardiovascular diseases**" - **Berg C**
Chair: Jill Barnes

Mansoureh Eghbali, UCLA - *Estrogen rescues advanced heart failure in mice*

Leslie Leinwand, University of Colorado, Boulder - *A woman is not a small man*

Fadi Charchar, Federation University - *Y chromosome: Function and involvement in coronary artery disease*

Soban Umar, UCLA - *Genistein, a phytoestrogen for the treatment of pulmonary arterial hypertension and right ventricular failure*

13:15-14:15 **Lunch – Berg A**

Mentor/Mentee Lunch – Berg B

14:15-16:00 **SESSIONS V AND VI**

Session V: "**Sleep and Sex**"- **Berg B**
Chair: David Ehrmann

Kristen Knutson, University of Chicago - *The impact of sleep disturbances on metabolism in women and in men*

Jessica A. Mong, University of Maryland - *Sex differences and the role of estrogen in sleep: what rodents can tell us about mechanism*

Fiona C. Baker, University of the Witwatersrand - *Menstrual cycle and menopause: Hormonal modulation of sleep*

David Garbe, University of Pennsylvania - *Sex differences in Drosophila sleep patterns*

Session VI: "**Sex determination, intersex and transsexualism**"- **Berg C**

Co-Chairs: Peter Koopman, Fadi Charchar

Blanche Capel, Duke University - *The battle of the sexes: Molecular pathways of male and female development*

Vincent Harley, Monash University - *A link between gender identity and genes involved in sex hormone signalling*

Peter Koopman, University of Queensland - *DSD advocacy: What can science bring to the debate?*

 **Elizabeth Young Award: Sahin Naqvi**, Whitehead Institute, MIT - *Survival on mammalian sex chromosomes is associated with a unique combination of transcription factor binding and microRNA-mediated repression*

16:30-17:30 **Organized walks: meet at Berg Lobby**

17:30 **Free time**

THURSDAY, APRIL 23

7:30-8:30 **Breakfast** - **Berg A**

8:30-10:15 **SESSIONS VII AND VIII**

Session VII: "**Epigenetic dynamics of sexual dimorphisms**"- **Berg B**
Co-Chairs: Claudine Junien, Carolyn Brown

Claudine Junien, National Institute For Agricultural Research - *Sex-specific epigenetics in transgenerational responses to environmental impacts : facts, gaps and new approaches for prevention and treatment of diseases*

David J. Waxman, Boston University - *Mechanisms of growth hormone-regulated, sex-dependent liver gene expression revealed by genome-wide analysis of mouse liver chromatin states*

Carolyn Brown, University of British Columbia - *Sex differences in X-linked gene expression: Human genes that escape from X-chromosome inactivation*

Xinxian Deng, University of Washington - *Dosage-sensitive transcriptional regulation by histone demethylases encoded by mouse genes that escape X inactivation*

Session VIII: "**Sex differences in sensory perception and cognition**"- **Berg C**
Chair: Katherine Sandberg

Claire Murphy, San Diego State University/UCSD - *Sex differences in taste responses*

Dolores Malaspina, New York University - *Olfaction and cognition in schizophrenia cases and healthy controls: sex matters*

Allan Reiss, Stanford - *Sex chromosomes, brain development and cognition*

Dena Dubal, UCSF - *The X Chromosome Confers Advantage in Alzheimer's Disease*

10:15-10:30 Break – Berg A

10:30-12:15 SESSIONS IX AND X

Session IX: "**Sex differences in neurocognitive aging**"- **Berg B**
Chair: Agnès Lacreuse

Naftali Raz, Wayne State University - *Aging of Human Brain and Cognition: Measurable Sex differences?*

Agnès Lacreuse, University of Massachusetts - *Sex differences in cognitive aging : a pressing need for nonhuman primate data*

Liisa Galea, University of British Columbia - *Sex and age differences in the regulation of neuroplasticity and cognition by sex hormones*

Joshua Talboom, Arizona State University - *Sex differences in the influence of cognitive training in aged rodents*

Session X: "**Sex and stress**"- **Berg C**
Co-Chairs: Gretchen Neigh, Nafissa Ismail

Gretchen Neigh, Emory University - *Sex differences in susceptibility and resiliency: it all depends on where you look*

Brian Trainor, UC, Davis- *Sex differences in effects of stress on the aversive properties of kappa opioid receptor*

Nafissa Ismail, University of Ottawa - *The sexed and stressed pubertal brain*

Katie Morrison, University of Pennsylvania - *Dynamic sex differences during PFC maturation and their disruption by stress*

12:15-13:30 **Lunch – Berg A**

Biology of Sex Differences **Editorial Board meeting** - LKSC Room 102

13:30-15:15 **SESSIONS XI AND XII**

Session XI: "**Sex, Obesity, and Diabetes**"- **Berg B**
Chair: Art Arnold

Karen Reue, UCLA - *Sex chromosomes and obesity*

Susan Fried, Boston University - *Female and male adipocytes are different: mechanisms and implications for metabolic health*

Franck Mauvais-Jarvis, Tulane University - *Sex differences and sex hormones in glucose homeostasis and diabetes*

 **Elizabeth Young Award: Sanne Peters,** University of Utrecht - *Greater excess risk of all-cause mortality and vascular events in women than in men with type 1 diabetes: a systematic review with meta-analysis*

Session XII: "**The X chromosome in neurodevelopmental disorders**"- **Berg C**

Chair: William Davies

Rebecca Knickmeyer, University of North Carolina - *The impact of X-chromosome loss on brain structure and function in infancy*

William Davies, Cardiff University - *Steroid sulfatase: an X chromosome-encoded modulator of attention and impulsivity phenotypes*

Armin Raznahan, National Institute of Mental Health - *The neuroanatomy of X-monosomy and autism spectrum disorders*

Donna Werling, UCSF - *Sex-differential gene expression patterns in the human brain and genetic risk for autism*

15:15-15:30 **Break – Berg A**

15:30-16:30 **CAPSTONE ADDRESS - Berg B+C**

Sponsored by the Stanford Cardiovascular Institute

Vera Regitz-Zagrosek, "*Sex and sex hormones in physiological and pathological cardiovascular stress – implications to management of human disease*"

16:30-18:30 **POSTER SESSION II – Berg Lobby**

18:30-19:30 **General OSSD membership meeting – LKSC Room 120**

19:30-22:00 **Banquet / Awards - Berg B+C**

SPEAKER ABSTRACTS – TUESDAY APRIL 21, 2015

PRE-CONFERENCE WORKSHOP: 9:00am - 12:00pm

How to study sex differences

Chair: **Virginia M. Miller** (Mayo Clinic)

Presenters: Arthur P. Arnold[1], Kathryn Sandberg[2], Jill B. Becker[3], Margaret M. McCarthy[4], Gillian Einstein[5], Cara Tannenbaum[5], Londa Schiebinger[6]

[1]Editor of the Biology of Sex Differences,[2] Director, Center for the Study of Sex Differences in Health, Aging and Disease, Georgetown University,[3]Senior Research Scientist, Molecular and Behavioral Neuroscience Institute, University of Michigan,[4]Department of Pharmacology, University of Maryland,[5]Canadian Institute of Health Research, University of Toronto,[6]Director, Gendered Innovations in Science, Health & Medicine, Engineering, and Environment, Stanford University

This workshop is designed to answer real questions investigators are asking following the new National Institutes of Health initiatives to include sex as a biological variable in experimental design. Leaders from the OSSD and Canadian Research Institutes will provide guidelines for how to develop sex-based research questions and how to frame sex compared to gender differences in research design, including budget considerations. They will use examples from their own research, grant submissions and published articles to develop case-based examples. Attendees are invited to bring examples of their own work with them or to submit them ahead of time through the ossdworkshop@ossdweb.org for critique.

PRESIDENTIAL SYMPOSIUM – April 21, 2015 1:45pm – 3:45pm

Policy, Advocacy and Innovation; the Future of Sex Differences Research

Chair: Louise McCullough, M.D. (University of Connecticut, Farmington CT)

The landscape of scientific and biomedical research policies and procedures are changing. Females have been consistently underrepresented in both clinical research and early phase drug studies, and this is even more prevalent in pre-clinical laboratory based research studies. The speakers in this symposium will discuss how sex differences will be incorporated into funding policies, identify resources that are available to researchers, and highlight the importance of advocating for change to improve the quality of research for both sexes. The interaction between gender and sex will also be discussed. The selected speakers have been instrumental in advocating for sex difference research and will demonstrate ways to expand approaches/knowledge of sex and gender research. Discussion on strategies to become a more active advocate of sex difference research and how new policies will impact funding and grant evaluations will be provided.

The View from Washington: Importance of Advocacy to Biomedical Research

Martha Nolan (Society for Women's Health Research)

SWHR will address the key role of advocacy in Washington and its impact on scientific and biomedical research. This talk will examine the role of advocacy organizations, what they do and how they accomplish change to policy, and in particular how they engage scientists in the advocacy process. Over the 25 years since its founding, SWHR has had a tremendous impact on science and policy, both in how research is conducted and how it is funded. SWHR's advocacy work broke down barriers to the inclusion of women and minorities in clinical trials, and transformed the landscape of women's health research and the science of sex and gender differences research at our federal health agencies and across the country. More recently, significant legislative and regulatory advancements have been made that will have a direct impact on the field of sex and gender differences research and the practice of medicine. These achievements are a direct result of advocacy efforts which cannot be obtained without the critical voice of scientists. This presentation will address the process and its importance and the different roles and opportunities for engagement that exist for scientists in advocacy whether close to home, in Washington or on Wall Street.

Gendered Innovations: How sex and gender interact

Londa Schiebinger, M.A., Ph.D. (History of Science, and Director, Gendered Innovations, Stanford University)

Much attention has been given to sex differences in basic and applied research. To expand that approach, this talk focuses on gender analysis, and interactions between sex and gender. This talk introduces the Gendered Innovations project: Gendered Innovations: 1) develops state-of-the-art methods of sex and gender analysis; and 2) provides 24 case studies as concrete illustrations of how sex and gender analysis leads to new ideas and excellence in research. Several case studies will be discussed. All case studies can be found at: http://genderedinnovations.stanford.edu/.

Sex as IS a Biological Variable

Janine A. Clayton, M.D. (Office of Research on Women's Health, National Institutes of Health, Bethesda, MD)

The National Institutes of Health (NIH) funds basic, translational, and clinical research aimed at deepening knowledge about human biology. From basic research to clinical care, studying both sexes is a guiding principle to aid in experimental design, hypothesis-generation and -testing, and in quantifying and expanding knowledge toward turning discovery into health for both women and men. Numerous factors coalesced toward the need for NIH policy, announced in May 2014, to ensure that sex is considered a basic biological variable in NIH-funded preclinical research. These include scientific progress emerging in NIH-funded laboratories, congressional interest and support, and ongoing NIH efforts to enhance reproducibility and transparency in preclinical research. An NIH-issued request for information in fall 2014 revealed that a large majority (nearly 90 percent) of scientist respondents agree that sex is a biological variable that affects rigor and transparency in research. A considerable proportion listed perceived impediments as cost and methodological/experimental complexity. The NIH community is working diligently to configure this policy, including potential changes to application and review language, and associated educational and training resources. Participants include several working groups, the NIH Office of Extramural Research, the NIH Center for Scientific Review, the Office of Research on Women's Health, and NIH senior leadership. Selecting an appropriate preclinical model that considers the role of sex in the context of the specific research question of interest is central to the scientific inquiry process. A continual growth in knowledge about the influence of sex in biomedicine is imperative to the NIH mission of turning discovery into health.

KEYNOTE ADDRESS – April 21, 2015 4:15pm – 5:15pm

Sex and disease: Do males and females read their genomes differently?

David C. Page, MD PhD (Whitehead Institute, Howard Hughes Medical Institute, and Department of Biology, Massachusetts Institute of Technology)

“Nothing in biology makes sense except in the light of evolution.”
Theodosius Dobzhansky, 1973

Dobzhansky’s oft-quoted dictum is highly relevant to our understanding of the manifold differences between males and females in health and disease, both within and beyond the reproductive tract. From the origins of sexual reproduction, in single-celled organisms, to the morphing of our own sex chromosomes from ordinary autosomes during the past 200-300 million years, comparative and evolutionary analyses offer deep, biologically grounded insights into the epigenetic, genomic, and phenotypic differences between the sexes. The emerging evolutionary view serves as an alternative, or complement, to the model (chromosomal sex → gonadal sex → phenotypic sex) that has guided teaching and research for the last half century. The opportunity now presents itself to capitalize upon this emerging evolutionary view of sex differences and their origins.

Most recently, my colleagues and I have conducted comparative genomic and evolutionary studies of the sex chromosomes of humans, other mammals, and birds. These studies have revealed that the Y chromosome’s gene content became specialized, through natural selection, to maintain the ancestral dosage of homologous X-Y gene pairs that function as broadly expressed “readers” of the genome; these X-Y gene pairs regulate transcription, translation and protein stability (Bellott et al. [2014] Nature 508: 494). As a result, there exists a fundamental sexual dimorphism, at a biochemical level, and throughout the body, that derives directly from genetic differences between the X and Y chromosomes. This fundamental sexual dimorphism may play an unappreciated role in health and disease in both males and females.

SPEAKER ABSTRACTS – WEDNESDAY APRIL 22, 2015

Special Session 8:00am - 9:00am

Angina in the Absence of Obstructive Coronary Artery Disease: Is There Truly a Sex Difference?

Jennifer A. Tremmel, MD, MS (Stanford University Medical Center, Department of Medicine (Cardiovascular)

More than 20% of patients presenting to the cardiac catheterization laboratory with angina have normal appearing coronary arteries. Women are significantly more likely than men to have angina, but they're also significantly less likely to have obstructive coronary artery disease (CAD). Symptoms in women have been attributed to various occult coronary abnormalities, such as endothelial or microvascular dysfunction, but little work has investigated these abnormalities in similarly presenting men. I will present data on sex differences in endothelial dysfunction, microvascular dysfunction, and myocardial bridging. I will also discuss how the measurements we use might vary between the sexes, and how this has implications for the interpretation of past studies and the design of future studies.

Funding: NIH K23 HL092233-05

Contact Information: Stanford University Medical Center, 300 Pasteur Drive, Room H2103, Stanford, CA 94305, Email: jtremmel@stanford.edu; Tel: (650) 723-0180

SESSION I & II – April 22, 2015 9:30am – 11:15am

SESSION I: Sex and Vaccines

Chairs: Mark Davis (Stanford University, Stanford CA)
Sabra Klein (Johns Hopkins University, Baltimore MD)

The biological differences associated with the sex of an individual affect immune responses to vaccination. Females consistently mount higher humoral and cellular immune responses to live-attenuated and killed vaccine antigens than their male counterparts. Females also experience more frequent and severe adverse reactions to vaccines than males. The speakers in this proposed symposium will demonstrate that sex is a fundamental source of variation in the outcome of vaccination that should be considered in the design of both clinical and preclinical trials. The speakers selected will demonstrate that sex differences are apparent in the immune responses to and safety of vaccines, in humans, animal models, and cell culture systems. Discussion of the role of immunogenetics and hormones will be provided.

Sex differences and the effects of sex hormones on vaccine efficacy

Sabra Klein, Ph.D. (W. Harry Feinstone Department of Molecular Microbiology & Immunology, Johns Hopkins University Bloomberg School of Public Health)

Biological (i.e., sex) differences as well as cultural (i.e., gender) norms influence the acceptance and efficacy of vaccines for males and females. These differences are often overlooked in the design and implementation of vaccination strategies. Using seasonal and pandemic influenza vaccines, I will document profound differences between the sexes in the acceptance, correlates of protection, and adverse reactions following vaccination in both young and older adults. Females develop higher antibody responses, experience more adverse reactions to influenza vaccines, and show greater vaccine efficacy than males. Our preclinical animal models further demonstrate that elevated immunity following vaccination in females leads to greater cross protection against novel influenza viruses in females compared with males. Sex steroid hormones, including progesterone and testosterone, affect immune responses to influenza virus infection and vaccination. One goal for vaccines designed to protect against influenza and even other infectious diseases should be to increase the correlates of protection in males and reduce adverse reactions in females in an effort to increase acceptance and vaccine-induced protection in both sexes.

Funding: R21AI112838, HHSN272201400007C, and SWHR Medtronic Award

Contact Information: 615 North Wolfe Street, Baltimore, MD 21205-2103, Email: sklein2@jhu.edu; Tel: (410) 955-8898

Primary cell cultures as models to identify sex-specific effects on virus replication and host innate immune responses

Andrew Pekosz, Ph.D. (W. Harry Feinstone Department of Molecular Microbiology & Immunology, Johns Hopkins University Bloomberg School of Public Health)

Influenza causes significant morbidity and mortality in the human population on an annual basis and this is particularly evident during influenza pandemics. Influenza vaccines are widely available and come either as an inactivated (the flu shot) or a live attenuated (LAIV or FluMist) form. The age and sex of an individual can

contribute to the severity of disease after infection and to the effective immune response generated after influenza vaccination. Both influenza and LAIV replicate initially in the upper respiratory tract, but only influenza A virus is able to spread to the lower respiratory tract. As a model system for studying influenza and LAIV replication, we utilize a primary, differentiated human nasal epithelial cell culture (hNEC) system that generates multiple epithelial cell types from epithelial progenitor cells isolated from human nasal tissue. The hNEC cultures from female donors supported greater levels of infectious virus production with both influenza A virus and LAIV when compared to cultures derived from male donor tissue. Female-derived hNEC cultures also responded to influenza A virus and LAIV infection with a stronger host innate immune response when compared to cultures derived from male donors. The stronger host responses included pathways associated with the recruitment of immune cells to sites of infection and pathways associated with pro-inflammatory responses. These data demonstrate that influenza- and LAIV-infected epithelial cells can contribute to the sex-specific immune responses generated to infection or vaccination and these responses may help explain the stronger immune responses to influenza infection and vaccination seen in females of reproductive age.

Funding: NIH R01AI097417; ORWH/NIH supplement for sex/gender differences; HHS N272201400007C

Contact Information: 615 North Wolfe Street, Baltimore, MD 21205-2103, Email: apekosz1@jhu.edu; Tel: (410) 502-9306

Sex considerations in vaccine safety and efficacy

Renata J. M. Engler, M.D., FAAAAI, FACAAI, FACP and Colonel (retired), Medical Corps, USA (Uniformed Services University of the Health Sciences (USUHS) and Walter Reed National Military Medical Center (WRNMMC), Bethesda, MD)

Immunization healthcare driven by one-size-fits-all public health disease preventing vaccine schedules has come under criticism for not addressing both efficacy and safety considerations in the context of biodiversity and personalized medicine questions. Within the larger discussions about how we currently vaccinate children and adults, sex-based differences in vaccine responses, ranging from immune reaction patterns, local reactions, pain, impacting systemic side effects, and rare but serious adverse events are of growing interest. Pre-licensure data generally fails to detail sex-aligned responses and are not powered to detect serious adverse events associations. In the 21st century, hypersensitivity myocarditis, predominantly in males receiving an adult primary dose of smallpox vaccine, has been newly characterized despite delivery of billions of doses in the past. Dose response sex differences in both side effect severity and in quantitative antibody responses can be seen with inactivated influenza vaccine. Yellow fever vaccine, a powerful live virus vaccine construct, activates inflammatory genes in women at a much higher rate than men. Improved understanding of sex differences in vaccine safety and side effect profiles as well as efficacy is needed for clinical guidelines supporting personalized vaccinology.

Funding: Review of published data funded by presenter; relevant studies funded through the Military Health System and associated grants as cited in publications.

Disclaimer: The views expressed are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Army, or Air Force, the Department of Defense, or the U.S. Government.

Contact Information: Walter Reed National Military Medical Center, 8901 Rockville Pike, Bldg 17A, 2nd Floor (ICHP), Bethesda, MD 20889; Tel: (301) 400-1111 and cell - (301) 526-6682 Renata.engler@gmail.com, Renata.j.engler.ctr@mail.mil, and Renata.engler@usuhs.edu

Testosterone influences humoral immune responses to the influenza vaccine in males

Furman D[1], Hejblum BP, Simon N, Jojic V, Dekker CL, Thiébaut R, Tibshirani RJ, Davis MM.

[1]Institute for Immunity, Transplantation and Infection, Stanford School of Medicine

Sex differences in vaccine responses have long been noted. We used a systems biology approach to identify differences between males and females' immune response in an unbiased fashion. We identify a set of inflammatory mediators increased in females as well as higher levels of influenza-specific antibodies at day 28 after administration of an inactivated influenza vaccine. None of these inflammatory mediators correlated with the increased vaccine response. However, a module of genes likely regulated by testosterone could explain these sex-related differences. Accordingly, men with the highest levels of testosterone exhibited the weakest responses whereas in those men with low testosterone levels, expression of such gene signatures was not significantly associated with vaccine responsiveness. Thus, sex hormones appear to be important modulators of an immune response to vaccination.

Funding: NIH U19s AI057240 and AI090019, and Howard Hughes Medical Institute

Contact Information: 279 Campus Drive, Stanford, CA 94305, Email: furmand@stanford.edu Tel: (650) 498-7759

SESSION II: Sex differences in brain networks

Chair: Ivanka Savic (Department of Womens and Childrens Health, Karolinska Institute, Stockholm, Sweden)

During the last decade there has been mounting indications that the perception of *self* and *own body* is mediated by a group of structures in the brain, located along the midline and constituting the so-called default mode network (DMN). This network emerges already in the fetus, is active during rest, and seems to be affected in neuropsychiatric conditions involving a distorted perception of self. Interestingly, several of these conditions, e.g. depression, schizophrenia, anorexia nervosa are associated with sex differences, and reportedly triggered by perturbations of sex hormones. This raises the question whether there are sex differences in the cerebral midline structures, what is governing these differences, how they may be involved in the perception of gender identity, and in the core symptoms of transsexuality, anorexia and autism. The symposium presents cutting edge data in the field including new information about genetic and neural control of sexually dimorphic behaviors mediated via hypothalamic connections. In addition, we will hear about chronic alcohol-induced aberrant plasticity of brain networks.

Modular genetic and neural control of sexually dimorphic behaviors

Nirao M. Shah, M.D., Ph.D. (University of California San Francisco, San Francisco, CA, USA)

We aim to understand the mechanisms via which genes and neural circuits control social behaviors. We are tackling these mechanisms as they relate to sexually dimorphic displays of sexual and aggressive behaviors in mice. These behaviors are quantifiable, can be elicited by natural stimuli without prior training, and are regulated by sex hormones. These features have allowed us to make significant inroads into the mechanisms that control these behaviors using tools from genetics, molecular biology, endocrinology, behavioral analysis, and electrophysiology. We have identified specific chemosensory pathways and hormonal signals that promote aggressive displays in males and in females. Our group is the first to molecularly identify long-sought hypothalamic neurons that control aggression. We recently demonstrated that these neurons control aggression in males and sexual behaviors in both sexes. Ongoing studies focus on understanding how these neurons control such different social behaviors.

We will discuss recent advances that show that innate social behaviors are controlled in a modular manner such that different components of a behavior are regulated by specific hormonal signaling events, separable genetic pathways, and distinct neuronal populations. We will also discuss the broader implications of our findings on the general mechanisms whereby neural circuits encode complex social behaviors.

Funding: This study was funded by grants from The Ellison Medical Foundation and the NIH (NINDS).

Contact Information: Nirao M. Shah, University of California San Francisco, 1550 Fourth Street, RH345, MC2722, San Francisco, CA 94158; 1-415-476-0873; nms@ucsf.edu

---

Sex-typical and sex-atypical white matter microstructure in gender dysphoric children and adolescents – a Diffusion Tensor Imaging study

Sarah M. Burke Ph.D.[1,2], Ilja M. J. Saris M.Sc.[3], Baudewijntje P. C. Kreukels Ph.D.[1], Janniek M. Wester M.Sc.[4], Martijn Steenwijk Ph.D.[5], Peggy T. Cohen-Kettenis Ph.D.[1], Dick J. Veltman Ph.D., M.D.[6], Daniel T. Klink Ph.D., M.D.[7], Julie Bakker Ph.D.[1,2,8]

[1]Center of Expertise on Gender Dysphoria, Neuroscience Campus Amsterdam, Department of Medical Psychology, VU University Medical Center, Amsterdam, the Netherlands; [2]Neuroendocrinology Group, Netherlands Institute for Neuroscience, Amsterdam, the Netherlands, [3]Academic Outpatient Clinic for Depression and Anxiety Disorders, GGZ InGeest, Amstelveenseweg 589, 1081 JC Amsterdam, the Netherlands, [4]The Amsterdam Brain & Cognition Center, University of Amsterdam, Nieuwe Achtergracht 129, 1018 WS Amsterdam The Netherlands, [5]Department of Radiology, VU university Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, the Netherlands, [6]Department of Psychiatry, VU university Medical Center, Amsterdam, the Netherlands, [7]Department of Pediatric Endocrinology, VU University Medical Center, Amsterdam, the Netherlands, [8]GIGA Neuroscience, University of Liege, Avenue de l'Hôpital 1, 4000 Liege, Belgium

White matter microstructure, assessed by means of diffusion tensor imaging, varies as a function of gender. Men show higher overall, and region-specific fractional anisotropy (FA) values compared to women, suggesting differences in axonal organization and myelination. Diffusion measures such as FA are highly sensitive to neurodevelopmental changes of white matter cellular architecture during adolescence. In the present study we investigated whether 35 prepubertal children (15 natal girls) and 41 adolescents (21 natal girls) diagnosed with Gender Dysphoria (GD) exhibit sex-atypical (in accordance with their experienced gender), rather than sex-typical (in accordance with their natal sex) white matter microstructural characteristics. All adolescents with GD were receiving puberty suppressing medication. We first identified sexually dimorphic white matter brain areas in age-matched prepubertal (20 girls, 18 boys) and adolescent (21 girls, 20 boys) control groups and then compared the mean FA values for each of these regions between groups. Sex differences in FA (with males having higher values than females) in the prepubertal controls were less pronounced than in the adolescent control groups, suggesting pubertal sex hormone effects on white matter development. Both, prepubertal and adolescent natal boys with GD did not differ significantly from either the control boys or the control girls in the majority of the sexually dimorphic brain areas, indicating they had intermediate values between the sexes. In contrast, the prepubertal natal girls with GD had significantly masculinized FA values (similar to control boys) in all sexually dimorphic white matter areas, whereas the adolescent natal girls with GD predominantly had sex-typical (similar to control girls) FA values. Our findings suggest different white matter developmental trajectories for natal males and natal females with GD, and confirm important influences of puberty (suppressing) hormones on white matter brain development.

Funding: This study was funded by a VICI grant (453-08-003) from the Dutch Science Foundation (Nederlandse Organisatie voor Wetenschappelijk Onderzoek) to JB.

Contact information: Sarah M. Burke, VU university medical center, Department of Medical Psychology / Center of Expertise on Gender Dysphoria, De Boelelaan 1117 (HB 3H07), 1081 HV Amsterdam, +31 20 444 29 90, s.burke@vumc.nl

---

Sex differences in functional brain connectivity and relationships to obsessive-compulsive disorder symptoms

Jamie D. Feusner, M.D., Teena Moody, Ph.D., Giulia Salgari, M.S., Tsz Man Lai, B.A., Courtney Sheen, M.A., & Joseph O'Neill, Ph.D.

Department of Psychiatry and Biobehavioral Sciences, University of California Los Angeles, Los Angeles, CA

Obsessive-compulsive disorder (OCD) shows sexually dimorphic characteristics in symptom dimensions, as well as younger age of onset and higher rates of comorbid tic disorders in males. Sexual dimorphism has also been noted in brain morphometry, yet this has been little studied in regards to brain activity. We aimed to determine if functional brain connectivity in OCD, and relationships between connectivity and symptoms, differ by sex. We hypothesized that, as in previous studies in controls, males would have greater modularity and higher clustering, and both would be associated with worse symptoms. We acquired resting-state fMRI data from adults with OCD (22F; 21M) and healthy controls (8F; 13M). BOLD connectivity matrices were extracted from all pairwise partial correlation coefficients between nodes (160, covering the whole brain), which were analyzed to yield global graph-theory metrics: small-worldness, clustering coefficient, modularity, global efficiency, and local efficiency. We tested the effect of sex, diagnostic group, and their interaction on the connectivity metrics. Males demonstrated significantly higher small-worldness and clustering coefficient than females, with a trend for higher global efficiency in females, yet did not differ by diagnostic group. However, male and female patients differed significantly in their relationship between local efficiency and OCD symptoms severity; in females there was a positive association and in males a negative association. In sum, sexual dimorphism is evident in global functional connectivity patterns, with males showing greater efficiency of local information transfer and females with greater efficiency of long-distance information transfer. Moreover, in females but not males, more efficient local connectivity is associated worse OCD symptoms. Results may have clinical implications in light of studies showing treatment-related alterations of brain connectivity networks, in that biomarkers may differ by sex.

Funding: This study was funded by an NIMH grant (R01MH085900) to JDF and JON.

Contact Information: Jamie D. Feusner, 300 UCLA Medical Plaza, Suite 2200, Los Angeles, CA 90095. +1-310-206-4951. jfeusner@mednet.ucla.edu

---

Sex-specific effects of chronic voluntary alcohol consumption on limbic neuronal function

Kristen E. Pleil, Ph.D.[1], Kathleen A. Grant, Ph.D.[2], & Thomas L. Kash, Ph.D.[1]

[1]Department of Pharmacology & Bowles Center for Alcohol Studies, University of North Carolina School of Medicine, Chapel Hill, NC, USA; [2]Division of Neuroscience, Oregon National Primate Research Center, Oregon Health and Science University, Beaverton, OR, USA

Females are at greater risk than males of developing a host of negative behavioral and health consequences of chronic voluntary alcohol consumption, including alcohol dependence and mood disorders. The bed nucleus of the stria terminalis (BNST) is a sexually dimorphic limbic brain region implicated in these neuropsychiatric diseases that may be a key site of chronic alcohol-induced aberrant plasticity. Here, we performed whole-cell patch-clamp electrophysiological recordings in BNST neurons from male and female rhesus monkeys that self-administered alcohol for 12 months (EtOH) and age-matched controls (CON). BNST neurons in females had lower hyperpolarization-activated cation currents (Ih) than those in males; and, chronic voluntary alcohol drinking

decreased this measure in both sexes suggesting that both sex and chronic alcohol exposure affect the function of HCN "pacemaker" channels. Further, chronic alcohol exposure led to increased membrane resistance and a depolarized resting membrane potential of BNST neurons in females but not males. In contrast, chronic EtOH caused an increase in the frequency of spontaneous inhibitory postsynaptic currents (sIPSCs) but did not alter excitatory synaptic transmission, leading to an overall shift toward inhibitory synaptic drive onto BNST neurons, in males but not females. Together, our results suggest that chronic voluntary alcohol drinking alters a number of neuronal functions, leading to increased excitability of BNST neurons in females that may be attenuated in males by a homeostatic increase in inhibitory synaptic tone. The lack of compensatory inhibition in the female BNST may confer increased susceptibility to the negative effects of chronic alcohol exposure, including anxiety and alcohol use disorders. Given the dense expression of a multitude of steroid hormone receptors in the BNST, ongoing analyses are examining the potential contributions of sex and stress hormone levels to these reported effects.

Funding: This study was funded by National Institute on Alcohol Abuse and Alcoholism (NIAAA) grants AA021043 to KEP; AA013541 and AA109431 to KAG; and AA019454, AA020911 and AA011605 to TLK.

Contact Information: Kristen E. Pleil, Department of Pharmacology & Bowles Center for Alcohol Studies, UNC School of Medicine, CB #7178, 104 Manning Dr., Room 5023, Chapel Hill, NC 27599; 1-919-843-7867; kpleil@email.unc.edu

SESSION III & IV – April 22, 2015 11:30am - 1:15pm

SESSION III: Sex effects in early adversity

Session Chairs: Julia Zehr (National Institute of Mental Health)
Tracy Bale (University of Pennsylvania)

Early adversity encompasses a wide range of potential experiences, including exposure during development to maltreatment, trauma, violence, poverty, nutritional stress, or institutional care. Although there are clear associations between early life adversity and later risk for psychopathology, the underlying biological mechanisms through which adversity impacts neurodevelopmental trajectories of risk and resilience are only beginning to be understood. Moreover, sex differences in biological responses to adversity during development are even less well characterized. This symposium will highlight how experience alters risk for mood and anxiety disorders through multiple biological pathways across the lifespan in males and females. Common themes across talks will include: the impact of adversity on neurodevelopmental trajectories; variation in experience and individual differences in risk and resilience; and relationships among behavioral and neurobiological measures.

Sex differences in the neurobiology of stress inoculation

David M. Lyons, Alex. G. Lee, Christine L. Buckmaster, Samuel D. Peaslee, Roxanne Capanzana, Paul S. Buckmaster, & Alan F. Schatzberg.

Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA

Stress inoculation entails intermittent exposure to mildly stressful situations that present opportunities to learn, practice, and improve coping in the context of exposure psychotherapies and resiliency training. Stress inoculation training sessions and exposure psychotherapies are generally administered by psychologists and psychiatrists, but these interventions build on conditions that appear to spontaneously occur without instruction or guidance. Previously, we showed that stress inoculation training sessions modeled by brief intermittent social separations enhance subsequent indications of resilience in juvenile monkeys. More recently, we found that stress inoculation is not restricted to critical or sensitive periods in development and protects adult monkeys against subsequent stress

induced anhedonia measured by sucrose preference tests. Despite similarities in behavior and neuroendocrine measures of stress inoculation, sex differences in the underlying neurobiology have emerged. Stress inoculation increases hippocampal neurogenesis in adult males but not female monkeys. Microarray analysis indicates numerous sex-by-stress inoculation interactions for the expression of genes in anterior cingulate cortex. These findings suggest that well-known sex differences in the prevalence of stress related mood and anxiety disorders may reflect sex differences in the neurobiology of coping with stressful life events.

Funding: Supported by MH47573, DA35503, and the Pritzker Consortium.

Contact Information: 1201 Welch Rd, MSLS Room P104, Stanford University School of Medicine, Stanford, CA 94305-5485; 1-650-725-5931; dmlyons@stanford.edu

---

Genotype and childhood trauma effects on development of sex differences in biomarkers of fear and anxiety

Tanja Jovanovic, Ph.D.[1], Dorthie Cross, Ph.D.[1], Rebecca Roffman[1], Bekh Bradley, Ph.D.[1,2;]

[1]Department of Psychiatry & Behavioral Sciences, Emory University, Atlanta, GA, USA; [2]Atlanta VA Medical Center, Decatur, GA, USA

Fear conditioning studies in adults have found that post-traumatic stress disorder (PTSD) is associated with heightened fear responses and impaired discrimination. The objective of the current study was to examine the association between PTSD symptoms and fear conditioned responses in children from a highly traumatized urban population. Children between 8 and 13 years old participated in a fear conditioning study in addition to providing information about their trauma history and PTSD symptoms. Results showed that females showed less discrimination between danger and safety signals during conditioning compared to age-matched males. In boys, intrusive symptoms were predictive of fear responses, even after controlling for trauma exposure. However, in girls, conditioned fear to the danger cue was predictive of self-blame and fear of repeated trauma. This study suggests there are early sex differences in the patterns of fear conditioning and that these sex differences may translate to differential risk for trauma-related psychopathology. In addition, we recently found that children of abused mothers show elevated dark-enhanced startle. Using a sample of children of traumatized mothers, we have extended this research by examining effects of the *PAC1R* polymorphism on dark-enhanced startle. Based on our prior studies with adults, we hypothesized that *PAC1R* risk genotype would interact with sex to increase dark-enhanced startle in girls but not boys. However, we found that the same gene polymorphism associated with PTSD risk in adult females is also associated with increased startle responses in both male and female children prior to puberty onset.

Funding: This study was funded by a NARSAD, a R01 from NIMH (TJ) and a R01 from NICHD (BB).

Contact Information: Tanja Jovanovic, Grady Trauma Project, Emory University, 49 Jesse Hill Jr Dr, NE, Atlanta, GA 30303. Tel: 404-778-1485. Email: tjovano@emory.edu

---

The role of adverse childhood experiences and lifelong social supports on cognitive aging and risk for depression at menopause

C. Neill Epperson, M.D.[1,2], Mary D.Sammel, Ph.D.[3], Tracy L. Bale, Ph.D.[4], Ellen W. Freeman, Ph.D.[2]

[1]Department of Psychiatry, [2]Obstetrics and Gynecology, [3]Biostatistics and Epidemiology, Perelman School of Medicine at the University of Pennsylvania, [4]School of Veterinary Medicine at the University of Pennsylvania, Philadelphia PA, USA,

After puberty and before a woman is postmenopausal, her risk for a major depression episode (MDE) is greater than for her male counterparts. Even among women with no previous history of MDE, their risk increases by 2-fold during the menopause transition. Likewise, the menopause exerts an age-independent detrimental effect on verbal memory and cognitive processing speed. Early life adversity (ELA) is a known risk factor for depression and other psychiatric disorders in both males and females across the lifespan, but non-human primate studies would suggest that ELA may play a special role for risk of depression and cognitive decline during menopause when estradiol levels are erratic and declining. For example, the enhancing effects of estradiol on tryptophan hydroxylase type 2, the rate-limiting enzyme for serotonin synthesis, gene expression is modified by exposure to early life and chronic stress. We examined the relationship between ELA, whether pre or post-pubertal in onset, and cognition and mood in a community cohort of women from Philadelphia County who participated in the 17 year-long Penn Ovarian Aging Study. Women were enrolled during the premenopause and studied yearly with a battery of evaluations ranging from hormonal assessments to evaluations of sexual functioning, perceived stress, economic status, mood and cognition, to name a few. With roughly 3000 observations in over 230 women who are now postmenopausal, we have had sufficient power to determine the relationship between pre-pubertal and post-pubertal adverse childhood events and our behavioral outcomes of interest. We will share these findings as well as the results from our initial investigation of factors that may contribute to resiliency in the face of ELA.

Funding: This study was funded in part by the Specialized Center of Research P50 grant mechanism from the National Institute of Mental Health and Office of Research on Women's Health (CNE, MDS, TLB, EWF; P50 MH099910)) and a R01 (CNE, MDS, EWF; R01 AG048839) from the National Institute on Aging.

Contact Information: C. Neill Epperson, M.D., Professor of Psychiatry and Obstetrics and Gynecology, Director, Penn Center for Women's Behavioral Wellness, Perelman School of Medicine at the University of Pennsylvania, 3535 Market Street, Rm 3001, Philadelphia, PA 19104, (tel) 215-573-8871, (fax) 215-573-8881, email: cepp@mail.med.upenn.edu, web: www.med.upenn.edu/womenswellness

---

Western Diets during Gestation and Lactation: A Novel Model for Postpartum Depression and Sex-Specific Developmental Programming?

Jessica L. Bolton, BS[1], Leigh Ann Simmons, PhD[2], Melanie Wiley, BS[1], Bailey Ryan[1], Samantha Truong[1], Cristina L. Sanchez-López, PhD[3], Cynthia Kuhn, PhD[3], and Staci D. Bilbo, PhD[1]

[1]Department of Psychology & Neuroscience, Duke University, Durham, NC, USA; [2]Duke University School of Nursing, Durham, NC, USA; [3]Department of Pharmacology & Cancer Biology, Duke University School of Medicine, Durham, NC, USA

Maternal obesity during gestation/lactation can "program" offspring long-term for increased obesity themselves, along with increased vulnerability to mood disorders. Emerging evidence suggests that this programming by perinatal diet is propagated via inflammatory mechanisms, specifically linked to two components that are enriched in a "Western diet": saturated fatty acids and branched-chain amino acids (BCAA). To test the interaction of these components, we placed female mice on one of 4 diets: 1) high-fat diet (HFD), 2) low-fat diet (LFD), 3) HFD supplemented with BCAA (HFD+BCAA), or 4) LFD supplemented with BCAA (LFD+BCAA) for 6 weeks prior to breeding. The combination of HFD and BCAA resulted in markedly greater weight gain in the mothers than either dietary component alone, but paradoxically, smaller birth weights for their offspring. PCR array analysis of 84 immune genes in mid-gestation placentas revealed that maternal diet altered the expression of multiple inflammatory genes in a sex-specific manner, as well as disrupted placental serotonin synthesis—a placental function critical for embryonic brain development. One week after birth, BCAA-supplemented mothers exhibited increased depressive-like behavior and lower-quality maternal behavior, and their offspring were smaller at weaning. RT-PCR analysis of post-partum mother and offspring brains revealed that HFD and BCAA altered expression of both serotonergic and immune genes, as in the placenta. Despite placement on a LFD at weaning,

HFD offspring exhibited increased anxiety-like behavior in adulthood, in conjunction with increased serotonin turnover in the frontal cortex. Moreover, the male, but not female, offspring of this group were hyperactive and had altered dopaminergic metabolism, suggesting that the long-term effects of maternal nutrition are also sex-specific. In sum, perinatal diet can modulate postpartum depression risk for mothers, as well as program brain development and behavior of offspring.

Funding: This study was funded by an internal Duke University Bass Connections interdisciplinary research initiative.

Contact information: Jessica L. Bolton, Psychology & Neuroscience Department, Duke University**,** 417 Chapel Drive**,** Box 91050**,** Durham, NC 27708**;** (919) 660-5700**;** jessica.bolton@duke.edu

SESSION IV: Sex effects in cardiovascular diseases

Chair: Jill N. Barnes (Mayo Clinic, Rochester MN)

Significant sex differences exist in the pathophysiology of cardiovascular disease. While there is evidence for a sexual dimorphic effect of testosterone on the development of cardiovascular disease, estrogen is increasingly understood to be important for both sexes. Moreover, the effect of testosterone may be mediated to a significant degree by the conversion of testosterone to estrogen. The objective of this symposium is to review current evidence from both animal and human models evaluating the mechanisms and interactions by which sex steroids and sex chromosomes may mediate sex differences in normal cardiovascular physiology and the development of cardiovascular disease. This symposium will include presentations by both expert investigators and trainees.

The heart has all the machinery to biosynthesize estrogen from testosterone by aromatase. It has been suggested that the level of estrogen is altered in heart failure, and this session will discuss the effect of exogenous estrogen therapy in a model of heart failure. In addition to disease states, the aspects of the cardiovascular system that are specific to males and females in healthy conditions will also be discussed. A molecular, cellular, and whole animal approach is necessary to understand this. At the molecular level, 2000 genes are differentially expressed in male and female hearts. At baseline, many more signaling pathways are activated in female cardiac myocytes compared to male myocytes. Furthermore, the responses of each pathway to pathological stimuli are distinct. The mechanisms underlying sex differences with a focus on the cardiac myocyte will be examined. Finally, the last presentation will focus on cardiopulmonary structure and function, and the effect of phytoestrogens. The changes induced by phytoestrogens may have a beneficial effect on the heart and lungs in a model of pulmonary hypertension. Taken together, this symposium will encompass the role of sex chromosomes and the effect of endogenous and exogenous sex hormones in the development of cardiovascular diseases and the mechanisms underlying sex differences in the within the cardiac myocyte.

Estrogen rescues advanced heart failure in mice

Andrea Lorga, Jingyuan Li, Salil Sharma, Soban Umar and **Mansoureh Eghbali**

Department of Anesthesiology, Division of Molecular Medicine, David Geffen School of Medicine at University of California, Los Angeles, CA, USA

The heart has all the machinery to biosynthesize estrogen from testosterone by aromatase. However, it is unknown if the levels of estrogen in plasma and heart are altered in heart failure. Although estrogen pretreatment attenuates the development of heart hypertrophy, it is not known whether estrogen could also rescue pre-existing heart failure (HF). Here we hypothesized that local heart estrogen concentration is reduced in HF and examined whether exogenous estrogen therapy after the onset of advanced HF induced by pressure overload can rescue

HF. Severe HF was induced by transaortic constriction. Mice with HF were treated with estrogen or with estrogen receptor alpha (ERα) or -beta (ERβ) agonists for ten days. We found that local heart estrogen concentrations, as well as cardiac aromatase transcript levels were significantly reduced in HF. Estrogen therapy of HF mice increased the levels of estrogen, and aromatase transcripts in the heart. More importantly, estrogen therapy rescued pre-existing HF by restoring cardiac function. Stimulation of cardiac angiogenesis by estrogen is one of the key mechanisms, as in the presence of anangiogenesis inhibitor, estrogen failed to rescue HF. Furthermore, estrogen therapy also reversed HF-induced fibrosis and inflammation. Estrogen rescue is mediated potentially through ERβ since the ERβ agonist DPN rescued HF by stimulating cardiac angiogenesis and reversing fibrosis. Estrogen rescues pre-existing HF by increasing cardiac estrogen, restoring testosterone and aromatase transcripts, stimulating cardiac angiogenesis, suppressing fibrosis, inflammation and activation of ERβ pathway.

Funding: This study was funded by National Institutes of Health grants R01HL089876 and R56HL119886.

Contact Information: Mansoureh Eghbali, Ph.D, Department of Anesthesiology, Division of Molecular Medicine, 650 Charles E Young Dr South BH-160 CHS Los Angeles, CA 90095; 310-206-0345; meghbali@ucla.edu

---

A Woman is Not a Small Man

Leslie Leinwand, Ph.D. (University of Colorado, Boulder)

Many clinical studies, drugs, devices, and even animal studies have not considered sex. We have spent many years understanding sex differences in the heart, with a focus on cardiac myocytes. We and others have shown that male and female hearts have very different gene expression profiles (about 2000 genes are differentially expressed). And male and female hearts respond to stimuli very differently. For example, female mice run voluntarily almost twice as much as males, but more importantly, when normalized to the amount run, their hearts undergo much more physiologic hypertrophy than male hearts. This difference also applies to pathological stimuli, where females fare better in most settings of heart disease ranging from genetic to acquired disease. To understand the mechanisms underlying these differences, we have taken a number of approaches ranging from sex-specific myocyte function and intracellular signaling using phospho-proteomic approaches. We have found that at baseline, female cardiac myocytes have much higher activation of receptor tyrosine kinases and intracellular signaling molecules. We believe that this higher basal activation state renders them more sensitive to chemotherapeutic cardiotoxicity. We have also shown that it not purely sex hormones that drive these differences.

Contact information: Dr. Leslie A. Leinwand, University of Colorado Boulder JSC Biotech Building 596 UCB Boulder, CO 80309 Tel: 303-492-7606 Email: leslie.leinwand@colorado.edu

---

Y chromosome: Function and involvement in coronary artery disease

Elsa Molina[1] Ph.D. Student, Guat S. Chew[1] Ph.D., Stephen A. Myers[1] Ph.D., James Eales[2] PhD, Maciej Tomaszewski[2] M.D., **Fadi J. Charchar[1] Ph.D.**

Biomedical Research Laboratory, Faculty of Science and Technology, Federation University Australia, Ballarat, VIC, Australia

Coronary artery disease (CAD) is one of the leading causes of morbidity and mortality in the world. Recently, we have shown that the human Y chromosome may harbor genes that contribute to CAD in men that could explain why CAD is more prevalent in men. Studies from our group and others have also revealed that the Y influence 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 3,000 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 CAD by 50%. To determine potential molecular pathways regulated by haplogroup I, mRNA was isolated from macrophages that were derived from monocytes, representing the differentiation of monocytes during the development of atherogenic plaques. In the macrophages of haplogroup I carriers, 30 gene pathways were differentially expressed compared to those derived from non-carriers; 19 were interconnected by genes related to inflammation and immunity. In particular, those associated with adhesion of leukocytes to other blood elements and their adhesion to and migration through the vascular endothelium. In this context, we are interested in determining the Y-specific molecular factors that contribute to CAD including long non-coding RNAs (lncRNAs), a new class of regulatory RNA molecules. Our study provides the first evidence of Y-specific genes and a new lncRNA role in modulating CAD.

Funding: National Health and Medical Research Council of Australia, British Heart Foundation, Wellcome Trust and the Collaborative Research Network (CRN) funded this study.

Contact Information: Fadi Charchar, Biomedical Research Laboratory, Faculty of Science and Technology, Federation University Australia, Mount Helen Campus, Ballarat, 3350 VIC, Australia, +61 353 276 098, f.charchar@federation.edu.au

---

Genistein, a Phytoestrogen, for the Treatment of Pulmonary Arterial Hypertension and Right Ventricular Failure

Soban Umar, M.D., Ph.D., Salil Sharma, Ph.D, Humann Matori, B.Sc, Alex Centala, B.Sc, Mansoureh Eghbali, Ph.D

Department of Anesthesiology, Division of Molecular Medicine, David Geffen School of Medicine at University of California, Los Angeles, CA, USA

Pulmonary hypertension (PH) is a progressive lung disease associated with increased pulmonary arterial pressure leading to right ventricular (RV) failure and death. We examined whether genistein, a phytoestrogen, rescues pre-existing established PH. PH was induced in male rats by a single injection of 60 mg/kg of monocrotaline and 21 days later when PH was well established, rats received daily injection of genistein (1 mg/kg per day) for 10 days or were left untreated to develop RV failure by day 30. We discovered that genistein rescues advanced PH by significantly improving lung and heart function. Genistein also restored PH-induced downregulation of estrogen receptor-β expression in the lung and right ventricle. To unravel the molecular mechanisms underlying genistein-induced rescue of PH, we performed microRNA-microarray analysis on the lung samples from control, PH and genestein-rescue group. We found that miR206 which was robustly upregulated to ~11 fold by PH was completely normalized to control levels by genistein treatment. Next, we examined whether knockdown of miR206 could reverse established PH. Rats received three intratracheal doses of either miR206 antagomir (10mg/kg body weight) or scrambled miR control at days 17, 21 and 26 after MCT. Knockdown of miR206 resulted in significant improvement in the cardiopulmonary function as RV pressure was significantly reduced to 38.6±3.61mmHg from 61.2±5.4mmHg in PH (P<0.05) and RV hypertrophy index was decreased to 0.35±0.04 from 0.59±0.037 in PH (P<0.05). Knock down of miR206 restorated PH-induced loss of capillaries in the lungs by targeting vascular endothelial growth factor-A (VEGF-A). In conclusion, genistein rescues established PH by normalizing the upregulation of miR206. Furthermore miR206 antagomir therapy improved cardiopulmonary function and structure and rescued pre-existing severe PH in MCT-rat model possibly by stimulating angiogenesis in the lung.

Funding: This study was funded by National Institutes of Health grants HL089876 and HL089876S1.

Contact Information: Soban Umar, M.D., Ph.D, Department of Anesthesiology, Division of Molecular Medicine, 650 Charles E Young Dr South BH-508 CHS Los Angeles, CA 90095; 310-825-1562; sumar@mednet.ucla.edu

SESSION V & VI – April 22, 2015 2:15pm - 4:00pm

SESSION V: Sleep and Sex

Chair: David A. Ehrmann (University of Chicago)

Both qualitative and quantitative disorders of sleep are more common among women compared to men. The overarching objective of this Session is to examine the impact of and mechanisms responsible for these differences. Data will be presented from studies conducted in human, rodent, and *Drosophila* models. Causal relationships between obstructive sleep apnea (OSA) and the development of both obesity and disordered glucose tolerance in adult men and women will be addressed by Knutson and Van Cauter from The University of Chicago. To gain insight into sex differences in the hormonal modulation of sleep, data from studies in male and female mice will be presented by Mong, et al. from the University of Maryland. Data from their studies support a sex difference in the sleep promoting effect of a dual orexin antagonist. Sleep disruption in peri- and postmenopausal women is highly prevalent. A multicenter collaboration undertaken by Baker and colleagues will show that there is a positive association between elevated levels of follicle stimulating hormone and objective measures of sleep disruption seen on polysomnographic recordings. Finally, Garbe and colleagues from the University of Pennsylvania will discuss a *Drosophila* model that has been developed to examine the neuronal and molecular mechanisms responsible for sex-specific differences in sleep behavior and post-mating sleep patterns.

The impact of sleep disturbances on metabolism in women and in men

Kristen L. Knutson and Eve Van Cauter

Sleep, Metabolism and Health Center, Department of Medicine, University of Chicago

There are well-documented sex differences in human sleep regulation. In particular, women sleep longer and spend more time in deep non-REM sleep than men and the intensity of non-REM sleep as assessed by EEG spectral power in the delta range (0.5- 4.0 Hz) is higher in women than in men. There is also a sex disparity in the prevalence of the two most common sleep disorders, insomnia (more frequent in women) and obstructive sleep apnea (OSA; more frequent in men). In the past 15 years, evidence has accumulated from both epidemiologic and laboratory studies to indicate that insufficient sleep duration and poor sleep quality, including OSA, have adverse metabolic consequences and may increase the risk of obesity and diabetes. Conversely, the epidemic of obesity has increased the prevalence of sleep disorders in both sexes, but particularly in women. OSA is no longer a rare condition in women. This presentation will focus on sex differences in the metabolic impact of insufficient sleep and OSA. We will review evidence from epidemiologic studies suggesting that the risk of incident diabetes associated with short sleep may be lower in women than in men. Recent data on the increase in prevalence of OSA in women and on sex differences in the clinical and polysomnographic presentation of this sleep disorder will be discussed. While the prevalence of OSA in adults who have normal glucose tolerance is clearly higher in men than in women, even after adjusting for the degree of obesity, this sex disparity is no longer present in individuals who have prediabetes or diabetes. Evidence suggestive of an increased risk of incident diabetes in overweight and obese women with OSA as compared to men of similar age and BMI will be presented.

Sex differences and the role of estrogen in sleep: what rodents can tell us about mechanism

Jessica A. Mong, Ph.D., Danielle M. Cusmano, Ph.D., and Shaun Viechweg, B.S.

Program in Neuroscience and Department of Pharmacology, University of Maryland, School of Medicine, 655 W. Baltimore St., Baltimore, MD, 21201 USA.

Sleep disruptions are more commonly reported in women and typically coincide with periods of hormonal fluctuation. The reason for this sex difference in sleep is unknown. In females, findings from clinical and basic research studies strongly implicate a role for sex steroids in sleep modulation. Here, we sought to address the mechanism by which sex steroids modulate sleep in females. In rodents, we found that sex differences in sleep resulted from activational effects of estradiol (E2) on sexually differentiated brain circuitry. We have identified the median preoptic nucleus (MnPN), a sleep-promoting region, as a key site of E2 action. E2 reduces the activation of sleep-associated MnPN neuron and antagonism of estrogen receptors within the MnPN attenuates the E2-mediated effects on sleep. To promote sleep, the MnPN sends inhibitory projections to arousal nuclei like the lateral hypothalamus. Orexinergic neurons in the lateral hypothalamus are regulated by MnPN activity and orexin is a key neuropeptide involved in arousal. Thus, we hypothesized that orexin may act as a mediator of E2's effects on sleep. To test this hypothesis, we administered a dual orexin receptor antagonist (DORA-12, gift from Merck) in the presence or absence of E2. Blocking orexin signaling did not affect estrogenic modulation of sleep. However, a comparison between males and females revealed a sex difference in the sleep-promoting effect of the dual orexin receptor antagonist. Females experienced prolonged wake suppression compared to males suggesting that sex differences in sleep circuitry and/or drug metabolism may contribute to increased sleep promotion in females. Together, these data begin to address major gaps in our knowledge regarding sex differences and hormonal modulation of sleep. Advancing our understanding of the mechanisms underlying hormonal modulation of sleep is imperative for better treatment of sleep disruption in women.

Funding: This work was funded by an R01 from NHLBI (JAM) and a F31 NRSA from NINDS (DMC).

Contact Information: Jessica A. Mong Department of Pharmacology, University of Maryland, School of Medicine, 655 W. Baltimore St., Baltimore, MD, 21201; 410-706-4295; jmong@som.umaryland.edu

Menstrual Cycle and Menopause: Hormonal Modulation of Sleep

Fiona C. Baker, Ph.D.[1,2], Massimiliano de Zambotti[1], Adrian Willougby[1], Stephanie Sassoon[1], Ian M Colrain IM[1,3]

[1]Center for Health Sciences, SRI International, Menlo Park, CA, USA, [2]Brain Function Research Group, School of Physiology, University of the Witwatersrand, Johannesburg, South Africa, [3]Melbourne School of Psychological Sciences, The University of Melbourne, Parkville, Victoria, Australia

Within women, fluctuating reproductive hormones during the menstrual cycle, pregnancy, and menopause transition, are associated with changes in sleep. The most dramatic change in sleep across the menstrual cycle in young women is increased spindle frequency EEG activity and increased spindle density during sleep in the luteal phase, when progesterone is high, compared with the follicular phase. The menstrual cycle also influences rapid eye movement (REM) sleep, which is marginally reduced in the luteal phase. Higher progesterone and estradiol levels correlate with less REM sleep, implying a role of these hormones in the REM sleep changes in the luteal phase. Sleep homeostasis, as reflected by sleep onset latency and slow wave activity during sleep, however, does not change across the menstrual cycle. In midlife women, sleep is impacted by the hormonal changes associated

with the approach to menopause. Sleep problems are one of the most prevalent and bothersome symptoms during perimenopause, being reported by about 40% of women, with frequent night-time awakenings being the most common and severe symptom. Our recent findings show a positive association between higher follicle stimulating hormone (FSH) levels and objective measures of sleep disturbance, including polysomnographic-defined wakefulness after sleep onset and number of awakenings and arousals, in perimenopausal women without sleep complaints independent of age, body mass index and hot flashes. Taken together, these findings suggest an interaction between the hypothalamic-pituitary ovarian axis and the sleep-wake regulatory system in women.

Funding: Grants HL103688 and HL088088 (FCB).

Contact Information: Fiona C. Baker, Center for Health Sciences, SRI International, 333 Ravenswood Avenue, Menlo Park, CA 94025, USA; 650-859-3062; Fiona.baker@sri.com

---

Sex differences in *Drosophila* sleep patterns

David S. Garbe, PhD[1], Abby Vigderman, BS[1], & Amita Sehgal, PhD[1,2]

[1] Neuroscience Department, [2] Howard Hughes Medical Institute, University of Pennsylvania, Philadelphia, PA USA

Sensory perception directly impacts health and behavior in several species, including humans and *Drosophila*. Yet how external environmental cues and internal physiological states are sensed, integrated, and conveyed to appropriate behavioral circuits has yet to be resolved. Recent studies have shown that *Drosophila* Sex Peptide (SP), which is transferred from a male to a female during copulation, triggers stereotypical female post-mating behavioral responses including increases in egg laying and decreases in sexual receptivity; changes which are critical for reproductive success. Interestingly, while baseline amounts of daytime sleep are different in male and female flies, copulation further exacerbates this imbalance. These data support the idea that altering female sleep:wake activity may also contribute to an adaptive reproductive response. However, it is unclear if the sensory and inter-neurons required for modifying sexual receptivity and egg laying are identical to the ones responsible for altering sleep. In one situation, the same set of neurons might receive SP and transmit this signal via a common pathway to divergent circuits in higher brain centers to elicit various behavioral responses.

Alternatively, distinct sets of neurons may receive male mating cues thereby eliciting changes in behavior via parallel, non-overlapping circuits. Lastly, how these post-mating behaviors are ultimately coordinated is not understood. We are interested in uncovering the neuronal and molecular mechanisms responsible for 1) sex-specific differences in baseline sleep behavior and 2) eliciting changes in female post-mating sleep patterns. Additionally, we hope to gain insight into how an organism interprets external cues and internal states to tune its behavior in response to an ever-changing environment.

Funding: This study was supported by the Howard Hughes Medical Institute and funding from the Ellison Medical Foundation awarded to AS.

Contact Information: David S. Garbe, Neuroscience Department, University of Pennsylvania, Smilow Center for Translational Research, Building 421, 3400 Civid Center Boulevard, 10-165, Philadelphia, PA 19104; 215-898-1177; garbe@mail.med.upenn.edu

SESSION VI: Sex determination, intersex and transsexualism

Chairs: Peter Koopman (University of Queensland, Australia)
Fadi J. Charchar (Federation University, Australia)

This symposium will explore the genetic and developmental basis of intersex (otherwise known as Disorders of Sex Development, Differences of Sex Development, or variant sex development), gender identity, and gender dysphoria. The vast majority of people (and other animals) are born as male or female, but for many the distinction is not so clear. In recent years there has been a revolution in our understanding of how intersex arises, how it impacts, and what can or should be done about it. In particular, accurate genetic diagnosis is the key to appropriate management, yet in most cases a molecular diagnosis is unavailable. This symposium will review our current understanding of the developmental biology and molecular genetics of sex development, look at how these mechanisms can sometimes falter and lead to one of the many kinds of intersex or DSD, and examine the interrelationship of sex and gender. It looks at how scientists, doctors and intersex/transsexual people can work together to raise awareness and improve outcomes. Through better awareness and understanding on a scientific level, we hope that society can more adequately and fairly cater for those for whom the common categories of sex and gender don't apply.

The Battle of the Sexes: Molecular pathways of male and female development

Anirudh Natajan, Steve Munger, Danielle Maatouk, Samantha Jameson and **Blanche Capel**

4034 GSRB II, Department of Cell Biology, Duke University Medical Center, Durham, NC 27710 USA

The gonad is an outstanding experimental model for the study of cell fate determination because it is a *bipotential primordium* where a primary fate decision has the dramatic outcome of controlling the sex of the organism. My lab has focused on how this fate decision is executed and how it is maintained both at the level of organogenesis of a testis or ovary, and at the more global level of the transcriptional network that regulates the process. Transcriptome analysis of the three principle precursor populations in the bipotential XX and XY gonad (supporting cell precursors, steroidogenic cell precursors, and germ cells) identified distinct signatures specific to each lineage, shared in XX and XY gonads. Overall, more genes associated with the female pathway are expressed in XX and XY supporting cell precursors at the bipotential stage, suggesting a female bias in lineage priming. In mammals, divergence along the male pathway is initiated by the expression of the Y-linked gene, *Sry*, in supporting cell precursors. We conducted a transcriptome analysis comparing XX and XY gonads at 4 hour intervals during the period of *Sry* expression (E.11.0-E12.0), and determined how sexually dimorphic expression patterns were established. The expression level of all genes is nearly identical in XX and XY gonads at E11.0, and gradually resolves in one direction or the other. Expression of *Sry* initiates a cascade of expression of male pathway genes in XY gonads. However, repression of the female pathway genes in XY gonads is equally important in establishing the male pathway. Deletion of *Fgf9*, a repressor of the female pathway, leads to male to female sex reversal and ovary development in XY offspring. To investigate the chromatin landscape in pre-Sertoli cells, we identified DNAse hypersensitivity sites (DHS) in chromatin of E13.5 and E15.5 Sertoli progenitors. DHS identified regions of open chromatin both in genes associated with the male pathway and actively transcribed in Sertoli progenitors, and those that were silent and associated with the female pathway. Chromatin immunoprecipitation (ChIP) analysis using an antibody against the active chromatin mark, H3K27ac distinguished those DHS peaks that are associated with active transcription from those that are likely associated with factors that repress expression, defining the genomic landscape that regulates male sex determination.

Funding: This study was funded by grants from NICHD and NIDDK to BC.

Contact Information: Blanche Capel, Box 3471, DUMC, Durham, NC 27710; phone: 919-684-6390; blanche.capel@duke.edu

A link between gender identity and genes involved in sex hormone signalling

Kate York PhD[1], Lauren Hare PhD[1], Kara Balakrishnan BSc[1], Jaco Erasmus MD[2], Fintan Harte MD[2], Eric Vilain MD PhD[3], and **Vincent Harley PhD[1]**

[1]Sex Determination & Gonadal Development, MIMR-PHI, Clayton, VIC, Australia; [2] Monash Gender Clinic, Monash Health, Melbourne, VIC, Australia; [3] Institute for Society and Genetics, University of California, CA, USA

Little is known about the aetiology of transsexualism and both environmental and biological factors may contribute. Anatomical and MRI studies reveal that sexually dimorphic brain structures in male-to-female (MtF) gender dysphoria individuals (transsexuals) are more similar to females than males. It is also likely that there is a heritable component, and genes involved in sex steroidogenesis are good candidates. Previously, *androgen receptor* (*AR*), *aromatase* (*CYP19*) and *oestrogen receptor* (*ER*) have been the focus of studies by us (Hare L, Bernard P, Sanchez FJ, Baird PN, Vilain E, Kennedy T,and V Harley Androgen receptor repeat length polymorphism associated with male-to-female transsexualism. *Biol Psychiatry*. 2009;65:93-6) and others, with variable results. Our hypothesis is that sex steroidogenesis is variant in people with gender dysphoria. A genetic association study was conducted with 380 MtF transsexuals and 344 Caucasian male control subjects. Eight genes in the sex steroidogenesis pathway were analysed, with functional (disease-associated) repeat length gene polymorphisms; *androgen receptor* (*AR*), *aromatase* (*CYP19*), *oestrogen receptorβ* (*ERβ*), *oestrogen receptor α* (*ERα*), *CYP11A1*, *progesterone receptor* (*PGR*), *CYP17* and *5-alpha reductase* (*5αR*). Gene-gene interactions were also analysed. The significant associations of specific gene variants between transsexual male control populations, and possible functional consequences will be discussed, which suggest reduced androgen signalling in the MtF brain.

Funding: NHMRC (Australia)

DSD advocacy: What can science bring to the debate?

Peter Koopman, PhD

Institute for Molecular Bioscience, The University of Queensland, Brisbane, QLD 4072, Australia; National Health and Medical Research Council Program in Disorders of Human Sex Development.

As scientists, we continue to advance our understanding of the molecular and cellular mechanisms that determine our sex – an important biological issue that in turn shapes our gender identity and societal roles. These insights also inform the causes of disorders of sex development (DSD), otherwise known as differences in sex development, or intersex. A challenge for the research scientist is to convey these research outcomes to the groups who need it most – in the case of sex research, those affected by DSD and clinicians who manage DSD. I set out to established a website, www.dsdgenetics.org, directed at parents and clinicians who need to participate in decisions that affect how a DSD child is raised, and what treatment, if any, the child will receive. It aims to provide up-to-date research findings relating to the genetics and biology of sex development, and the causes, frequencies and repercussions of DSD, filling a gap left by websites established by patient advocacy groups and clinical groups. But presenting science in a publicly digestible, socially aware and ethically responsible manner calls for a whole different skillset. Acquiring these skills has involved liaising with many different stakeholders including clinicians and advocacy groups; these efforts have presented unexpected challenges. In dealing with these issues, I have also adopted a broader role in facilitating dialogue between medical and patient groups, and helping to develop a plan for working together to improve DSD management in Australia. I will describe the progress made and the challenges that lie ahead. While some distance from the lab bench, these efforts may encourage other scientists to be more active in publicizing the role basic research can play in enriching lives and improving health.

Funding: This work was funded by the National Health and Medical Research Council of Australia.

Contact information: Peter Koopman, PhD, FAA, Professor of Developmental Biology, NHMRC Senior Principal Research Fellow, Institute for Molecular Bioscience, The University of Queensland, Brisbane, QLD 4072, AUSTRALIA. Tel +61 7 3346 2059. p.koopman@imb.uq.edu.au; www.dsdgenetics.org

---

Survival on mammalian sex chromosomes is associated with a unique combination of transcription factor binding and microRNA-mediated repression

Sahin Naqvi, A.B. [1, 2], Daniel W. Bellott Ph.D. [1], & David C. Page M.D. [1, 2]

[1]Whitehead Institute and Howard Hughes Medical Institute, Cambridge MA 02142; [2]Department of Biology, Massachusetts Institute of Technology, Cambridge MA 02139

Comparisons of eight mammalian Y chromosomes have identified a set of genes with ancestral homologs on the X chromosome that survived Y-linked degeneration (X-Y pairs). Genes in X-Y pairs are likely to be important for differences between the sexes due to their exposure to both male-specific and non-sex-specific selective pressures. Survival of such Y-linked genes is due to selection to maintain expression of broadly expressed gene pairs sensitive to under-expression, suggesting that X-Y pairs are likely subject to unique modes of gene regulation. However, the nature of such regulation is poorly understood due to a limited understanding of the regulatory role of non-coding sequence in sex chromosome evolution. Here, we show that X-Y pairs' dosage is controlled by two widely studied gene regulatory mechanisms. First, we provide evidence that X-Y pairs are sensitive to over-expression and thus extensively targeted by microRNAs (miRNAs) in order to tune expression levels. Other X-linked genes sensitive to over-expression throughout mammalian evolution, i.e. genes that evolved to undergo X-inactivation, also show increased miRNA-mediated regulation. Second, the promoters of X-Y pairs are highly bound by sequence-specific transcription factors (TFs). Other broadly expressed ancestral X genes are also highly TF-bound but not subject to extensive miRNA targeting, indicating that two largely orthogonal regulatory mechanisms have converged on X-Y pairs. Our results are consistent with a model in which the combination of TF- and miRNA-mediated regulation maintains the expression of X-Y pairs within narrow windows across tissues and cell-types.

Funding: Supported by National Institutes of Health and Howard Hughes Medical Institute

Contact information: Sahin Naqvi, Whitehead Institute, 9 Cambridge Center, Cambridge MA 021412, 617-258-8420, snaqv@mit.edu; David Page, Whitehead Institute, 9 Cambridge Center, Cambridge MA 021412, 617-258-5203, dcpage@wi.mit.edu

SPEAKER ABSTRACTS – THURSDAY APRIL 23, 2015

SESSION VII & VIII – April 23 2015, 8:30am - 10:15am

SESSION VII: Epigenetic dynamics of sexual dimorphisms

Chairs: Claudine Junien (National Institute For Agricultural Research (BDR INRA) France)
Carolyn Brown (University of British Columbia, Vancouver Canada)

The epigenetic origins of sexual dimorphism are due not only to the chromosomal sex (XX or XY) at conception prior to gonad differentiation, but also to a complex intermingling of both hormones and X and Y genes regulating autosomal genes later on. Sexual dimorphism may also date back to the sex of ancestors who experienced exposure to different environmental factors and transmitted their "imprint" in a sex-specific manner, either through the maternal or paternal lineage, or both, and in a manner that may also depend on the sex of the offspring. Observed sexual dimorphism is the result of a subtle entanglement of these different origins and pathways, further dependent on the timing of early or life-long environmental exposures, which leads to specific responses and outcomes for men and women. The four speakers in this session will highlight the complexity of the different mechanisms involved in sexual dimorphism, both in humans and animal models. Sex differences in gene expression in human and mouse are due in part to genes that escape from X-chromosome inactivation. Among these are genes that encode histone demethylases that regulate transcription throughout the genome in a dosage-sensitive sex-specific mode. Genome-wide analysis of mouse liver chromatin states reveal how growth hormone can impart dramatic sex-dependent liver gene expression in a manner that is largely independent of sex chromosomal status. Disruption of genetic and epigenetic sexual dimorphisms may represent a novel approach to identifying sex-specific mechanisms for coping with deleterious environments and diseases.

Sex-specific epigenetics in transgenerational responses to environmental impacts: facts, gaps and new approaches for prevention and treatment of diseases

Claudine Junien, Pharm.D. Ph.D., Qihan Wu, PhD & Linda Attig, PhD, Anne Gabory Ph.D, INRA, UMR1198 Biologie du Développement et Reproduction, F-78350 Jouy-en-Josas, France

Non-genetic and non-cultural heritability of susceptibility/resilience to common chronic diseases often shows differences between men and women. In line with the new paradigm of the Developmental Origins of Health and Disease (DOHaD), and throughout the life cycle of ancestors, parents and offspring, the environmental factors to which an individual is exposed throughout his life can leave an epigenetic footprint on the genome that dictate the coordinate expression of genes. Thus SD is due not only to the chromosomal sex (XX or XY) before gonad differentiation, but later on, to a complex intermingle of both hormones and X and Y genes regulating autosomal genes. Moreover the origins of SD also date back to the sex of the ancestors or parents who experienced exposure to different environmental factors and transmitted their "imprint" in a sex-specific manner, either through maternal or paternal lineage or both, depending also on the sex of the offspring. A crucial period is the early development, where the individual's epigenome is particularly sensitive to the effects of the environment, building up his health capital to respond more or less well to the vagaries of life and most often in a sex-specific manner. So all these sex differences lead to SD throughout life, resulting from a subtle entanglement of all these different roots and pathways and how the early exposures did interact with them and thus provided specific reactions and outcomes for men and women. Changes in SD for epigenetic marks and modifiers also revealed the existence of different adaptation mechanisms in males and females. Our findings provide proof-of-concept that the disruption, recovery or change in direction of basic sexual dimorphism may represent a novel approach to

identify sex-specific mechanisms for coping with deleterious environments and diseases. The discovery of such factors represents new strategies for use in the development of different preventative and treatment strategies more precisely adapted to males and females.

Funding: This study was funded by Operating Grants (OSEO, ANR, FCA) to CJ.

Contact Information: Claudine Junien BDR Biologie du Développement et Reproduction UMR INRA, 1198 Domaine de Vilvert, Bâtiment 230, deuxième étage, pièces 254-255. F-78352 Jouy en Josas; Tel 33680152385 email: claudine.junien@jouy.inra.fr

---

Mechanisms of growth hormone-regulated, sex-dependent liver gene expression revealed by genome-wide analysis of mouse liver chromatin states

David J. Waxman, PhD, Andy Rampersaud, BS, Gracia Bonilla, BS, Dana Lau Corona, MD and Jeannette Connerney, MD PhD.

Department of Biology and Program in Bioinformatics, Boston University, Boston, MA 02215.

Sex differences in mammalian liver gene expression are widespread, affecting ~1,000 protein-coding genes, non-coding RNA genes, and miRNAs. These sex-differences are regulated by the sex-dependent temporal patterns of pituitary growth hormone (GH) secretion, which induce sex-dependent activation of the transcription factor STAT5. Downstream gene targets of liver STAT5 include the male-enriched repressor BCL6 and the female-specific repressor CUX2, which cooperate with STAT5 to regulate liver sex differences. These and other liver transcription factors bind nearby many sex-specific genes and their associated regulatory sites in a sex-dependent manner. This sex-differential binding is strongly enriched at sites with differences in local chromatin accessibility between male and female liver, i.e., male-enriched and female-enriched DNase hypersensitive sites (DHS). Many male-enriched DHS coincide with sites of male-enriched STAT5 binding and are dynamically opened by GH at the time when STAT5 is activated by each successive male plasma GH pulse. In females, the more continuous plasma GH profile closes these DHS but opens other sites characterized as female-enriched DHS. Chromatin state maps developed for male and female mouse liver based on genome-wide DHS datasets and datasets for six histone-H3 chromatin marks revealed that sex-differential chromatin states frequently characterize distal sex-biased DHS regions, but not sex-biased gene bodies and their flanking sequences, indicating distal regulation. However, a gene subset comprised of the most highly sex-specific genes was additionally characterized by local sex-specific chromatin states. Further, H3-K27me3 was identified as a major sex-biased repressive mark at highly female-specific but not at highly male-specific genes. GH regulation of liver chromatin states, both local and distal, is thus a major determinant of sex-differences in liver chromatin accessibility, transcription factor binding, and sex-specific gene transcription.

Funding: Supported in part by NIH grant DK33765 (to DJW).

Contact Information: Dr. David J. Waxman**,** Dept. of Biology, Boston University**,** 5 Cummington Mall, Boston MA 02215**;** Email: djw@bu.edu

---

Sex differences in X-linked gene expression: Human genes that escape from X-chromosome inactivation

Carolyn J. Brown Ph.D., Allison M. Cotton Ph.D., & Bradley Balaton B.Sc.

Department of Medical Genetics, Molecular Epigenetics Group, University of British Columbia

X-chromosome inactivation serves to offset the dosage difference for X-linked genes between males and females.

Despite the extremely stable silencing caused by the recruitment of multiple heterochromatic modifications to the inactive X chromosome, over 15% of human X-linked genes continue to show expression from the otherwise inactive chromosome. We study these exceptions to silencing with the goal of identifying the underlying features enabling the spread of silencing and to simultaneously generate a catalog of genes escaping X inactivation. These genes may underlie some sexually dimorphic traits, and additionally could contribute to inter-female differences and identify X-linked genes more sensitive to reactivation in disease states.

We have identified genes escaping from inactivation using gene expression as well as DNA methylation as a surrogate marker for silenced genes. Combining results from multiple studies allows the prediction of an inactivation status for 639 genes (over 85% of the X-linked protein-coding genes excluding the testes-specific cancer antigen family). 60-70% of genes are subject to inactivation, 10-15% escape from inactivation and the proportion of genes that have differing inactivation statuses between individuals is more variable between studies at 13–30%. Variability is observed in the level of expression from the inactive X relative to the active X; between inactivation status for the same gene between different females; and between the inactivation status for a single gene between tissues. Both expression and DNA methylation show a continuum rather than gradated levels, and for escape genes the amount of expression from the inactive X (relative to the active X) inversely correlates with amount of DNA methylation at the CpG-rich promoter. Twin studies support a strong genetic component underlying the variability between X chromosomes. We find that variability between tissues is less pronounced for DNA methylation studies than expression studies. Comparisons between the studies identify genes that show a robust inactivation status, but also genes that may be prone to reactivation, and thus may be more readily disrupted in cancer.

Funding: This study was funded by Operating Grants (MOP-13690 and MOP-119586) to CJB.

Contact Information: Carolyn Brown, Department of Medical Genetics, Life Sciences Institute, 2350 Health Sciences Mall, University of British Columbia, Vancouver BC CANADA V6T 1Z3. (1-604-822-0908), email: Carolyn.Brown@UBC.CA

Dosage-sensitive transcriptional regulation by histone demethylases encoded by mouse genes that escape X inactivation

Xinxian Deng Ph.D[1], Joel B. Berletch Ph.D[1], Gengze Wei Ph.D[2], Wenxiu Ma Ph.D[3], Ana Dinca[1], Tianyi Zhou[1], Jay Shendure M.D., Ph.D[3], William S. Noble Ph.D[3], Jun Xu Ph.D[2], Christine M. Disteche Ph.D[1,4]

[1]Department of Pathology, University of Washington, Seattle, WA 98195, USA; [2]Department of Integrative Physiology and Neuroscience, Washington State University, Pullman, Washington 99164 USA; [3]Department of Genome Sciences, University of Washington, Seattle, WA 98195, USA; [4]Department of Medicine, University of Washington, Seattle, WA 98195, USA

X chromosome inactivation (XCI) silences most genes on one X chromosome in female mammals, but some genes escape XCI. We recently identified escape genes in vivo by analyzing the allele-specific expression of X-linked genes in mouse tissues with skewed XCI and distinguishable alleles based on single nucleotide polymorphisms. Both common and tissue-specific escape genes were identified. Such escape genes are candidates for tissue-specific sex differences and for a role in symptoms associated with sex chromosome aneuploidy. The persistence of a common set of escape genes between human and mouse indicates that these genes are probably dosage-sensitive for female/tissue-specific function. Indeed, we discovered dosage-sensitive regulatory roles for KDM5C and KDM6A, two important histone demethylases encoded by escape genes. In particular, we found female-biased regulation of two members of the X-linked *Rhox* (reproduction-related homeobox) cluster, *Rhox6* and *-9*, by KDM6A in mouse ES cells. Furthermore, modifying *Kdm5c* levels by over-expression or RNAi knockdown led to dysregulation of specific genes important for neuronal functions as well as phenotypic effects such as

alterations in cell growth and neurite length. These findings provide important insights on the regulation of dosage-sensitive X-linked genes and their roles in sex difference and sex-chromosome aneuploidy.

Funding: This study was funded by NIH grants and a Junior Faculty Pilot Award from the Department of Pathology at the University of Washington.

Contact Information: Xinxian Deng (dengx2@uw.edu) and Christine M. Disteche (cdistech@uw.edu); Department of Pathology, University of Washington, Seattle, WA 98195, USA; 1-206-685-2801

SESSION VIII: Sex differences in sensory perception and cognition

Chair: Kathryn Sandberg (Georgetown University)

This symposium focuses on sex differences in taste, olfaction and cognition in health and disease states. Dr. Claire Murphy (University of California, San Diego) will open the symposium by presenting her research on sex differences in taste in healthy young adult men and women. She will discuss her findings from functional magnetic resonance imaging of brain activation during the motivational states of hunger and satiety. Next, Dr. Dolores Malaspina (New York University) will talk about sex differences in odor detection sensitivity (acuity) and smell identification. Her laboratory investigates sex differences in the association of schizophrenia with olfactory processing dysfunction. Dr. Allan Reiss (Stanford University) will follow with a discussion of the effects of sex chromosomes on genetically- based neurodevelopmental disorders including fragile X syndrome, Turner syndrome and Klinefelter syndrome. His findings of sex differences in higher order cognition, including humor, creativity, social interaction and cooperative behavior will also be presented. Lastly, Dr. Dena Dubal (University of California, Los Angeles) will discuss the impact of one's sex on incidence and outcomes in Alzheimer's disease. She will also present her research investigating the effects of the sex chromosomes on the human amyloid precursor protein transgenic mouse model of the disease.

Sex differences in taste responses

Claire Murphy, Ph.D. [1,2,3], Erin Green, Ph.D. [3], Lori Haase, Ph.D. [3]

[1]Department of Psychology San Diego State University, [2]Department of Surgery University of California, San Diego, [3] San Diego State University/ University of California, San Diego Joint Doctoral Program, San Diego, CA, USA

Although males and females differ in eating behavior and prevalence rates for eating disorders and obesity, little is known about gender differences in cortical activation to pleasant and unpleasant pure tastes during the physiological states of hunger and satiety. To examine gender differences in fMRI activation during the motivational states of hunger and satiety, we investigated brain activation in healthy young adult females and males, using functional magnetic resonance imaging. During the scan participants rated the pleasantness of four pure tastants of differing qualities (i.e., salty, sour, bitter, sweet). There was greater change in fMRI activation from hunger to satiety in males than females, regardless of taste quality, within the middle frontal gyrus (BA 10), insula, and cerebellum. Males also had greater change in activation from hunger to satiety, relative to females, in limbic regions including dorsal striatum, amygdala, parahippocampal gyrus, and posterior and anterior cingulate; however, in these areas activation was stimulus dependent, despite equivalent ratings in perceived pleasantness and intensity. Interestingly, males and females showed significant change from hunger to satiety in response to citric acid, a sour-tasting stimulus, suggesting that in addition to gender and physiological condition, stimulus quality is an important factor in taste fMRI activation. These results will be discussed in the context of the literature on gender differences in taste sensitivity and preference. Gender differences in taste may have implications for the pathophysiology of eating disorders and obesity.

Funding: Supported by NIH grant number R01AG004085-26 to CM. We gratefully acknowledge the contributions of Barbara Cerf-Ducastel, Aaron Jacobson, the members of the SDSU Lifespan Human Senses Laboratory, the UCSD Center for fMRI, and the participants.

Contact information: Dr. Claire Murphy, SDSU/UCSD Joint Doctoral Program, 6363 Alvarado Ct., Suite 101, San Diego, CA 92120-4913; 619 594 4559; cmurphy@mail.sdsu.edu

---

Olfaction and cognition in schizophrenia cases and healthy controls: sex matters

Dolores Malaspina M.D., M.S., M.S.P.H.

Department of Psychiatry and Child Psychiatry, New York University, New York, N.Y., US

Olfactory processing shows clear and consistent sex differences. Of interest, olfactory testing is commonly employed for research in schizophrenia and other neuropsychiatry conditions. The sexes are rarely stratified however, even in schizophrenia studies where the disease entails robust sex differences in onset, symptoms and course. This study examined odor detection sensitivity (acuity) and smell identification with respect to symptoms and other cognitive capacities in cases with schizophrenia and healthy controls. While detection is a primary sensory capacity, odor acuity can be modulated by the activity at higher neural centers. First of all, in the healthy males, better odor detection sensitivity significantly predicted smell identification performance. Conversely, in the male schizophrenia cases, those with greater detection sensitivity did more poorly on smell identification. Lack on higher-level (top down) modulation could produce flooding by olfactory stimuli. The capacities of odor detection and smell identification were nonetheless associated in both male groups. Secondly, odor detection and smell identification were unassociated in the healthy females and in the females with schizophrenia. Finally, olfactory processing was strongly linked to the core negative symptoms in the disease but the relationship to either acuity or smell identification differed by sex. Smell identification was related to the negative symptoms in males with schizophrenia, whereas increased odor detection (hypensitivity) predicted these features in females. In males, detecting and processing odors appears to be directly linked, whereas the modulation of odor sensitivity in female patients may be under different constraints, presumably a more active orbitofrontal network subserves the evaluation of odor cues in females, which is damaged in the disease.

Funding: This study was funded by a R01 grant and a K24 grant from NIMH to dm.

Contact Information: Dolores Malaspina; Department of Psychiatry and Child Psychiatry, 1 Park Avenue, 8th floor, Rm 222, New York, N.Y. 10016; 718-877-5708; Dolores.malaspina@nyumc.org

---

Sex chromosomes, brain development and cognition

Allan L. Reiss, M.D. (Center for Interdisciplinary Brain Sciences, Department of Psychiatry & Behavioral Sciences, Stanford University, Stanford, CA, USA)

Despite decades of research investigating sex differences in brain development and cognition, there is much to be learned about this important topic. Lack of replication across previous studies likely reflects differences in methodological approaches as well as complex gene x environment influences differentially affecting outcome. Further, when considering higher-level cognitive processes, even less is known about the neuroscience of sex differences. Accordingly, this talk will consist of two parts. In the first, I will provide an overview of our center's research focused on genetically based neurodevelopmental disorders where sex effects on brain development and cognition are clearly evident (e.g., fragile X syndrome, Turner syndrome and Klinefelter syndrome). In the second part of my talk, I will describe our research investigating sex differences in higher order cognition, including humor, creativity and social interaction including preliminary data from our ongoing functional (near-infrared spectroscopy) imaging study designed to investigate, through hyperscanning, how sex pairings affect cooperative behavior and correlated brain activity.

Funding: This study was funded by R21 and R01 grants from the NIMH, a R01 grant from the NICHD, a grant from the Hasso Plattner Foundation and a gift from the Albert Yu and Mary Bechmann Foundation.

Contact Information: Allan L. Reiss, M.D., Department of Psychiatry & Behavioral Sciences, Stanford University School of Medicine, 401 Quarry Road, Stanford, CA 94305; areiss1@stanford.edu

---

The X Chromosome Confers Advantage in Alzheimer's Disease

[1]Lauren Broestl, [1]Kurtresha Worden, [1]Dan Wang, [2]Nino Devidze, [1]Bruce L. Miller, [3]Arthur P. Arnold, [1,2]Lennart Mucke, [1]**Dena B. Dubal**

[1]Department of Neurology, University of California, San Francisco, CA 94158; [2]Gladstone Institute of Neurological Disease, San Francisco, CA 94158; [3]Department of Physiological Science, University of California, Los Angeles, CA 90095

Males die before females. This male disadvantage extends worldwide, spans the animal kingdom and is relevant to the diseased brain. Men succumb to death faster with neurodegenerative conditions, including Alzheimer's disease (AD), the most common dementia. Fundamental mechanisms underlying this male disadvantage are unknown. Here we show that sex chromosomes impact AD-related vulnerability and mortality – through biology that depends upon the X-chromosome. In parallel with human AD, male mice that model AD via expression of the human amyloid precursor protein (hAPP) died sooner than females. They were also more vulnerable to cognitive deficits. Genetically modified XY-hAPP mice with a testicular or ovarian phenotype suffered worse mortality and deficits than XX-hAPP mice with either gonadal phenotype. Since sex chromosomes, and not gonadal phenotype, impacted mortality and deficits, we next examined whether the Y chromosome confers disadvantage or the X chromosome confers advantage. In the presence or absence of the Y, hAPP mice with one X died faster – while those with two lived longer. Thus, harboring two X chromosomes conferred resilience; adding a Y did not alter this effect. Our results define a critical role for the X chromosome in AD – and the lack of one as a key contributing mechanism underlying male vulnerability. Understanding how the X confers resilience in AD could lead to novel therapeutic targets for men and women.

Funding: Supported by NIH grants AG034531 (D.B.D), NS043196 (A.P.A.), DK0835361 (A.P.A), Coulter-Weeks (DBD) and Bakar Family Foundations (DBD), the American Federation for Aging Award (DBD), the Glenn Foundation (DBD).

Contact Information: Dena Dubal, Dept of Neurology, UCSF, 675 Nelson Rising Lane, Rm 212B, San Francisco, CA 94158; 415-502-7237; Dena.Dubal@ucsf.edu

SESSION IX & X – April 23, 10:30am - 12:15pm

SESSION IX: Sex differences in neurocognitive aging

Chair: Agnès Lacreuse (University of Massachusetts, Amherst MA)

Sex differences in human brain and cognition are well documented, but it remains unclear whether these sex differences persist in old age and whether men and women follow different trajectories of age-related cognitive decline. The paucity of longitudinal studies and sex-based analyses in animal models contribute to our poor understanding of this issue. The four presentations of this symposium will summarize the current state of knowledge on sex differences in neurocognitive aging, based on clinical and animal findings. Dr. Naftali Raz will begin the discussion by presenting mixed evidence for sex differences in neurocognitive aging in humans and highlighting the challenges associated with this research. Dr. Agnès Lacreuse will describe cross-sectional

work in nonhuman primates suggesting that males may be more vulnerable to age-related cognitive decline than females and emphasize the need for longitudinal studies addressing cognitive aging in nonhuman primates of both sexes. Dr. Liisa Galea will discuss the role of sex hormones and reproductive experience in modulating neuroplasticity and hippocampal-dependent cognition in older rodent models. Dr. Joshua Talboom will conclude the symposium by presenting recent data on the differential effects of cognitive training in aged male and female rats. The symposium will highlight the importance of incorporating sex-based analyses in research investigating cognitive aging in humans or animal models.

Aging of Human Brain and Cognition: Measurable Sex Differences?

Naftali Raz

Institute of Gerontology, Wayne State University, Detroit, MI, USA and Department of Psychology, Wayne State University, Detroit, MI, USA

Sexual dimorphism in body size is the rule for mammalian species, and multiple sex differences in cognition and behavior have been attributed to the influence of sex hormones. *In vivo* neuroimaging studies reveal multiple sex differences in regional brain volumes, with men usually showing greater volumes of many brain structures. However, these differences are not consistently replicated across studies and usually disappear once the dimorphism in head or body size is taken into account. The preponderance of structural MRI studies points to the greater age-related differences in total and regional brain volumes in men compared to women. Conversely, many studies show no difference in age effects or steeper slopes for women. Moreover, the specific foci of sex-differential aging vary widely across studies. Longitudinal studies of volume, white-matter hyperintensities and white-matter microstructure fail to reveal consistent sex differences in trajectories of brain aging. The apparent lack of consistent measurable sex differences in brain structure and in structural brain aging will be discussed in the context of attempts to understand neural foundations of sex differences in behavior and cognition.

Funding: This study was funded by a R37AG011230-20 from NIA.

Contact Information: Naftali Raz, Institute of Gerontology, Wayne State University, Detroit, MI, USA 48202, 313-577-2277; nraz@wayne.edu

---

Sex differences in cognitive aging: a pressing need for nonhuman primate data

Agnès Lacreuse, Ph.D.

Department of Psychological and Brain Sciences, University of Massachusetts, Amherst, MA, USA

Whether normal cognitive aging and dementia differ between men and women remains unclear. Because human cognition is strongly influenced by socio-cultural and environmental factors, studies in animal models, for which such confounds are minimized, can provide considerable insight into the biological bases of sex differences in cognitive aging. However, very few animal studies have compared age-related cognitive decline between males and females. In particular, studies in nonhuman primates have been critically lacking. We have found in cross-sectional studies in rhesus monkeys (*Macaca mulatta*) that relative to females, males are more vulnerable to the detrimental effects of aging for selective cognitive and motor abilities. Recently, we have established paradigms in aged common marmosets (*Callithrix jacchus*) that also demonstrate sex differences in reversal learning performance and emotional reactivity. Together, these findings put forth a compelling argument that longitudinal studies addressing cognitive aging in nonhuman primates of both sexes are critically needed. Using our established marmoset model, we are pursuing such studies to (1) determine whether males and females follow different trajectories of age-related cognitive decline and (2) identify their biological correlates and (3) develop sex-specific interventions to alleviate cognitive aging.

Funding: Studies described in this talk were supported by NIH grants AG00001, MH61817, RR00165, MH091492 and AG046266.

Contact Information: Agnès Lacreuse,Ph.D., Department of Psychological and Brain Sciences, 135 Hicks Way, University of Massachusetts, Amherst, MA 01003, USA; Phone: 413-545-2183; email: alacreuse@psych.umass.edu

---

Sex and age differences in the regulation of neuroplasticity and cognition by sex hormones

Liisa A.M. Galea

Department of Psychology, University of British Columbia, Vancouver, BC, CANADA

Women are more likely to be diagnosed with Alzheimer's disease but not other dementias. Estrogens and androgens may be neuroprotective and hormone therapies (HTs) can offset cognitive decline in postmenopausal women and aging men. HTs in women differ by in their composition of estrogens. Estradiol is the most potent estrogen and is the predominant estrogen in younger women, while estrone is a weaker estrogen and is the predominant estrogen in postmenopausal women. Meta-analyses indicate that estradiol-based HTs are beneficial, while estrone-based HTs can be detrimental to cognition and dementia risk. My talk will focus on how these different estrogens affect hippocampus-dependent neuroplasticity and cognition and how reproductive experience can moderate these effects during aging. Estradiol facilitates hippocampus-dependent learning and memory, while estrone has more limited and often impairing effects on hippocampus-dependent learning and memory. Chronic estradiol, but not estrone, increases neurogenesis and expression of the immediate early gene (IEG) product, zif268, in new neurons after spatial memory retrieval in adult female rats. Further reproductive experience modulates the ability of the hippocampus to respond to estrogens in middle-age females, such that an estrone-based HT improved learning in nulliparous but impaired learning in primiparous middle-aged rats. Further primiparous, but not nulliparous, rats showed a reduction in neurogenesis and zif268 expression with estrone-based HT. These findings suggest that previous parity permanently alters the hippocampus to respond to estrogens in older female rodents. Finally I will present data to indicate a shift in the effects of androgens to promote neurogenesis in male and females across the lifespan. Together these studies show that estrogens and androgens differentially affect neuroplasticity and cognition in both adult and older females. These findings have implications for the treatment of age-related neurodegenerative disorders in women and men.

Funding: This study was funded by a CIHR (LAMG).

Contact Information: Liisa Galea, Department of Psychology, University of British Columbia, Vancouver, BC CANADA, V6T1Z4; 604-822-6536; lgalea@psych.ubc.ca

---

Sex differences in the influence of cognitive training in aged rodents

Joshua S. Talboom[1,3], Stephen G. West[2,3], Elizabeth B. Engler-Chiurazzi[2,3], Craig K. Enders[2], Ian Crain [2], Heather A. Bimonte-Nelson[2,3]

[1]Banner Sun Health Research Institute, AZ, USA, [2]Department of Psychology, Arizona State University, Tempe, AZ, USA, [3]Arizona Alzheimer's Consortium, Phoenix, AZ, USA

Aging is associated with progressive changes in learning and memory. A potential approach to attenuate age-related cognitive decline is cognitive training. In our study, adult male and female rats were given either repeated exposure to a T-maze, or no exposure to any maze, and then tested on a final battery of cognitive tasks. Two groups of each sex were tested from 6 to 18 months old on the same T-maze; Group one received a version testing spatial reference memory, and Group two received only the procedural testing components with minimal

cognitive demand. Groups three and four of each sex had no maze exposure until the final maze battery, and were comprised of aged or young rats, respectively. The final maze battery included the practiced T-maze plus two novel tasks, one with a similar, and one with a different, memory type to the practice task. Group five of each sex was not maze tested, serving as an aged control for the effects of maze testing on neurotrophin protein levels in cognitive brain regions. Our results showed that adult intermittent cognitive training enhanced performance on the practice task when aged in both sexes, cognitive training benefits transferred to novel tasks only in females, and that cognitive demand was necessary for these effects, since rats receiving only the procedural testing components showed no improvement on the final maze battery. Further, for both sexes, rats that showed faster learning when young demonstrated better memory when aged. Age-related increases in neurotrophin concentrations in several brain regions were revealed, which were related to performance on the training task only in females. Our study supports the tenet that cognitive training can help one remember later in life, with broader enhancements and associations with neurotrophins in females.

Funding: This study was funded by a R21 from the NIA (HBN) and a R01 from the NIA (HBN).

Contact Information: Joshua S. Talboom, Ph.D., Banner Sun Health Research Institute, 10515 W Santa Fe Dr. Sun City, AZ 85351, Office: 623-832-7653, Email: Joshua.Talboom@bannerhealth.com

SESSION X: Sex and stress

Chairs: Gretchen Neigh (Emory University**)**
Nafissa Ismail (University of Ottawa)

Puberty is a critical period of development during which sexual maturity is attained. The pubertal period is also a time of change in an animal's response to stress. Exposure to stress during this period causes enduring changes in the brain and behavior and can impact mental health later in life. Many stress-related psychopathologies, like anxiety and depression, onset during puberty and are more prevalent in women versus men has been recognized for years, but only recently have substantial efforts been made to understand the biological mechanisms contributing to this phenomenon. Recent findings show important age and sex differences in pubertal stress response that may shed light on understanding the link between pubertal stress exposure and mental illness.

Sex differences in susceptibility and resiliency: it all depends on where you look

Gretchen N. Neigh, Ph.D.[1,2], Constance S. Harrell[1,2], Sean D. Kelly[1,2], Mandakh Bekhbat[1,2], and Sydney Rowson[1,2]

[1]Department of Physiology, Emory University, Atlanta, GA, USA, [2]Department of Psychiatry & Behavioral Sciences, Emory University, Atlanta, GA, USA

Although stress is part of life, the incidence of "toxic stress" is increasing among our youth. This increased exposure to toxic levels of stress has substantial consequences and can precipitate and augment chronic mental and somatic health conditions throughout adulthood. While both men and women suffer the consequences of early life stress, the precise manifestation of chronic developmental stress varies in a sex-dependent manner. Chronic stress during adolescence is particularly harmful because of interactions of stressor exposure with the maturation of the hypothalamic-pituitary-adrenal (HPA) axis and the reproductive axis. Alterations in these endocrine axes exert pervasive effects because many of the receptors for the hormones of these axes are transcription factors. Exposure to chronic mixed modality stress during adolescence, a paradigm that includes social as well as physical stress, causes a sustained increase in anxiety-like behaviors in female, but not male, rats. These behavioral changes are accompanied by alterations in the modulation of the glucocorticoid receptor, a transcription factor. Although males appear to be behaviorally unaffected by adolescent exposure to chronic mixed modality stress, they manifest both metabolic and immune changes. Males are not, however,

behaviorally resistant to adolescent environmental perturbations. Exposure of adolescent rats to a high fructose diet induces profound anxiety-like behaviors, which are accompanied by dramatic changes in gene expression in the hypothalamus. Sex differences in susceptibility to types of stressors, as well as, sex differences in the manifestation of stress-induced pathology, are reflections of important underlying variances in mechanisms between males and females. These contrasts may help to inform the collective understanding of individual differences in stress-induced pathology.

Funding: This study was funded by a R21 from NIMH (GNN) and a R01 from NINR (GNN).

Contact Information: Gretchen N. Neigh, Department of Physiology, Emory University, 615 Michael Street, Suite 600, Atlanta, GA 30322; 404-727-9022; gmccand@emory.edu

---

Sex differences in effects of stress on the aversive properties of kappa opioid receptor

Brian C. Trainor[1,2], Abigail Laman-Maharg[1,2], Marissa Z. McMackin[3], Katharine L. Campi[1], Cristian Jaramillo[1], Ian E. Doig[1], Evelyn O. Sanchez[1]

Department of Psychology, University of California, Davis, CA[1]; Center for Neuroscience and Neuroscience Graduate Group, University of California, Davis, CA[2]; Molecular and Cellular Integrative Physiology Graduate Group, University of California, Davis, CA[3]

The aversive properties of kappa opioid receptors (KOR) are well established, and there is strong evidence that psychosocial stress induces activation of KOR. Activation of KOR also mediates behavioral responses to stress, which suggests that KOR antagonists could have important therapeutic properties. In addition to short term effects on brain and behavior, psychosocial stress also induces long term changes in brain function that can take several days to manifest. Evidence from several sources suggests these long term changes have important implications for KOR function. We examined the effects of social defeat stress in California mice, a monogamous species in which social defeat can be applied in both males and females. Our studies suggest that two weeks after social defeat stress, the behavioral effects of KOR activation are profoundly altered in females but not males. A dose of the KOR agonist U50,488 that reduces social interaction behavior in females naïve to defeat reversed stress-induced decreases in social interaction behavior. In contrast, the inhibitory effects of U50,488 on social interaction behavior were stronger in stressed males compared to control males. One possible mechanism contributing to this effect is KOR modulation of serotonergic signaling. Previous studies in males showed that KOR activation inhibited serotonergic activity. Serotonin neurons in the dorsal raphe stained for phosphorylated extracellular signal regulated kinase (pERK) as an indirect marker of cellular activity. Cell count data suggest that females exposed to defeat have hyperactive serotonin neurons and that acute U50,488 treatment blunts this effect. These data suggest that KOR agonists could be beneficial for counteracting long term effects of psychosocial stressors.

Funding: Supported by R01 MH103322 from NIMH (BCT).

Contact information: Brian C. Trainor, Department of Psychology. 1 Shields Ave., Davis, CA 95616, USA. 530-752-1672. bctrainor@ucdavis.edu

The Sexed and Stressed Pubertal Brain

Nafissa Ismail Ph.D.

School of Psychology, University of Ottawa, Ottawa, Canada

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 response to an immune challenge. 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 vasopressin expression. These findings propose potential mechanisms through which exposure to an immune challenge can cause enduring alterations in reproductive and non-reproductive behaviors when administered during puberty but not in adulthood.

Funding: This work was funded by the University of Ottawa and a NSERC discovery grant to NI.

Contact Information: Nafissa Ismail, School of Psychology, University of Ottawa, 136 Jean-Jacques Lussier, Vanier 2076B, Ottawa, ON, Canada

Dynamic sex differences during PFC maturation and their disruption by stress

Kathleen E. Morrison Ph.D.

Department of Animal Biology, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA, USA

Environmental adversity, such as neglect or abuse, substantially increases neuropsychiatric disease risk, especially when it occurs during the years preceding puberty. Peripubertal stress experience may uniquely affect neurodevelopment in males and females, evidenced by significant sex biases in neuropsychiatric disease onset, prevalence, and symptom presentation. Maturation of the prefrontal cortex (PFC) is of particular importance, as it undergoes significant development during adolescence and plays a well-defined role in neuropsychiatric disease. We hypothesized that peripubertal PFC development in the mouse is sex-specific, and that exposure to environmental adversity shifts the trajectory of PFC maturation. We examined male and female mice at time points across the peripubertal window (postnatal day (PN) 21, PN28, and PN35), exposing a subset of animals to chronic variable stress. We found sex differences in gene expression in the peripubertal PFC through microarray analysis, identifying dynamic patterns consistent with the multi-factorial regulation of PFC maturation, potentially regulated by gonadal hormones, sex chromosome complement, and epigenetic regulators. Importantly, sex differences in cortical development are reflected in behavioral outcomes of PFC function, such as the acoustic startle response. Sex differences in neurotransmitter levels in the PFC are consistent with behavioral sex differences, as HPLC analysis reveals significantly lower levels of GABA and norepinephrine in females. Notably, all observed sex differences in peripubertal PFC maturation, with the exception of chromosomally-mediated gene expression, were disrupted by chronic variable stress. These data demonstrate that peripuberty is an important window for sexual differentiation of the cortex and provide an opportunity to examine mechanisms by which peripubertal adversity results in sex biased negative outcomes.

Funding: These studies were funded by NIH Grants MH073030, MH091258, MH087597, MH099910, and MH104184 to Tracy Bale.

Contact Information: Kathleen E. Morrison, Department of Animal Biology, School of Veterinary Medicine, 380 S University Ave, 437 Hill Pavilion, Philadelphia, PA, 19104; 215-898-1368; kmorr@vet.upenn.edu

SESSION XI & XII – April 23 1:30pm - 3:15pm

SESSION XI: Sex, Obesity, and Diabetes

Chair: Arthur P. Arnold (University of California, Los Angeles CA)

Males and females differ in the distribution of body fat, and the risk, development, and manifestations of obesity-related conditions such as diabetes and cardiovascular disease. This session will discuss sex differences caused by cell-autonomous factors, such as the number of X chromosomes, as well as by exogenous factors such as gonadal hormones, that regulate obesity and diabetes, in mice and humans. In mouse models, recent studies show sex differences in the amount of fat and lipid homeostasis are controlled in part by the number of X chromosomes. X genes that escape inactivation are expressed higher in XX than XY tissues, and are being evaluated for their role in regulating adiposity. Women have more body fat than men, and a different distribution of fat in the body. Fat cells from the two sexes, and from different regional fat depots, show different properties correlated with varying glucose and fat homeostasis, and diabetes outcomes. Pre-adipocytes show cell-autonomous sex- and region-specific differentiation *in vitro*. Sex differences in diabetes occur starting before puberty and into reproductive senescence. In women, estrogen favors glucose homeostasis via estrogen receptors (ERs) by improving insulin sensitivity. In men, testosterone is converted to estrogen and maintains fuel homeostasis via estrogen and androgen receptors, which share related functions to improve insulin secretion and sensitivity.

Sex chromosomes and obesity

Karen Reue[1,2], Xuqi Chen[3], Jenny Link[1], and Arthur P. Arnold[3]

[1]Departments of Human Genetics and [2]Medicine, and [3]Laboratory of Neuroendocrinology of the Brain Research Institute, University of California, Los Angeles, California

Obesity is a complex disease regulated by many genetic and environmental factors. It is well known that males and females differ in risk, development, and manifestations of obesity-related conditions such as diabetes and cardiovascular disease. To provide better diagnosis and treatment for both sexes, it is of interest to identify the factors that underlie sex differences in obesity. We have used the Four Core Genotypes mouse model to interrogate the contributions of gonadal sex and sex chromosome complement on body weight and composition, and susceptibility to diet-induced obesity. We find that in addition to the effect of male/female gonadal secretions on these traits, the presence of two X chromosomes (XX female and XX male) *vs*. one X chromosome (XY female and XY male) promotes increased adiposity and related co-morbidities. The effect of the second X chromosome on adiposity is due, in part, to increased food intake during the inactive period of the circadian cycle. Importantly, the effects of XX chromosome complement on food intake and adiposity are evident even in the presence of the large sex-biasing effect of gonadal secretions. We hypothesize that the metabolic effects of the XX chromosome complement are imparted by increased expression levels of gene(s) that escape X chromosome inactivation. To test this hypothesis, we are generating mouse models with global or tissue-specific haploinsufficiency of individual X chromosome genes and evaluating the effects on obesity. Our data thus far suggest that one or a few genes may be responsible for the effects on body weight and adiposity imparted by the XX chromosome complement.

Funding: We gratefully acknowledge support from the National Institutes of Health R01 DK083561.

Contact: Karen Reue, reuek@ucla.edu

Female and male adipocytes are different: mechanisms and implications for metabolic health

Susan K. Fried, Ph.D.[1], Steven R. Smith, M.D. [2], Kalypso Karastergiou[1], M.D., Ph.D. and Mi-Jeong Lee[1], Ph.D.

[1]Department of Medicine, Boston University School of Medicine, Boston MA 02118, and [2]TRI-Florida Hospital, Orlando, FL

Women have higher total body fat, most of which (80-90%) is stored in subcutaneous depots, and a more 'pear-shaped' fat distribution due to the expansion of lower body, gluteal-femoral fat depots. In contrast, men tend to have a more central obesity with preferential expansion of visceral fat depots. Expansion of lower body subcutaneous (sc) depots in women is associated with protection from impairments in glucose-insulin homeostasis and hypertriglyceridemia, and lower risk for developing type 2 diabetes and cardiovascular disease. The mechanisms involved are poorly understood, but are thought to involve the more efficient storage of fatty acids in lower body subcutaneous adipose depots and their capacity to expand by hyperplasia. Consistent with this idea, the increased mass of lower body adipose tissues in females is due in part to an increase in adipocyte size and partly to an increase in number. Our studies of adipose progenitors in primary culture unexpectedly indicated a lower capacity of gluteal compared to abdominal adipocytes of both men and women to differentiate. Nevertheless, these results together with our studies of HOXC13 and the long non-coding RNA HOTAIR, both of which are expressed exclusively in gluteal/femoral adipose tissues are consistent with the idea that adipocyte from different depots have cell autonomous properties. Intriguingly, transplant of female subcutaneous adipose tissue to the subcutaneous compartment of males improved glucose homeostasis, while transplant of male subcutaneous adipose tissue had little effect. Comparisons of the transcriptome of male and female gluteal and abdominal adipose tissues indicate sex dependent depot differences. We conclude that there is a clear need for further studies of cell and molecular mechanisms that determine sex differences in adipose tissue.

Funding: R24DK087669, Affinity Research Collaborative – DOM Evans Medical Foundation (Sex differences in adipose tissue), Isis Foundation, Society for Women's Health Research; Boston Nutrition Obesity Research Center (P30DK046200)

Contact Information: Susan K. Fried (skfried@bu.edu)

Sex differences and sex hormones in glucose homeostasis and diabetes

Franck Mauvais-Jarvis, MD, PhD

Department of Medicine, School of Medicine, Tulane University Health Sciences Center, New Orleans, LA, USA

There are fundamental aspects of the control of glucose homeostasis that are regulated differently in males and females and may influence both the development of diabetes and the response to pharmacological intervention. There are gender differences in diabetes pathophysiology and prevalence and there are more diabetic men before puberty, while there are more diabetic women after menopause. The prevalence of pre-diabetic symptoms such as impaired fasting glucose and impaired glucose tolerance also differs by sex. Some result from the action of estrogens and androgens on glucose homeostasis after puberty and in adults. In females, estrogen favors glucose homeostasis via estrogen receptors (ERs) by ameliorating insulin secretion and sensitivity. In males, testosterone is converted to estrogen and maintains fuel homeostasis via ERs and the androgen receptor, which share related functions to improve insulin secretion and sensitivity

Funding: This work was supported by grants from the National Institutes of Health (DK074970, HD044405) the American Heart Association (11IRG5570010) and the American Diabetes Association (7-13-BS-101)

Contact Information: Franck Mauvais-Jarvis, MD, Ph.D., Section of Endocrinology, Tulane University Health Sciences Center, New Orleans, LA 70112, USA. Tel: 504-988-5990; Fax: 504-988-6271. Email: fmauvais@tulane.edu

Greater excess risk of all-cause mortality and vascular events in women than in men with type 1 diabetes: a systematic review with meta-analysis

Rachel R. Huxley DPhil,[1,2] **Sanne A.E. Peters PhD,**[3,4] Gita D. Mishra PhD[1] and Mark Woodward PhD[2,4,5]

[1] School of Population Health, University of Queensland, Brisbane, Australia; [2] The George Institute for Global Health, University of Sydney, Sydney, Australia; [3] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands; [4] The George Institute for Global Health, Nuffield Department of Population Health, University of Oxford, Oxford, UK; [5] Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA

Background: Studies have suggested sex differences in the mortality rate associated with type 1 diabetes. We performed a meta-analysis to provide reliable estimates of any sex differences in the effect of type 1 diabetes on risk of all-cause mortality and cause-specific outcomes. *Methods:* PubMed MEDLINE was systematically searched for studies published between January 1, 1966 and November 26, 2014. Selected studies reported sex-specific estimates of the standardized mortality ratio (SMR) or hazard ratios associated with type 1 diabetes either for all-cause mortality or cause-specific outcomes. Random effects meta-analyses with inverse variance weighting were used to obtain sex-specific SMRs and their pooled ratio (women: men) for all-cause mortality, for fatal cardiovascular disease, renal disease, cancer, and accident and suicide and for incident coronary heart disease and stroke associated with type 1 diabetes. P-values <0.05 were considered statistically significant. *Results:* Data from 26 studies including 214,114 individuals and 15,273 events were included. The pooled ratio of the SMR for all-cause mortality was 1.37 (95% CI: 1.21-1.56), for incident stroke 1.37 (1.03-1.81), for fatal renal disease 1.44 (1.02-2.05) and for fatal cardiovascular diseases 1.86 (1.62-2.15). For incident coronary heart disease the sex difference was more extreme; the pooled ratio was 2.54 (95% CI: 1.80–3.60). There was no evidence of a sex difference for mortality associated with type 1 diabetes from cancer, or accident and suicide. *Conclusion:* Women with type 1 diabetes have approximately 35-40% greater excess risk of all-cause mortality, and twice the excess risk of vascular events, compared with similarly affected men.

Funding: None

Contact Information: Dr. Sanne A.E. Peters; The George Institute for Global Health; Nuffield Department of Population Health; University of Oxford; 34 Broad Street, Oxford OX1 3BD, United Kingdom; T: +44 1865 617 200; E: sanne.peters@georgeinstitute.ox.ac.uk

SESSION XII: The X chromosome in neurodevelopmental disorders

Chair: William Davies (Cardiff University, Cardiff United Kingdom)

Neurodevelopmental disorders, including autism spectrum conditions and attention deficit hyperactivity disorder (ADHD)**,** affect up to 6% of the population and can present significant problems for affected individuals, for their families and careers, and for society at large. These disorders are diagnosed significantly more frequently in males than in females, a bias that is likely to be accounted for largely by biological factors in addition to ascertainment processes. There is now convincing evidence that genetic and epigenetic factors are important in mediating the risk of developing such conditions, but these have yet to be fully specified. In this symposium, four speakers of international repute from across the USA and Europe will consider how (epi)genetic differences between the sexes (notably with regard to the X chromosome) might theoretically contribute towards the male bias in prevalence of neurodevelopmental disorders, and will discuss ongoing work designed to test these predictions. The presenters will describe basic and clinical work in animal models and humans and will emphasise the utility of such cross-species approaches; multiple experimental techniques designed to assay downstream effects of sex-specific genetics at the molecular, cellular, neuroanatomical, neurochemical, endocrinological and behavioural levels will be referred to.

The impact of X-chromosome loss on brain structure and function in infancy

Wendy Neuheimer, MA[1], Xuijuan Geng, Ph.D.[2], Aditya Gupta, Ph.D.[3], Sandra Woolson, M.Ph.[4], Robert M. Hamer, Ph.D.[1], Martin Styner, Ph.D.[1], John H. Gilmore, M.D.[1], Rebecca Edmonson-Pretzel, Ph.D.[1], Debra Reinhartsen, Ph.D.[5], Margaret DeRamus, M.S., CCC-SLP[6], Steven Hooper, Ph.D.[5], Marsha Davenport, M.D.[7], & **Rebecca C. Knickmeyer**, Ph.D.[1]

[1]Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [2]Centre for Genomic Sciences, University of Hong Kong, Hong Kong, PRC, [3]Children's Hospital of Pittsburgh, University of Pittsburgh, Pittsburgh, PA, USA, [4]VA Medical Center, Durham, NC, USA, [5]Allied Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [6]Carolina Institute for Developmental Disabilities, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [7]Department of Pediatrics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.

Many childhood-onset behavioral disorders are male-biased, including autism spectrum disorders, attention-deficit hyperactivity disorder, and early onset persistent antisocial behavior. It has been hypothesized that these differences result from sex chromosome effects on the development of brain structure and function. Behavioral and neuroimaging studies of individuals with partial or complete X monosomy (Turner Syndrome or TS) provide an unparalleled opportunity to test this hypothesis. However, all studies of TS to date have been carried out in adults and older children. The study presented here is the first to test whether brain structure and function is altered in infants with TS. Our central hypothesis was that infants with TS would show altered gray matter volumes, anatomical connectivity, and functional connectivity in the neural circuits for social cognition and executive function. High-resolution structural magnetic resonance imaging revealed that infants with TS had decreased gray matter volumes in parietal cortex and increased gray matter volumes in insular cortex compared to XX females. Findings are highly similar to neuroanatomical studies of older children with TS, suggesting a stable phenotype with origins in the prenatal or early postnatal period. Diffusion tensor imaging (DTI) revealed that infants with TS did not exhibit the extensive reductions in FA seen in older children, but did show focal reductions in FA in several regions, suggesting that global reductions in FA arise after two years of age. Resting state functional connectivity analyses suggested reduced fronto-parietal connectivity in infants with TS, a lack of typical connectivity between caudate and frontal lobe, and increased connectivity with the insula. Results provide new insight into the impact of X-chromosome loss on neurodevelopment in early life.

Funding: This study was funded by the NIH (K01MH083045 to RCK, P50MH064065 & R01HD053000 to JHG), the NC TraCS $50K Pilot Grant Program (MLD), and Pfizer Global Pharmaceuticals (WS426679 & WS1365413 to MLD).

Contact Information: Rebecca C. Knickmeyer, 343 Medical Wing C, University of North Carolina at Chapel Hill, NC 27599-7160. Phone: 919-966-2216. Email: rebecca_knickmeyer@med.unc.edu

Steroid sulfatase: an X chromosome-encoded modulator of attention and impulsivity phenotypes

William Davies Ph.D[1], Simon Trent Ph.D[1], Tommaso Cassano Ph.D[2], Jonathan Fry Ph.D[3], Amelia Fisher B.Sc[1], Obah A. Ojarikre[4], Lawrence S. Wilkinson Ph.D[1], Trevor Humby Ph.D[1]

[1]Schools of Medicine and Psychology, Cardiff University, Cardiff, UK; [2]Medical School, University of Foggia, Foggia, Italy; [3]Department of Neuroscience, Physiology and Pharmacology, University College London, London, UK; [4]Medical Research Council National Institute for Medical Research, London, UK

Attention deficit hyperactivity disorder (ADHD) is a common condition characterized by impaired attention, pathological impulsivity and hyperactivity; it is diagnosed considerably more frequently in males than females, and

more frequently in females with Turner syndrome (45,X) than without (46,XX), suggestive of a X-linked genetic influence on its pathogenesis. Using a mouse model of Turner syndrome (39,XO) we previously identified the sex-linked *Sts* gene (encoding the neurosteroid-modulating enzyme steroid sulfatase) as a candidate modulator of attention; steroid sulfatase exhibits sexually dimorphic expression/activity in humans. Through using additional genetic and pharmacological mouse models in which the *Sts* gene is absent, or the associated enzyme is inhibited, respectively, we have definitively demonstrated that steroid sulfatase can modulate attention, impulsivity (specifically response inhibition) and hyperactivity; we have suggested that abnormal behavioral phenotypes in Sts-deficient mice may be partially explained by serotonergic dysfunction and specific alterations in brain gene expression. In parallel human work, we have shown that *STS* is expressed in regions of the developing brain involved in attention and response inhibition, and that genetic variation within *STS* is associated with attention in both subjects diagnosed with ADHD and in healthy individuals. Overall, our work provides converging evidence for steroid sulfatase as a modulator of sexually dimorphic ADHD-related phenotypes, and suggests possible underlying biological mechanisms.

Funding: This work was funded by a Research Councils UK Fellowship and a Medical Research Council UK New Investigator Research Grant to WD, and by Cardiff University.

Contact Information: Dr William Davies, Schools of Medicine and Psychology, 2F41, Haydn Ellis Building, Maindy Road, Cardiff CF24 4HQ, United Kingdom; +44-29-2087-0152; daviesw4@cardiff.ac.uk

---

The Neuroanatomy of X-monosomy and Autism Spectrum Disorders

Armin Raznahan MD PhD

Child Psychiatry Branch, National Institute of Mental Health, Intramural Research Program, NIH, Bethesda, MD, USA

Autism Spectrum Disorders (ASD) are significantly more prevalent in males than females. The magnitude and robustness of this sex bias suggests that biological differences between males and females probably modify exposure and/or tolerance to ASD risk factors. The foundational biological difference between males (XY) and females (XX) is unequal sex chromosome dosage, and several observations suggest that X-chromosome gene dosage may shape risk for neurodevelopmental disorders: enriched brain expression for X-linked vs. non X-linked genes; the large number of X-linked intellectual disability syndromes; and the patterns of psychopathology that can accompany altered X-chromosome dosage in human Sex Chromosome Aneuploidy (SCA). We have begun addressing the hypothesis that X-chromosome dosage may influence brain systems involved in social cognition and ASD, by using structural neuroimaging data to: (i) specify patterns of altered brain development in idiopathic ASD, (ii) model brain anatomy in human and murine SCA to identify which regions are most sensitive to X-chromosome dosage effects, and (ii) examine cognitive/behavioral correlates of altered brain anatomy in ASD and SCA groups. These three inter-related strands of research have yielded the following conclusions. First, despite the marked inconsistency of neuroimaging findings in idiopathic ASD, the superior temporal sulcus (STS) emerges as a component of the “social brain” that is repeatedly implicated in ASD. Second, there is replicable evidence for regionally specific effects of X chromosome aneuploidy on both human and murine brain anatomy. In mice, these effects are prominent within a distributed set of brain regions linked to social interaction. Third, diverse approaches to structure-function mapping suggest that X-chromosome dosage effects preferentially strike human brain systems that are critical for adaptive social behavior. However there appears to be marked overlap in the neuroanatomical effects of altered X- and altered Y-chromosome dosage in humans – suggesting that these effects are unlikely to drive sex-differences in ASD risk. In summary, altered dosage of X and Y chromosome genes can modify the structural development of social brain systems, although the relevance of these effects for normative sex-differences in ASD risk remains unclear. Our laboratory is currently merging neuroimaging data with transcriptomic studies in an effort to prioritize potential molecular mediators of X-chromosome dosage effects on mammalian brain development.

Funding: This work was funded by an Clinical Research Fellowship Grant from the UK Medical Research Council (AR), and NIH Intramural Research Program Federal funding to the Child Psychiatry Branch.

Contact Information: Armin Raznahan, Child Psychiatry Branch, rm 4C108, Building 10, 10 Center Drive, Bethesda, MD 20892; 301-435-7927; raznahana@mail.nih.gov

---

Sex-differential gene expression patterns in the human brain and genetic risk for autism

Donna M. Werling[1], Neelroop N. Parikshak[2,3], Daniel H. Geschwind[3,4,5,6]

[1]Department of Psychiatry, UCSF, San Francisco, CA, USA, [2]Interdepartmental PhD Program in Neuroscience, UCLA, Los Angeles, CA, USA, [3]Center for Neurobehavioral Genetics, Semel Institute, Geffen School of Medicine, UCLA, Los Angeles, CA, USA,. [4]Program in Neurogenetics, Department of Neurology, Geffen School of Medicine, UCLA, Los Angeles, CA, USA, [5]Center for Autism Research and Treatment, Semel Institute, Geffen School of Medicine, UCLA, Los Angeles, CA, USA, [6]Department of Human Genetics, Geffen School of Medicine, UCLA, Los Angeles, CA, USA.

Autism spectrum disorders (ASDs) are a group of pervasive developmental conditions with heterogeneous presentation and a comparably heterogeneous genetic architecture. The identification of hundreds to 1000 genes harboring risk-increasing variants is expected as sample sizes continue to grow. ASDs also have a consistently male-biased prevalence, and although genetic findings support a role for protective factors in females, the precise mechanisms responsible for this sex difference in risk are not known. We hypothesize that ASD risk genes and typical sexually dimorphic biological processes interact in one of two general mechanisms to confer sex-differential liability in the population. For one, ASD risk genes could exhibit sexually dimorphic expression and function such that variants in these genes have different impact on male and female neurodevelopment. Alternatively, ASD risk genes may not show sexual dimorphism, but instead interact with molecular or cellular pathways that are sexually dimorphic. We reasoned that sex-differential gene expression patterns in healthy human neural tissue can inform us of such interactions or overlaps with ASD risk genes, thus implicating potential mechanisms for male-biased risk. We have investigated sexually dimorphic gene expression levels in three independent data sets from adult and prenatal human neocortical tissue, and evaluated known ASD risk genes, genes with distinct expression patterns in ASD brain, and neural cell type markers for evidence of sex-biased expression. We find no evidence for systematic sex-differential expression of ASD risk genes. Instead, we observe that genes expressed at higher levels in males than females are significantly enriched for genes co-expressed and up-regulated in ASD brain and for glial marker genes. These findings suggest that male-biased ASD risk does not result from sex-differential regulation of genes carrying ASD risk variants. Instead, our results suggest that naturally occurring sexually dimorphic processes, potentially including neuron-glial interactions, may act to modulate the impact of ASD risk variants in the human brain, and thus contribute to the sex-skewed prevalence of ASD.

Funding: This work was funded by a Ruth L. Kirschstein National Research Service Award F31 from the National Institute of Mental Health (DMW) and UCLA Institutional Funds.

Contact information: Donna M. Werling, Department of Psychiatry, UCSF, 1550 4th Street, Room RH 447, San Francisco, CA, 94158; 415-502-2776; donna.werling@ucsf.edu

CAPSTONE ADDRESS – April 23, 2015 3:30 pm – 4:30 pm

Sex and sex hormones in physiological and pathological cardiovascular stress – implications to management of human disease

Prof. Dr. Dr. h.c. Vera Regitz-Zagrosek, Director of the Institute for Gender in Medicine (GiM), Charité Berlin

My work focuses on sex differences and the role of sex hormones in physiological and pathological cardiovascular stress. Increased circulating volume, pressure overload and mineralocorticoid excess contribute differently to cardiovascular pathophysiology in women and men, in male and female rodents. In order to understand sex specific mechanisms, underlying protection or maladaptation in females and males, we analyze different stressors like exercise, pressure overload and myocardial ischemia and their sex specific effects on heart, kidney and peripheral fat.

We developed animal models and cell culture models of hemodynamic and neurohormonal stress as well as animal models with modified sex hormone receptor expression- ER alpha and ER beta cell specific knockouts and overexpression. We studied the interaction of the stressors with sex and sex hormone effects. According to their effects on the heart, stressors were characterized as inducers of physiological or pathological myocardial hypertrophy. We further analyzed effects on energy metabolism, fibrosis and Calcium signaling. We translated the findings to the human clinical situation.

Exercise leads to physiological myocardial hypertrophy. Females develop more physiological myocardial hypertrophy than males with better metabolic adaptation. Pressure overload and/or mineralocorticoid excess lead to pathological myocardial hypertrophy. Fibrosis, a hallmark of pathological myocardial hypertrophy, is more prominent in males than in females. Estrogen is protective in females but may be harmful in males in some conditions. Estrogen receptor alpha and beta activation have different effects on fibrosis and metabolism in females and males. Female animals under stress maintain energy metabolism better than males and have more favourable Calcium signaling. Women with aortic stenosis develop less excentric myocardial hypertrophy with less fibrosis than men and this is associated with better myocardial survival.

Conclusions: Adaptation to cardiovascular stress and end organ damage are sex specific. Females exhibit less down-regulation of metabolic pathways and males an up-regulation of maladaptive, e.g. pro-fibrotic, mechanisms. This can be translated to the human situation.

POSTER ABSTRACTS – TUESDAY APRIL 21st

1. Title: Sexually dimorphic gene expression in human left ventricle tissue

Authors List: Kolsoum Inanloo Rahatloo Ph.D.[1], Grace Liang B.S[1], Davis Vo B.S[1], Ivy Nguyen[1], Antje D. Elbert Ph.D[1], Joseph C. Wu MD, Ph.D.[1], Patricia Nguyen, MD [1]

Author Affiliations: [1]Stanford Cardiovascular Institute, Stanford University School of Medicine, Stanford, CA 94305, USA. Department of Medicine, Division of Cardiology, Stanford University School of Medicine, Stanford, CA 94305, USA. Institute of Stem Cell Biology and Regenerative Medicine, Stanford University School of Medicine, Stanford, CA 94305, USA.

Abstract: Sex differences in heart development and in the prevalence of cardiovascular disorders such as atherosclerosis have been reported. The molecular basis of these differences remains unclear. Sex differences in human heart might be related to patterns of gene expression. Recent studies have shown sex specific differences in gene expression in tissues including the brain, kidney, skeletal muscle, and liver. Similar data, however, is limited for the heart. Here we address this issue by using donor and post-mortem adult human heart samples originating from 50 control individuals to study whole-genome gene expression in human left ventricle. Gene expression patterns in male and female left ventricle were profiled using the illumine RNA sequencing. We found that genes located on sex chromosomes were the most abundant ones among the sexually dimorphic genes. Male specific expression of Y-linked genes was observed in human left ventricle (e.g. RPS4Y1, KDM5D and DDX3Y). Higher expression levels of X-linked genes were detected in female left ventricle for XIST and TSIX. Furthermore, genes on autosomal chromosomes encoding cytochromes of the monoxygenase family (e.g. CYP26B1), chemokines with inflammatory functions (e.g. CCL4, CX3CL1) and Vascular Cell Adhesion Molecule-1 (VCAM1) were identified with sex and/ or age-specific expression levels. This study underlines the relevance of sex and age as modifiers of cardiac gene expression. The majority of differentially expressed genes are involved in inflammation, atherosclerosis and IL signaling. These results have important implications in understanding the different physiology of male and female's heart and how they lead to different sex specific difference in human cardiac health and its control.

Funding: This study was funded by Stanford WSDM and Stanford CVI.

Contact Information: Kolsoum Inanloo Rahatloo, Department of Medicine , Stanford University School of Medicine, 300 Pasteur Drive, Grant Building S114, Stanford, CA 94305-5111, Phone: 650-736-2863, Fax: 650-736-0234, Email: kinanloo@stanford.edu

---

2. Title: Sex Differences in Myocarditis

Author Affiliations: Patricia Nguyen, MD,[1,2,3] Joseph Wu, MD, PhD,[2,3] Mark Davis, MD, PhD,[3,4] and Sean Wu, MD, PhD[2,3]

Author Affiliations: [1]Veteran's Affairs Palo Alto Health Care System, [2]Department of Cardiovascular Medicine, Stanford Cardiovascular Institute, [3]Department of Microbiology and Immunology, Stanford, California

Abstract: Viral myocarditis is a leading cause of sudden death in young adults with infection with Cocksackievirus B (CVB). Currently, there is no effective treatment for viral myocarditis. Numerous studies have demonstrated that men and peripartum women are more likely to develop the disease and also have a worse prognosis. In animal models, it has suggested that a decline of estrogen in the peripartum women and increased testosterone (or lower estrogen) in men raise their susceptibility to infection and may alter their immune response. Hence, sex difference may underlie either the persistence or the response against the virus long-term. Indeed, chronic

viral infection has been associated with progressive left ventricular dysfunction and the development of dilated cardiomyopathy (DCM). To date, however, there has been no method available to validate the role of sex hormones in the susceptibility of human cardiomyocytes (CMs) to viral infection due to the lack of an accessible cell source for *in vitro* study. Furthermore, the sex differences in human T cell response to cardiotropic viral infection has not been evaluated rigorously. We hypothesize that estrogen level regulates either the expression of CVB receptor and/or the viral replication rate in CMs to cause the male-specific increase in viral myocarditis. This increased viral presence is also exacerbated by a sex-specific difference in T cell response to CVB infection. To address these hypotheses, we propose the following experiments. First, we will compare the expression of CVB receptor in CMs derived from 15 male and 15 female human induced pluripotent stem cell (hiPSC) lines in the presence and absence of sex steroids and measure the rate of viral expansion. We will also use hiPSC-CMs to test candidate antiviral agents to determine whether a sex-specific difference in drug-mediated survival is present. We will then isolate naïve CD4+ T cells from ten males and ten females who have had exposure to CVB and treat them with CVB in the presence or absence of sex steroids to determine whether there are sex differences in the TH1 response by CD4+ T cells. We will correlate the pattern of immune response in these individuals with those in the literature to determine whether there is a sex-specific pattern that predicts greater likelihood of developing DCM after acute myocarditis in men.

Funding: This study was funded by Women's Heart Health at Stanford University.

Contact Information: Patricia Nguyen, Division of Cardiovascular Medicine, Grant Building S114, 300 Pasteur Drive, Stanford, California 94305

---

3. Title: Diet-induced obesity enhances the severity of experimental autoimmune encephalomyelitis in female, but not male mice

Authors List: J. Jennifer Ahn[1], Xavier S. Revelo Ph.D.[2], Sue Tsai Ph.D., Daniel A. Winer M.D.[1,2], and Shannon E. Dunn Ph.D.[1,2,3]

Author Affiliations: [1]Department of Immunology, University of Toronto, [2]Toronto General Research Institute, University Health Network, [3]Women's College Research Institute, Women's College Hospital, Toronto, ON, Canada

Abstract: Obesity in childhood is recognized to be a risk factor for multiple sclerosis (MS), and this association appears to be stronger for females. It has been speculated that obesity increases MS risk because of higher levels of pro-inflammatory adipokines that serve to enhance T cell activation. The objective of this study was to investigate whether obesity increases T helper (Th) cytokine responses and autoimmune susceptibility in experimental autoimmune encephalomyelitis (EAE), a model of MS. For this, female and male C57BL/6J mice were given a high-fat diet (HFD) or normal chow diet (NCD) for three weeks, after which EAE was induced by immunization with the myelin antigen, myelin oligodendrocyte glycoprotein (MOG)35-55, in Complete Freund's adjuvant. The activity of MOG35-55-specific T cells was examined *ex vivo* using 3H-thymidine incorporation and cytokine ELISAs. We observed that males on HFD diet gained significant weight and became insulin-resistant over four weeks. In comparison, female gained less weight and remained insulin-sensitive. Upon induction of EAE, female mice on HFD developed more severe clinical symptoms compared to NCD controls, which correlated with more severe demyelination in the spinal cord. On the other hand, there was only a trend for more severe EAE in males on HFD. The more severe EAE in females correlated with higher production of IFN-γ by MOG35-55-specific cells. Our *in vitro* experiments revealed that a soluble factor(s) in the serum of HFD females enhanced the proliferation and IFN-γ production by MOG35-55-specific T cells *ex vivo*. Upon profiling the serum for soluble factors, we observed that in HFD females, only leptin and CCL2 were upregulated, and adiponectin was downregulated, compared to NCD females. In conclusion, diet-induced obesity has a sex-specific effect on T helper immunity, resulting in increased autoimmunity in female, but not male mice.

Funding: This study is funded by a CIHR grant (MOP 136884) to SED and DAW. JJA is supported by a studentship and SED by a Don Paty award from the MS Society of Canada.

Contact Information: Shannon Dunn, 67 College St. Rm 4-421, Toronto, ON, Canada, M5G 2M1; 1-416-340-4423; sdunn@uhnresearch.ca.

---

4. Title: Effects of high fructose and glucose on metabolic parameters and aortic endothelial function in female rats

Authors List: Farjana Akther M.S[1], Gemma Sangüesa M.S [1&2], Sonali Shaligram M.S[1], Marta Alegret Ph.D. [2], Juan Carlos Laguna Ph.D.[2], and Roshanak Rahimian Ph.D[1]

Author Affiliations: [1]Department of Physiology and Pharmacology, Thomas J. Long School of Pharmacy, University of the Pacific, Stockton, CA, USA. [2]Department of Pharmacology and Therapeutic Chemistry, School of Pharmacy, University of Barcelona, Barcelona, CIBERObn, IBUB, Spain

Abstract: Intake of high fructose, especially in soft drinks, has shown to contribute to variety of metabolic disorders. Limited data is available on the relative effects of high fructose and glucose intake on vascular reactivity and metabolic parameters in female rats. The objective of this study was to compare the effects of high glucose (HG) and high fructose (HF) (20% w/v in drinking water for 8 weeks) consumption on female rat's metabolic parameters and aortic endothelial function. Body weight, food and drink intake and blood pressure (BP) were monitored. Organ weight and plasma analytes were also measured. Endothelium-dependent vasodilation (EDV) to acetylcholine (ACh; 10-8 to 10-5M) and bradykinin (BK; 10-9 to 10-5 M) and endotheliumindependent vasodilation to sodium nitroprusside (SNP; 10-9 to 10-5 M) were measured in aortic rings pre-contracted with phenylephrine (PE). Furthermore, constrictor response curves to PE (10-8 to 10-5 M) were generated. Total caloric intake and systolic BP were significantly elevated in both HG and HF groups. Triglyceride (TG), insulin, as well as liver and body weights were significantly higher only in HF group. The EDV to ACh was preserved in both HF and HG groups. HF ingestion, but not HG, significantly decreased maximal relaxation to BK. The potency of endothelium-independent vasodilation to SNP was augmented in aortic rings from HG. Accordingly, the PE-induced contraction was decreased in HG fed rats. HF ingestion, however, significantly attenuated the potency of relaxation to SNP. Our data suggest that an increase in the sensitivity of smooth muscle to NO may in part contribute to the decreased PE contractile responsiveness in HG. An increased level of insulin and TG and a decrease in sensitivity of vascular smooth muscle to NO along with the impaired vasodilatory responses to BK of HF groups suggest that HF ingestion may have a higher impact in inducing metabolic and aortic dysfunction compared to HG ingestion in female rats.

Funding: This study was supported by NIDCR.

Contact Information: **Dr.Roshanak Rahimian,** Department of Physiology and Pharmacology, Thomas J. Long School of Pharmacy, University of the Pacific, Stockton, CA. 209 946 2373 rrahimian@pacific.edu.

---

5. Title: Sex differences in regulation of gene expression and their relevance to human cardiovascular health

Authors List: Charlotte L Anderson MRes[1], Michael Tadao Inouye PhD[2] and Fadi Charchar PhD FAHA[1,2]

Author Affiliations: [1]Faculty of Health, School of Health Sciences and Psychology, Federation University; [2]Faculty of Medicine, Dentistry and Health Sciences, Department of Pathology, University of Melbourne

Abstract: Cardiovascular disease has a well documented sexual dichotomy with regard to age of onset, symptoms and response to treatment. Males are more commonly affected than age-matched females, however the number

of incidence in women surpassed men at older ages and outcomes are worse. A vast array of phenotypic differences exist between males and females, however genetically they are nearly identical. In most other species the male and female genomes differ by only a few genes located on sex specific chromosomes. This suggests that sexually dimorphic traits arise by an alternative mechanism. It has also been suggested that it is the differential expression of genes that are present in both sexes that most likely gives rise to the disparity between male and female. Previous studies of sex biased gene expression, initially with microarrays using mouse models, indicate that a large number of individuals provide the power to detect relatively small differences.

Motivated by the ability of RNA-seq technology to study gene expression, we hypothesise this is causing the resulting manifestations in phenotypes between sexes seen in cardiovascular disease. We set out to characterise the fold changes detectable between males and females using the RNA-seq dataset generated by the Geuvadis Consortium. We utilised the lymphoblastoid cell lines of individuals from the 1000 Genome Project, which has a population similar to that of a data collected in cardiovascular disease studies. Secondly we used the same data to quantify the accuracy of the fold changes detected. Finally, we evaluated the potential of RNA-seq data sets to uncover small fold changes in gene expression. The next phase is to utilise RNA-seq to detect changes in gene expression responsible for phenotypic manifestations seen in cardiovascular disease.

Funding: This study was funded by NHMRC and BHF.

Contact Information: Charlotte L Anderson, Federation University Australia, Building Y, University Drive, Mount Helen VIC 3350 Australia; charlotteanderson@students.federation.edu.au

---

6. Title: Sex differences in renewal of conditioned responding to food cues: role of estradiol

Authors List: Lauren C. Anderson, MA & Gorica D. Petrovich, Ph.D.

Author Affiliations: Department of Psychology, Boston College, Chestnut Hill, MA, USA

Abstract: Cues associated with food can stimulate food consumption independently of hunger. Renewal, or reinstatement, of responding to food-cues after extinction may explain our inability to resist palatable foods and change maladaptive eating habits, similar to the mechanisms of drug use relapse. First, we found sex differences in context-induced renewal of responding to food cues, such that males showed renewal, but females did not. We hypothesized that estradiol is important for females during renewal of responding. Next, we compared behaviors of ovariectomized female rats (OVX), OVX with estradiol replacement (OVX+E) and intact female rats during acquisition, extinction and test for renewal. Context-induced renewal involves conditioning and extinction in different contexts and the renewal of responding is induced by return to the conditioning context ("ABA renewal"). Control groups remain in the same context during conditioning, extinction and test. Rats were conditioned to associate a tone with food pellets during acquisition, received tone only presentations during extinction, and were tested for renewal with tone only presentations. Food cup behavior (time spent in and around food receptacle) indicated learning. Rats in all treatment groups learned similarly during acquisition and extinction. Similar to the original findings, intact and OVX rats in the experimental groups did not show renewed conditioned responding and had similar rates of food cup behavior as control groups. The OVX+E rats in the experimental group, however, showed renewal responding, and had significantly higher food cup behavior compared to OVX+E rats in the control group. The results demonstrate estradiol is an important mediator of renewal of extinguished conditioned responses to food cues in female rats. These experiments provide novel insights into the sex differences in responding to food cues and an important role of estradiol in contextual processing and appetitive associative learning.

Funding: Research was supported by NIH Grant R01DK085721 and Boston College funds to GDP.

Contact Information: Lauren C. Anderson, Department of Psychology, Boston College, 300 McGuinn Hall, Chestnut Hill, MA 02467; 1-508-525-0334; andersvz@bc.edu

7. Title: The relationship between 17b-estradiol and cognitive functioning in women

Authors List: April Au M. A.[1], Deborah Schwartz M. A.[1], Andrea Eisen M.D.[2], Amy Finch Ph.D.[3], Elizabeth Hampson Ph.D.[4], Wendy Meschino M.D.[5], Steven Narod M.D.[3,6], Mary C. Tierney Ph.D.[2], & Gillian Einstein Ph.D.[1,6]

Author Affiliations: [1]Laboratory of Cognitive Neuroscience & Women's Health, Department of Psychology, University of Toronto, Toronto, ON, CA; [2]Sunnybrook Health Sciences, Toronto, ON, CA; [3]Women's College Research Institute, Toronto, ON, CA; [4]Department of Psychology, University of Western Ontario, London, ON, CA; [5]Genetics, North York General Hospital, Toronto, ON, CA; [6]Dalla Lana School of Public Health, University of Toronto, Toronto, ON, CA

Abstract: Sex hormones in humans are not limited to producing physical sexual dimorphisms, but also cognitive differences between and within sexes. The relationship between estrogens and cognitive functioning have been studied prominently in the context of the menopause transition; however, findings in the literature are mixed. The present study investigates how a low estrogen milieu affects cognition in young women who have undergone bilateral salpingo-oophorectomy (BSO: surgical removal of the ovaries and fallopian tubes) up to 10 years ago using an accelerated longitudinal design. Cognitive tasks assessing attention, memory and working memory were selected to explore functioning of the prefrontal cortex and hippocampus, where estrogen receptors are expressed in the brain. In addition, urine samples were collected to determine levels of ovarian steroids at the time of testing. In our preliminary results, we found that women with BSO recalled significantly fewer details on the Logical Memory task, a test of verbal, episodic memory, compared to age-matched controls. A significant association between estrogen levels and performance on the Rey Auditory Verbal Learning Test was also found, where higher levels were predictive of better scores. Furthermore, time since BSO was negatively associated with measures of verbal ability after controlling for age. Taken together, these results suggest that BSO affects verbal memory in women, and this effect may be exacerbated by time since estrogen deprivation. The sustained differences observed in women with BSO compared to the control group provide evidence that 17b-estradiol, produced in the ovaries, is implicated in the maintenance of cognitive functioning.

Funding: This study is funded by grants from the Canadian Breast Cancer Foundation and the Canadian Institutes of Health Research to GE. AA is supported by a scholarship from the Enid Walker Estate.

Contact Information: April Au, Laboratory of Cognitive Neuroscience and Women's Health, Sidney Smith Hall 4F c/o Psychology, 100 St. George Street, Toronto ON M5S 3G3; 1-416-978-6582; april.au@mail.utoronto.ca

---

8. Title: How to get Gender Medicine into Medical Training

Authors List: Dr.[in] Angelika Bader, Dr.[in] Heidi Siller & Univ.-Prof.[in]Dr.[in] Margarethe Hochleitner

Author Affiliations: Medical University of Innsbruck, Women's Health Centre, Austria/Europe

Abstract: Gender Medicine needs to be incorporated in the curriculum of all medical degree programs. This as usual meets with strong resistance on the part of students due to increased course load and exam burden. We decided to incorporate Gender Medicine in the compulsory curriculum to make it a "normal" course. These efforts were supported by various legal and ministerial "Gender subsidies and guidelines." At Innsbruck Medical University in 2008, Gender Medicine was incorporated in the compulsory curriculum of all medical degree programs, human medicine, dental medicine and molecular medicine, namely in Semesters 3 and 10. Moreover, Gender Medicine is compulsory in the Clinical-PhD-program. In 2013, Gender Medicine was introduced as a key word for registration of diploma and PhD-theses and without advertising this fact already identified 127 diploma and eight PhD-theses in the first year. The model for implementation of Gender Medicine in compulsory medical education and as part of the examinations has over the years, as anticipated, caused it to be viewed as "normal"

despite initial resistance. Meanwhile, even the benefits of Gender Medicine, namely various possibilities for subsidies, have been recognized and utilized. Gender Medicine can and should be incorporated in all compulsory medical curricula. For science it offers new research approaches and possibilities for subsidies as well as being the basis for tailored offerings in prevention, diagnosis, therapy and rehabilitation for our patients.

Funding: Medical University of Innsbruck.

Contact Information: Univ.-Prof.in Dr.in Margarethe Hochleitner, Medical University of Innsbruck, Women's Health Centre, Innrain 66, A-6020 Innsbruck, Austria/Europe; Phone +43.512.504.25710, fax +43.512.504.25719; margarethe.hochleitner@i-med.ac.at

---

9. Title: Gender Medicine in Physician Clinical Training; Results of a Large, Single Center Survey

Authors List: May Bakir MD, Erika Jones MD, Shivani Dhawan MS, Sarah Kilpatrick MD PhD, C. Noel Bairey Merz MD

Author Affiliations: Barbra Streisand Women's Heart Center, Cedars-Sinai Heart Institute, Los Angeles, CA

Abstract: Background. Gender Medicine is a novel medical discipline that takes into account the effects of sex and gender on the health of women and men. The Institute of Medicine in the USA declared in its 2001 and 2010 statements that being a woman or a man significantly impacts the course of diseases and therefore this fact must be considered in diagnosis and therapy. We evaluated the representation of Gender Medicine in clinical training at Cedars-Sinai Medical Center, a large, tertiary, non-profit, academic medical training center in the Western United States. **Methods.** Post-graduate physician trainees (residents and fellows) in all medical departments (medicine, surgery, ob-gyn, pediatrics, anesthesiology, pathology, urology, EP, pulmonary critical care, cardiology, women's heart, medical genetics, radiology, neurosurgery and radiation oncology) were surveyed on-line; 80 (55% and 45% female and male residents respectively) responded to questions regarding gender medicine. **Results.** Seventy percent of post-graduate physician trainees indicated that gender medicine concepts are never or only sometimes discussed/presented in their training program (Figure 1). Slightly greater than 70% of the trainees indicated that gender concepts are never or only sometimes incorporated into didactic lectures (Figure 2) or clinical teaching (Figure 3). However, more than 65% felt that gender medicine concepts are important and 60% agreed that gender medicine curriculum should be implemented and taught in their clinical program. **Conclusions.** Current physician trainees endorse both a current lack of and need for Gender Medicine clinical training

Funding: Barbra Streisand Women's Heart Center.

Contact Information: Noel Bairey Merz MD, Women's Heart Center, Cedars-Sinai Medical Center, 127 S San Vicente Blvd, #A9-300, Los Angeles, CA 90048. 310.423.9680.

---

10. Title: Protection conferred by Y-chromosome against pulmonary hypertension is not due to *Ddx3y* gene

Authors List: Mariam Barseghyan BS BA[1], Soban Umar MD PhD [2], Alex Centala BS[2], Yuichiro Itoh PhD[1], Ryan Mackie BS[1], Arthur P. Arnold PhD [1], Mansoureh Eghbali PhD [2]

Author Affiliations: [1] Department of Integrative Biology and Physiology, University of California Los Angeles, Los Angeles, Los Angeles, CA, USA; [2] Department of Anaesthesiology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA

Abstract: Pulmonary arterial hypertension (PAH) is an incurable vascular disease characterized by elevated pulmonary arterial pressure and vascular remodelling, and lesions leading to right heart failure. It is 4 times more likely to occur in females than males. Our previous work showed that in gonadectomized (GDX) Four Core Genotypes (FCG) mice (XX and XY males, XX and XY females, C57BL6/J), XY mice (XYM, XYF) develop less severe PAH than XX (XXM, XXF). In the GDX XY* C57BL/6J model, right ventricular systolic pressure (RVSP) in mice with Y-chromosome (ChrY) (XY, XXY) was significantly lower than that of mice without a ChrY (XO, XX). Since RVSP directly correlates with pulmonary hypertension (PH) severity, we concluded that ChrY confers protection against PH in GDX mice. Four ChrY genes are expressed consistently in lung and heart (Ddx3y, *Kdm5d, Uty, Eif2x3y*) and are thus candidate protective genes.

In this study we asked if the Y gene *Ddx3y*, a cellular growth suppressor, is protective. Since *Ddx3y* transgenic mice were available on an outbred MF1 background, we first examined the ChrY protective effect in MF1 XY* mice (n=5/grp). Secondly, we compared PH in MF1 XX female mice with and without a transgenic copy of *Ddx3y* (n=10/grp). Mice were GDX at 75d and 4 weeks after GDX exposed to hypoxia (10% O_2) for 3 weeks. Right ventricular pressure was measured through direct catheterization. We confirmed that in MF1 XY* mice ChrY protects against hypoxic insult as it does in C57BL6/J mice. RVSP was significantly lower in XXY or XY mice compared to XX or XO mice ($p=0.03$). We did not find a significant difference between the RVSP of XX mice with or without a transgenic copy of *Ddx3y*. Thus, we conclude that *Ddx3y* does not confer protection against PH. In the future study we plan to investigate effects of the other Y candidate genes *Kdm5d, Uty,* and *Eif2x3y*.

Funding: NIH 1R56HL119886. Thanks to Paul Burgoyne for gift of the transgenic mice.

Contact Information: Mariam Barseghyan, Department of Integrative Biology and Physiology, University of California Los Angeles, Terasaki Life Science Building Room 1146, 610 Charles E. Young Drive South, Los Angeles, CA 90095-8347; 310-825-9340; mbarseghyan@ucla.edu

---

11. Title: Obesity-induced hypertension involves sex-specific mechanisms

Authors List: Eric J. Belin de Chantemèle[1], Anne-Cécile Huby[1], Joseph Cannon[2] and Miriam Cortez-Cooper[2].

Author Affiliations: [1]Physiology Department, Medical College of Georgia, Georgia Regents University, Augusta, GA. [2]College of Allied Health Sciences, Georgia at Georgia Regents University, Augusta, GA.

Abstract: The recent obesity epidemic that affects more women than men worldwide is a major risk factor for hypertension (HTN). Obesity is associated with inappropriately high levels of the mineralocorticoid hormone aldosterone, which positively correlate to the level of adiposity and blood pressure (BP) in women but not in men. The mechanisms controlling aldosterone secretion in obesity and by which obesity sensitizes women to HTN remain however unknown. The adipocyte-derived hormone leptin is a main contributor to obesity-related hypertension in men. As women secrete 4 times more leptin than men, we hypothesized that excessive levels of leptin trigger HTN via aldosterone-dependent mechanisms in obese females. We combined the analysis of the cardiovascular phenotype of male and female mice presenting either a hypersensitivity to leptin (PTP1B KO mice) or high leptin levels (Obese Agouti mice), to the study of the interaction between percentage of body fat, leptin and aldosterone levels in adult Caucasians. Increasing leptin sensitivity with PTP1B deletion or leptin levels in Obese Agouti mice induced a similar increase in BP, in both males and female mice. High leptin sensitivity or levels increased sympathetic activity (drop in BP in response to ganglionic blockade) in males but not in females that presented increased aldosterone levels and high level of aldosterone synthase (*CYP11B2*). Chronic treatment with the mineralocorticoid receptor antagonist sprironolactone reduced BP in female PTP1B KO and Agouti mice only. In parallel, we reported a positive correlation between adiposity and aldosterone, and between leptin and aldosterone in adult women only. These data suggest that leptin is a new regulator of aldosterone secretion and demonstrated that obesity-mediated HTN involves sex-specific mechanisms and is aldosterone-

dependent in females. These discoveries highlight the need for sex-specific therapies and provide new avenues for the treatment of obesity-related HTN.

Funding: This study was supported by Scientist Development Grant (EBC) from the American Heart Association.

Contact Information: Eric J. Belin de Chantemele, Ph.D, FAHA, Assistant Professor, Physiology Department, Medical College of Georgia at Georgia Regents University, 1120 15th Street, Augusta, GA 30907. Tel: 706 721 7805. Email: ebelindechanteme@gru.edu

---

12. Title: Targeted deletion of selenium transport and recycling pathways in mice: gender-specific neurological and metabolic consequences

Authors List: Marla J. Berry Ph.D., Lucia A. Seale Ph.D., Ashley Ogawa, Penny Kremer, Ann C. Hashimoto M.S., and Matthew W. Pitts Ph.D.

Author Affiliations: Department of Cell and Molecular Biology, John A. Burns School of Medicine, University of Hawaii at Manoa, Honolulu, HI, USA

Abstract: Selenoproteins function in multiple essential biological functions, are particularly known for their key roles in antioxidant defense, and are synthesized via a unique translational mechanism involving recoding of UGA codons to specify selenocysteine instead of stop. Selenoprotein P (Sepp1) is distinctive among selenoproteins in that it contains multiple selenocysteine residues and is thought to act in selenium transport. Selenocysteine lyase (Scly) recycles selenium from selenoproteins via decomposition of selenocysteine to alanine and selenide, the latter of which is utilized for new selenoprotein biosynthesis. Genetic deletion of Sepp1 combined with feeding a selenium-deficient diet results in severe neurological dysfunction and widespread brainstem neurodegeneration. We hypothesized that mice lacking Scly might exhibit similar deficits. Surprisingly, Scly KO mice raised on a Se-adequate diet exhibit hyperinsulinemia, hyperleptinemia, glucose intolerance, and hepatic steatosis, and this phenpotype was more pronounced in male mice. Upon dietary Se restriction, male Scly KO animals develop several characteristics of metabolic syndrome, such as obesity, fatty liver, and hypercholesterolemia, with aggravated hyperleptinemia, hyperinsulinemia, and glucose intolerance. In addition, they exhibit mild neurological deficits. We created novel transgenic mice constitutively lacking both genes and characterized the phenotype. Deletion of Sepp1 and Scly further aggravates the phenotypes of either single knockout male mouse, as these mice needed supraphysiological selenium supplementation to survive, and surviving mice exhibited impaired motor coordination, audiogenic seizures, and brainstem neurodegeneration. These findings provide the first in vivo evidence that Scly and Sepp1 work cooperatively to maintain selenoprotein function in the mammalian brain, and that these functions exhibit gender-specific differences.

Funding: This project was supported by NIH grants G12MD007601 from NIMHD and R01DK047320 from NIDDK to MJB.

Contact Information: Marla J. Berry, Department of Cell and Molecular Biology, John A. Burns School of Medicine, University of Hawaii at Manoa, Honolulu, HI 96813; 1-808-692-1506; mberry@hawaii.edu

---

13. Title: Epigenetic role of Histone Deacetylase 9 (HDAC-9) as a repressor of intrarenal angiotensinogen (AGT): A novel mechanism to explain sex disparities in hypertension

Authors List: Camille T Bourgeois, MS[1], Ryosuke Satou, PhD[1-3], and **Minolfa C. Prieto, MD, PhD**[1-4].

Author Affiliations: [1]School of Medicine, [2]Department of Physiology and Hypertension and [3]Renal Center of Excellence, [4]Tulane-BIRCWH Program, Tulane University, New Orleans, LA.

Abstract: Young females are protected from the development of hypertension and related end-organ damage compared to males. Inappropriate activation of intrarenal renin-angiotensin system (RAS) is a major contributor to hypertension and the development of kidney injury. Females exhibit lower excretion of AGT in urine suggesting that lower levels of intrarenal AGT in females may be protective against the development of hypertension. Thus, in this study to determine if epigenetic factors determine sex differences in intrarenal AGT expression levels, we measured AGT mRNA and protein levels in renal cortex of male and female Sprague Dawley rats by real time-PCR and Western blot analyses. We found that AGT mRNA and protein levels in renal cortex of females were significantly lower than in males (0.15 ± 0.01 in mRNA, 0.41 ± 1.15 in protein, ratio to male). To determine if epigenetic factors repress AGT transcription, we examined the effects of histone deacetylases (HDAC) and co-repressors on AGT expression in the kidney of females using a chromatin modification enzyme PCR array. As result, only HDAC9 exhibited higher expression in renal cortex of females compared to males (7.09± 0.88, ratio to male). Higher levels of HDAC9 protein in renal cortex of female were observed by immunoblotting. Because HDAC9 is expressed in rat proximal tubule cells (PTC), we examined the relationship between HDAC9 and AGT, using gene silencing of HDAC9 in cultured rat PTC. Knockdown with HDAC9 siRNA augmented AGT mRNA (1.92 ± 0.35, ratio to control) and protein (2.25 ± 0.50, ratio to control) levels compared to scrambled siRNA transfected cells. Our data indicate that HDAC9 is a novel suppressing epigenetic factor involved in the regulation of AGT gene in the renal PTC and support an association between HDAC9 and hypertension. This may represent a novel mechanism to explain sex disparities in hypertension and kidney injury associated with intrarenal RAS dysregulation.

Funding: This study was funded by the Tulane-BIRCWH Program, the CoBRE grant from the Institutional Developmental Award Program of the NIH of General Medical Sciences (P30GM103337), and the LACaTs grant award.

Contact Information: Minolfa C. Prieto, MD, PhD. Tulane University, SOM. Department of Physiology, (SL39). 1430 Tulane Avenue. New Orleans, LA 70112; mprieto@tulane.edu

---

14. Title: Sex differences in soluble ST2 (sST2) predict heart failure during acute myocarditis and DCM in patients and mice

Authors List: ***Katelyn A. Bruno[1,2]***, *Michael J. Coronado[1], Leslie T. Cooper Jr.[2], Adriana Bucek[1], Madeleine W. Cunningham[3], DeLisa Fairweather[1,2]*

Author Affiliations: [1]Johns Hopkins Bloomberg School of Public Health, [2]Mayo Clinic, [3]University of Oklahoma Medical Center

Abstract: The Th2-associated cytokine IL-33 was found to be upregulated during acute myocarditis in microarray studies in mice. ST2 pairs with IL-1RAP as the membrane bound receptor for IL-33 that is associated with activation of the inflammasome and NF-KB and MAP kinase pathways. The soluble form of the ST2 receptor (sST2) binds IL-33 to regulate its function. In atherosclerosis patients elevated sera sST2 is known to be associated with heart failure. We have found in a mouse model of lymphocytic myocarditis (LM) and clinical samples from patients with lLM that elevated sera sST2 was associated with heart failure according to ejection fraction and NYHA classification in men, but not in women. In contrast, patients with fulminant myocarditis, giant cell myocarditis, or eosinophilic myocarditis had higher sera ST2 that correlated with heart failure in women. LM was increased in ST2 receptor knockout mice and associated with increased IL-1b and IFNg. When recombinant ST2 was administered to mice it decreased LM and IL-33 levels in the heart as well as preventing progression of males to DCM. When gonadectomy (Gdx) and hormone replacement was performed on male mice we found that testosterone increased LM and sST2 in the sera. These findings suggest that sera sST2 may be a good biomarker for risk of heart failure in myocarditis patients that differs by sex and type of myocarditis.

Funding Sources: This research was supported by funding from NIH HL111938, ES024414 and AHA 12GRNT12050000 to DeLisa Fairweather and the Katelyn Bruno was funded by an NIH training grant ES07141.

Contact Information: DeLisa Fairweather, 615 N Wolfe St E7628 Baltimore, MD 21205, (410) 502-3644, dfairweather@jhu.edu

---

15. Title: Gender differences in the impact of dysfunctional coping in a hypertensive population

Authors List: [1]**RM Bruno**, [2]L Palagini, [2]M Mauri, [2]L Ghiadoni, [3]S Cervia, [2]S Taddei R Biancheri,

Author Affiliations: [1] Institute of Clinical Physiology – CNR, Pisa, Italy, [2] Department of Clinical Experimental Medicine, University of Pisa, Italy, [3] Department of Social Sciences, University of Pisa, Italy

Abstract: Hypothesis: Chronic stress and coping strategies might influence cardiovascular health in a gender-dependent manner. Aim of this study is to investigate their impact on blood pressure control in men and women attending for the first time a visit in a Hypertension Outpatient Clinic.

Methods: Data from 330 patients were analyzed (males 51%, mean age 57±13 years, antihypertensive treatment 84%, previous CV events 9%, diabetes 7%, obesity 24%, smoking 13%, hypercholesterolemia 67%). Office blood pressure (BP) was measured, and medical history collected. Perceived Stress Scale (PSS), Brief-COPE, Pittsburgh Sleep Quality Index (PSQI), Beck Depression Inventory (BDI), and State-Trait Anxiety Inventory (STAY-Y2) were administered.

Results: Women were older and less obese, and showed lower office BP than men. Sleep quality was similar among men and women, while women showed higher STAI-Y2 and BDI values. Despite similar perceived stress, women showed higher emotion-focused and dysfunctional coping. In the overall population, univariate regression analysis showed that systolic BP was directly correlated with triglycerides and dysfunctional coping and inversely correlated with HDL. These correlations were confirmed in men, but not in women.

In men, a multiple regression model, considering age, body mass index, diabetes, HDL, Triglycerides, number of antihypertensive drugs, STAI-Y2, BDI and dysfunctional coping, as independent variables, demonstrated that only diabetes (beta 12.9, p=0.04), number of antihypertensive drugs (beta -3.39, p=0.05) and dysfunctional coping (beta 0.91, p=0.03) were significantly associated with systolic BP. The model explained 23% of the variance of systolic BP, while dysfunctional coping 6%. Conversely in women only diabetes (p=0.049) was positively associated with systolic BP.

Conclusions: Maladaptive coping strategies seems to translate into unfavorable cardiovascular outcome in men but not in women.

Funding: none.

Contact information: Rosa Maria Bruno, Institute of Clinical Physiology – CNR, Via Moruzzi 1, 56125, Pisa, Italy**,** tel: +39 050 3152377**,** fax:+39 050 3152355**,** email: rosam.bruno@gmail.com

---

16. Title: Depressive symptoms are associated with salivary C-reactive protein in adolescents: Effects of sex and BMI.

Authors List: Michelle L. Byrne, Ph.D.[1,3]**,** Neil M. O'Brien-Simpson, Ph.D.[2], Eric C. Reynolds, Ph.D.[2], Katrina A. Walsh, Ph.D.[2], Katrina Laughton, Ph.D.[2], Nicholas B. Allen, Ph.D.[1,3]

Author Affiliations: [1] The University of Melbourne, Melbourne School of Psychological Sciences, Parkville, VIC, Australia; [2] The University of Melbourne, Melbourne Dental School, Carlton, VIC, Australia; [3] The University of Oregon, Department of Psychology, Eugene, OR, USA.

Abstract: Inflammation has been proposed to be a mechanism relevant to depression. However, research is limited by the paucity of lifespan studies, making it difficult to address temporal relationships and the onset of risk factors. Furthermore, the role of individual differences, such as sex and adiposity, has not been fully explored. This study investigated the temporal relationship between inflammation and depressive symptoms in a sample of 67 adolescents (40 males) recruited from the community and the moderating effects of sex and adiposity, using a longitudinal design measuring depressive symptoms at three phases and salivary C-reactive protein (CRP) at Phase II. We hypothesized that elevated inflammation would be associated with increased depressive symptoms and that female sex and high body-mass-index (BMI) would be associated with a stronger relationship between these measures. We also hypothesized that elevated inflammation would prospectively predict an increase in depressive symptoms over time. Results showed that salivary CRP was cross-sectionally associated with depressive symptoms ($p = 0.007$), even when controlling for age, family history of cardiovascular disease, pubertal status, and socio-economic status. There were also significant interactions with female sex ($p = 0.034$) and higher BMI ($p = 0.014$). CRP did not predict levels of depressive symptoms longitudinally. Inflammation was only measured at one time point (Phase II), so it was not possible to examine the effect of depressive symptoms on levels of CRP. This is the first study to show that CRP measured in saliva is associated with depressive symptoms cross-sectionally. Furthermore, the moderating effects of female sex and high BMI are factors that may contribute risk to both depressive and inflammatory disorders and should be considered by researchers in further studies and by clinicians in treatment of these disorders.

Funding: This work was supported by funding from the Australian Research Council and The University of Melbourne, Melbourne School of Psychological Sciences.

Contact Information: Michelle L. Byrne, Department of Psychology, 1227 University of Oregon, Eugene, OR 97403; 1-541-346-3936; mbyrne@uoregon.edu

---

17. Title: Sex Differences in the Association of Cardiovascular Risk Factors with Peripheral Endothelial Function in Individuals with Lower than Normal Endothelial Function

Authors List: Alice Y. Chang, MD, MSc,[1, 2] Yasushi Matsuzawa, MD, PhD,[2, 3] Rebecca Cilluffo, MD, [2, 3] Amir Lerman, MD[2, 3]

Author Affiliations: [1]Division of Endocrinology, Metabolism, Diabetes and Nutrition, [2]Department of Internal Medicine, [3]Division of Cardiovascular Disease, Mayo Clinic, Rochester, Minnesota

Abstract: Previous studies suggest that endothelial dysfunction is more strongly associated with cardiovascular (CV) risk factors in healthy women than men. We compared women with insulin resistance and lower than normal endothelial function to age- and BMI-matched men. We hypothesized that there would be no sex differences in the association of CV risk factors with endothelial function when comparing higher risk individuals. Participants on lipid-lowering therapy or previously diagnosed diabetes were excluded. Peripheral flow-mediated dilation was assessed using digital arterial tonometry. The reactive hyperemia index (RHI) was calculated as changes in tonometry before and after brachial cuff inflation normalized to baseline and indexed to the contralateral arm. We compared 16 women with Polycystic Ovary Syndrome (PCOS) and 17 men matched by age (W: age 28 [24.5–33] years; M 30 [26-36] years, p=0.27) and BMI in the obese range. There was no difference in RHI between sexes (W: RHI 1.82 [1.55–2.25]; M: RHI 1.9[1.5-2.1], p=0.50), and the medians for both sexes were below normal (≥2). There were no sex differences in waist circumference, lipids, fasting glucose, blood pressure or highly sensitive C-reactive protein. The prevalence of impaired fasting glucose (W 18.8% vs M 5.9%, p=0.35) and metabolic

syndrome (W 37.5% vs M 11.8%, p=0.11) were greater in women than men but not statistically significant. The prevalence of hypertension was significantly lower in women than men (W 0% vs M 29.4%, p=0.04). In linear regression models, there was a significant interaction of sex in the association of metabolic syndrome and hypertriglyceridemia with RHI. Stratifying by sex, metabolic syndrome and hypertriglyceridemia were significantly associated with RHI in women but not men. In conclusion, metabolic syndrome and hypertriglyceridemia are significantly associated with endothelial dysfunction in women with PCOS, not men, even among individuals with lower than normal endothelial function.

Funding: Office of Women's Health Research (Building Interdisciplinary Careers in Women's Health award K12HD065987), St. Jude's Cardiovascular Research Award, This project was supported by Grant Number UL1 TR000135 from the National Center for Advancing Translational Sciences (NCATS). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

Contact Information: Alice Y. Chang, Mayo Clinic, 200 First Street, Rochester, MN 55905, 507-284-2191, chang.alice1@mayo.edu

---

18. Title: Boy Crisis? Sex Differences in Self-injurious Behaviors and the Effects of Gender Role Conflicts among College Students in China

Authors List: Qiuling Chao, Ph.D [1], Dr. Xueyan Yang[2,3], Dr. Cheng Luo[4]

Author Affiliations:[1] Higher Education Research Institute, School of Public Policy and Administration, Xi'an Jiaotong University, P.R.China, [2] Institute for Population and Development Studies, School of Public Policy and Administration, Xi'an Jiaotong University, P.R.China; [3] Morrison Institute for Population and Resource Studies, Department of Biology, Stanford University; [4] Cheng Luo, PH.D, Associate Professor and Associate Research Fellow at Institute for Rural Development of Shaanxi Social Science Academy

Abstract: Background. In western research, self-injurious behaviors are commonly viewed as "feminine" behavior that is most likely to occur among female adolescents aged 15–19 (Van Camp, Desmet & Verhaeghe, 2011). Studies in China, however, tell yet another story: the prevalence of self-injurious behaviors among male adolescents is significantly higher than among female adolescents. For example, Wang's (2007) study among 371 college students in China reported that the prevalence of self-injurious behaviors is 18.4% among males and 13.8% among females but without statistical significance (Wang, Lu & Li, 2007). Another study conducted among students from 12 universities reported a significantly higher prevalence of self-injurious behaviors among male students (39.1%) than among female students (19.5%) (Wang, 2010). Huang et al.'s study (2011) among 1525 students from 8 universities in Hunan of China reported the same pattern, with the prevalence of self-injurious behaviors among male students (12.19%) being significantly higher than among female students (8.19%). Although these studies in China suggest a different gender pattern for self-injurious behaviors compared to that in western countries, they do not provide any reasonable explanations.

Using the data from a survey conducted among first- and second-year college students in a university in western China, this present study aimed to analyze the sex difference in self-injurious behaviors among college students and to try to explain the self-injurious behaviors among college students by sex through looking at gender role conflicts and violent experiences.

Methods: The data was collected in September and October of 2013 via "A Survey for Adolescents' Health Risk Behaviors" conducted at Xi'an Jiaotong University. Students in four disciplines—science, engineering, medicine, and literature—and from 11 schools—Science, Mechanics, Electrical Engineering, Dynamic, Telecommunications, Life Science, Spaceflight, Medical Science, Economics and Finance, Public Policy and Administration, and Humanities—took part in the survey. Out of 1200 questionnaires issued, 960 were returned.

The three schools from which the most students participated were Medical Science, Telecommunications, and Mechanics, followed by Electrical Engineering, Life Science, Public Policy and Administration, and Humanities. The mean age for the respondents is 18.69, with the eldest being 24 and the youngest 15; in addition, 33.2% of respondents are from rural areas and 67.8% from urban areas. In order to measure adolescents' self-injurious behaviors, Non-Suicidal Self-Injury Assessment Tool (NSSI-AT) developed by Janis Whitlock and Amanda Purington (Whitlock & Purington, 2007) was adopted. A comparison analysis was conducted on the prevalence, frequency, wounded location, forms, motivation, and consequences of self-injurious behaviors among college students by sex. Based on the results, the binary logistic analysis method was further adopted, with the likelihood of self-injurious behaviors as the dependent variable, to construct a series of associated factors models for self-injurious behaviors among college students by sex.

Results. The descriptive analysis demonstrates that, as reported in the data, the prevalence of self-injurious behaviors and frequency of severe self-injurious behaviors among male students are significantly higher than among female students. At the same time, there are some slight gender differences in the wounded locations, forms, and motivations for self-injurious behaviors among college students; in other words, self-injurious behaviors are more aggressive and violent among male students than among female students. The results of the analysis on factors associated with self-injurious behaviors identified that gender role conflicts have a positive impact on self-injurious behaviors among both male and female college students, but the significance and the explanation power are different between males and females. The impact of gender role conflicts on male students' self-injurious behaviors is significant ($p < 0.001$), and the explanation power is also large (Cox and Snell R2 = 0.05; Nagelkerke R2 = 0.08), indicating that gender role conflicts can well explain male students' self-injurious behaviors; among female students, by way of contrast, gender role conflicts affect female students' self-injurious behaviors to some extent but with limited significance and explanation power ($p < 0.05$; Cox and Snell R2 = 0.01; Nagelkerke R2 = 0.02), indicating that variables other than gender role conflicts may explain female students' self-injurious behaviors. This suggests that in the context of Chinese culture and reality, gender role conflicts is the most important variable for providing a good explanation of the "boy crisis" in self-injurious behaviors, which is also apparent in previous research. For example, the dimensions of "competition" and "motivation for success" are the protective factors for male adolescents' suicidal behaviors, while "emotional disclosure with anxiety or negativity" are risk factors for male adolescents' suicidal behaviors (Galligan, Barnett, Brennan, & Israel, 2010). Other studies have also pointed out that gender role stress can accurately predict anxiety and other risky health behaviors among males (Eisler, Skidmore & Ward,1988) . Further analysis revealed that violent experiences have a significant impact on both males' and females' self-injurious behaviors, with the male and female students who have experienced verbal violence being more likely to use self-injurious behaviors. Besides, visual and sexual violence have a significant impact on female students' self-injurious behaviors, with the female students who have experienced visual and sexual violence being more likely to use self-injurious behaviors. It is worthwhile to notice that in this study, although the impacts of sexual violence on female students' self-injurious behaviors are significant at the level of $p < 0.1$, the regression coefficients are large (6.03, 7.87), whether or not the control variables are included in the model. This suggests that sexual violence experiences, such as sexual assault and sexual abuse, are much significantly associated with female self-injurious behaviors, but owing to the small number reported in the sample (only six female students reported violent experiences, which was only about 1.4% of the total sample), the significance is lower.

Conclusions. To some extent, there is a boy crisis in self-injurious behaviors among college students in China, and gender role conflicts are the important variable for explaining this crisis; in addition, verbal violence leads to self-injurious behaviors among both male and female college students, while visual and sexual violence leads to self-injurious behaviors among female students.

Fundings and Acknowledgements: This research was jointly supported by a project sponsored by The China Ministry of Education of Humanities and Social Science project (Grant number: 13YJAZH118), the Fundamental

Research Funds for the Central Universities (Grant number: SK2013025), the 985-3 Project of Xi'an Jiaotong University and Shaanxi Laboratory for Population and Development Research. The authors would like to acknowledge the contribution of Janis Whitlock (Research Scientist in Cornell University) who generously sent her questionnaires (NSSI-AT) for our reference.

Contact information: Mailing Address: Xueyan Yang, 653 Arastradero RD., Palo Alto, CA, 94306. Email: xueyan@stanford.edu; Tel and Fax: 650-724-3566 (O) Cell: 650-285-9300

---

19. Title: Sex differences and the role of IL-10 in ischemic stroke recovery.

Authors List: Sarah E. Conway B.A.[1], Meaghan Roy-O'Reilly M.S.[2], Ilene Staff Ph.D.[3], Gil Fortunato M.B.A.[3], Louise D. McCullough M.D. Ph.D.[1,2]

Author Affiliations: [1]Department of Neurology, School of Medicine, University of Connecticut, Farmington, Connecticut.[2] Department of Neurology and Neuroscience, University of Connecticut Health Center, Farmington, Connecticut. [3]Research Program, Hartford Hospital, Hartford, Connecticut.

Abstract: It is known that sex differences exist in stroke especially with regards to recovery. Women have poorer recovery post-stroke than men, and many factors contribute to this female disadvantage including sex-specific comorbidities, varying social support, and higher depression rates. Women also have higher rates of post-stroke immunosuppression leading to worse acute outcomes. IL-10 is an anti-inflammatory cytokine produced by Th2 CD4+helper T cells. In ischemic stroke an excessive IL-10 response contributes to post-stroke immunosuppression and increases the risk of post-stroke infection leading to poor outcomes. However, it is unknown if sex differences exist in IL-10 after ischemic stroke. In this study we investigated the relationship between IL-10 levels and stroke outcomes in men and women who suffered an acute ischemic stroke. Serum samples were drawn from 155 patients (70 women and 85 men) at 24±6 hours post-ischemic stroke. IL-10 levels were measured using a multiplex ELISA (BioRad). The primary outcome was in hospital mortality or hospice. Secondary outcomes were change in NIHSS, modified Rankin score (mRs) at 3 and 12 months, modified Barthel index (MBI) at 3 and 12 months, mortality at 3 and 12 months, and rate of post-stroke infection. Only in women were higher levels of IL-10 associated with death or hospice (p=0.018). In addition, in women only higher levels of IL-10 were associated with more severe strokes as measured by NIHSS on admission (p=0.049), development of post-stroke urinary tract infections (p=0.003), and 3 (p=0.035) and 12 month "poor" composite outcomes (p=0.022) defined as death or disabled with a mRs greater than 2. In conclusion, higher levels of IL-10 are associated with worse acute and chronic ischemic stroke outcomes in women but not in men. Future studies are needed to further assess the role of IL-10 in stroke and why these sex differences exist.

Funding: Hartford Hospital Research Department

Contact Information: Sarah E. Conway; sconway01@hhchealth.org

---

20. Title: Hypothalamic estrogen receptor alpha signaling modulates energy expenditure but not food intake in female mice

Authors List: Stephanie M. Correa, Ph.D., William C. Krause, Ph.D., Candice B. Herber, Ph.D, and Holly A. Ingraham, Ph.D.

Author Affiliations: Department of Cellular and Molecular Pharmacology, University of California San Francisco, San Francisco, CA 94143.

Abstract: Estrogen receptor alpha (ERa) signaling is required for normal energy homeostasis. Indeed global or CNS-specific ERa ablation leads to obesity due to lower energy expenditure and higher food intake. In

females, estrogen-responsive changes in thermogenesis and locomotion have been linked to the ventromedial hypothalamic nucleus (VMH) using *Sf1Cre*, while changes in feeding have been linked to the arcuate nucleus (ARC) using *PomcCre*. However, recent lineage tracing studies find that the *PomcCre* driver marks other neuronal populations within and outside the ARC, calling into question the specificity of *PomcCre*-mediated gene ablation. We ablated all hypothalamic ERa using the *Nkx2-1Cre* driver (*Esr1*$^{Nkx2\text{-}1Cre}$). Consistent with the female-specific roles of ERa in the VMH, *Esr1*$^{Nkx2\text{-}1Cre}$ female mice exhibit reduced brown adipose tissue (BAT)-induced thermogenesis and decreased locomotion. Compared to *Esr1*$^{f/f}$ littermates, *Esr1*$^{Nkx2\text{-}1Cre}$ females exhibit a whitening of BAT and lower *Ucp1* expression in BAT of females housed at 22°C and 4°C. Similarly, total and ambulatory movement are reduced in *Esr1*$^{Nkx2\text{-}1Cre}$ females, while physical activity is unaffected in *Esr1*$^{Nkx2\text{-}1Cre}$ males. Surprisingly, food intake was not affected by loss of hypothalamic ERa, suggesting that hypothalamic ERa signaling is important for normal thermogenesis and locomotion but dispensable for normal food intake. Indeed, estrogen induces phosphorylation of ribosomal subunit S6, a robust marker of neuronal activity, in the VMH, but the ARC appears less sensitive. These studies raise the possibility that estrogen modulates food intake via extra-hypothalamic *Pomc* neurons. Future studies will directly test the role of estrogen signaling in the ARC and other brain regions using functional and pharmacogenetic technologies that confer anatomical and molecular specificity. Defining the estrogen-responsive feeding centers will begin to uncover sex differences in the neural circuits that regulate feeding behavior.

Funding: This study was funded by grants to HAI (NIDDK R01DK099722, AHA Grant-in-Aid 13GRNT16120004) and SMC (NIDDK K01DK098320).

Contact Information: Stephanie Correa, UCSF Department of Cellular and Molecular Pharmacology, 1550 4th St. Box 2611, San Francisco, CA 94143; lab: 415-476-3401; stephanie.vanveen@ucsf.edu

---

21. Title: Developmental changes in Y chromosome gene expression in the mouse cortex and hippocampus

Authors List: Alex Dang, Chris Armoskus, Saori Taniguchi, Lester Fulay, and Houng-Wei Tsai, Ph.D.

Author Affiliations: Department of Biological Sciences, California State University, Long Beach, Long Beach CA 90840

Abstract: To elucidate the genetic mechanism that governs differences in brain structures and circuits underlying distinct cognitive and social behaviors between the sexes, we have previously used gene expression microarrays to identify 90 candidate genes differentially expressed in the neonatal cortex/hippocampus between male and female mice, including three genes, *Ddx3y*, *Eif2s3y*, and *Kdm5d*, located on the non-recombining region (NRY) of the Y chromosome. Without undergoing recombination with the X chromosome, NRY genes are exclusively expressed in males, but it still remains unclear if their levels change during development. In the present study, we hypothesize that expression of NRY genes is altered during early development, which might be responsible for masculinization of brain development and behavior. To test our hypothesis, we used reverse transcription with real time polymerase chain reaction (RT-qPCR) to measure mRNA levels of six NRY genes, *Ddx3y*, *Eif2s3y*, *Kdm5d*, *Uba1Y*, *Usp9y*, and *Uty*, in the male and female mouse cortex/hippocampus collected at birth (PN0), 7 (PN7), 14 (PN14), and 21 (PN21) days after birth. In consistent with the literature, the six Y-linked genes we measured were exclusively expressed in the male, but not female, cortex/hippocampus during early development. With analysis of one-way ANOVA or Kruskal-Wallis test, we discovered significant changes in relative mRNA levels of these genes with age. For *Ddx3y*, *Kdm5d*, and *Uba1y*, a significant rise in mRNA levels was observed on PN21 when comparing to PN0. Similar to those genes, *Uty* expression significantly increased with age, but occurred on both PN14 and PN21 while a decrease in mRNA levels was observed for *Usp9y* on PN21. In contrast, two elevations of *Eif2s3y* mRNA were found on PN7 and PN21. Our data demonstrate that for the first time expression of NRY genes in the mouse cortex/hippocampus is age-dependent, suggesting that these genes might differentially participate in brain masculinization.

Funding: This work was supported by National Institutes of Health Grant SC3GM102051.

Contact Information: Houng-Wei Tsai, Department of Biological Sciences, California State University Long Beach, 1250 Bellflower Blvd., Long Beach, CA 90840; 562-985-5649; Houng-Wei.Tsai@csulb.edu

---

22. Title: Sex differences in the mitochondrial pathophysiology of neonatal hypoxic ischemia

Authors List: T.G. Demarest , M.S.[1], Schuh R.A., PhD, [3] J. Waddell, PhD [2], M.C. McKenna, PhD [2], G. Fiskum, PhD[1]

Author Affiliations: Department of Anesthesiology and Shock, Trauma, Anesthesiology Research (S.T.A.R.) Center[1], Department of Pediatrics and Program in Neuroscience[2], Department of Neurology[3], University of Maryland School of Medicine, Baltimore, Maryland 21201,

Abstract: Clinical and experimental studies of neonatal cerebral hypoxic-ischemia (HI) suggest long-term cognitive impairments are greater in males than females with no obvious histopathological sex differences. Given that mitochondrial bioenergetic dysfunction contributes to ischemic injury, we tested the hypothesis that secondary bioenergetic dysfunction occurs 20 hours following neonatal HI of 7 day old rat pups in a sex dependent manner. Respiration of isolated mitochondria 20 hr following HI revealed complex I-dependent respiratory rates from both sexes were impaired, with male rates significantly lower than females, in both hemispheres. While respiratory impairment in both hemispheres was observed for Complex II-dependent respiration, there was no obvious sex difference. The fact that uncoupler (FCCP)-stimulated respiration was impaired similarly to that of state 3 respiration indicates that inhibition of the ATP synthase or ATP/ADP translocase are not responsible for respiratory impairment. Mitochondrial biogenesis (mtDNA:nDNA) was increased 1.5 fold in the ipsilateral cortex vs. sham in both sexes suggesting mitochondrial respiratory impairment is a functional deficit and not due to quantity of mitochondria. Oxidative stress was assessed as a contributing factor to the observed sex difference in mitochondrial respiratory impairment assessment of the glutathione antioxidant system. Results indicate females have ~40% more reduced glutathione (GSH) vs. males in sham animals and that GSH is decreased in females but not males following HI. The inability of male pups to utilize reduced GSH following HI is associated with a decrease in mitochondrial glutathione peroxidase 4. Based on our results, we conclude that sexually dimorphic impairment of brain mitochondrial respiration and antioxidant defense systems by HI contribute to HI pathophysiology and are targets for neuroprotective interventions that should be tested in both sexes.

Funding: Supported by NIH 5P01 HD016596-27.

Contact Information: Tyler G. Demarest, Department of Anesthesiology and Shock, Trauma, Anesthesiology Research (S.T.A.R.) Center, 685 W. Baltimore Street, MSTF 5-54, Baltimore, MD 21201; (410) 706-2990; tdemarest@anes.umm.edu.

---

23. Title: X-linked histone demethylase Kdm6a regulates motor coordination and depression-like behavior in mice

Authors List: Terri Driessen Ph.D.[1], Anna Aversa[1], Caroline Baer[1], Matthew Landowski B.S.[1], Ge Kai Ph.D.[2], Jun Xu Ph.D.[1]

Author Affiliations: [1]Department of Integrative Physiology and Neuroscience, Washington State University, Pullman, WA 99164, USA; [2]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD 20814, USA

Abstract: Kdm6a is an X-linked, dimorphically expressed gene which potentially contributes to sex differences in the brain. It encodes a histone demethylase that activates gene expression via removal of the repressive methylation mark at histone H3 lysine 27 (H3K27). In humans, KDM6A mutations cause Kabuki syndrome, a

disorder associated with intellectual disability and motor coordination deficits. To assess the role of Kdm6a in brain development and behavior, we generated a neuron-specific Kdm6aDEL mouse model. The Kdm6aDEL mice and wild type (WT) littermates have comparable body weight, reproductive behavior, and lifespan, different from the constitutive female Kdm6a KO mice which die prenatally. The Kdm6aDEL and WT mice scored similarly intests such as fear conditioning, anxiety (open field and elevated plus maze), locomotor activity, and grip strength. However, relative to WT mice, the Kdm6aDEL males exhibited less depression-like behavior and an adult-onset deficit in motor coordination. Following the motor coordination test, cFos immunohistology was performed which revealed increased neuronal activity in the cerebellum of Kdm6aDEL relative to WT mice. Also in the cerebellum, gene expression analysis detected a down-regulation of the NMDA receptor subunit 3b gene (Grin3b) in Kdm6aDEL, while other NMDA receptor genes quantified were similarly expressed between the mutant and WT mice. These results confirmed the importance of the X-linked chromatin enzyme Kdm6a in brain function and behavior. The phenotype of reduced depression-like behavior in Kdm6aDEL mice is intriguing, considering the higher prevalence of depression among women than men. Ongoing studies include a comprehensive analysis of the Kdm6aDEL females as well as mice with brain region-specific Kdm6a mutations.

Contact Information: Terri M. Driessen (terridriessen@vetmed.wsu.edu) and Jun Xu (junxu@vetmed.wsu.edu); Dept. of Integrative Physiology and Neuroscience, Washington State University, Pullman, WA 99164, USA; 1-608-338-5679

---

24. Title: Sex and gender integration into Canadian health research: The Canadian Institutes of Health Research's *Sex and Gender Champions*

Author Affiliations: Annie Duchesne[1], PhD, Abigail Forson[2], MA; Joy Johnson[2,3], RN, PhD; Cara Tannenbaum[2,4], MD, MSc, Gillian Einstein[1,2,5], PhD

Affiliations: [1]Department of Psychology, University of Toronto; [2]Institute of Gender and Health, Canadian Institutes of Health Research; [3]Simon Fraser University; [4]Université de Montreal; [5]Dalla Lana School of Public Health, University of Toronto

Abstract: The Canadian Institutes of Health Research (CIHR) and the National Institutes of Health have called for inclusion of males and females in both preclinical and clinical research. This is to ensure reliability of data, and guarantee equity in the burden of participation and benefit from the knowledge gleaned. The question remains: How do we mentor those who do not know how to integrate sex and gender (S/G) in their research program to ensure this goal is met?

CIHR, through its Institute of Gender and Health (IGH) is developing a framework for ensuring that research supported by CIHR integrates S/G. This framework includes: (1) a research application mandatory question about the inclusion of S/G; (2) reviewer training for evaluating that question's answer; and (3) the inclusion of *Sex and Gender Champions (SGCs)*, researchers who have expertise in areas under study as well as S/G who will advocate for meaningful integration of S/G considerations across the research program.

This poster describes IGH strategy including current best practices to guide the work of SGCs as they have been integrated in two pan-Canadian research programs. Current best practices include:

- Identifying key individuals on or brought on the team to forward methods, questions, and analyses that take S/G into account;
- Incorporating principles and procedures to ensure that all researchers understand the mandate;
- Including experts in S/G on advisory boards and program review criteria that include S/G;
- Establishing a publication policy requiring that papers using data emerging from the research address S/G in the choice of animals and participants;
- Devising inclusion and exclusion criteria that do not bias participants to one sex or the other;

- Collecting histories of surgeries such as oophorectomies and prostate removal as well as hormonal treatments and relevant biomarkers such as androgens, estrogens, and progestagens;
- Gathering information about gendered life experience.

Funding: The Institute of Gender and Health, Canadian Institutes of Health Research

Contact Information: Annie Duchesne, Department of Psychology, 100 St. George St., Toronto, ON M5S 3G3, Canada

---

25. Title: 17β-Estradiol (E2) And Estrogen Receptor (ER)-α Mediate Improved Right Ventricular Adaptation To Experimental Severe Pulmonary Hypertension (PH)

Authors List: Andrea L. Frump[1], Margie Albrecht[1], Alexandra Vayl[1], Amanda Fisher[1], Anthony Cucci[1], Todd Cook[1], and Tim Lahm[1,2]

Author Affiliations: [1]Indiana University School of Medicine and [2]Richard L. Roudebush VA Medical Center; all in Indianapolis, IN, USA.

Abstract: Background: PH is a sexually dimorphic disease characterized by excessive pulmonary artery vasoconstriction and remodeling that ultimately leads to right ventricular (RV) failure and death. Survival is primarily determined by RV function. Despite increased susceptibility to PH development, female patients survive longer and exhibit better RV function than male patients. This effect is likely due to at least in part to RV-protective effects of E2; however the underlying mechanisms are unknown. We **hypothesized** that improved RV function in females is mediated through E2- and ERα-dependent effects on pro-survival and anti-apoptotic signaling.

Methods: We used a well-characterized angioproliferative model of PH induced by administration of Su5416 and chronic hypoxia (SuHx-PH) in age-matched male and female Sprague-Dawley rats. Subgroups of female SuHx rats were ovariectomized (OVX) ± E2 repletion (75 mcg/kg/d). Subgroups of male rats were treated with E2 or ERα-agonist PPT (850 mcg/kg/d). $P<0.05$ by one-way ANOVA was considered significant.

Results: RV ERα expression was decreased by 30% in OVX rats but restored in E2 replete rats ($p<0.05$). E2 replete OVX rats exhibited decreased pro-apoptotic signaling (assessed by Bcl2/Bax ratio and cleaved caspase-3 activity). ERα was expressed in cardiomyocyes and its abundance correlated positively with physiological parameters indicating improved RV function, including cardiac output ($r=0.46$, $p<0.05$) and apelin expression (a marker of angiogenesis and pro-contractile signaling; $r=0.57$, $p<0.05$), and correlated negatively with SuHx-induced increases in RV systolic pressure ($r=-0.45$, $p<0.05$) and RV hypertrophy ($r=-0.61$, $p<0.05$). RV-protective E2 effects were replicated in male SuHx-PH rats treated with E2 or PPT; these animals exhibited improved RV function, increased apelin expression, and decreased pro-apoptotic signaling ($p<0.05$).

Conclusions: Our data suggest RV-protective, ERα-mediated effects of E2 in a model of severe PH.

Funding: This study was funded by Gilead PAH Research Scholars Program (TL), VA Merit 1I01BX002042-01A2 (TL) and NIH 5T32HL091816-05 (AF).

Contact Information: Andrea Frump, PhD, R3/Walther Hall, roomC407, 980 W. Walnut St, Indianapolis, IN 46202, 317-278-5397, anfrump@iu.edu.

---

26. Title: Stably expressed genes- Commonality and differences between the sexes

Authors List: James C. Fuscoe, Ph.D., Kejian Wang, Ph.D., and Vikrant Vijay, Ph.D.

Author Affiliations: Division of Systems Biology, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR

Abstract: Recently, we used RNA-Seq to profile gene expression levels across 11 organs at 4 developmental stages (from immature to old age) in both sexes of F344 rats (n=4/group; 320 samples). Expression changes (calculated as the maximum expression/ minimum expression for each gene) of >19000 genes across organs, ages, and sexes ranged from 2.6 to $>10^9$- fold, with a median of 262-fold. Genes whose expression varies within a narrow range (Stably Expressed Genes) may be involved in core cellular processes necessary for basic functions. The expression of 278 genes was found to vary ≤4-fold and these genes were significantly involved in protein catabolism (proteasome and ubiquitination), RNA transport, protein processing, and the spliceosome. Examination of Stably Expressed Genes separately in females and males identified more than twice as many genes whose expression varies ≤4-fold in females (928) as in males (455). 371 genes were stably expressed in both females and males, with 557 being stably expressed only in females and 84 being stably expressed only in males. The same stable pathways described above were found in females and males, although the specific genes involved were not identical, and there were no unique pathways identified in males. Several pathways were found to be stably expressed only in females, including mTOR signaling, endocytosis, and ribosome biogenesis. The chromosome location of the stably expressed genes was not significantly different between females and males, indicating that the sex-difference is not due to X-linkage of these genes. Such stably expressed genes and pathways across life-stages suggest that tight control of these processes is important in basic cellular functions and that perturbation by endogenous (e.g., genetics) or exogenous agents (e.g., drugs, environmental factors) may have adverse effects. The finding of sex-specific stable genes and pathways suggest that there may be sex-differences in susceptibility to such adverse effects.

Funding: US FDA

Contact: James C. Fuscoe, FDA-NCTR, 3900 NCTR Rd., Jefferson, AR 72079; 870-543-7126: James.Fuscoe@fda.hhs.gov

---

27. Title: Sex Differences: Association of Body Mass Index with Anatomical Architecture of Reward Network Regions in Healthy Subjects

Author Affiliations: Arpana Gupta (PhD)[1]**,** Emeran A. Mayer (MD)[1,3], John van Horn (PhD)[2], Mher Alaverdyan (MPH)[1], Connor Fling (BSc)[1], Kirsten Tillisch (MD)[1], Claudia Sanmiguel (MD)[1], Jennifer S. Labus (PhD)[1]

Author Affiliations: [1]Oppenheimer Family Center for Neurobiology of Stress and Pain and Interoception Imaging Network (PAIN), Division of Digestive Diseases, David Geffen School of Medicine at UCLA; [2]The Institute for Neuroimaging and Informatics, Keck School of Medicine, USC; [3]Ahmanson-Lovelace Brain Mapping Center, UCLA

Abstract: Alterations in key brain regions of the extended reward network have been linked to increased ingestive behaviors in obesity. The topology of the brain can be quantified using network metrics of centrality that index a brain region's contribution to the network's structural integrity and information flow. Regions with high *degree* are considered essential for facilitating functional integration. The ability of a region to propagate information across a network of regions is referred to as *local efficiency*. We hypothesized that differences in the degree and clustering coefficients of extended reward network regions would be related to BMI and sex. 99 healthy male and female subjects completed structural diffusion tensor imaging (DTI) MRI scans. Segmentation and parcellation of each brain into 165 regions was performed using Freesurfer. Deterministic tractography was performed using TrackVis and provided a measure of relative fiber DTI density between regions. Network metrics (degree, local efficiency) based on DTI were generated for the extended reward network using the Brain Connectivity Toolbox. Controlling for age, the general linear model was applied to test the hypotheses. BMI was positively associated with degree of reward regions (e.g. nucleus accumbens) but negatively associated with inhibitory cognitive regions (vmPFC). BMI was positively associated with local efficiency for reward regions but negatively associated with anterior insula and vmPFC. For degree, males had a positive correlation with dlPFC

and females had a positive correlation with NAcc. For local efficiency, males had a negative correlation with hippocampus. Findings indicate that higher BMI and being female is associated with more local and regional communication between regions with increased dopamine production, and less information propagation was observed in the cognitive frontal regions. Longitudinal studies need to address causality between BMI*sex and ingestive behaviors.

Funding: Supported by NIH grants P30 DK041301, R01 DK048351, P50 DK64539. UCLA Ahmanson-Lovelace Brain Mapping Center (Pilot Scanning)

Contact Information: Arpana Gupta, Oppenheimer Center for the Neurobiology of Stress, Ingestive Behavior and Obesity Program, CHS 42-210, 10833 Le Conte Avenue. Los Angeles, CA 90095, USA, Tel: (865) 406 0839, Fax: (310) 825 1919

---

28. Title: Dietary fructose induces hyperglycemia, hypertension, and pathologic changes in kidney and liver during rodent pregnancy

Author Affiliations: Linda Shortliffe MD, Olfat Hammam MD, **Xiaoyuan Han PhD**, Erik Kouba MD, Philip S. Tsao MD, Bingyin Wang MD

Author Affiliations: Stanford University, School of Medicine, Department of Urology, Stanford, CA

Abstract: The incidence of pregnancies complicated by hyperglycemia and hypertension is increasing along with associated morbidities to mother and offspring. The high fructose diet is a well-studied model that induces hyperglycemia and hypertension in male rodents, but has been reported not to affect females. We hypothesized that the physiologic stress of pregnancy may alter metabolic responses to dietary fructose. In this study female Sprague-Dawley rats were divided into two gestational dietary groups: 1) 60% carbohydrate standard rat chow (Pregnant-S--controls) and 2) 60% fructose enriched chow (Pregnant-F). Weekly body weight, blood pressure, blood glucose, triglycerides, and insulin were measured in pregnancy and during the post-partum period. Major maternal organ weights and histological changes were also assessed after delivery. By midpregnancy Pregnant-F rats had increased weight, elevated blood pressure, higher fasting glucose, and elevated triglycerides compared with Pregnant-S rats. Both groups demonstrated elevated gestational insulin levels with signs of insulin resistance (increased HOMA-IR). Pregnant-F rats showed significant histopathologic hepatic steatosis and renal tubular changes characterized by tubular dilation and glomerulosclerosis. In conclusion, our findings provide a model in which dietary change during pregnancy can be examined. We demonstrate, moreover, that high dietary fructose ingestion in pregnant rats results in profound systemic and pathologic changes not appreciated during routine rodent pregnancy.

Funding: none

Contact Information: Xiaoyuan Han, 300 Pasteur Dr., Stanford University, School of Medicine, Department of Urology, Palo Alto, CA 94035; 1-209-938-8859; xyhan@stanford.edu

---

29. Title: Sex differences in metabolic and pathologic responses to dietary fructose in rodent model

Author Affiliations: Xiaoyuan Han PhD, Winifred Owumi MD, Olfat Hammam MD, China Chien, Linda Shortliffe MD

Author Affiliations: Stanford University, School of Medicine, Department of Urology, Stanford, CA

Abstract: Elevated dietary high fructose corn syrup (HFCS) is associated with hypertension and metabolic disorder, but sex response is unclear. We hypothesize that HFCS has a sex based effect on dietary intake,

metabolism, and pathology. We divided Sprague-Dawley rats (27 females and 18 males) by sex equally among 3 dietary groups: a) standard chow and water (CW); b) standard chow and soft drink (FS, decarbonated Sprite—5.89% fructose solution); and c) 60% fructose chow and water (FW). For 8 weeks: weekly body weight (BW), fluid, and chow intake, were recorded, and serum assayed for fasting blood glucose (FBG), plasma insulin (I), triglyceride (TG) and creatinine (Cr). Liver, kidney, heart, and aorta were preserved and histology examined. Liver and kidney were evaluated using semi-quantitative histologic grading. Results showed that FS rats drank more fluid/BW compared with rats on water (CW, FW); this finding was greater in females than males. Overall caloric intake and BW gain were similar in dietary groups for both sexes, but greater caloric proportion of the FS diet was from soft drink. Notably, only males had elevated FBG, I, and TG, while females had no elevation. Both FS and FW were associated with lower plasma Cr in both sexes. While both FS and FF males and females developed renal glomerulosclerosis and tubular injury and hepatic inflammation and ballooning; these changes were more severe in females than males. There were no differences in heart or aortic thickness or collagen/muscle ratio. We conclude that dietary fructose in either liquid (FS) or solid form (FW) caused dietary aberrations; FS showed increased fluid intake. While males showed metabolic change (FBG, I, TG), and females did not, females still suffered profound renal and hepatic histologic changes even on the lower fructose soft drink diet (FS). This model suggests that dietary fructose has a sexually dimorphic response measured by consumption, metabolism and histopathology.

Funding: none

Contact Information: Xiaoyuan Han, 300 Pasteur Dr., Stanford University, School of Medicine, Department of Urology, Palo Alto, CA 94035; 1-209-938-8859; xyhan@stanford.edu

---

30. Title: SRY is a vulnerability factor that underlies male sex bias in Parkinson's disease

Authors List: Joohyung Lee[1,2], Paulo Garcia-Pinares[1,2], Daniel Czech[1], Hannah Loke[1], Seungmin Ham[1,], Eric Vilain[3], **Vincent R. Harley**[1,2]

Author Affiliations: [1]MIMR-Prince Henry's Institute of Medical Research, Melbourne, Australia, [2]Department of Anatomy and Developmental Biology, Monash University, Melbourne, Australia, [3]Human Genetics, University of California Los Angeles, USA

Abstract: Parkinson's disease (PD) results from the selective loss of dopaminergic neurons from the substantia nigra compacta (SNc). Male-sex is a strong risk factor in PD and mechanisms underlying dopamine cell death in PD remain elusive. We showed previously that in healthy males, HMG box protein SRY in the SNc controls movement by transcriptional regulation of multiple components of the dopamine machinery. Here we describe an unsuspected role for *SRY*_ENREF_1 in PD. In two rat models of PD showing male sex bias, toxin-induced injury upregulates endogenous *SRY*_ENREF_1 expression in the SNc. In these PD models SRY upregulation is transient lasting about 2 weeks and occurs via DNA damage inducible factor, GADD45g, which is responsible for phosphorylation of GATA4 via a MAPK cascade, and SRY promoter activation. Transcriptional mechanisms by which SRY increases cell death will be discussed. Lowering *SRY* mRNA levels, by infusion of antisense SRY oligonucleotides into the SNc, had a protective effect, reducing motor deficits and reducing dopamine cell loss in male PD rats. Thus in the male brain SRY is a double-edge sword, which controls movement in healthy males, but with the onset of PD, aberrant SRY overexpression occurs which exacerbates cell death and symptoms.

Dewing, P.*, et al.* Direct regulation of adult brain function by the male-specific factor SRY. *Curr Biol* **16**, 415-420 (2006).

Czech, D.P.*, et al.* The human testis-determining factor SRY localizes in midbrain dopamine neurons and regulates multiple components of catecholamine synthesis and metabolism. *J Neurochem* **122**, 260-271 (2012).

31. Title: Link Between Gender Identity and Genes Involved in Sex Hormone Signalling

Authors List: Kate York[1], Lauren Hare[2], Kara Balakrishnan[1], Jaco Erasmus[3], Fintan Harte[3], Eric Vilain[4], and **Vincent Harley**[1]

Author Affiliations: [1]Sex Determination & Gonadal Development, MIMR-PHI, Clayton, VIC, Australia, [2]Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia, [3]Monash Gender Clinic, Monash Health, Melbourne, VIC, Australia, [4] Institute for Society and Genetics, University of California, CA, USA

Abstract: Little is known about the aetiology of transsexualism and both environmental and biological factors may contribute. Anatomical and MRI studies reveal that sexually dimorphic brain structures in male-to-female (MtF) transsexuals are more similar to females than males. It is also likely that there is a genetic component and genes involved in sex steroidogenesis are good candidates. Previously, *androgen receptor* (AR), *aromatase* (CYP19) and *oestrogen receptor* (ER) have been the focus of studies by we (1) and others, with variable results. We sought to further investigate the genetic basis of transsexualism by examining additional genes involved in sex steroid synthesis and signalling in a larger cohort. A genetic association study was conducted with 380 MtF transsexuals and 344 Caucasian male control subjects. Eight genes in the sex steroidogenesis pathway were analysed, seven of which have functional repeat length gene polymorphisms; *androgen receptor* (*AR*), *aromatase* (*CYP19*), *oestrogen receptor* β (*ERβ*), *oestrogen receptor α* (*ERα*), *Cyp11A1*, *progesterone receptor* (*PGR*) and *5-alpha reductase* (*5αR*). *Cyp17* is a T/C SNP. A χ^2 test was used to analyse the number of short and long alleles in each of these genes. Logistic regression was used to compute the ORs and 95% CIs for the genotypes in all genes. Gene-gene interactions were also analysed by binary logistic regression. Significant associations were identified between transsexualism and variants in *5αR*, with transsexual individuals being more likely to possess the TA(0)/TA(0) genotype than the male control subjects (P≤0.001). Associations were also identified with *ERα*, with transsexual individuals being more likely to have the short allele (P≤0.03). There was a higher incidence of the *Cyp17* A2A2 genotype in transsexuals than the male control cohort (P≤0.04). These findings suggest a significant role for 5αR in transsexual patients. 5αR converts testosterone (T) to its more potent form dihydrotestosterone (DHT), which then binds to the AR to produce an active hormone-receptor complex. Transsexual patients with TA(0) have a shorter version of the gene, potentially leading to a lower rate of conversion of T to DHT. Minor contributions from *ERα* and *Cyp17* are also indicated. We speculate that the consequence of the functional variants overrepresented in the MtF population may result in reduced androgen signalling in the MtF brain.

1.Hare L, Bernard P, Sanchez FJ, Baird PN, Vilain E, Kennedy T,and V Harley Androgen receptor repeat length polymorphism associated with male-to-female transsexualism. *Biol Psychiatry*. 2009;65(1):93-6.

32. Title: Sex- and gender-based medicine curriculum project: Slide library

Authors List: Heather Patel, Marjorie Jenkins, MD, Jongpil Cheon, EdD, Steven Crooks, PhD, Michael Song, PharmD, RPh, Robert Casanova, MD

Author Affiliations: Texas Tech University Health Sciences Center.

Abstract: Problem: Many healthcare teaching institutions lack proper medical education pertaining to sex and gender disparities in the progression and management of diseases.[1,2] Some educators do not realize they should incorporate this information into their lectures. Others may not have the time or the resources necessary to fully integrate sex and gender material into their lectures.

Approach: Multi-disciplinary teams including faculty and learners will work together to facilitate sex and gender integration into healthcare curricula. Not only are these teams raising awareness of the importance of including this material in lectures, they also aim to provide a means by which smooth incorporation can be achieved.

Students from several different schools are asked to create annotated PowerPoint slides explaining evidence-based sex discrepancies in many major disease states. Teachers will be able to download specific slides or entire slide sets and conveniently assimilate them into their lectures.

Results: The Sex and Gender Based Medicine Curriculum Project includes interactive modules, an integrated simulation case roadmap, and a slide library. The slide sets will be a part of the slide library and will be accessible on this website. My contribution to the slide library includes the slide sets on osteoporosis, diabetes, urinary tract infections, and sexually transmitted diseases. Additionally, I authored a How-To Guide for creating these slide sets, so that future slide set contributors will know how to approach a topic.

Significance: With the emergence of customized medical care, rising healthcare professionals need to be introduced to interpersonal differences such as gender discrepancies. Integrating sex and gender differences into medical education is a key part of creating evidence-based personalized medicine for men and women. With this mindset, future healthcare providers will begin to think dynamically for a diverse population of patients.

References: McGregor AJ, Templeton K, Kleinman MR, Jenkins MR. Advancing sex and gender competency in medicine: sex & gender women's health collaborative. Biology of Sex Differences. 2013; 4:11.

Miller VM, Rice M, Schiebinger L, Jenkins MR, Werbinski J, Nunez A, Wood S, Viggiano TR, Shuster LT. Embedding concepts of sex and gender health differences into medical curricula. J Womens Health. 2013 Mar; 22(3):194-202. Epub 2013 Feb 15.

Funding: Grants from the Laura W. Bush Institute for Women's Health.

Contact Information: Heather Patel; 223 Indiana Ave. Apt. 2109; 469-737-0262; heather.patel@ttuhsc.edu.

---

33. Title: Female IBS patients show altered brain responses during uncertain, but not certain expectation of painful stimulation of the abdominal wall

Authors List: Jui-Yang Hong M.S.[1,3], Bruce Naliboff Ph.D.[1], Jennifer S. Labus Ph.D.[1], Arpana Gupta Ph.D.[1], Lisa A. Kilpatrick Ph.D.[1], Connor Fling[1], Cody Ashe-McNalley[1], Jean Stains[1], Suzanne R. Smith[1], Nuwanthi Heendeniya[1], Kirsten Tillisch M.D.[1], Emeran A. Mayer M.D.[1,2]

Affiliations: [1]Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA; [2]Ahmanson-Lovelace Brain Mapping Center, UCLA; [3]Department of Bioengineering, UCLA

Abstract: Irritable bowel syndrome (IBS), a common chronic visceral pain disorder, is more prevalent in women. Prior studies have used cued designs in which a specific cue gives the subject information about the probability of an aversive stimulus. It is hypothesized that symptom anxiety may be more related to context threat, in which there is no explicit threat cue but the experimental environment itself is associated from prior experience with aversive stimulation. We aimed to determine if uncertainty related to expected abdominal pain influences sex-specific group differences in brain responses between IBS patients and healthy controls (HCs). A functional magnetic resonance imaging technique was used to investigate the brain responses of 37 healthy controls (18 females) and 37 IBS patients (21 females) during three conditions: 1. a cued safe condition 2. a cued expectation of an electric shock 3. an ambiguous condition with no specific cue. Brain responses for cued anticipation and ambiguous contextual threat were evaluated by contrasting the regressions for the three conditions. Statistical significance was achieved with a minimum cluster size of 120 contiguous voxels. Female IBS patients had significantly greater anxiety and depression scores compared to female HCs. During contextual threat condition versus safe condition, IBS patients showed greater brain activations in affective (amygdala, ventral anterior insula), sensory (thalamus), and attentional (middle frontal gyrus) regions, and in the precuneus. These disease-

related differences were primarily seen in female subjects. In contrast, no disease-related differences were observed during cued expectation of abdominal threat condition versus safe condition. The observed greater engagement of cognitive and emotional brain networks in IBS patients especially in female patients during ambiguous contextual threat may reflect the propensity of female IBS patients to make prediction about the likelihood of future pain.

Funding: This study was supported by NIH grants P50 DK064539, R01 DK048351, U01 DK082370, and P30 DK041301. Pilot scans were provided by the Ahmanson-Lovelace Brain Mapping Center, UCLA.

Contact information: Jui-Yang Hong, Oppenheimer Family Center for Neurobiology of Stress, 10833 Le Conte Avenue, CHS 42-210 MC 737818, Los Angeles, CA 90095-7378; +1 (310) 206-0192; usagilberthong@hotmail.com

---

34. Title: Sex-specific effects of arsenic on global levels of histone mark H3K36me2 in peripheral blood mononuclear cells from Bangladeshi adults.

Authors List: Caitlin G. Howe[1]; Megan N. Hall, Ph.D.[2]; Xinhua Liu, Ph.D.[3]; Vesna Ilievski[1]; Vesna Slavkovich[1]; Faruque Parvez, DrPH.[1]; Abu B. Siddique, MBBS, MPH.[4]; Hasan Shahriar, MBBS [4]; Nasir Uddin, MS[4]; Tariqul Islam, MS.[4]; Joseph H. Graziano, Ph.D.[1]; Max Costa, Ph.D.[5]; Mary V. Gamble, Ph.D.[1]

Author Affiliations: [1]Department of Environmental Health Sciences, [2]Department of Epidemiology, [3]Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, New York; [4]Columbia University Arsenic Project in Bangladesh, Dhaka, Bangladesh; [5]Department of Environmental Medicine, Langone Medical Center, New York University, New York, New York

Abstract: In Bangladesh, more than 57 million individuals are chronically exposed to arsenic (As) at concentrations that exceed the WHO guideline for safe drinking water. This is a critical public health problem, because As is associated with multiple adverse health outcomes, with susceptibility differing by sex. Although the mechanism by which As induces disease remains unknown, As alters epigenetic marks in vitro, including histone marks H3K36me2 and H3K36me3. For this study, peripheral blood mononuclear cells collected from 318 As-exposed, Bangladeshi adults enrolled in the Folic Acid and Creatine Trial (FACT) were used to determine: 1) if exposure to As is associated with global levels (%) of histone marks, including H3K36me2, H3K36me3, and H3K79me2, 2) if these associations differ by sex, and 3) if As-induced changes in histone marks are reversed when As exposure is reduced due to the use of As-removal filters. In generalized linear models, urine As was positively associated with %H3K36me2 in males, both before (P = 0.02) and after (P = 0.03) adjusting for age, education, and BMI. However, As was not significantly associated with %H3K36me2 in females (Ps > 0.05). Furthermore, %H3K36me2 decreased significantly (P < 0.01, N=56) after the use of As-removal water filters for 12 weeks. Arsenic was not significantly associated with %H3K36me3 or %H3K79me2 in either men or women. These findings have two major implications that warrant further study: 1) As-induced alterations in epigenetic marks, such as %H3K36me2, may explain some of the sex-specific effects of As and 2) As-induced increases in %H3K36me2 may be reversible.

Funding: This study was funded by NIH grants P42 ES10349, RO1 CA133595, and T32 ES007322

Contact Information: Caitlin Howe, Ph.D. Candidate, Environmental Health Sciences, Mailman School of Public Health, Columbia University, 11th Floor, 722 W. 168th Street, New York, NY, 10032, 212-305-1205, cgh2121@cumc.columbia.edu

35. Title: Organizational influences of sex steroid hormones on corticosteroid receptor responses in male and female rats.

Authors List: Leyla Innala BSc, Yi Yang BSc, Adam Anonuevo MS, and Victor Viau PhD

Author Affiliations: Department of Cellular and Physiological Sciences, University of British Columbia, BC, Canada.

Abstract: The sex steroid milieu during the neonatal period in the rat exerts marked effects on the development of the hypothalamic-pituitary-adrenal (HPA) endocrine axis, including programming the process of stress habituation. Thus, previous findings in our lab indicate that blocking androgen receptors or preventing the conversion of testosterone to estrogen during the postnatal period impedes the normal decline in glucocorticoid steroid hormone responses seen during repeated stress. Using Western blot analysis of the glucocorticoid receptor protein in the hippocampus, we are currently examining in adult animals how postnatal alterations in androgen exposure in males and females are met by changes in glucocorticoid receptor signaling responses. As we intend on extending this analyses to other putative glucocorticoid negative feedback sites in the brain, we hope to reveal the sex- and region-specific nature by which the sex steroid hormones may come to permanently alter HPA axis function. Therefore, in this study we are interested in whether neonatal sex steroids have similar organizational effects on the HPA axes in female rats as we have previously seen in male rats. Secondly, if these changes in HPA output and habituation are due to neonatal sex steroid effects on the corticosteroid receptors.

Funding: Research supported by the National Sciences and Engineering Council of Canada (NSERC) and Canadian Institutes of Heath Research (CIHR) grants to VV.

Contact Information: Leyla Innala, Department of Cellular and Physiological Sciences, University of British Columbia, 2350 Health Sciences Mall, Vancouver, BC, Canada, V6T 1Z3; 1-604-822-9736; leyla@mail.ubc.ca

---

36. Title: Sex differences in neurosteroid and hormonal responses to metyrapone in posttraumatic stress disorder.

Authors List: Sabra Inslicht, Ph.D.[1,2,3], Anne Richards, MD[1,2,3], Erin Madden, MA[1,3], Madhu N. Rao, MD[1,3,4], Aoife O'Donovan, PhD. [1,2,3], Lisa Talbot, Ph.D.[1,2,3], Evelyn Rucker, MA[1,3], Thomas J., Metzler, MA[1,3], Richard L. Hauger, MD,[5,6] Thomas C. Neylan, MD[1,2,3].

Author Affiliations: [1]Stress and Health Research Program, San Francisco VA Medical Center, 4150 Clement St. (116P), San Francisco, CA, 94121, USA, [2]Department of Psychiatry, University of California, San Francisco, San Francisco, CA 94143, USA, [3]Northern California Institute for Research and Education (NCIRE), The Veterans Health Research Institute, San Francisco, CA, 94121, USA, [4]Department of Medicine-Division of Endocrinology, University of California, San Francisco, San Francisco, CA, 94143, USA, [5]Center of Excellence for Stress and Mental Health, San Diego VA Healthcare System, 3350 La Jolla Village Drive, San Diego, CA, 92161, USA, [6]Department of Psychiatry, School of Medicine, University of California, San Diego, CA, 9500 Gilman Drive, La Jolla, San Diego, CA 92093, USA

Abstract: RATIONALE: Mechanisms contributing to sex differences in the regulation of acute stress responsivity and their effect on the increased incidence of posttraumatic stress disorder (PTSD) in women are poorly understood. The reproductive hormone, progesterone, through conversion to allopregnanolone (ALLO), suppresses the hypothalamic pituitary adrenal (HPA) axis and has potent anxiolytic effects. The potential that progesterone and allopregnanolone reactivity modulate HPA axis responses and account for sex differences in PTSD has not been previously examined. **OBJECTIVE:** The present study examined the effects of sex and PTSD on adrenocorticotropic hormone (ACTH), progesterone, and allopregnanolone responses to metyrapone and whether progesterone and allopregnanolone reactivity could affect the ACTH response in PTSD. **METHODS:**

Healthy medication-free male and premenopausal follicular phase female participants with chronic PTSD (n = 43; 49% female) and controls (n = 42; 50% female) completed an overnight metyrapone challenge and ACTH, progesterone, and allopregnanolone were obtained by repeated blood sampling. **RESULTS:** The increase in ACTH response to metyrapone was higher in PTSD subjects compared to controls and in women compared to men. Contrary to our initial prediction of an inverse relationship, progesterone and allopregnanolone were positively associated with ACTH. Progesterone and allopregnanolone partially mediated the relationship between PTSD and ACTH. **CONCLUSIONS:** Our findings of increased ACTH to metyrapone in PTSD and in women may reflect heightened hypothalamic CRF hypersecretion. Progesterone and allopregnanolone partially mediated the ACTH response in PTSD. Further characterizing sex differences in these processes will advance our understanding of the pathophysiology of PTSD, and may ultimately lead to better-targeted, more effective treatment.

Funding: This research and development project was conducted by the Stress and Health Research Program at the San Francisco VA Medical Center and is made possible by a research grant that was awarded and administered by the US Army Medical Research and Materiel Command (USAMRMC) and the Telemedicine & Advanced Technology Research Center (TATRC), at Fort Detrick, MD (SI: W81XWH-05-2-0094). This study was also supported by the National Institute for Mental Health (TCN: 5R01MH073978-04, 5R34MH077667-03), the Veterans Health Research Institute, the Mental Illness Research and Education Clinical Center of the US Veterans Health Administration, and the Clinical Research Center of the National Center for Advancing Translational Sciences, National Institutes of Health, through UCSF-CTSI Grant Number UL1 RR024131. RLH was supported by a BLR&D Merit Review grant from the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, the VA Center of Excellence for Stress and Mental Health (CESAMH), and a NIH/NIMH (MH074697) RO1 grant.

Contact Information: Sabra Inslicht, Ph.D., San Francisco VA Medical Center, 4150 Clement St. (116P), San Francisco, CA 94121, 415-221-4810 x3341, sabra.inslicht@ucsf.edu

---

37. Title: Sex Differences in Slow Wave and REM Sleep in PTSD and Healthy Control Subjects

Authors List: Anne Richards, MD, MPH[1,2]**,** Thomas J. Metzler, MS[2], Leslie M. Ruoff, BA[2], Sabra S. Inslicht, PhD[1,2], Madhu Rao, MD[1,2], Lisa S. Talbot, PhD[2], Thomas C. Neylan, MD[1,2]

Author Affiliations: [1]University of California, San Francisco, CA, [2]San Francisco Veterans Affairs Medical Center, San Francisco CA

Abstract: **Background**: A growing literature shows prominent sex effects for risk for PTSD and associated medical comorbid burden. Prior research indicates that PTSD is associated with reduced slow wave sleep (SWS), which may have implications for overall health, and abnormalities in REM sleep, which have been implicated in specific PTSD symptoms. A major limitation of existing research is that most research has been conducted in male subjects. We therefore sought to compare SWS and REM sleep in male and female PTSD subjects with age and sex-matched control subjects. **Hypotheses**: Our primary hypothesis, confirming prior research, was that PTSD is associated with greater visually scored slow wave sleep and cumulative NREM delta power (i.e: delta energy), and that this finding would be most pronounced in males. Exploratory analyses examined overnight power in all frequency bands in both NREM and REM sleep, although based on recent findings we did not predict that PTSD would be associated with higher power in the higher frequency bands. Additionally, exploratory analyses of spectral power were performed to test for group (PTSD vs. control) by sex interactions. **Methods**: We used a cross-sectional, 2x2 design (PTSD/control x female/male) involving 83 medically healthy, non-medicated adults aged 19-39 in the inpatient sleep laboratory. **Results**: Visual analysis of EEG demonstrated that PTSD was associated with lower SWS duration ($F(3,82)=7.63$, $p=.007$) and SWS percent ($F(3,82)=6.11$, $p=.016$). There was also a group by sex interaction effect for REM duration ($F(3,82)=4.08$, $p=.047$) and REM percent ($F(3,82)=4.30$,

p=.041), explained by greater REM sleep in PTSD females as compared to control females, a difference not seen in male subjects. Quantitative EEG analysis demonstrated that PTSD was associated with lower energy in the delta spectrum (F(3,82)=6.79, p=.011) in NREM sleep. SWS and delta findings were more pronounced in males. **Conclusions**: These findings support prior evidence that PTSD is associated with impairment in the homeostatic function of sleep, especially in men with the disorder. Interaction effects of sex and PTSD status on REM sleep raise intriguing questions about the role of REM sleep in sexual dimorphism in PTSD pathophysiology.

Funding: National Institute of Mental Health grant (R01-MH73978) to Dr. Neylan

Contact Information: Anne Richards, MD, MPH, San Francisco VA Medical Center, 4150 Clement Street Box 116-C, San Francisco, CA 94121. Telephone: (415) 221-4810 x3312. E-mail: anne.richards@ucsf.edu

---

38. Title: Gender differences in plasma levels of anti-ANA and dsDNA antibodies in healthy donors, and these autoantibodies are not induced by influenza vaccination

Authors List: Wei Jiang[1*], Gary Gilkeson[2]

Author Affiliations: [1]Department of Microbiology and Immunology; Division of Infectious Diseases, Department of Medicine, Medical University of South Carolina; [2]Division of Rheumatology, Department of Medicine, Medical University of South Carolina

Abstract: The ratio of female to male is 9:1 in the prevalence of SLE. Double strand anti-DNA (anti-dsDNA) autoantibody plays a key role in SLE disease. In the current study, we investigate the mechanisms of gender bias in autoreactive antibody production in controls after influenza (flu) vaccination. Method. Plasma levels of anti-nuclear antibody (ANA) and anti-dsDNA autoantibody in a cohort of 5 healthy men and 11 healthy women received vaccines at 2012-2013 and 2013-2014 seasons. Blood draws were taken at 0, 7, and 14 days after the latest vaccination. Vaccine responses were defined by neutralization activities in plasma. Flu-specific antibody avidity was tested by ELISA. The levels of autoantibodies were analyzed in plasma by ELISA. Results: Women have higher levels of all 3 autoantibodies than men at D0, but not the flu-specific neutralizing activities or flu-specific antibody avidities. The median plasma levels of anti-ANA antibody (OD) at D0 were 0.2281 (IQR, 0.2058 – 0.2338) and 0.3697 (IQR, 0.2918 – 0.4261); and the median plasma levels of anti-dsDNA antibody (IU/mL) were 122.3 (IQR, 91.86 – 175.8) and 197.3 (IQR, 131.2 – 389.8), for men and women respectively ($P < 0.05$, Mann Whitney U). The levels of anti-ANA IgG were directly related to the levels of anti-dsDNA ($P < 0.05$, Spearman correlation test). Influenza vaccination did not change the titer of autoantibodies at any time point. Conclusions: Women have increased levels of autoantibodies than men, and these autoantibodies are not resulted from repeated influenza vaccination.

Funding: This study was funded by NIH AI091526, AI077283, AR062755, VA CSRD MERIT CX001211, and MUSC MCRC internal grant.

Contact Information: Wei Jiang, 173 Ashley Ave. BSB207. Charleston, SC, 29425. Phone: 843-8762457, email: jianw@musc.edu

---

39. Title: Microarray analysis of copy number variants on the human Y chromosome reveals novel and frequent duplications overrepresented in specific haplogroups

Authors List: Martin M Johansson[1*], Anneleen Van Geystelen [2], Maarten H.D. Larmuseau[2,3], Srdjan Djurovic[4,5], Ole A. Andreassen[6], Ingrid Agartz[6,7] and Elena Jazin[1*]

Author Affiliations: [1]Department of Organismal Biology, EBC, Uppsala University, Sweden [2]Laboratory of Socioecology and Social Evolution, Department of Biology, KU Leuven, Belgium [3]Forensic Biomedical Sciences,

Department of Imaging and Pathology, KU Leuven, Belgium. [4]Department of Medical Genetics, Oslo University Hospital, Oslo, Norway [5]NORMENT, KG Jebsen Centre for Psychosis Research, Department of Clinical Science, University of Bergen, Bergen, Norway [6]NORMENT, KG Jebsen Centre for Psychosis Research, Division of Mental Health and Addiction, Oslo University Hospital & Institute of Clinical Medicine, University of Oslo, Norway [7]Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, Norway

Abstract: The human Y chromosome is almost always excluded from genome-wide investigations of copy number variants (CNVs) due to its highly repetitive structure. This chromosome should not be forgotten, not only for its well-known relevance in male fertility, but also for its involvement in clinical phenotypes such as cancers, heart failure and sex specific effects on brain and behavior. We analyzed Y chromosome data from Affymetrix 6.0 SNP arrays and found that the signal intensities for most of 8179 SNP/CN probes in the male specific region discriminated between a male, background signals in a female and an isodicentric male containing a large deletion of the q-arm and a duplication of the p-arm of the Y chromosome. Therefore, this SNP/CN platform is suitable for identification of gain and loss of Y chromosome sequences. In a set of 1718 males, we found 24 different CNV patterns, many of which are novel. We confirmed some of these variants by PCR or qPCR. The total frequency of individuals with CNVs was 13.9%, including 9.3% with duplications, 4.5% with deletions and 0.1% exhibiting both. Hence, a novel observation is that the frequency of duplications was more than twice the frequency of deletions. Another striking result was that 10 of the 24 detected CNVs were significantly overrepresented in one or more haplogroups, demonstrating the importance to control for haplogroups in genome-wide investigations to avoid stratification. NO-M214(xM175) individuals presented the highest percentage (95%) of CNVs. If they were not counted, 12.3 % of the rest included CNVs, and the difference between duplications (9.4%) and deletions (2.9%) was even larger.

Our results demonstrate that currently available genome-wide SNP platforms can be used to identify duplications and deletions in the human Y chromosome. Future association studies of the full spectrum of Y chromosome variants will demonstrate the potential involvement of gain or loss of Y chromosome sequence in different phenotypes.

Funding: This study was funded by the Swedish Research Foundation, grant name: Sex determination factors in the brain encoded in the Y chromosome (Project number K2012-61X-22089-01-3)

Contact Information: Martin M Johansson, Department of Organismal Biology, Evolutionary Biology Centre, Uppsala University, Norbyvagen 18a 75236 Uppsala Sweden; +0046 (0)765-826899 martin.johansson@ebc.uu.se

---

40. Title: Portfolio Analysis of Sex and Gender Differences Research Awardees of Infectious and Immune Mediated Conditions - Funding the cutting edge of sex and gender difference science

Authors List: Tamara E. Lewis Johnson, MPH, MBA

Author Affiliations: Office of Extramural Research Policy and Operations, Division of Extramural Activities, National Institute of Allergy and Infectious Diseases

Abstract: Awardees of infectious disease and immune mediated sex and gender differences research grants were more likely to be independent researchers who proposed novel methods/techniques for conducting sex and gender differences research. Three rounds of the infectious diseases and autoimmune related research awardees were analyzed to better understand the characteristics of awardees and the areas of science in which they conduct sex and gender differences research in response to the Administrative Supplements for sex and gender differences research initiative sponsored by the National Institute of Health's Office of Research and Women's

Health. Research awardees were analyzed by the type of funding mechanism, areas of science, demographics, stage of career, research environment, cost of proposed research, and type of methods/techniques employed to study sex and gender difference science. It was predicted that research awardees would be established investigators with expertise in clinical research. Findings indicate that investigators were more likely to be a range of researchers including early stage investigators and merit award winning scientists. Areas of science tended to vary from foundational immunological basic research to human studies of familiar conditions such as HIV. Awardees were more likely to be funded through an independent research grant rather than a research network. Methods and techniques included innovative analyses, such as bioinformatics, as well as adding animals or patients to power a study to determine whether sex differences were statistically significant. These findings indicate that sex and gender differences research could enhance research design of vaccine, diagnostics and therapeutic studies and potentially advance the health of individuals living with infectious diseases and immune mediated conditions.

Funding: The portfolio analysis were supported by the National Institutes of Health, USA.

Contact Information: Tamara E. Lewis Johnson, Division of Extramural Activities, National Institute of Allergy and Infectious Diseases, 5601 Fishers Lane, Rockville, MD 20875; 1-240-669-2934; lewisjohnsont@niaid.nih.gov

---

41. Title: An Initiative to Increase Women Leadership in Academic Medicine: National Survey Results

Authors List: Erika Jones MD[1], May Bakir MD[1], Shivani Dhawan MS[1], Molly Carnes MD[2], Marjorie Jenkins MD[3], Paula A. Johnson MD, MPH[4], Wendy S. Klein MD[5], Noel Bairey Merz MD[1]

Author Affiliations: [1]Cedars-Sinai Heart Institute, Barbara Streisand Women's Heart Center, Los Angeles, California USA.[2] University of Wisconsin, Center for Women's Health Research, Madison, Wisconsin USA. [3] Texas Tech University Health Science Center, Center for Women's Health and Gender-Based Medicine, Amarillo, Texas USA.[4]Brigham and Women's Hospital, Connors Center for Women's Health & Gender Biology, Boston, Massachusetts USA. [5] Virginia Commonwealth University, Institute for Women's Health, Richmond, Virginia USA.

Abstract: Background: Women's leadership indicated by women deans, department and division chairs in Internal Medicine and Medicine Subspecialties has declined in the last decade (AAMC data). Holding an endowed chair is an important means of achieving a leadership voice in academic medicine. The value, experience, opportunities and barriers to endowed chair development in women's health (WH) is unknown.

Methods: We identified and surveyed 25 existing Endowed Chairs in Women's Health in Internal Medicine and Medicine Subspecialties using an online survey. **Results:** Overall results are depicted in the Table. Most see WH Endowed Chairs as valuable and an opportunity for advancing women in academic leadership. A majority endorsed WH Endowed Chairs increased the stature of WH as a discipline, and promoted inclusion of WH in clinical care, education and research. Barriers and opportunities were identified, including limited experience in grateful patient fundraising. **Conclusion**: Women's Health Endowed Chairs are perceived as an opportunity for advancing women in academic leadership in Internal Medicine and Medicine Subspecialities, as well as a route for inclusion of WH to improve clinical care, teaching and research. Attention to institutional barriers, academic-industry collaboration and grateful patient fundraising training appear to be areas of opportunity for WH Endowed Chair development.

Table: Women's Health Leadership Summit Survey Results

	% Agree with statement, [n=25]
WH is an opportunity for academic leadership	92%
Endowed Chairs in WH increase stature of women's health as a discipline	64%
Women's academic leadership leads to WH inclusion in clinical care, teaching, research	64%
Institutional policies prevent WH fundraising initiatives	52%
Academic-industry collaboration is acceptable when guidelines are clear	72%
I am comfortable with grateful patient fundraising experience	28%

Funding: The Barbra Streisand Women's Heart Center and the Linda Joy Pollin Women's Heart Health Program.

Contact Information: Noel Bairey Merz MD, The Barbra Streisand Women's Heart Center, Cedars-Sinai Medical Center, 127 S San Vicente Blvd, #A9-300, Los Angeles, CA 90048. 310.423.9680

---

42. Title: Sex and gender-roles relate differently to cortisol functioning, allostatic load, and mental health

Author Affiliations: Robert-Paul Juster[1, 2, 3], Jens C. Pruessner[4, 5], Alexandra Bisson Desrochers[1, 4, 6], Olivier Bourdon[1], Nadia Durand[1, 2], Nathalie Wan[1, 2], Valérie Tourjman[2, 8], Edouard Kouassi[2, 7], Alain Lesage[2, 8], Sonia J. Lupien[1, 2, 8*]

Author Affiliations: [1]Centre for Studies on Human Stress, Institute universitaire en santé mentale de Montréal; [2]Research Centre, Institute universitaire en santé mentale de Montréal; [3]Integrated Program in Neuroscience, McGill University; [4]Research Centre, Douglas Mental Health University Institute; [5]Departments of Psychiatry and Psychology, McGill University; [6]Department of Psychology, Université du Québec à Montréal; [7]Department of Medicine and Medical Specialties, Université de Montréal; [8]Departement of Psychiatry, Université de Montréal.

Abstract: Sandra Lipsitz Bem (1944 – 2014) proposed that androgynous individuals adaptively alternate between masculine and feminine gender-roles. Among 204 adults, we hypothesized that androgynous individuals of both sexes would evidence lower concentrations of cortisol, less multi-systemic 'wear and tear' known as allostatic load (AL), and better mental health than undifferentiated individuals who self-endorse low masculinity and low femininity. We found sex differences only for cortisol functioning: women had greater cortisol awakening responses than men who had higher AL than women when using a formulation that does not account for sex differences for 20 biomarkers. Using a sex-specific formulation, androgynous men showed lower AL than undifferentiated men who also had higher levels than undifferentiated women. Regardless of sex, androgynous individuals experienced higher self-esteem and well-being as well as lower depressive symptoms in comparison to undifferentiated individuals. In summary, both sex and gender-roles explain stress-related outcomes differently.

Funding: This study was funded by a grant (222055) from the Canadian Institutes of Health Research to S.J.L. who holds a Senior Investigator Chair on Gender and Mental Health from the Canadian Institute of Gender and Health (GSC 91039).

Contact Information: Robert-Paul Juster, Centre for Studies on Human Stress, Fernand-Seguin Research Centre of the Louis-H. Lafontaine Hospital, 7401 Hochelaga, Louis Riel Pavilion, Unit 226, Room RI-2678, Montreal, Quebec, Canada H1N 3M5. Tel.: +1 514 251 4000x3253; robert.juster@mail.mcgill.ca

43. Title: Sex-specific cardiomyocyte death in heart failure: influence of sex-specific calcium remodeling

Authors List: Georgios Kararigas Ph.D.[1], Cristina E. Molina Ph.D.[2], Holger Summer M.Sc.[3], Istvan Baczko M.D.[4], Stefan Golz Ph.D.[3], Vera Regitz-Zagrosek M.D.[1]

Author Affiliations: [1]Institute of Gender in Medicine and Center for Cardiovascular Research, Charite University Hospital, Berlin, Germany, [2]Cardiovascular Research Centre (CSIC-ICCC), Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [3]Bayer HealthCare, Wuppertal, Germany, [4]Department of Pharmacology and Pharmacotherapy, University of Szeged, Szeged, Hungary.

Abstract: In heart failure (HF), prognosis differs between men and women and there are major sex differences in cardiomyocyte death. However, the underlying mechanisms are unclear. We hypothesized significant sex differences in the cardiac transcriptome of end-stage non-ischemic dilated cardiomyopathy (DCM) patients. We compared left ventricular (LV) transcriptomes of closely-matched DCM men (n = 5; 53 ± 6 y) and women (n = 5; 55 ± 7 y) with male (n = 10; 56 ± 4 y) and female (n = 8; 56 ± 5 y) controls by genome-wide expression profiling. We identified 4273 transcript clusters regulated in male, 1344 in female and 2817 in both male and female LVs (adjusted P < 0.01). Pathway analysis (adjusted P < 0.05) revealed induction of ECM-receptor interaction and several inflammatory pathways in male LVs, while oxidative phosphorylation and proteasome pathways were repressed. In female LVs, the Wnt and Hedgehog signaling pathways were induced, while the mTOR signaling pathway was repressed. Although the Ca2+ signaling pathway was induced in both sexes, male LVs had a significantly higher induction of ca. 30% of genes encoding ion channels, accessory beta subunits and regulatory proteins than female LVs. In isolated ventricular myocytes (VMs) from DCM patients, while there were no sex differences in sarcoplasmic reticulum Ca2+ load, there was a 2-fold increase in L-type Ca2+ current density in male vs. female VMs (n = 6-8 cells/group; each cell originated from a different individual; P < 0.05). Pro-apoptotic cytochrome *c* release was significantly higher in male than female LVs (P < 0.05), while the anti-apoptotic protein BCL2 was higher in female than male LVs (P < 0.05). Ca2+-mediated dephosphorylation of pyruvate dehydrogenase was higher in male than female LVs (P < 0.01) indicating more Ca2+ present in male mitochondria. We conclude that sex-specific regulation of Ca2+ homeostasis may account for sex differences in cardiomyocyte death in HF, thereby affecting clinical prognosis.

Funding: This work was supported by the DZHK (German Center for Cardiovascular Research).

Contact Information: G. Kararigas; Charite University Hospital, Institute of Gender in Medicine & Center for Cardiovascular Research, Hessische Str. 3-4, 10115 Berlin, Germany; +4930450525355; george.kararigas@charite.de.

44. Title: Sex differences in the relationship between trait resilience and the intrinsic connectivity of the salience and default mode networks of the brain

Author Affiliations: Lisa A. Kilpatrick[1,2], Joshua J. Istrin[1], Arpana Gupta[1,2], Bruce Naliboff[1-4], Kirsten Tillisch[1-4], Jennifer S. Labus[1,2], Emeran A. Mayer[1-5]

Author Affiliations: [1]Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress, Departments of [2]Medicine, [3]Psychiatry, [4] Division of Digestive Diseases, David Geffen School of Medicine, UCLA, Pain and Interoception Network (PAIN) and [5]Ahmanson-Lovelace Brain Mapping Center, UCLA

Abstract:Background: Increased resilience is associated with better health outcomes and reduced morbidity in response to injury and homeostatic perturbations. Two brain networks potentially relevant for resilience are the salience network (SN) and the default mode network (DMN). Although sex differences exist in stress response patterns, preferred coping styles, and protective factors involved in resilience, the potential impact of sex/gender has been largely ignored in the study of the neurobiological correlates of resilience.

Aims: To identify relationships between a resilient personality profile and connectivity of the SN and DMN. We hypothesized that variations in trait resilience would be reflected in SN integrity and interaction with the DMN. Furthermore, we hypothesized that sex differences exist in the neurobiology of trait resilience.

Methods: 82 healthy subjects (46 female; 36 male) completed a resting fMRI scan and NEO personality inventory. Partial Least Squares was performed to examine sex differences and commonalities in the relationship between intrinsic connectivity and a resilient NEO personality profile.

Results: The PLS analysis identified 2 significant brain-behavior patterns reflecting mainly sex differences in the relationship between trait resilience and connectivity patterns among SN and DMN subnetworks. **Conclusions:** While the integrity of the anterior insula within the SN is important for resilience in both men and women, the results suggest that increased functional integration of the anterior DMN, a network involved in emotion regulation, preferentially benefits women while increased functional integration of the posterior DMN, a network involved in learning and memory, preferentially benefits men in terms of resilience. These findings may relate to previous literature demonstrating that men and women engage different behavioral strategies to achieve resilience and highlight the importance of considering sex and gender in resilience research.

Funding: P50 DK064539, R01 DK048351, K01 DK085133

Contact: Lisa Kilpatrick, Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress, 10833 Le Conte Avenue, CHS 42-210 MC 737818, Los Angeles, CA 90095-7378, 310-206-0547, lisa@lisakilpatrick.com

---

45. Title: Estrogen Receaptor Beta (ERβ) is required on CD11c expressing cells for ERβ-ligand mediated neuroprotection during EAE

Author Affiliations: Roy Y. Kim B.S.[1,2], Alexandra Hoffman[2], Rojan Kavosh[2], Noriko Itoh M.S.[2], Rhonda R. Voskuhl M.D.[2]

Author Affiliations: [1]Molecular Cellular and Integrative Physiology Interdepartmental Ph.D. Program [2]Multiple Sclerosis Program, University of California, Los Angeles

Abstract: Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS). Estriol, an estrogen that is only produced in significant amounts during pregnancy, has been shown to have neuroprotective effects in experimental autoimmune encephalomyelitis (EAE) and in a Phase II Trial for relapsing-remitting MS in women. Considering its safety record and binding preference to estrogen receptor β (ERβ) over ERα, the neuroprotective effects are suggested to work through ERβ activation. Here, we investigate the mechanisms of ERβ activation using a cell specific approach. Microglia and dendritic cells (DC), antigen presenting cells (APC) of the CNS, have the ability to initiate and propagate Th1/Th17 immune responses during EAE. To understand whether these cell types have an important role in ERβ-ligand mediated neuroprotection, we used CD11c promoter as the cre driver to generate conditional knockout (CKO) mice of ERβ (CD11c-CKO-ERβ) using Cre-loxP system. CD11c is known to be a marker for DC, however, recent studies reported a subset of microglia cells also express CD11c during EAE. We induced EAE in CD11c-CKO-ERβ mice and wildtype littermate control (CD11c-WT-ERβ) mice. Concurrently, we have started vehicle or ERβ-ligand treatment for both groups of mice. Our results demonstrated that, ERβ-ligand treatment did not ameliorate EAE clinical disease scores nor prevent axonal and myelin loss in the dorsal spinal cord of CD11c-CKO-ERβ mice compared to CD11c-WT-ERβ mice. Interestingly, ERβ-ligand treatment in both groups did not reduce T cell and macrophage infiltration into the dorsal spinal cord. Given that ERβ-ligand has anti-inflammatory effects on microglia cells, we looked at M1 (MHCII) vs M2 (Arg1) polarization among total Iba1$^+$ cells in the dorsal spinal cord. We found that ERβ-ligand treatment in CD11c-WT-ERβ mice reduced MHCII$^+$Iba1$^+$ cells, without having an effect on Arg1$^+$Iba1$^+$ cells, however, this effect was abolished in CD11c-CKO-ERβ mice. Together, our data show that ERβ is required on CD11c expressing cells for

ERβ-ligand mediated neuroprotection during EAE and that these cells mediate a direct neuroprotective effect by reducing M1 polarization in the dorsal spinal cord, despite having no effects on infiltrating immune cells.

Funding; RYK; UCLA Laboratory of Neuroendocrinology grant T32 HD07228-26 and Department of Neurology, RRV; NIH grant K24NS052117, NMSS grants RG4033 and RG4364

Contact Information: Roy Y. Kim, BS, 635 Charles E. Young Drive South, Neuroscience Research Building Room 480CO, Los Angeles, CA 90095-1489, Telephone: 310-206-4640, Email: roykim81@ucla.edu

---

46. Title: The Role of Sex and Gender in Anterior Cruciate Ligament Reconstructive Surgery Outcome

Authors List: Sabrina Kolker, MD[1], Jas Chahal, MD FRCSC MSc[1,2] Monique Gignac, PhD[3], [4] Paul Marks, MD FRCSC[5] Aileen Davis, PhD[1,6]

Author Affiliations: [1]Institute of Health Policy, Management and Evaluation, University of Toronto; [2]Division of Orthopaedics, University Health Network and University of Toronto; [3]Dalla Lana School of Public Health, University of Toronto; [4]Institute of Work and Health, Toronto; [5]Division of Orthopaedics, Sunnybrook Health Sciences Centre Holland Orthopaedic & Arthritic Centre and University of Toronto; [6]Health Care and Outcomes Research, Toronto Western Research Institute, University Health Network

Abstract: Women are three times more likely to tear their ACL compared to men. In young, active individuals ACL reconstructive surgery (ACLR) is most often the standard practice of care for patients hoping to return to their pre-injury level of activity. Following ACLR outcomes are not always ideal. Given the identified differences in risk, anatomy and physiology in males and females with ACL tears some literature has evaluated outcomes between males and females. However, the influence of sex on outcomes following ACLR remain unclear, with some reporting no difference between sexes, while others report poorer outcomes in female patients. Previous attempts to look at differences in ACLR outcomes between the sexes were based on an inclusion of a variable defined as male/female (M/F). However, “sex” refers to the biological differences between male and female and “gender” refers to socio-cultural characteristics of maleness and femaleness. While the two terms, sex and gender, are frequently acknowledged in the literature, they are often used interchangeably, where “gender” is usually used as a synonym for “sex”. The incorrect use of the terms leads to confusion about the contributions of sex and gender to overall health, and missed opportunities for developing appropriate conclusions in health research. We hypothesize that by using a sex and gender sensitive approach, important outcome differences in ACLR between men and women will become apparent that otherwise would have been masked looking at sex alone. We will perform secondary analysis on a longitudinal data set. Using the parent study data dictionary as a reference, outcome variables, derived variables representing sex, gender and Sex and Gender (SG) using patient reported outcome measure questions and functional assessment tools will be derived. A Multivariable regression model will be used to identify predictors of Health Related Quality of Life (HRQOL) among those who have had ACLR. Variables potentially representing biological sex differences (e.g. knee strength) will be entered into the model. Then, variables potentially representing sociocultural gender differences (e.g. perception of overall health) will be added. Finally, variables representing both SG (e.g. pain) will be added to the model to assess for fit. This research project is currently underway. Anticipated results are that Gender differences are expected to be more common than sex differences with women expected to be more likely to report poorer HRQoL based on their SF-36 scores compared to men at 1 year following ACLR. The results of this study could more accurately identify the specific needs of men and women and identify areas of similarity and difference in ACLR. Furthermore, the results could help provide evidence for the necessity of a sex and gender sensitive approach and help influence and improve models of care, including policies and management plans so as to ensure optimum outcomes for women and men following ACLR.

Funding: This research was funded by the Surgeon Scientist Program, Department of Surgery at the University of Toronto. **Contact Information:** Sabrina Kolker, 893 Dovercourt Road. Toronto Ontario Canada M6H2X6. 416-705-1375. Sabrina.kolker@mail.utoronto.ca

---

47. Title: The impact of pubertal immune stress on learning and memory between the sexes

Author Affiliations: Daria Kolmogorova (BSc Psychology), Catherine Paré(BSc Psychology), Sarah Kostuck (BA Psychology), Nafissa Ismail (PhD Psychology)

Author Affiliations: School of Psychology, University of Ottawa

Abstract: Research into puberty as a critical developmental period suggests that early activation of the innate immune response influences various aspects of brain function and cognition, including learning and memory. However, the enduring effects of a pubertal immune challenge on spatial memory and its relation to the sexes remain to be investigated. The objective of the current study is to examine sex differences in short- and long-term hippocampal-dependent visuo-spatial memory and cognitive flexibility following a single pubertal exposure to the bacterial endotoxin lipopolysaccharide (LPS). A sample of 20 male and 20 female CD-1 mice was shipped at three weeks of age. At six weeks of age (i.e. pubertal), male and female mice were injected intraperitoneally with LPS (1.5 mg/kg) or 0.9% sterile saline control (1.5 mg/kg). To examine the effects of gonadal hormones on learning and memory, mice underwent either gonadectomy or sham-operation upon at nine weeks of age. Following one week of recovery, at ten weeks of age (i.e. in adulthood), the mice were tested in the Barnes Maze and Morris Water Maze during their dark cycle. An open field test was used to assess differences in locomotor activity. Based on previous research, it is expected that (1) LPS-injected mice outperform their saline counterparts and (2) males outperform females regardless of treatment, and (3) that gonadectomized females will perform better than sham-operated females on visuo-spatial memory tasks. Taken together, these findings suggest important interactions between pubertal immune stress and gonadal hormones on cognitive function.

Contact Information: Email: dkolm072@gmail.com Telephone: 613-882-2789, Address: NISE Laboratory, Faculty of Social Sciences, 136 Jean-Jacques Lussier, Vanier Hall, Room 2076B, Ottawa, Ontario, Canada, K1N 6N5

---

48. Title: Sex differences in platelet toll-like receptors and their association with cardiovascular risk factors.

Authors List: Milka Koupenova Ph.D[1*], Eric Mick Sc.D.[2], Ekaterina Mikhalev B.S.[1], Emelia J Benjamin M.D.[3,4,5], Kahraman Tanriverdi Ph.D.[1], and Jane E. Freedman M.D.[1]

Author Affiliations: Department of Medicine, [1]Divisions of Cardiovascular Medicine, and [2]Quantitative Health Sciences University of Massachusetts Medical School, Worcester, MA 01605, USA. [3]Departments of Medicine, and [4]Whitaker Cardiovascular, Boston University School of Medicine, Boston, MA 02118, USA. [5]NHLBI and Boston University's Framingham Heart Study, Framingham, MA 01702, USA.

Abstract: Platelets contribute to thrombosis, and platelet toll-like receptors (TLRs) are central in pathogen detection, potentially mediating infection-induced vascular occlusion. Using a large community-based cohort study, we sought to examine if platelets express all known TLR transcripts and analyze their association with cardiovascular risk factors. We hypothesized that platelets exhibit sex differences in TLR expression in these differences are associated with distinct cardiovascular risk factors. Messenger RNA (mRNA) levels for TLRs were measured in isolated platelets by high-throughput quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) in 1625 participants (mean age 66.6±9, 54% women) of the Framingham Heart Study. We measured circulating inflammatory and thrombotic markers (CRP, IL6, MCP1, ICAM1, TNFR1, and P-selectin),

and analyzed TLRs and their association with sex and cardiovascular risk factors by multivariable logit regression model adjusted for confounding factors. We show that, platelets expressed all ten TLR-transcripts, and all TLRs were co-expressed. Women had higher platelet TLR expression, which associated with different cardiovascular risk factors as compared to men. In women, TLR1, TLR3, TLR6, and TLR7 were associated with BMI, and TLR5, TLR7, and TLR10 were associated with total cholesterol to HDL ratio. In men, TLR1, TLR2, and TLR3 were associated with lipid and TLR8 with hypertension treatment. Similarly, TLR expression in men was more commonly associated with circulating inflammatory markers (TNFR1, ICAM1), whereas in women TLR expression was associated with P-selectin levels. We report, the first study to demonstrate that platelets express all TLR transcripts using a large community-based observational cohort. These transcripts are more abundant in women and have distinct associations with cardiovascular risk and inflammatory biomarkers that vary by sex.

Funding: This work was funded by grants from the National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH) to J.E.F and E.J.B.

Contact Information: Milka Koupenova, University of Massachusetts Medical School, Albert Sherman Center, 368 Plantation St, S7-1014, Worcester, MA 01605, (508) 856-6937, email: milka.koupenova@umassmed.edu

---

49. Title: Exacerbation of autoimmune neuroinflammation by dietary sodium is genetically controlled and sex-specific

Authors List: Dimitry N. Krementsov Ph.D.[1], Laure K. Case Ph.D.[1], William F. Hickey Ph.D.[2], Cory Teuscher Ph.D.[1]

Author Affiliations: [1]Department of Medicine, Immunobiology Program, University of Vermont, Burlington, VT 05401, USA; [2]Department of Pathology, Dartmouth Medical School, Hanover, NH, USA

Abstract: Multiple sclerosis (MS) is a debilitating neuroinflammatory disease of autoimmune etiology, influenced by genetics and the environment. MS incidence in females has approximately tripled in the last century, suggesting a sex-specific environmental influence. Recent animal studies have implicated dietary sodium as a risk factor in MS, whereby high sodium augmented the generation of Th17 cells and exacerbated experimental autoimmune encephalomyelitis (EAE), the principal autoimmune model of MS. However, whether dietary sodium interacts with sex or genetics remains unknown.

Here, we show that high dietary sodium exacerbates EAE in a strain- and sex-specific fashion. In C57BL6/J mice, exposure to a high salt diet exacerbated disease in both males and females, while in SJL/J mice it did so only in females. In further support of a genetic component in the response to dietary sodium, we found that a high sodium diet failed to modify EAE course of C57BL6/J mice carrying a 129/Sv-derived congenic interval on chromosome 17. In contrast to previous studies, we found that the high salt diet did not augment Th17 or Th1 responses, but it did result in increased blood-brain barrier permeability and more severe brain pathology. Taken together, our results demonstrate that the effects of dietary sodium on autoimmune neuroinflammation are: 1) sex-specific, 2) genetically controlled, and 3) CNS-mediated. These findings identify dietary sodium as a sex-specific MS risk factor, and reveal novel underlying mechanisms.

Funding: This work was supported by National Institute of Health grants NS069628 and NS076200 to CT. This work was also supported a postdoctoral fellowship FG1911-A-1 from the National Multiple Sclerosis Society to DNK, and a pilot project grant PP2123 from the National Multiple Sclerosis Society to CT.

Contact Information: Dimitry Krementsov, D305 Given building, 89 Beaumont Ave, University of Vermont, Burlington, VT, 05405; (802)338-1640; dkrement@uvm.edu;

50. Title: Sex and Gender-Based Medicine Online Multimedia Case-Based Learning

Authors List: M. Jenkins[1], R. Casanova[1], S. Crooks[2], J. Cheon[2]

Authors Affiliations: [1]Texas Tech University Health Sciences Center, Lubbock, Texas, [2]Texas Tech University, Lubbock, Texas

Abstract: The goal of SGBM online case-based learning is to advance understanding of sex/gender differences, increase awareness of gender-specific health issues, and improve knowledge of sex/gender evidence based medicine. In addition to the lack of teaching related to Sex and Gender-Based Medicine, there are typical challenges in higher education due to the differences between classroom problem-solving (well-structured problem solving) and real world problem-solving (ill-structured problem solving). Teaching students to reason with basic content knowledge can be difficult without scaffolding strategies that enhance thinking skills. These online instructional resources are based on an evidence-based pedagogical framework that has been proven to enhance problem-solving and decision-making skills in real-world settings. Multidisciplinary teams, including faculty and learners, create module materials and instructional design experts create instructional strategies and delivery methods. Interprofessional education is also included within the modules. The modules are presented in three parts and include a progressively higher order application of Bloom's Taxonomy. This online instruction can be used throughout the curriculum as a stand-alone or supplementary instructional resource. Online multimedia cases provide students with authentic learning opportunities that integrate the learning of SGBM with more traditional clinical knowledge and skills. This instructional framework is designed to engage students in developing real-world medical problem solving and clinical decision-making skills that can be transferred to the clinical practice of SGBM. Pre and post knowledge and application assessments have been integrated within each module and data is collected to support the efficacy of the design. In addition, national dissemination is foundational to this work.

Funding: Funding provided by Texas Tech University Health Sciences Center and the Laura W. Bush Institute for Women's Health

Contact Information: Marley Hoggatt, Laura W. Bush Institute for Women's Health, TTUHSC, 1400 Wallace, Amarillo, TX 79106, 806-414-9946

---

51. Title: Gene-sex interaction in Alzheimer's disease

Authors List: Andre Altmann Ph.D.[1], Valerio Napolioni Ph.D.[1], Hua Tang Ph.D.[2], Michael D Greicius MD[1]

Author Affiliations: [1] Department of Neurology and Neurological Sciences, [2] Department of Genetics, Stanford University, Stanford, CA, USA

Abstract: Background: Alzheimer's disease (AD) is an increasingly prevalent, ultimately fatal neurodegenerative disorder for which there are no disease-modifying treatments. The E4 allele of the Apolipoprotein E gene (APOE4) is a potent genetic risk factor for sporadic and late-onset familial AD. A critical, and commonly overlooked, feature of the APOE4 link to AD is that several case-control studies suggest it is far more pronounced in women than in men.Shortly after the identification of APOE as a risk factor for AD, a study found an interaction between sex and APOE: women in their sixties with one APOE4 allele had a 4-fold increased risk whereas male APOE4 heterozygotes did not bump their risk much. In this study, we screened genome-wide association studies (GWAS) for (i) further genes with a gene-by-sex interaction on AD risk and (ii) genes with an APOE-by-gene-by-sex interaction on AD risk.

Methods: We used the single nucleotide polymorphism (SNP) data of 15 AD GWAS collected by the AD genetics consortium (ADGC) comprising in total 10491 controls and 11449 AD subjects. For each study we applied logistic regression models to compute the association strength of the interaction term (i) SNP-by-sex and (ii) SNP-by-sex-by-APO with AD while controlling for age, population structure and the main effects of sex, APOE and SNP. Effect sizes from each study for each of the 7.1 mio SNPs were combined in a meta-analysis using the inverse variance weighted method implemented in METAL.

Results: Our analysis confirmed the main effects of previously identified AD genes.

However, no SNP passed the level of genome-wide significance (P=5x10-8) for the SNP-bysex interaction or for the SNP-by-sex-by-APOE interaction. Conclusion: We did not identify new genes with a SNP-by-sex interaction. However, we are currently using the established APOE-by-sex interaction to define a group of healthy older APOE4 carriers and are searching their whole genome sequence for protective variants.

Funding: This work was supported by the Stanford WSDM Center.

Contact Information: Andre Altmann, Functional Imaging in Neuropsychiatric Disorders, Department of Neurology and Neurological Sciences, Stanford University, Stanford, CA, USA; 1-650-7366679; altmann@stanford.edu

---

52. Title: Neonatal Limited Bedding Stress Influences Basal and Post-Stress Visceral Sensitivity in a Sex-Dependent Manner in Adult Wistar Rats.

Authors List: Muriel Larauche, Ph.D.*[1,2], Mandy Biraud, B.S.[1,2], Jenny Molet, Ph.D.[3], Mulugeta Million D.V.M., Ph.D.[1,2], Yvette Taché, Ph.D.[1,2]

Authors Affiliations: [1]Department of Medicine, UCLA, Oppenheimer Family Center for Neurobiology of Stress and CURE: Digestive Diseases Research Center, David Geffen School of Medicine, Los Angeles, CA, United States, [2]VA Greater Los Angeles Healthcare System, Los Angeles, CA, United States, [3]Department of Anatomy and Neurobiology, University of California, Irvine, Irvine, CA, United States.

Abstract: Early life adversity contributes to the development of stress-sensitive disorders such as irritable bowel syndrome (IBS) with higher occurrence in females. The limited bedding stress (LBS) model was recently validated as a model of maternal neglect and abuse in rodents, but its influence on visceral sensitivity in adult rats under basal or stress conditions is unknown. Time-pregnant Wistar females (E15, Harlan) were used. From PND2 to PND10, dams were then housed under control (direct contact bedding + 1 paper towel) or LBS conditions (wire bottom floor + ½ paper towel). Once adult, rats (9-14 wks, n=6-14) received a basal colorectal distension (CRD, 10, 20, 40, 60 mmHg, 20 sec, 4 min intervals) before being exposed to repeated water avoidance stress (rWAS, 10 days, 1h/day) or no stress. The visceromotor response (VMR) was monitored non-invasively using manometry. Additional CRDs were performed immediately (IMM), 24h and 72h after the last stress session. Control and LBS female rats had similar baseline VMR, while LBS male rats exhibited a decrease in VMR at 40 mmHg vs control males ($p<0.05$). Females' VMR was higher than males at 60 mmHg in controls ($p<0.01$), but present at both 40 and 60 mmHg in LBS ($p<0.05$ and $p<0.0001$) animals. Repeated WAS induced visceral analgesia at 40 mmHg, IMM and 72h post stress in control males and at 60 mmHg IMM, 24h and 72h post stress in control females. In contrast, LBS-raised males and females lost their analgesic responses and males developed visceral hyperalgesia IMM and 24h post rWAS. Repeated CRDs did not affect the VMR of control or LBS-raised rats. Our data show that neonatal LBS induces a basal visceral analgesia in adult Wistar male rats but not females and leads to a loss of stress-induced visceral analgesia and the development of stress-induced hyperalgesia. These findings suggest that early life events affect both the basal and stress-related visceral pain response of rodents in a sex-dependent manner.

Funding: Supported by NIH P50-DK-64539 (YT, MM), DK 57238 (YT), 1K01DK088937 (ML)

Contact information: Muriel Larauche, UCLA Division of Digestive Diseases, Oppenheimer Family Center for Neurobiology of Stress and CURE: Digestive Diseases Research Center, GLA VA HS, Bldg. 115/Rm 111, 11301 Wilshire Blvd., Los Angeles, CA 90073; (310) 478 3711 ext 41827; mlarauche@mednet.ucla.edu

---

53. Title: Role of Sex Hormones and Sex Chromosomes in Mechanically-Induced Visceral Hyperalgesia in Mice

Authors List: Muriel Larauche Ph.D.*[1,2], Mandy Biraud B.S.[1,2], Mulugeta Million D.V.M., Ph.D.[1,2], Ryan Mackie B.S.[3], Art Arnold Ph.D.[3], Yvette Taché Ph.D.[1,2]

Authors affiliations: [1]Department of Medicine, UCLA, Oppenheimer Family Center for Neurobiology of Stress and CURE: Digestive Diseases Research Center, David Geffen School of Medicine, Los Angeles, CA, United States; [2]VA Greater Los Angeles Healthcare System, Los Angeles, CA, United States; [3]Department of Integrative Biology & Physiology, UCLA, Los Angeles, CA, United States.

Abstract: Characterized by recurrent abdominal pain and altered bowel habits, irritable bowel syndrome is more common in women, but the reasons for this prevalence remain unclear. Sex differences in phenotype are linked to direct effects of gonadal hormones (organizational or activational) and/or of genes represented unequally in the genome because of their X- or Y-linkage. To address the role of sex hormones vs. sex chromosomes in the modulation of visceral sensitivity, we used the “four-core genotypes” (FCG) mice. Intact and gonadectomized (GDX) FCG male (XY(Sry+) and XX(Sry+)) and female (XX and XY) (4-6 months old; n=6-8/group) were subjected to 4 sets of isobaric phasic distensions (each set: 3 CRDs at 55 mmHg, 10-s duration, 5-min intervals). Visceromotor response (VMR) was recorded using manometry. The 1st CRD set served as a baseline response. Repeated noxious CRD induced visceral hypersensitivity in intact XX, XY(Sry+) and XX(Sry+) mice but not in XY mice. The VMR between groups of males (XY(Sry+) and XX(Sry+)) and females (XY and XX) was similar. When pooled together, intact gonadal males and females exhibited visceral hyperalgesia at the 4th and 3rd set of CRD ($p<0.05$), respectively, with males showing higher VMR than females to all CRD sets. Gonadectomy reduced the basal VMR in all groups compared to intact mice. GDX XX, XY(Sry+), XX(Sry+) and XY mice had similar VMR and presented a strong visceral hyperalgesia at the last two sets of CRD. When pooled together, GDX males and females exhibited visceral hyperalgesia at the 2nd, 3rd and 4th set of CRD ($p<0.01$), and their VMR were comparable. Males GDX exhibited lower VMR at all sets of CRD compared to intact males, unlike GDX females which except for the 1st set, had the same VMR than intact females. These data support a major role of sex hormones, but not sex chromosomes, in the modulation of basal visceral pain and in response to repeated noxious colorectal distensions under non stress conditions.

Funding: Supported by NIH DK-57238 (YT), 1K01DK088937 (ML), 1R01NS043196 (AA).

Contact information: Muriel Larauche, UCLA Division of Digestive Diseases, Oppenheimer Family Center for Neurobiology of Stress and CURE: Digestive Diseases Research Center, GLA VA HS, Bldg. 115/Rm 111, 11301 Wilshire Blvd., Los Angeles, CA 90073; (310) 478 3711 ext 41827; mlarauche@mednet.ucla.edu

---

54. Title: Aberrant activation of the sex-determining gene in early embryonic development results in postnatal growth retardation and lethality in transgenic mice

Authors List: Tatsuo Kido Ph.D., Zaoyu Sun Ph.D., Yunmin Li Ph.D. & **Yun-Fai Chris Lau, Ph.D.**

Author Affiliations: Department of Medicine, VA Medical Center, and Institute for Human Genetics, University of California, San Francisco, California, USA.

Abstract: Sexual dimorphisms are prevalent in development and various human diseases, particularly in neural diseases and neurodevelopment. Currently, the role of the Y chromosome in such phenomena has not been clearly defined. Among the Y chromosome genes, the sex-determining gene, *SRY*, could be a significant candidate capable of exerting male-specific effects on sexual dimorphisms. *SRY* is the founder of the SRY-box (*SOX*) genes, which are key regulators for various developmental processes. SRY and SOX proteins harbor a conserved HMG box DNA/protein binding domain. In a previous study, we have identified the targets of SRY and SOX9 at the time of sex determination and differentiation in the mouse. Our results showed that SRY and SOX9 share a significant number of common targets, and are capable of regulating each other's target genes. Further, a sizable number of SRY targets are neural genes, suggesting that an ectopically expressed SRY could compete with the SOX factors in regulating the respective SOX targets, thereby disrupting the corresponding developmental processes. To test this hypothesis, we have established a transgene activation system in the mouse, in which a human *SRY* transgene responder could be activated by a tissue-specific Cre driver. The Ddx4-Cre transgenic line expresses the Cre recombinase exclusively in the germ lines of both sexes. When a female Ddx4-Cre driver is crossed with a male SRY responder, the Cre recombinase is transferred to the single-cell embryo from the fertilized oocyte, thereby activating the SRY transgene in and single-cell embryo and subsequently in all tissues. However, when a male Ddx4-Cre driver is crossed with a female SRY responder, the *SRY* transgene could not be activated till much later in germ cells. Hence, *SRY* transgene could be activated differentially with the respective sex of the Ddx4-Cre mice. Our results show that early activation of *SRY* transgene during embryonic development results in significant postnatal growth retardation of the offspring, which do not survive beyond two weeks of age while late and male germ cell activation of *SRY* transgene result in normal postnatal development. Characterization of the pups with early *SRY* transgene activation shows significant abnormalities in the heart, liver, lung and brain development. Comparative transcriptome analysis of the brains between mutant and control pups shows increases in organismal death, hypoplasia, abnormalities in head and cerebrum, and lack of dentate gyrus development and significant decreases in transcription, cell quantity, dendritic cell migration, long-term potentiation, neuritogenesis, behavior, learning, cognition, and dendritic growth/branching. Golgi staining of neurons shows a significant reduction in dentritic spine densities in various portions of the SRY-expressing brain, thereby confirming the impairment in neurodevelopment. Our results suggest that ectopic activation of *SRY* in non-gonadal tissues could have significant disruptive effects in embryonic development, including neurodevelopment while a mild *SRY* activation could be responsible for dimorphisms observed between the sexes.

Funding: This study was partially funded by a Concept grant from the Department of Defense Autism Research Program and a Merit grant from the Department of Veterans Affairs, and a pilot project grant from the Clinical and Translational Institute of UCSF. Y-FCL is a Research Career Scientist of the Department of Veterans Affairs.

Contact Information: Yun-Fai Chris Lau, Department of Medicine, VA Medical Center, University of California, San Francisco, 4150 Clement Street, San Francisco, CA 94121; 1-415-379-5526; chris.lau@ucsf.edu

---

55. Title: Sex differences in sensorimotor mechanisms for dynamic function of the upper and lower extremities

Authors List: Emily L. Lawrence, M.S.[1], Inge Werner, Ph.D.[2], Susan M. Sigward, Ph.D.[3], & Francisco J. Valero-Cuevas, Ph.D.[1, 3]

Author Affiliations: [1]Department of Biomedical Engineering, University of Southern California, Los Angeles, CA, USA, [2]Institute for Sports Science, University of Innsbruck, Innsbruck, Austria, [3]Division of Biokinesiology and Physical Therapy, University of Southern California, Los Angeles, CA, USA

Abstract: Appropriate mechanisms for sensorimotor processing are critical to skilled motor function of the fingers for dexterous manipulation, and the legs for balance and locomotion. We have developed the Strength-Dexterity (SD) paradigm to quantify dexterity in the fingers and legs. We define dexterity as the ability to control

instabilities when participants compress compliant, unstable springs with the fingers, or the isolated leg. Both tests evaluate dynamic function (i.e., dexterity) independently of strength because they require very low forces. We find several instances of sex differences in dynamic function of the fingers and legs. First, males exhibit better performance throughout adulthood (finger: n=147, p=0.021;leg: n=188, p=0.002). A subset of these participants performed the tests with their dominant limbs separately (n=81), and we found a stronger correlation between finger and leg dexterity in females (females $\rho = 0.529$, $p = 0.004$;males $\rho = 0.403$, $p = 0.003$). We speculate that dexterity is the sum of two components: basic systemic plus limb-specific. The higher correlation in females suggests they have a greater systemic component. We also investigated balance ability young adults (n=37) with a set of five outcome measures and find females show correlations among balance measures, while males do not, suggesting potential sex differences in balance control mechanisms or strategies. We know that women are disproportionately prone to anterior cruciate ligament (ACL) tears and osteoarthritis (OA); and there are reports that older women fall more often than men. Proposed reasons include sex differences in hormonal levels, joint alignment, ligament laxity, and strength. The sex differences in low-level sensorimotor mechanisms in multiple contexts we report provide an alternative reason, and have profound implications for health, sports, and rehabilitation of both the upper and lower extremities.

Funding: Research reported in this publication was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health (NIH) under Award Numbers AR050520 and AR052345 to FVC. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Contact Information: Emily L. Lawrence, Department of Biomedical Engineering, University of Southern California, 3710 McClintock Ave, RTH 421, Los Angeles, CA 90089; 1-713-289-9669; ellawren@usc.edu

---

56. Title: Mast cells regulate early life programming of sex differences in social behavior

Authors List: Steven Platko, Anabel Galan, BA, and **Kathryn M. Lenz, PhD**

Author Affiliations: Departments of Psychology and Neuroscience; The Ohio State University

Abstract: Perinatal inflammation increases risk for neurodevelopmental disorders, including autism. Autism is also four times more common in males than females. We aim to understand how sex differences in the brain's innate immune environment regulates sex-specific brain development, and ultimately, sex-specific programming of behavior by inflammatory events. Mast cells are a type of innate immune cell that is present in the brain yet their role in brain development is largely unknown. We have found that thousands of mast cells reside in the developing rat brain, with over 90% situated in or near the hippocampus, thalamus, habenula, and amygdala. Males have 40% more mast cells in the brain than females during the neonatal period; by adulthood both males and females have only a few hundred brain-resident mast cells. The goal of these experiments was to determine whether this mast cell population in the neonatal brain regulates the development of social behaviors. We utilized a prenatal allergic immune challenge on embryonic day 15 to induce physiologically relevant mast cell activation during development. We tested juvenile social behavior post-weaning and found that males that experienced allergic challenge in utero engaged in less social play behavior than controls and females were unaffected. We also found that this early life activation of mast cells led to life-long increases in the brain mast cell population. Currently underway experiments will determine the effects on allergic challenge on the number of mast cells in the in brain regions that may regulate social behavior during the neonatal period and assess immediate early gene expression following mast cell activation. Together these studies show that mast cells may play a key role in the early life programming of sex differences in brain and behavior following early life perturbations.

Funding: The Ohio State University startup funds

Contact information: Kathryn M. Lenz, PhD. Psychology Building, 1835 Neil Ave, Columbus, OH 43210, USA. Phone: 614-292-8565. Email: lenz.56@osu.edu

---

57. Title: Assessment of the effect of genistein diet on jejunum contractility, and morphology in lean and obese/diabetic male and female mice

Authors List: Lana Leung, B.Sc., Sydney Schacht, BSc., Robert Dolan, BSc., Ashesh Bhakta, BSc., and Layla Al-Nakkash, Ph.D.

Author affiliations: Department of Physiology, Arizona College of Osteopathic Medicine, Midwestern University, 19555 N. 59th Ave, Glendale, AZ. 85308

Abstract: The goal of this study was to characterize intestinal function with respect to contractility, and morphology to better understand whether the intestinal dysfunction (delayed gastrointestinal transit) seen in a clinically relevant mouse model of diabetes and obesity (*ob/ob*) was comparable for both males and females. We examined the effects of a 4-week genistein-containing diet (600 mg genistein/kg food, 600G) in *ob/ob* male and female mice with comparisons to lean controls. Contractility (tension) of freshly isolated segments of jejunum in response to incrementally increased concentrations of KCl was assessed. In lean mice, the maximal tension generated was significantly greater in females (0.77±0.07 g, n=8, $P<0.05$) versus males (0.49±0.07 g, n=5). This was not associated with changes in jejunum total smooth muscle wall thickness, inner circular smooth muscle depth, nor, outer longitudinal smooth muscle depth (as determined from measures of H&E stained sections). Whether this sex-dependent effect is similar in the *ob/ob* mice, remains to be seen. Since the enteric nervous system plays an important role in the control of local gastrointestinal functions, we visualized clusters of acetylcholine receptors, AChR, in the jejunum wall. Our data suggest that *ob/ob* females fed standard diet have significantly less AChR's (49.3±5.0, n=9, $P<0.05$) than lean counterparts (84.1±7.6, n=10). There was no change in the numbers of AChR's in male *ob/ob* versus lean mice. Interestingly, lean females had a 1.4-fold greater number of AChR clusters than male counterparts. Our data suggest that sex-dependent differences are evident in lean mice: (1) contractility was greater in females versus males, and (2) AChR number was increased in females versus males.

Funding: This study was funded by the Soy Health Research Program, Diabetes Action & Research Foundation, and Midwestern Intramural Funds.

Contact Information: Layla Al-Nakkash, PhD., Professor**,** Department of Physiology**,** Midwestern University**,** 19555 N. 59th Avenue**,** Glendale. AZ. 85308. Tel: (623) 572-3719**.** Fax: (623) 572-3673**.** Email: lalnak@ midwestern.edu

---

58. Title: The Y-encoded SRY competitively disrupts the SOX10 regulation of the RET promoter: Implication for SRY contribution to sexual dimorphisms in Hirschsprung Disease

Authors List: Yunmin Li Ph.D.[1,2], Tatsuo Kido Ph.D. [1,2], Z. Laura Tabatabai M.D.[3] & Yun-Fai Chris Lau Ph.D. [1,2]

Author Affiliations: Departments of Medicine[1] and Pathology[3], VA Medical Center, and [2]Institute for Human Genetics, University of California, San Francisco, California, USA.

Abstract: The Hirschsprung disease (HSCR) is a complex congenital disorder, arising from abnormalities in enteric nervous system (ENS) development. There is a gender disparity among the patients, with the male to female ratio as high as 5:1. Loss-of-function mutations of HSCR genes and haploinsufficiency of their gene products are the primary pathogenic mechanisms for disease development. Recent studies identified over half of the HSCR disease susceptibility genes as targets for the sex-determining factor SRY, suggesting that this Y-encoded transcription factor could be involved in sexual dimorphism in HSCR. Expression analysis demonstrated that

SRY expression could be detected in male HSCR diseased tissues, but not normal controls. Among the SRY targets, the tyrosine kinase receptor RET represents the most important disease gene, whose mutations account for half of the familial and up to one-third of the sporadic forms of HSCR. RET is regulated by a distal and a proximal enhancer at its promoter, in which PAX3 and NKX2-1 are the resident transcription factors respectively. We show that the SRY-box 10 (SOX10) co-activator interacts and forms transcriptional complexes with PAX3 and NKX2-1 in a sequence-independent manner and exacerbates their respective transactivation activities on the RET promoter. SRY competitively displaces SOX10 in such transcription complexes and represses their regulatory functions on RET (Figure 1). Hence SRY could be a Y-located negative modifier of RET expression; and if it is ectopically expressed during ENS development, such SRY repression could result in RET protein haploinsufficiency and promotion of HSCR development, thereby contributing to sexual dimorphism in HSCR.

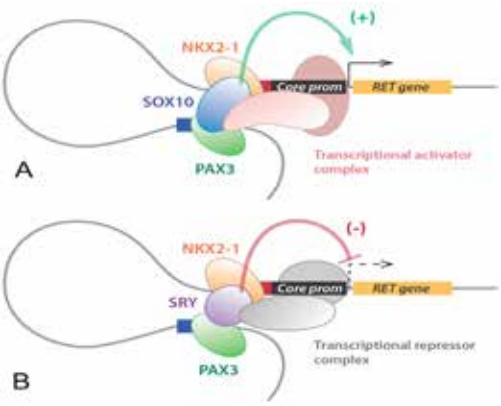


Figure 1. A) Model of SOX10 interactions with NKX2-1 and PAX3 transcription complex in regulation of RET gene. B) SRY competitively displaces SOX10 and disrupts the NKX2-1-SOX10-PAX3 complex in transactivation of the RET gene.

Funding: This study was partially funded by a Concept grant from the Department of Defense Autism Research Program and a Merit grant from the Department of Veterans Affairs, and a pilot project grant from the Clinical and Translational Institute of UCSF. Y-FCL is a Research Career Scientist of the Department of Veterans Affairs.

Contact Information: Yun-Fai Chris Lau, Department of Medicine, VA Medical Center, University of California, San Francisco, 4150 Clement Street, San Francisco, CA 94121; 1-415-379-5526; chris.lau@ucsf.edu

---

59. Title: Sex Differences in Hypoxic-Ischemic Encephalopathy and Inflammation

Authors list: Mehwish A. Mirza, Rodney Ritzel, Yan Xu, Louise D. McCullough, **Fudong Liu**

Author Affiliations: Department of Neuroscience, University of Connecticut Health, Farmington, Connecticut

Abstract: Neonatal hypoxic-ischemic encephalopathy (HIE) is an important cause of motor and cognitive impairment in children. Clinically, male infants are more vulnerable to ischemic insults and suffer more long-term deficits than females; however, the mechanisms underlying this sex difference remain elusive. Inflammatory processes initiated by microglial activation are fundamental in the pathophysiology of ischemia. Recent studies report a sexual dimorphism in microglia numbers and expression of activation markers in the neonatal brain under normal conditions. How these basal sex differences in microglia affect HIE remains largely unexplored. We hypothesize that ischemia induces sex-specific brain injury in male and female neonates and that microglial activation and inflammatory responses play an important role in this sexual dimorphism. HIE outcomes, CX3CR1 signaling in microglial activation and inflammatory responses were investigated. Male and female C57BL6 and CX3CR1$^{gfp/+}$ mice were subjected to 60-minute Rice-Vanucci Modeling at post-natal day 10 (P10) to induce HIE. C57BL6 P10 males had significantly larger infarct size and worsened neurological deficits than females at 3d, 7d, 30d but not 24h of HIE. Correspondingly, male animals demonstrated increased microglial activation and up-regulated inflammatory responses compared with females at 72 hours. More CX3CR1-gfp positive cells and higher MFI (mean fluorescence intensity) of CX3CR1-gfp signals by flow cytometry were seen in female vs. male

brains 72h after HIE; however, males had higher ratio of MHCII$^+$ cells than females. There was no sex difference in hormone levels in neonatal mice at 1d and 3d of HIE. HIE leads to an equivalent primary brain injury in male and female neonates at the acute stage that develops into sexually dimorphic outcomes at later time points. An innate immune response secondary to the primary injury may contribute to the sexual dimorphism in HIE.

Funding: This work was supported by the NIH/NINDS (grants NS050505 and NS055215 to Louise D MCCULLOUGH), and by the American Heart Association (grant 12SDG9030000 to Fudong LIU).

Contact Information: Fudong Liu, Department of Neuroscience, University of Connecticut Health, 263 Farmington Ave, Farmington, CT-06030; 860-679-3508; fliu@uchc.edu

---

60. Title: A successful strategy to integrate gender and sex aspects into a newly developed undergraduate medical curriculum

Authors List: Sabine Ludwig Dipl. oec., MA[1], Sabine Oertelt-Prigione MD, MScPH[2,3], Christine Kurmeyer, PhD, MA[4], Manfred Gross, MD[5], Annette Grüters-Kieslich, MD[6], Vera Regitz-Zagrosek, MD[2,3], Harm Peters, MD[1]

Author Affiliations: [1]Dieter Scheffner Centre for Medical Education and Educational Research, Charité – Universitätsmedizin Berlin, Germany; [2]Institute of Gender in Medicine, Charité – Universitätsmedizin Berlin, Germany; [3]German Centre for Cardiovascular Research (DZHK), Berlin, Germany; [4]Office for Equal Opportunities, Charité – Universitätsmedizin Berlin, Germany; [5]Department of Audiology and Phoniatrics, Charité – Universitätsmedizin Berlin, Germany; [6]Institute of Experimental Pediatric Endocrinology, Charité – Universitätsmedizin Berlin, Germany

Abstract: A new integrated, modular medical curriculum was introduced at Charité - Universitätsmedizin Berlin in 2010. The key stated goal was to systematically integrate gender and sex aspects into the curriculum to make sure that future doctors have adequate gender and sex-related knowledge and skills as far as the etiology, pathogenesis, clinical presentation, diagnosis and treatment are concerned and are able to consider gender and sex dimensions in their research. A change agent was directly assigned into the curriculum development team to ensure direct interactions with the key players of the curricular change and development process. The gender change agent established a supporting organizational framework and developed a ten-step approach according to the regular module planning cycles. This systematic approach included the identification, selection and implementation of relevant gender and sex-related issues into the new curriculum as well as the consultation and support of faculty members and the monitoring and finalization of the curriculum planning process for each module. With this approach, gender and sex-related issues were widely integrated into the new curriculum throughout all teaching and learning formats, ranging from lectures to clinical skills and communication skills courses. Gender and sex aspects and perspectives of health differences in diseases were successfully incorporated from early basic science to later clinical modules and represent an integral part of the assessment program. In conclusion, the appointment of a gender change agent allows the development of systematic approaches that can be key to successfully integrate gender and sex aspects into a new medical curriculum. The change agent serves a dual purpose: firstly, to establish and maintain a network of stakeholders for the incorporation of gender and sex aspects into medical education. Secondly, to directly facilitate the implementation of gender and sex aspects along the general curriculum development process.

Funding: The study was funded by a grant from the Berlin state government within the program “Promotion of Gender Equality in Research and Higher Education.”

Contact Information: Sabine Ludwig, Dieter Scheffner Center for Medical Education and Educational Research, Charité – Universitätsmedizin Berlin, Medical Faculty of Free University and Humboldt University Berlin, Charitéplatz 1, 10117 Berlin, Germany, tel: +49 (0) 30 450 576 082, fax: +49 (0) 30 450 576 952, sabine.ludwig@charite.de

61. Title: An XX sex chromosome complement markedly promotes the severity and progression of angiotensin II-induced abdominal aortic aneurysms in hypercholesterolemic male mice

Authors List: Yasir Alsiraj MS, Sean Thatcher PhD, and Lisa Cassis PhD

Author Affiliations: Department of Pharmacology and Nutritional Sciences, University of Kentucky, Lexington, KY

Background: Male sex is a strong non-modifiable risk factor for the formation and progression of abdominal aortic aneurysms (AAAs) in both mice and humans. We previously demonstrated that testosterone promotes the formation and progression of angiotensin II (AngII)-induced AAAs in hypercholesterolemic male and female mice. However, our results suggest that while testosterone promotes AAA formation and progression in both sexes, other factors contribute to sexual dimorphism of AngII-induced AAAs. In this study, we hypothesized that sex chromosome complement influences the severity and progression of AngII-induced AAAs in gonadally intact male mice.

Methods and Results: Male transgenic mice with deletion of *Sry* from the Y-chromosome expressing *Sry* on autosomes (8-12 weeks of age) were bred to female *Ldlr*-/- mice to generate male mice with an XY or an XX sex chromosome complement. Mice were fed a western diet and were implanted with osmotic micropumps to infuse AngII (1,000 ng/kg/min) for either 28 (AAA formation) or 56 days (AAA progression). Suprarenal aortic lumen diameters were monitored by ultrasound throughout the study to quantify AAA formation and progression. At day 28 of AngII infusion, XX males had significantly increased aortic lumen diameters compared to XY males (XX, 1.77 ± 0.08; XY, 1.59 ± 0.06 mm; $P<0.05$). Moreover, the maximal diameter of cleaned AAAs at study endpoint was significantly increased in XX compared to XY males (XX, 2.12 ± 0.17; XY, 1.55 ± 0.12 mm; $P<0.05$). With more prolonged AngII infusions (on day 56), XX males continued to have increased abdominal aortic lumen diameters compared to XY males (XX, 2.72 ± 0.29; XY, 2.23 ± 0.13 mm, $P<0.05$).

Conclusions: These results suggest that an XX sex chromosome complement promotes the severity and progression of AngII-induced AAAs in gonadally intact male mice.

Funding: These studies were supported by the National Institutes of Health Heart Lung and Blood Institute (R01 HL107326; LC) and from the American Heart Association (YA; predoctoral fellowship 14PRE20030018).

Contact information: Yasir Alsiraj, 300 Alumni Drive apt#105, Lexington KY 40503, yaal223@g.uky.edu, Tel: 859-536-1238

---

62. Title: Is there an association between the serotonin receptor 2A polymorphisms and obsessive-compulsive disorder: A systematic review of the literature

Authors List: Gabriella F. Mattina M.Sc Candidate[1,2], Meir Steiner MD, MSc, PhD, FRCPC[1,2]

Author Affiliations: [1]Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Ontario, Canada, [2]Women's Health Concerns Clinic, St. Joseph's Healthcare, Hamilton, Ontario, Canada

Abstract: Due to the heterogeneous nature of obsessive-compulsive disorder, the underlying genetics of the disorder remain unclear. Clinically, serotonergic dysfunction is implicated in OCD due to the efficacy of selective serotonin-reuptake inhibitors in treating OCD. Evidence from a recent meta-analysis is pointing towards examining genetic associations of OCD with polymorphisms in the gene coding for the serotonin receptor 2A (HTR2A). A review of all published studies cited in PubMed, MedLine, and Embase, using the search terms "OCD" and "HTR2A" or "serotonin polymorphism," was conducted. Out of 232 publications identified, only 14 studies examined the association. Two genetic variants have been found to be significantly associated with OCD: -1438G/A (rs6311) and 516C/T (rs6305). The A allele of rs6311 has been linked to OCD in both adults and

adolescents and in those with early onset, but results were inconsistent. There is some evidence that the effect may be sexually dimorphic, specific to females. The C allele of rs6305 was found to be associated with OCD, however this has yet to be replicated. Some studies failed to see any association with either SNPs. Another SNP that was repeatedly tested in relation to OCD was 102T/C (rs6113), with no positive results. However, 102T/C polymorphism has been demonstrated to be in complete linkage disequilibrium with the -1438G/A polymorphism, despite the varying findings between the two. With only a few studies examining the relationship between HTR2A polymorphisms and OCD, there is some promising evidence that the -1438G/A SNP may confer risk to developing OCD, which may be specific to women. There is a substantial amount of evidence identifying etiologically distinct forms of OCD based on sex and age of onset. Many studies failed to examine the association by these subtypes, which should be considered in future studies and may be the key in replicating findings.

Funding: None

Contact Information: Gabriella Mattina, Women's Health Concerns Clinic, St. Joseph's Healthcare, 301 James Street South, Hamilton, ON L8P 3B6, Canada; 1-905-522-1155 ext. 34173; mattingf@mcmaster.ca

---

63. Title: Informing women's cardiovascular health through genomic analysis of extreme endurance athletes

Authors List: C. Mikael Mattsson PhD[1,4], **Daryl Waggott MSc**[1], Matthew Wheeler MD, PhD [1,2,3], Aleksandra Pavlovic BS[1], Kristin Reese BS[1], & Euan A. Ashley MD, PhD[1,2,3]

Author Affiliations: [1]Ashley Lab, Department of Cardiovascular Medicine, School of Medicine, Stanford University, Stanford, CA, USA; [2]Center for Inherited Cardiovascular Disease, Stanford University, Stanford, CA, USA; [3]Undiagnosed Disease Network, Stanford University, Stanford, CA, USA; [4]Åstrand Laboratory of Work Physiology, The Swedish School of Sport and Health Sciences, Stockholm, Sweden

Abstract: Cardiovascular health exists as a spectrum of wellness and disease states. We hypothesize that interrogating the tail ends of the distribution for individuals with extreme phenotypes, such as high VO_2max in endurance athletes, will inform prevention, cause and treatment of pathogenic conditions. Mounting literature suggests that the physiological path to athletic performance is different among males and females. Traits with published sexual dichotomy include lactate threshold, efficiency, heat management, and fat metabolism. To define the genetic roots of this dichotomy, we propose to investigate sex-specific genetic determinants of VO_2max among elite endurance athletes. We have recruited 36 female (VO_2max>63 ml/kg; >99.99th percentile) and 129 male (>75 ml/kg) elite athletes (n=167) who have been consented and undergone enhanced whole exome sequencing. Even with differential eligibility, skewed recruitment (1:3.5) is a challenge. We will recruit a total of 100 female and 156 male elite athletes, and analyze these 256 exomes for burden of rare genetic variation that may impact sex-specific determinants of VO_2max. We will combine these data with an additional 1850 samples of elite athletes to evaluate for common variants that have sex-specific effects on VO_2max. Lastly, we will do a sex specific genetic cohort comparison of endurance athletes with existing collections of cardiovascular disease patients. Our preliminary results show tantalizing evidence for several highly plausible sex specific genes, including androgen receptor (AR) and FTO. The AR is the target of several known performance enhancing drugs, such as testosterone. FTO is associated with numerous aspects of body composition, energy management and even some evidence for age of menarche. While already promising, rigorous analysis, increased sample size and orthogonal replication is required as our next step.

Funding: SAP/Stanford Sequencing Initiative, Women's Heart Health at Stanford.

Contact information: Euan A. Ashley, Falk Cardiovascular Research Center, Quarry Road Extension, Palo Alto, CA 94304, phone: (650) 498-4900, email: euan@stanford.edu

64. Title: Sex differences in fat storage, cell size, and gene expression in subcutaneous abdominal adipose cells

Authors List: Tracey McLaughlin MD[1], **Bryan McColgan MD[1]**

Author Affiliations: [1]Department of Endocrinology and Metabolism, Stanford University Medical Center, Stanford, CA, USA

Abstract: Women have multiple anatomical differences in fat storage compared to men, including greater total body fat, greater subcutaneous relative to visceral fat, and larger abdominal and gluteofemoral adipose cell size. Metabolically, women also have a greater propensity to store fat in subcutaneous adipose tissue. This topic is of particular interest as the male pattern of fat distribution is associated with adverse health consequences such as insulin resistance, type 2 diabetes, and cardiovascular disease. We hypothesized that women would have larger and more metabolically active adipose cells in abdominal subcutaneous fat, which could confer insulin sensitivity. In order to investigate this question, 34 females with an average age of 50.8 years and 20 males with an average age of 54.3 years were examined for cell size and genetic expression of their subcutaneous abdominal adipose tissue. Through fat biopsies, our results showed women had significantly larger adipose cells (116+15 μm vs. 102+13 μm, p=<0.001). In addition, women also had significant differences in several genes for fatty acid storage, adipose cell differentiation, and mitochondrial oxidation genes as demonstrated by PCR. In terms of fatty acid storage gene expression, fatty acid synthase (p=0.09), hormone sensitive lipase (p=0.003), and lipoprotein lipase (p=0.016) were all significantly elevated in women. There was not a significant difference in free fatty acid lipoxygenase between the sexes (p=0.75). Women also had higher expression of the following adipose cell differentiation genes: CEBPα (p=<0.001), CEBPβ (p=0.017), PPARδ (p=0.006). Finally, women also had significantly increased expression of mitochondrial oxidation genes ATP5B (p=0.037), ATP5C1 (p=0.001), and NDUFS1 (p=0.037). However, a trend towards significance was noted in women with regard to steady-state plasma glucose compared to men (114+83 mg/dL vs. 183+64 mg/dL, p=0.06). In terms of fatty acid lipoxygenase, we did not observe a statistically significant difference between sexes, but regression analysis showed fatty acid lipoxygenase was directly associated with adipose cell size independent of sex (p=0.04). These data suggest that women have a metabolically more active reservoir of adipose cells that could possibly confer a reduced risk of diabetes and cardiovascular disease through alterations in insulin sensitivity and fatty acid metabolism.

Funding: NIH/NIDDK 1 R01 DK071309-01, 5RO1DK071333, 5K23 RR16071

Contact Information: Bryan McColgan, Stanford University Medical Center, Endocrinology Clinic, Boswell Building, 1st Floor, A175, Stanford, CA 94305; 1-650-723-6961; mccolgan@stanford.edu

---

65. Title: The Impact of Body Mass Index and Gender On Patient Survival After Therapeutic Hypothermia Following Resuscitation

Authors List: Nishaki Mehta Oza[1], Khadijah Breathett[1], Vedat Yildiz[2], Erik Abel[3], Ruchika Husa[1]

Author Affiliations: [1]Division of Cardiovascular Medicine, The Ohio State University Wexner Medical Center, Columbus, OH, USA, [2]Division of Statistics, The Ohio State University Wexner Medical Center, Columbus, OH, USA, [3]Division of Pharmacy, The Ohio State University Wexner Medical C enter, Columbus, OH, USA

Abstract: BACKGROUND: Therapeutic hypothermia has been established to improve survival in patients following cardiac arrest; yet the impact of body mass index (BMI) and gender on survival post hypothermia is lesser known. Given the obesity paradox in heart failure and the gender differences in cardiovascular outcomes, we hypothesized that men and higher BMI patients would have better survival post therapeutic hypothermia than women and lower BMI patients.

METHODS: We retrospectively evaluated 183 patients who underwent therapeutic hypothermia following resuscitation at our two large academic centers from 1/2012 to 9/2014. Logistic regression analysis was used to assess for survival based upon BMI, gender, and comorbidities.

RESULTS: The average BMI was 30.5 (standard deviation 9.7 kg/m2). There were 67% men (n=122). Therapeutic hypothermia was performed in 75% patients (n=138) for cardiac arrest, while the rest were cooled for neurologic indications. Mortality post therapeutic hypothermia was 60% (n=110). There was a significantly higher mortality for patients with BMI >30kg/m2 compared to BMI ≤30kg/m2 [Odds Ratio OR 1.94 (95% Confidence Intervals CI 1.04, 3.62), p=0.034, Figure 1]. There was no difference in mortality based upon gender [OR 1.57 (95% CI 0.8, 2.9), p= 0.166] or other comorbidities.

CONCLUSIONS: BMI >30kg/m2 was a significant risk factor for mortality post therapeutic hypothermia protocol, while gender was not a factor. Larger studies will be needed to validate these findings.

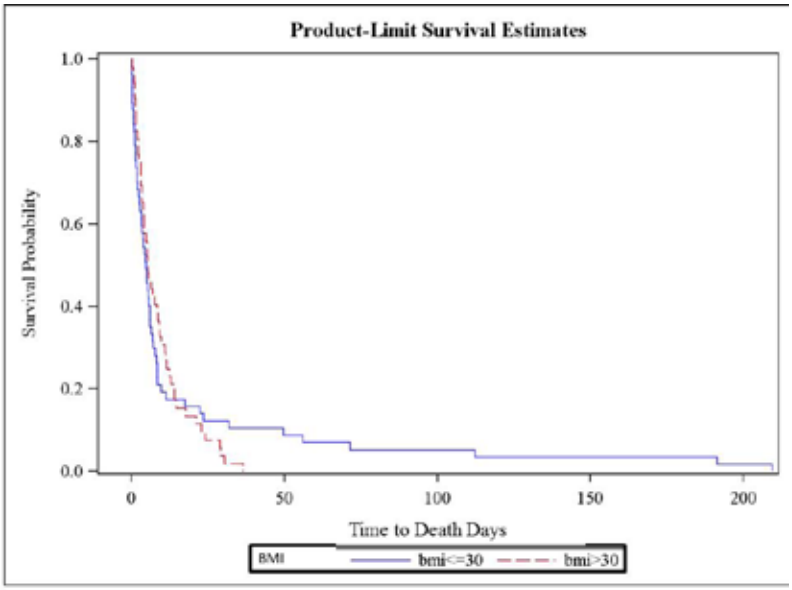


Figure 1: Relationship of BMI with mortality in patients who underwent therapeutic hypothermia following resuscitation.

Funding: None

Contact information: Nishaki Mehta Oza, MD, Division of Cardiovascular Medicine, The Ohio State University, Columbus, Ohio 43221, (T) 508 523 9673, Email: drnishakimehta@gmail.com

---

66. Title: Intrinsic excitability varies by sex in prepubertal striatal medium spiny neurons

Authors List: David M. Dorris[1], Jinyan Cao M.D./PH.D.[1,2], Jaime A. Willet[1,2,3], Caitlin A. Hauser[1], **John Meitzen Ph.D.**[1,2,4]

Author Affiliations: [1]Department of Biological Sciences, North Carolina State University, Raleigh, NC, [2]W.M. Keck Center for Behavior Biology, North Carolina State University, Raleigh, NC, [3]Graduate Program in Physiology, North Carolina State University, Raleigh, NC, [4]Center for Human Health and the Environment, Center for Comparative Medicine and Translational Research, North Carolina State University, Raleigh, North Carolina

Abstract: Sex differences in neuron electrophysiological properties were traditionally associated with brain regions directly involved in reproduction in adult, postpubertal animals. There is growing acknowledgement that sex differences can exist in other developmental periods and brain regions as well. This includes the dorsal striatum (caudate/putamen), which shows robust sex differences in gene expression, neuromodulator action (including

dopamine and 17β-estradiol), and relevant sensorimotor behaviors and pathologies such as the responsiveness to drugs of abuse. Here we examine whether these sex differences extend to striatal neuron electrophysiology. We test the hypothesis that passive and active medium spiny neuron (MSN) electrophysiological properties in prepubertal rat dorsal striatum differ by sex, a developmental period widely employed for electrophysiological recordings. We made whole cell recordings from male and females MSNs from acute brain slices. The slope of the evoked firing rate to current injection curve was increased in MSNs recorded from females compared with males. The initial action potential firing rate was increased in MSNs recorded from females compared with males. Action potential after-hyperpolarization peak was decreased, and threshold was hyperpolarized in MSNs recorded from females compared with males. No sex differences in passive electrophysiological properties or miniature excitatory synaptic currents were detected. These findings indicate that MSN excitability is increased in prepubertal females compared with males, providing a new mechanism that potentially contributes to generating sex differences in striatal-mediated processes. Broadly, these findings demonstrate that sex differences in neuron electrophysiological properties can exist prepuberty in brain regions not directly related to reproduction.

Funding: NC State University Start Up Funds, Grass Foundation, Howard Hughes Medical Institute Undergraduate Science Education Grant.

Contact: 144 David Clark Labs, Campus Box 7617, Raleigh, NC, 27695-7617; 919-515-4496; jemeitze@ncsu.edu

---

67. Title: Novel preclinical models to study sex differences in obesity-linked metabolic dysregulation

Authors List: Suresh Mishra Ph.D.[1,2], Sudharsana R. Ande* Ph.D.[1], Khanh H. Nguyen* Ph.D.[1], G. Pauline Padilla-Meier Ph.D.[1], B. L. Grégoire Nyomba. M.D., Ph.D.[1] * Contributed equally

Author Affiliations: [1]Department of Internal Medicine, University of Manitoba, Winnipeg, MB, Canada; [2]Department of Physiology & Pathophysiology, University of Manitoba, Winnipeg, MB, Canada

Abstract: Sex differences are known to exist in obesity- and immune-associated diseases and their complications. Recent studies have highlighted the potential relevance of white adipose tissue mitochondria in adipose tissue homeostasis and its impact on metabolic regulation. However, a potential role of adipose tissue mitochondria in obesity associated sex differences in metabolic consequences is not explored. To this end, we developed a transgenic obese mouse model (**Mito-Ob**) by prohibitin mediated mitochondrial remodeling in adipocytes. Interestingly, Mito-Ob mice develop obesity in sex-neutral manner; however, only male Mito-Ob mice had impaired glucose homeostasis and developed insulin resistance, whereas female mice had normal glucose homeostasis and insulin sensitivity. The metabolic phenotype of Mito-Ob mice is consistent with our hypothesis that obesity and obesity associated sex-dimorphic metabolic dysregulation may develop due to primary changes in adipose tissue or adipocyte mitochondria. For example, priming of adipose tissue and/or adipose tissue mitochondria by environmental factors during critical stages of development such as prenatal and puberty may underlie the obesity epidemic that warrants further investigations. On the basis of Mito-Ob mice, we also developed a **mutant-Mito-Ob** mouse to investigate sex differences in adipose-immune interactions, because it has emerged as a driver for obesity-associated abnormalities including insulin resistance, type 2 diabetes and some forms of cancer. Mutant-Mito-Ob mice share the metabolic phenotype of Mito-Ob mice. In addition, mutant-Mito-Ob mice develop histiocytosis with lymphadenopathy in obesity-associated insulin resistance dependent manner, suggesting a role for sex differences in adipose-immune interactions in obesity-linked cancer development. We anticipate that our novel preclinical models will prove valuable tools to better understand obesity associated metabolic defects and diseases in a sex-specific manner.

Funding: Supported by funding from Natural Sciences and Engineering Research Council of Canada and Research Manitoba.

Contact Information: Suresh Mishra, Department of Internal Medicine**,** University of Manitoba, 843 JBRC/ 715 McDermot Avenue, Winnipeg, MB, R3E 3P4, Canada Ph. 1-204-977-5629, Email: suresh.mishra@umanitoba.ca

---

68. Title: Effect of age on sexually dimorphic expression of selected X chromosome genes in the mouse cortex and hippocampus

Authors List: Debbie Moreira, Chris Armoskus, Saori Taniguchi, Oliva Jimenez, Khary Filer, and Houng-Wei Tsai Ph.D.

Author Affiliations: Department of Biological Sciences, California State University, Long Beach, Long Beach CA 90840

Abstract: Using microarrays and reverse transcription with quantitative polymerase chain reaction (RT-qPCR), we have previously identified five X chromosome genes differentially expressed in the neonatal male and female mouse cortex/hippocampus. Among those X-linked genes, three (*Eif2s3x*, *Kdm6a*, and *Xist*) are located on the non-pseudoautosomal portion (NPX) while two (*Erdr1* and *Mid1*) reside in the pseudoautosomal region. We hypothesized that in the developing mouse cortex/hippocampus, dimorphic expression of these genes might be temporally dynamic, responsible for the development of sex differences in structures and circuits that mediate sex-biased function controlled by these two brain regions. To test our hypothesis, we measured mRNA levels of these genes in the male and female mouse cortex/hippocampus collected on the day of birth (PN0), and 7 (PN7), 14 (PN14), and 21(PN21) days after birth. We found significant effects of age and sex on *Eif2s3x* expression in the mouse cortex/hippocampus, but no interaction between these two factors. While female mice expressed higher *Eif2s3x* mRNA levels than males during early development, an age-dependent decrease in *Eif2s3x* expression occurred at PN7 and PN14 as compared to PN0. We also discovered significant effects of sex, age, and interaction on mRNA levels of *Kdm6a* and *Erdr1* in the developing mouse cortex/hippocampus. The female-biased expression of the former was observed only at PN0 and PN21 while such female-biased expression of the latter didn't appear until PN21. Unlike *Eif2s3x*, *Erdr1*, or *Kdm6a*, the *Kdm5c* gene showed no sex difference, but a significant increase with age and interaction, with male- and female-biased expression on PN7 and PN14, respectively. Based on our data, we concluded that during early development, dimorphic expression of the four X-linked gene in the mouse cortex/hippocampus dynamically changes with age, suggesting that these genes might participate in brain feminization at different developmental stages.

Funding: This work was supported by National Institutes of Health Grant SC3GM102051.

Contact Information: Houng-Wei Tsai, Department of Biological Sciences, California State University Long Beach, 1250 Bellflower Blvd., Long Beach, CA 90840; 562-985-5649; Houng-Wei.Tsai@csulb.edu

---

69. Title: Sex differences in knowledge of reproductive potential

Authors List: Mariko Ogawa M.D, Akane Miyata M.D., Kiyoshi Takamatsu M.D., Masumi Yoshimaru M.D., Sayaka Uchida M.D., and Joji Yoshida M.D.

Author Affiliations: Department of Obstetrics and Gynecology, Tokyo Dental College Ichikawa General Hospital, Chiba, Japan

Abstract: While the reproductive potential of women declines with age, there is limited information available on this. Our aim was to investigate the knowledge of couples who desire infertility treatment. Participants were 51 couples who visited the reproduction center to undergo testing and receive infertility treatment, and responded to a questionnaire. The questionnaire, which asked about women's reproductive potential, was distributed to the

men and women individually. The results were as follows: (1) For the question “What is the maximum age that women can get pregnant?”, women and men responded that it was 41.7 and 43.5 years on average, respectively. (2) For the question that asked the participants to state their perceived success rate of assisted reproductive technologies, women and men stated 25.9 and 32.5%, respectively. (3) As their sources of information, the most common answer was the press reporting the pregnancy of famous people, the second was television programs, and the third was the Internet. Few participants responded that they had sought a professional opinion. There were no significant differences noted between males and females. In conclusion, we found that infertile men tend to optimistically estimate the reproductive potential of females, compared to infertile women. Additionally, they do not have sufficient ways to obtain accurate information. An educational system to learn about fertility should be established.

Funding: This study did not receive any funding.

Contact Information: Mariko Ogawa, Department of Obstetrics and Gynecology, Tokyo Dental College Ichikawa General Hospital, 5-11-13, Sugano, Ichikawa City, Chiba 272-8513, Japan. +81-47-322-0151; ogawam@tdc.ac.jp

---

70. Title: Operator volume and experience can overcome sex difference in procedural success of chronic total occlusion interventions

Authors List: Janet Okogbaa BA[1], David V. Daniels MD[2], William Lombardi MD[3], Jennifer A. Tremmel MD[4]

Author Affiliations: [1]Stanford University School of Medicine, Stanford, CA, USA; [2]Palo Alto Medical Foundation, Palo Alto, CA, USA; [3]University of Washington Medical Center, Seattle, WA, USA; [4]Stanford University Medical Center, Division of Cardiovascular Medicine, Stanford, CA, USA

Abstract: Chronic total occlusion (CTO) of the coronary arteries is a severe condition characterized by complete artery blockage persisting for at least three months. Though traditionally remedied with bypass grafts, CTO is more commonly treated with minimally invasive Percutaneous Coronary Intervention (PCI). Existing data suggests a sex difference in PCI for CTO, with men having a significantly lower procedural success rate than women (67.5% vs. 74.5%, P=0.03). However, it is also known that men with coronary artery disease (CAD) have more high-risk angiographic features and CTO success is improved with operator volume and experience. We aimed to determine if operator volume and experience might overcome the existing sex difference in CTO success. We investigated sex differences in angiographic and procedural characteristics in 480 consecutive patients undergoing PCI for at least one CTO by a single operator with a high CTO volume, retrograde expertise, and success rate (>90%). A total of 406 men and 74 women were treated. Procedural success rates were similar between women (92%) and men (90%, P=0.294). In addition, there were no significant sex differences in procedural characteristics such as CTO lesion length (24.4 mm vs. 27.0 mm), reference vessel diameter (2.8 mm vs. 2.9 mm), procedural time (87.5 minutes vs. 93.4 minutes), fluoroscopy time (31.3 minutes vs. 35.4 minutes), contrast used (197.6 ml vs. 230.8 ml), or use of the retrograde technique (52% vs. 48%). In conclusion, high operator volume and experience eliminates the previously observed sex difference in the success of PCI for CTO. This finding suggests that lower procedural success rates in men may be attributable to the higher-risk angiographic profile of this subset and variation in operator experience and skill level. Ongoing research is needed to identify methods for optimizing PCI outcomes for both men and women.

Funding: none

Contact Information: Janet Okogbaa, Li Ka Shing Center for Learning and Knowledge, 291 Campus Drive, Palo Alto, CA 94305; 1-813-842-8839; jokogbaa@stanford.edu.

71. Title: Mast cells and microglia mediate sexual differentiation of the preoptic area

Authors List: Lindsay A. Pickett[1,2], Kathryn M. Lenz[3] and Margaret M. McCarthy[1,2]

Author Affiliations: [1] Department of Pharmacology and [2] Program in Neuroscience, University of Maryland School of Medicine, Baltimore, MD; [3] Department of Psychology, The Ohio State University, Columbus, OH.

Abstract: The first neuroanatomical sex difference detected in the mammalian brain was reported in 1978 and named the sexually dimorphic nucleus (SDN) due to its larger size in males compared to females. The SDN is a dense collection of calbindin-expressing neurons located within the central division of the medial preoptic nucleus (MPNc) of the preoptic area (POA), a critical brain region for the control of copulatory, partner preference and maternal behaviors. Previous studies have established that both sexes generate the same number of neurons in the SDN and they selectively die early in life in females due to a lack of the endogenous survival factor, estradiol. This system is an excellent model for naturally occurring cell death versus neuroprotection in the developing brain but the involvement of non-neuronal cells in this model system has been largely ignored. We have previously established that innate immune cells of the brain, microglia, and inflammatory mediators such as prostaglandins direct the development of sex-specific synaptic patterns in the neonatal POA that correlate with sexual behavior in the adult rat. We now turn our attention to an additional inflammatory cell type, mast cells, which like microglia are of myeloid cell lineage with origins outside the nervous system. We determined there are more mast cells in the POA of neonatal males than females and pharmacological activation of mast cells in newborn females induces a male-typical microglial morphology, with higher numbers of ameboid microglia and lower numbers of ramified, phagocytic microglia. We are currently investigating whether mast cells modulate microglial primary phagocytosis (phagoptosis) and whether this contributes to the sexual differentiation of SDN volume by either primary or secondary phagocytosis. Collectively these results indicate non-neuronal cells are crucial and unappreciated factors shaping brain development and sex-specific physiological and behavioral outcomes.

Funding: R01MH52716 (MMM), F32NS076327 (KML).

Contact Information: Lindsay A. Pickett, Department of Pharmacology, University of Maryland School of Medicine, 655 W. Baltimore Street, Baltimore MD 21201, USA. Phone: (410) 706-2654; Email: lindsaypick46@gmail.com

72. Title: Emotional contexts exert a differential effect on event related potentials associated to response inhibition in men and women

Authors List: Julieta Ramos-Loyo Ph.D., Armando Angulo Psy., Luis Angel Llamas, Psy., & Andrés A. González-Garrido, Ph.D.

Author Affiliations: Instituto de Neurociencias, Universidad de Guadalajara, México.

Abstract: Some evidence indicates that women are more efficient in inhibitory processing and involve different cerebral areas than men. However, despite of sex differences in different levels of emotional processing have been widely reported, there is no evidence related to the effects that emotional contexts exert in the temporal course of inhibition processing. Therefore, the objective of the present study was to explore sex differences in the effects of emotional contexts over response inhibition through event related potentials (ERPs). Men and women performed a Go-NoGo response inhibition task under 4 context conditions: stimuli without context and contexts with neutral, pleasant and unpleasant emotional contents. Subjects had to press a key when an arrow located in the middle of the screen, coincided both in direction and color with a bar presented in the left or right edges (Go) and to withhold the response when it did not match (NoGo). Emotional contexts provoked lower number of correct inhibitions than non-emotional ones. No sex differences in performance were found. Unpleasant context elicited higher N2 amplitude and, the pleasant one, a longer P3 latency during inhibition. Women showed higher

N2 amplitude and longer latency than men at emotional contexts, whereas men showed higher P3 amplitude at the unpleasant one. In addition, higher N2 and P3 amplitudes and N2 latency correlated with higher number of inhibition responses only in men. Results suggest that emotional contexts attract attention making more difficult to inhibit a prepotent response than non-emotional ones, evidenced both in performance and ERPs. In addition, women invested more resources and took more time to process inhibition in earlier stages than men when emotional contexts were present. Meanwhile, men who required recruiting more attentive and inhibitory neural resources had more difficulties in order to achieve inhibition, particularly under emotional contexts.

Funding: This study was funded by CONACyT (155520).

Contact Information: Julieta Ramos-Loyo, Instituto de Neurociencias, Francisco de Quevedo 180, Arcos Vallarta, Guadalajara, Jal., México, 44520; 0152 37 77 11 50 ext. 33354; jramos@cencar.udg.mx

---

73. Title: Sex-specific regulation of CNS autoimmunity by the signal lymphocytic activation molecule (Slam) locus

Author List: Abbas Raza[1], Laure K. Case Ph.D.[1], Erin Osmanski[1], Dimitry N. Krementsov Ph.D.[1], Jonathan E. Boyson, Ph.D[2], Cory Teuscher Ph.D.[1]

Author Affiliations: [1]Department of Medicine, Immunobiology Program, University of Vermont, Burlington, VT 05405, USA; [2]Department of Surgery, University of Vermont, Burlington, VT 05405, USA

Abstract: Multiple sclerosis (MS) is a chronic demyelinating inflammatory disease of the central nervous system (CNS). Epidemiological studies have documented a 3-6 fold increase in MS incidence and prevalence in females over the last half-century, while remaining relatively stable in males. This rate of change clearly establishes that geneÅ~environmentÅ~sex interactions contribute to MS susceptibility. Genome-wide association studies (GWAS) of MS patients identified multiple candidate genes, including a locus containing the signal lymphocytic activation molecule (SLAM) family of receptors, a region rich in immune-relevant genes that is highly conserved between humans and mice. There are two major Slam haplotypes segregating in laboratory mice. Slam haplotype-1 is present in C57BL/6 (B6) mice and haplotype-2 is expressed in most other commonly used inbred laboratory strains, including 129 mice. The congenic B6.129c1 mouse possesses the 129-derived Slam haplotype-2 locus on the B6 background, which allows for assessing the potential contribution of SLAM family genes to MS susceptibility using the myelin oligodendrocyte (MOG) model of experimental autoimmune encephalomyelitis (EAE). We show that male B6.129c1 congenic mice demonstrate significant protection against MOG-EAE, but only in males. Furthermore, draining lymph nodes from immunized B6.129c1 males, but not females, had increased Foxp3+ regulatory T cells (Treg) and IL-10 levels compared with B6 controls, suggesting that SLAM/Slam haplotypes regulate autoimmunity by modulating the generation of immunoregulatory cells in a sex-specific manner. Taken together, our results support a role for the SLAM locus is MS pathogenesis, and reveal a novel sexual dimorphism in the genetic control of this autoimmune disease.

Funding: This work was supported by National Institute of Health grants NS069628 and NS076200 to CT and AI067897 to JEB.

Contact: Abbas Raza, D305 Given building, 89 Beaumont ave, University of Vermont, Burlington, VT, 05405; 802-656-8391; abbas.raza@uvm.edu

74. Title: Lamotrigine and $GABA_A$ Receptor Modulators Interact with Menstrual Cycle Phase and Oral Contraceptives to Regulate Mood in Women with Bipolar Disorder

Authors List: Thalia K. Robakis, MD, PhD; Jessie Holtzman; Pascale G. Stemmle, PsyD; Margaret F. Reynolds-May, MD; Heather A. Kenna, MS, MA; Natalie L. Rasgon, MD, PhD

Author Affiliations: Department of Psychiatry and Behavioral Science, Stanford University School of Medicine, 401 Quarry Road, Stanford, CA 94305

Abstract: *Objectives:* To examine the occurrence of menstrually-entrained mood cycling in women with treated bipolar disorder as compared to healthy controls, and to explore whether there is a specific effect of lamotrigine in dampening menstrually-entrained cyclicity of mood. *Methods:* Observational comparison study of daily self-ratings of mood, sleep, and insomnia obtained over a mean of four menstrual cycles in 42 women with bipolar disorder taking lamotrigine as part of their treatment, 30 women with bipolar disorder receiving mood stabilizing regimens without lamotrigine, and 13 healthy controls, all with physiological menstrual cycles. Additional exploratory analysis of interactions between psychopharmacological regimen and hormonal contraceptive use in the group of women with bipolar disorder, with the addition of 19 women with bipolar disorder who were using hormonal contraceptives. *Results:* Women treated for bipolar disorder manifested lower average mood, longer average nightly sleep duration, and greater fluctuations in mood and sleep across menstrual cycle phases than healthy controls. Women with bipolar disorder who were taking lamotrigine had less fluctuation in mood both within and across menstrual cycle phases, and were more similar to the control group than to women with bipolar disorder who were not taking lamotrigine in this respect. Additionally, medications with $GABA_A$ receptor modulating effects were found to result in improved mood ratings when combined with hormonal contraceptives. *Conclusions:* Menstrually-entrained mood fluctuation is present in women treated for bipolar disorder to a greater degree than in healthy controls. Lamotrigine may be of use in mitigating this fluctuation. $GABA_A$ receptor modulators in general may act synergistically with hormonal contraceptives to enhance mood in women with bipolar disorder; this hypothesis merits further study.

Funding: Financial support for this project was provided by the National Institutes of Health (R01 grant MH0066033), the National Center for Research Resources (M01 grant RR-00070), and by Glaxo Smith-Kline.

Contact Information: Dr. Thalia Robakis, Stanford University Department of Psychiatry and Behavioral Science, 401 Quarry Road MC 5723, Stanford, CA 94305; Email: trobakis@stanford.edu; Telephone: 650-724-9694

---

75. Title: The sex-specific link between eotaxin and ischemic stroke outcomes

Authors List: Meaghan A. Roy-O'Reilly M.S. [1], Sarah E. Conway B.A. [2], Ilene Staff Ph.D.[3], Gil Fortunado MBA[3], Louise D. McCullough M.D. Ph.D.[1,2]

Author Affiliations: [1]Dept. of Neurology and Neuroscience, Univ. of CT Health Center, Farmington, CT, [2]Department of Neurology, School of Medicine, Univ. of CT Health Center, Farmington, CT, [3]Research Program, Hartford Hospital, Hartford, CT

Abstract: Women who suffer an ischemic stroke have poorer functional outcomes and higher age-specific mortality than their male counterparts. Recently, sex-specific immune responses have been implicated in the distinct disease outcomes seen in males and females. We have demonstrated that the pro-inflammatory cytokine eotaxin increases significantly in mice following experimental ischemic stroke. Eotaxin levels increase with age, and are responsible for age-related deficits in neurogenesis in experimental models. However, little is known about its role in the stroke-induced immune response. Given that females often have a more robust immune response, we hypothesized that the increase in eotaxin following stroke may be sex-specific, with differential effects on acute and long-term outcomes. Serum samples were taken from 158 patients (88 male, 70 female) at 24±6 hours

after the onset of imaging positive ischemic stroke. Levels of serum eotaxin were quantified by multiplex ELISA (BioRad). The primary outcome of this study was in-hospital mortality or discharge to hospice care. Secondary outcomes included change in NIH stroke severity during hospital stay, incidence of post-stroke infection, and functional outcomes at 3 and 12 months as measured by modified Rankin score (mRs) and modified Barthel Index (MBI). Eotaxin levels showed no association with negative outcome measures and were not significantly different between sexes [females = 35.97 (23.6 - 48.0) and males = 31.5 (24.3 - 48.4)]. Interestingly, eotaxin levels were associated with positive outcomes in men, including an improved NIH score at discharge (p=.005), lower infection rates (p=.03), and improved functional scores as measured by mRS at 3 months (p=.024) and 12 months (p=.048). In conclusion, these associations suggest that eotaxin may represent a beneficial immune mechanism after an acute injury such as stroke. Further study of eotaxin signaling may provide insight into novel therapeutic targets for both sexes.

Funding Source: Hartford Hospital Research Department

Contact Information: Meaghan A. Roy-O'Reilly, royoreilly@uchc.edu, 860-617-7758 L-4008, 263 Farmington Avenue, Farmington, CT, 06032

---

76. Title: Hedonic sensitivity to low-dose ketamine is modulated by gonadal hormones in a sex-dependent manner

Authors List: Samantha K. Saland M.S. [1, 2], Kristin J. Schoepfer [1, 2], & Mohamed Kabbaj Ph.D. [1, 2]

Author Affiliations: [1]Department of Biomedical Sciences, [2]Program in Neuroscience, College of Medicine, Florida State University, Tallahassee, FL, USA

Abstract: We recently reported a greater sensitivity of female rats to the antidepressant-like effects of ketamine relative to male rats, which required both gonadal estrogen (E2) and progesterone (P4). However, baseline sex differences in these acutely-stressful behavioral paradigms interfere with the ability to tease apart hormone-dependent contributions to ketamine's response profile in this species. In addition, it is unclear how these hormones and testosterone (T) contribute to sex differences in anhedonia-like behaviors, and whether the duration of response to ketamine is modulated in a sex- and hormone-dependent manner. Here, a mixed between-/within-subjects approach was implemented to delineate hormonal contributions to ketamine's sex-dependent response profile in rats. Using a continuous-access sucrose preference paradigm, we systematically investigated the influence of T, E2 and P4 on initiation and maintenance of hedonic response to low-dose ketamine in gonadectomized and intact male and female rats receiving identical physiologically-relevant hormone treatments. Results showed that a single low dose of ketamine induced a robust increase of sucrose preference levels in female, but not male rats, which was both E2- and P4-dependent. Conversely, T failed to alter male treatment response. However, hedonic sensitivity to the same dose of ketamine could be significantly enhanced in male rats by concurrent treatment with P4 alone. Collectively, we provide novel evidence supporting activational roles for ovarian-, but not testicular-, derived hormones in mediating hedonic sensitivity to low-dose ketamine in female and male rats, respectively. Organizational differences may, in part, account for the persistence of sex differences following gonadectomy. Importantly, our data suggest the potential utility of P4 or P4-like neurosteroids as adjunctive treatments for enhancing the pro-hedonic effects of ketamine at suboptimal doses in males.

Funding: NIMH RO1MH087582 and RO1MH099085 to Mohamed Kabbaj.

Contact Information: Samantha K. Saland, Department of Biomedical Sciences, College of Medicine, Florida State University, 1115 W. Call St., Tallahassee, FL 32306; 1-515-371-0014; samantha.saland@med.fsu.edu

77. Title: Does Plasminogen Activator Inhibitor (1,2) Mediate Depression and Cardiovascular Disease During Pregnancy? A Review of the Literature

Authors List: Calan Savoy B.A., Ryan Van Lieshout MD Ph.D., Meir Steiner MD Ph.D.

Author Affiliations: Women's Health Concerns Clinic, St. Joseph's Healthcare, Hamilton, Ontario, Canada; Department of Psychiatry and Behavioural Neurosciences, McMaster University; McMaster Integrated Neuroscience Discovery and Study Program, McMaster University, Hamilton, Ontario, Canada

Abstract: Plasminogen Activator Inhibitor (PAI) increases coagulation by inhibiting plasmin, a protein responsible for clot degradation. Chronic dysregulation of this pathway may be implicated in the formation of atherosclerotic clots and other aspects of cardiovascular disease (CVD). Some research also proposes a link between PAI-1 and Major Depressive Disorder (MDD), suggesting a mechanism behind MDD and CVD comorbidity. This effect may be particularly evident during pregnancy because of the increased incidence of MDD and cardiovascular pathology. Of a preliminary pool of 7765 PubMed articles, 26 were selected for inclusion into this review based upon suitability of subject matter and robustness of study. MDD produces a number of discrete physiological changes that have independently been observed to influence PAI-1. For instance, serum PAI-1 concentration has been observed to be elevated during inflammatory cardiovascular pathologies. PAI-1 is also upregulated by pro-inflammatory cytokines. Likewise, MDD is characterized by a systemic inflammatory response. Additionally, MDD mediates HPA axis dysregulation, which can also elevate PAI-1 expression. These findings have special significance in the pregnant population. A second isoform of PAI (PAI-2) is secreted from the placenta during pregnancy, further explaining the increased propensity of pregnant women to MDD and cardiovascular pathology. Our review of the available literature suggests that PAI-1 and 2 mediate CVD and MDD through a number of candidate pathways. Further research is needed to explore this possibility and determine whether PAI may be predictive, rather than descriptive of illness. Of particular interest is the roles PAI-1 and 2 play during pregnancy, and how they may influence both MDD and CVD development in that high-risk patient population.

Contact Information: Calan Savoy, Women's Health Concerns Clinic, St. Joseph's Healthcare Charlton Campus, 301 James Street South, Hamilton ON L8P 3B6; (905) 522-1155 ext. 32953; savoycd@mcmaster.ca

78. Title: Infection of female and male mice reveals differences in bladder immune responses to urinary tract infection

Author List: **Anna Zychlinsky Scharff**[1,2,3], Tracy Canton[2,3], Matthew L. Albert, MD, PhD[2,3], Molly A. Ingersoll, PhD[2,3]

Author Affiliations: [1]Hannover Medical School, Hannover, Lower Saxony, Germany; [2]Immunobiology of Dendritic Cells Laboratory, Immunology Department, Institute Pasteur, Paris France [3]INSERM U818, Paris, France.

Abstract: Susceptibility to urinary tract infections (UTI) differs strongly between the sexes; adult women are 40 times more likely than men to develop an infection. The difference in disease susceptibility has long been attributed to the divergent lengths of the male and female urethra. However, experimental evidence for this hypothesis is lacking, and additional immune factors likely play a role. We developed a model of male UTI, bypassing the requirement of bacterial ascension of the urethra, to test whether the innate immune response to uropathogenic Escherichia coli (UPEC), the most common causative agent of UTI, differs between male and female mice. Paradoxically, we observed that while female mice resolved infection within 14 days, male mice continued to shed UPEC in their urine for up to 30 days. The type and number of infiltrating immune cells in male and female mice differed significantly, with females exhibiting more robust infiltration at 24h post infection, marked by higher levels of eosinophil infiltration. To understand the mechanism(s) underlying this phenotype, we first tested eosinophil depletion, however, this did not alter the sex-specific ability to resolve infection. We then hypothesized that sex hormones play a role in bacterial elimination. To test this, we treated female mice with continuous release testosterone implants. We observed that

females treated with testosterone exhibited persistent UTI, with bacteria present in the urine for up to 30 days, mimicking the phenotype observed in male mice. Notably, castration had no impact on the capacity of male mice to clear their infection. These data suggest that testosterone negatively impacts the animal's capacity to clear UPEC, and highlights the complexity of susceptibility to infection.

Contact Information: Corresponding Author: Molly Ingersoll**,** 25 Rue du Dr Roux 75005 Paris France, +33 1 4568 8071 (molly.ingersoll@pasteur.fr) Poster Presentation: Anna Zychlinsky Scharff, Tieckstrasse 18, 30625, Hannover, Germany (ankazychlinsky@hotmail.com)

---

79. Title: Context fear conditioning requires different processes in males and females

Authors List: Ashley A. Schmeling B.S. & Natalie C. Tronson Ph.D.

Author Affiliations: Department of Psychology, University of Michigan, Ann Arbor, MI, USA.

Abstract: Sex differences in fear-related learning have been observed in both prevalence of disordered fear in humans, and in animal models of fear conditioning. For example, women are almost three times more likely to develop post-traumatic stress disorder after a traumatic event than men. In contrast, in animal models of context fear conditioning, males typically show stronger fear conditioning compared with females. It is not clear whether sex differences in fear-related memories exist due to differential learning about context, the relationship between context and shock, or the modulatory effects of aversive stimuli on memory formation. Here we aimed to determine whether differential context learning by males versus females contributes to sex differences in fear conditioning. To do this, we trained male and female mice in context fear conditioning and tested fear responses in contexts identical, similar-to, and distinct-from the training box. We hypothesized that differences in learning about context would result in females showing less discrimination between similar contexts, and therefore greater fear (more generalization) to a similar context compared with males. Further, we anticipated that exposure to the training context prior to fear conditioning would alleviate this difference by increasing context learning in both males and females. We found that, in this fear conditioning protocol, females exhibited greater generalization of fear to a similar context than did males. In contrast, we found that pre-exposure to the training context increased fear in males but was only partially effective in alleviating generalization in females. Our results demonstrate that males show stronger learning of contextual information compared with females. However, reduced context learning in females is not sufficient to fully account for sex differences in context fear conditioning. How other factors contribute to fear-associated learning in males and females is yet to be determined.

Contact Information: Ashley A. Schmeling, Department of Psychology, East Hall, 530 Church Street, Ann Arbor, MI, 48109; 734-678-7070; aschmeli@umich.edu

---

80. Title: Bisphenol A increases acute myocarditis in female BALB/c mice by activating estrogen receptor beta, mast cells, and the inflammasome

Authors List: Ashley Scott[1,2], Katelyn A. Bruno[2,3], Adriana Bucek[1], Henry Greyner[1], Frank Molina[1], J. Augusto Frisancho[2,3], DeLisa Fairweather[2,3]

Author Affiliations: [1]University of Maryland Baltimore County, Baltimore, MD; [2]Johns Hopkins Bloomberg School of Public Health, Department of Environmental Health Sciences, Baltimore, MD; [3]Mayo Clinic, Department of Cardiovascular Medicine, Jacksonville, FL, United States

Abstract: Myocarditis is an inflammatory heart disease that is the leading cause of heart failure in young adults. Sex hormones play a crucial role in the development of myocarditis. Testosterone is the major driving force of the disease in males and estrogen mediates cardioprotection in females via Estrogen Receptor α (ERα). Since myocarditis is influenced by sex hormones, it is possible that endocrine disruptors (EDs), which interfere with

natural hormones, will play a part in the progression of the disease. Bisphenol A (BPA) is a known ED that is used as a monomer in various plastic materials including: baby bottles, water bottles and food containers. BPA has been found to function through ERβ in cardiomyoctes, worsening some cardiovascular diseases. To our knowledge no one has examined the effect of EDs such as BPA on myocarditis. We hypothesize that BPA will increase myocarditis by activating the ERβ as opposed to triggering the beneficial effects of ERα. Through quantitative-RT-PCR analysis, we found that clinically relevant doses (25 μg/L and 250 μg/L) of BPA diluted in water increased acute myocarditis when compared to control water. Furthermore, we found that BPA significantly increased ERβ, while ERα was significantly decreased in BALB/c mice with myocarditis. We also found that mast cells (cKit) and CD4 T helper cells were significantly increased in BALB/c mice. IL-1β, IFN-γ, TLR4, Caspase-1, Mmp9, and ST2 were all increased during myocarditis with BPA treatment, genes that are associated with more severe inflammation and fibrosis in male BALB/c mice. In summary, we found that BPA exposure increases myocarditis in female BALB/c mice by altering ERα and β expression. In future studies we will confirm whether BPA's effect is mediated via ERα or ERβ using knockout mice, the effect of BPA exposure in BALB/c males, and its effect on other mouse strains like C57BL/6 mice. This work was funded by NIH R01 HL111938, AHA 12GRNT12050000, and NIEHS training grant ES07141.

Contact Information: Katelyn Ann Bruno, Mayo Clinic, 4500 San Pablo Road Jacksonville, FL 32224, 832-452-7903; kbruno@jhu.edu

---

81. Title: Profiling sex and age differences in circulating microRNA to identify novel therapeutic targets for experimental stroke

Authors List: Amutha Selvamani, Ph.D., and Farida Sohrabji, Ph.D.

Author Affiliations: Women's Health in Neuroscience Program, Department of Neuroscience and Experimental Therapeutics, Texas A&M University, College of Medicine, Bryan TX

Abstract: *Background:* Circulating microRNA profile analysis in young and middle aged male and female rats revealed distinct expression patterns of post-stroke microRNAs (Selvamani et al., 2014), which correlate with sex and age difference in ischemia-induced infarction. Infarct volumes are significantly smaller in adult females as compared to age-matched males or middle-aged males and females. A time course analysis showed that one of these microRNA, mir363, rises in the acute phase of stroke (48h-5d) in adult females, fails to rise in the males, and is chronically low in middle-aged males and females. Based on this pattern, we hypothesized that mimicking this early rise in miR363 would be neuroprotective for older females. Additionally, such treatment would not be effective in young males, where the early elevation of miR363 occurred naturally. *Methods:* Middle aged (12 mo) female and adult male (6-7 mo) rats were subject to middle cerebral artery occlusion (MCAo). At 4h post-stroke, half the animals in each group received a tail-vein injection of miR-363 or scrambled control. Vibrissae-elicited forelimb placement (VIB) test was performed pre and post MCAo to assess motor deficits. All animals were terminated at 5d post MCAo and the brains processed for infarct analysis by standard histological procedures. *Results*: Infarct volumes (cortex and striatum), at 5d post stroke, were significantly reduced in the miR-363 treated middle-aged females as compared to age-matched controls ($p \leq 0.001$). VIB-test indicated significant motor recovery post-stroke in the contralateral limb in miR-363 mimic treated group as well. In contrast, miR-363 mimic treatment to middle aged males had no neuroprotective effect in the ischemic hemisphere and did not facilitate motor recovery, suggesting a sex difference in miR-363 mediated neuroprotection. *Conclusion:* The present study highlights the utility of sex and age differences in identifying therapeutic targets for acute disease.

Funding: Supported by NIH NS074895 to FS

Contact information: Amutha Selvamani, Department of Neuroscience and Experimental Therapeutics, Texas A&M University, College of Medicine, Bryan TX, 77807, 1-979 450-6750, aselvamani@medicine.tamhsc.edu.

82. Title: Sexual dimorphism in contribution of NO and EDHF to vascular reactivity in mesenteric arteries of zucker diabetic fatty (ZDF) rats

Authors List: Sonali Shaligram M.S[1], Xiaoyuan Han Ph.D.[1], Rui Zhang, Ph.D.[1], Leigh Anderson, Ph.D.[2], Roshanak Rahimian, Ph.D.[1]

Author Affiliations: [1]Department of Physiology and Pharmacology, Thomas J. Long School of Pharmacy, University of the Pacific, Stockton, CA, USA. [2] Department of Biomedical Sciences, Arthur A. Dugoni School of Dentistry, University of Pacific, San Francisco, CA, USA.

Abstract: Little is known about interaction of sex and diabetes in vasculature. Our study investigates the effects of type 2 diabetes (T2D) on endothelium-dependent and -independent relaxations in male and female of ZDF rats. Furthermore, we examined whether there are sex-based differences in the relative contributions of endothelium derived relaxing factors (EDRFs) in modulating vascular reactivity of MA from ZDF rats. Relaxation responses to acetylcholine (ACh) in pre-contracted MA with phenylephrine (PE) were obtained before and after pretreatment with indomethacin (cyclooxygenase inhibitor), L-NAME (NOS inhibitor) or barium chloride (Kir blocker) plus ouabain (Na^+-K^+-ATPase inhibitor). Vascular responses to sodium nitroprusside (SNP) were also measured in PE pre-contracted MA. The ACh-induced relaxations were significantly impaired in MA of diabetic rats, regardless of sex. In diabetic female MAs, the relative importance of endothelium derived hyperpolarizing factor (EDHF) in relaxation to ACh was reduced, while in diabetic males, role of nitric oxide (NO) was reduced. On the other hand, relaxation to SNP was enhanced in diabetic animals, irrespective of sex. Our data suggest that the relative importance of NO and EDHF in regulating vascular tone is altered in T2D with respect to sex. Increased smooth muscle sensitivity to NO may be an attempt to compensate for impaired endothelial function in the diabetic rats.

Funding: Research was funded by NIDCR.

Contact information: Dr. Roshanak Rahimian, Department of Physiology and Pharmacology, 751 Brookside Rd, Stockton, CA-95211, (209)-946-2373, Email: rrahimian@pacific.edu

---

83. Title: Effects of Poly(I:C) on thermoregulation in CD1 mice

Authors List: Rupali Sharma & Nafissa Ismail Ph.D.

Author Affiliations: Biomedical Sciences and School of Psychology, University of Ottawa, Ontario, Canada.

Abstract: Exposure to stress during critical periods of development can lead to enduring changes in the functioning of the brain and body that can impact physical and mental health. The objective of the current study is to examine age and sex differences in immune response following exposure to the viral mimetic polyinosinic:polycytidylic acid (Poly(I:C)). We hypothesized that there will be age and sex differences in Poly(I:C)-induced sickness behavior and changes in body temperature. To test this hypothesis, male and female mice received an intraperitoneal injection of either saline or Poly(I:C) at 6 (puberty) or 10 (adulthood) weeks of age. We also examined the effect of circulating gonadal hormones by gonadectomizing half of our mice. We predicted that Poly(I:C) would induce a significant rise in body temperature compared to saline treated controls based on previous literature. We predicted that adolescent mice would show a distinct body temperature profile and sickness behaviors in comparison to the adult mice. We also predicted that female mice would significantly differ from male mice in each age category. Finally, we predicted that gonadectomized females and intact males would display the same temperature profiles and sickness behaviors in each age category. These findings provide a better understanding of age and sex differences in immune response to a viral infection and the effect of circulating gonadal hormones in these differences. These results also suggest potential mechanisms of interactions between stress, immune response and gonadal hormones that cause enduring changes in brain functioning and behavior. Future research will attempt to identify age and sex differences in cytokine and corticosterone levels as well as cytokine expression in significant brain regions following exposure to Poly(I:C).

Funding: This work was funded by a NSERC grant to Nafissa Ismail.

Contact Information: Nafissa Ismail, NeuroImmunology, Stress, and Endocrinology (NISE) Laboratory, University of Ottawa, 136 Jean-Jacques Lussier, Ottawa, ON K1N 6N5; 1-613-562-5700 ext. 4176; nafissa.ismail@uottawa.ca, rshar069@uottawa.ca

---

84. Title: Sexually dimorphic development of external genitalia in guinea pig: a better model for congenital penile anomalies?

Authors List: Mingxin Shi MS, Dongqing Zhu MS, Zhengui Zheng Ph.D

Author Affiliations: Department of Physiology, Southern Illinois University, School of Medicine, Carbondale, IL, USA

Abstract: Congenital penile anomalies (CPAs) are birth defects of penis. CPAs affect approx. 1% of newborn boys. The most common anomaly is hypospadias. The etiology of hypospadias and other anomalies are largely unknown. Until now, the commonly used animal models to study genital development are mouse and rat. They play important roles in understanding external genital early patterning, cell signaling, and lineage during organogenesis. They are not ideal model for study disease related to sexually dimorphic development because of short gestation and morphological difference with human. Unlike mice and rats, the morphology of guinea pigs external genitalia showed many more similarities to human. We examined the external genital development in both male and female guinea pigs using light microscopy, scanning electronic microscopy (SEM) and histology in multiple stages. Genital swellings could be observed as early as embryonic day (E) 20, the early development is similar to mice except the distal part of genital tubercle enlarged to form a human like glans at E26. The early sign of sex differentiation was found at E28. The proximal bilateral swellings of male tubercle grew outwards to give rise to the prepuce, while the female tubercle started to extend and form a flat structure at E30. At E40, the fetal penis with a central tubular urethra has been formed in males. The female plate like structure then folded forward and fused to form clitoris and urethra (E40). Compared to mice, the sex differences of guinea pig initiated at prenatal stage like human. We also analyzed expression of androgen receptor (AR) and estrogen receptor alpha (ERα) using immunostaining during different stages. The results showed a significant nucleus staining of AR around male urethral and preputial epithelium, but not in females. Weaker ERα nucleus signal could be detected at the female tubercle, but not in male. Our findings suggest guinea pig may be a better model for studying human congenital penile anomalies.

Contact Information: Zheng ZG, Department of Physiology, SIU School of Medicine, Life Science III, 1135 Lincoln Drive, Carbondale, IL62901; 1-618-453-8430; zzheng57@siumed.edu

---

85. Title: Development of a PubMed based search tool for identifying sex and gender specific literature

Authors List: Michael M. Song Pharm.D.[1, 4], Cheryl K. Simonsen, MLIS [2], Joanna D. Wilson, D.O.[3, 4], Marjorie R. Jenkins, M.D.[3, 4]

Author Affiliations: [1]MD/PhD Program, Texas Tech University Health Sciences Center (TTUHSC) School of Medicine & Graduate School of Biomedical Sciences, Lubbock, TX, USA; [2]TTUHSC Libraries, Amarillo, TX, USA; [3]Department of Internal Medicine, TTUHSC School of Medicine, Amarillo, TX, USA; [4]Laura W. Bush Institute for Women's Health, Amarillo, TX, USA

Abstract: Sex and Gender Based Medicine (SGBM) aims to understand sex and gender differences through research and to effectively incorporate the new knowledge into the clinical decision making process. An effective literature search strategy is critical to achieving those aims. However, literature search for SGBM content is often

inefficient, with low specificity results. The objective of this project was to develop and validate a SGBM literature search tool that is readily and freely available to clinical researchers and practitioners. PubMed, a freely available database, was selected as the platform to build SGBM literature search tool. Combinations of MeSH terms, text words, and title words were evaluated for optimal specificity and sensitivity. The search tool was then validated against a list of references compiled for two disease states: diabetes and stroke. Key sex and gender terms and limits were bundled to create a search tool to facilitate PubMed SGBM literature searches. During validation, the search tool retrieved 50 of 94 (53.2%) stroke and 62 of 95 (65.3%) diabetes reference articles selected for validation. A general keyword search of stroke or diabetes combined with sex difference retrieved 33 of 94 (35.1%) stroke and 22 of 95 (23.2%) diabetes reference articles, with lower specificity and sensitivity for SGBM content. Currently, vague utilization of the terms “sex” and “gender” in published literature, as well as nonspecific MeSH headings to categorize published works, limit rapid SGBM literature procurement. Clarifications of MeSH headings will be critical to ensuring effective SGBM literature retrieval. The TTUHSC SGBM PubMed Search Tool is a straightforward and customizable tool that has a higher degree of specificity to sex and gender specific literature while maintaining high sensitivity. The tool and instructions for use can be accessed free of charge at www.texastechsgbm.org.

Funding: This project was funded by Laura W. Bush Institute for Women’s Health

Contact Information: Marjorie Jenkins, Laura W. Bush Institute for Women’s Health, Texas Tech University Health Sciences Center, 1400 Wallace Blvd., Amarillo, TX 79106; 806-356-4617 ext. 271; Marjorie.Jenkins@ttuhsc.edu

---

86. Title: Epigenetic regulation contributes to a sex difference in neonatal hippocampal proliferation

Authors List: Sara L. Stockman[1,2], J. Michael Bowers[1], Margaret M. McCarthy[1]

Author Affiliations: [1]Deptartment of Pharmacology and [2]Program in Neuroscience, University of Maryland School of Medicine, Baltimore, MD

Abstract: Sexual differentiation of the brain is an important process in normal development and has implications on later behavior and disease susceptibility. Our laboratory has identified a sex difference in neonatal hippocampal proliferation in which male rats exhibit increased cellular proliferation in multiple subregions of the hippocampus compared to females (Bowers et al., Biol. Sex Diff., 2010). While sex differences are traditionally accomplished through elevation of testosterone in neonatal males that is locally aromatized to estradiol in the brain, there is no sex difference in hippocampal estradiol content at this time (Konkle et. al, Endocrinology, 2011). Therefore, we examined alternative sources for this sex difference and have discovered contributions of epigenetic regulation. Canonical modes of epigenetic regulation include DNA methylation and histone acetylation. Pharmacological inhibition of methylation through bilateral intracerebroventricular injections of Zebularine on the day of birth and one day after reduced cell proliferation (measured by BrdU incorporation) in males to that of females without effecting proliferation in females. Conversely, increased histone acetylation via administration of the HDAC inhibitor, Trichostatin A, intraperitoneally to newborns elevated proliferation in females to levels comparable to males, but had no effect on male proliferation. These opposing results suggest neonatal hippocampal cell proliferation is regulated epigenetically in a sexually dimorphic manner whereby in females reduced acetylation silences pro-proliferation genes and in males methylation silences anti-proliferation genes. Currently, we are exploring the functional significance of this sex difference. A recent study has implicated a role for neurogenesis in forgetting. We propose that increased neonatal hippocampal proliferation in males promotes forgetting and may contribute to sex differences in susceptibility to the effects of adverse early life events.

Funding: R01NS050525 to MMM

Contact: Margaret M. McCarthy, 655 W. Baltimore St. BRB 4-008, Baltimore, MD, 21210, USA. Phone: (410) 706-2655; E-mail: mmccarth@umaryland.edu

---

87. Title: Sex differences in a murine model of complex regional pain syndrome

Authors List: Maral Tajerian, PhD [1-3], Peyman Sahbaie, MD [1-3], Yuan Sun, PhD [1-3], Wenwu Li, PhD [1-3], Ting Ting Huang, PhD [1,3], Wade Kingery, PhD [4], and J David Clark, MD/PhD [1-3]

Author Affiliations: [1]Veterans Affairs Palo Alto Health Care System Palo Alto, CA, 94304, USA; [2]Department of Anesthesiology, Stanford University School of Medicine, Stanford, CA; [3]Palo Alto Institute of Research and Education, Palo Alto, CA, 94304, USA; [4]Physical Medicine and Rehabilitation Service, Veterans Affairs Palo Alto Health Care System, Palo Alto, CA, 94304, USA

Abstract: Complex Regional Pain Syndrome (CRPS) is a major cause of chronic pain after surgery or trauma to the limbs. Despite evidence showing that the prevalence and severity of many forms of chronic pain, including CRPS, differ between males and females, laboratory studies on sex-related differences in animal models of CRPS are not available, and the impact of sex on the transition from acute to chronic CRPS pain and disability are unexplored. Here we make use of the tibia fracture/cast model of CRPS recapitulating the nociceptive, functional, vascular, trophic, inflammatory and immune aspects of CRPS. Our aim is to describe the timecourse of nociceptive, motor and memory changes associated with fracture/cast in male and female mice, in addition to exploring their underlying spinal mechanisms. Our behavioral data show that, compared to males, female mice display increased and persistent mechanical allodynia and motor dysfunction in response to tibia fracture. No such differences were observed in measures of edema and temperature in the affected hindpaw. Furthermore, they exhibit signs of increased latent sensitization even after the normalization of mechanical thresholds. Behavioral memory tests showed no differences between the two groups. Our biochemical data show differences in the spinal cord levels of the glutamate receptor NMDAR2b, suggesting sex differences in mechanisms of central sensitization that could account for differences in duration and severity of CRPS symptoms between the two groups.

Funding: Funded by National Institute of Health grant NS072168 to WSK and JDC (Palo Alto Institute of Research and Education, Palo Alto, CA, USA).

Contact information: Maral Tajerian, Veterans Affairs Palo Alto Health Care System Unit E4-218, Building 100; 3801 Miranda Ave., Palo Alto, CA 94304, Tel: 650-493-5000 ext. 68825; E-mail: maral@stanford.edu

---

88. Title: Gender differences in health related quality of life among people living with HIV on highly active antiretroviral in public health institutions in Mekele, North Ethiopia

Authors List: Amanuel Tesfay MPH,[1] Abebe Gebremariam (Professor),[1] Mulusew Gerbaba MPH,[1]and Hailay Abrha MPH.[2]

Author Affiliations: [1]Department of Population and Family Health, College of Public Health and Medical Sciences, Jimma University, Jimma, Ethiopia; [2] Department of Epidemiology, College of Public Health and Medical Sciences, Jimma University

Abstract: Health related quality of life is an important outcome measure for highly active antiretroviral treatment program. In Ethiopia, studies revealed that there are improved qualities of life among adult living with the viruses taking anti retro viral therapy but there is no explicit data showing gender differences in health related quality of life. Thus, the main aim of this study was to assess gender differences in health related quality of life and its associated factors among people living with HIV and on highly active antiretroviral therapy in public health institutions of Mekelle Town, Northern Ethiopia. A comparative cross sectional study was conducted among 494

adult people living with HIV taking ART services in public health institutions in Mekelle town. Quality of life was measured using the World Health Organization's Quality of Life HIV short form instrument (WHOQOL HIV BREF). Descriptive, independent sample t test, bivariate and multivariable logistic regression analyses were performed. Data were analyzed by SPSS for windows version 16 software. The mean age of the study participants was 35.5 (SD ±8.03) for females and 39.8(SD±7.85) for males. There was a statistically significant gender difference in health related quality of life among people living with HIV on HAART using physical, psychological, level of independence, environmental and spiritual domains and two general QOL items (P< 0.05). Females had low score in all domains when compared to the male counter parts. Females who had high perceived stigma were 2.89 times more likely to have poor psychological health as compared to individuals who had low perceived stigma [OR=2.89,95%CI(1.69,4.96)]. Females had low score in all domains. To enhance quality of life of PLHIV and address these gender differences in health related quality of life it's better to consider physical, psychological, social, environmental and spiritual health of PLHIV during treatment, care and support.

Funding: This study was funded by Jimma University.

Contact information: Amanuel Tesfay Gebremedhin, Department of Population and Family Health, College of Public Health and Medical Sciences, Jimma University,P.O. Box 2080, Phone: +251(0) 912743058; amanuelpraise@gmail.com Jimma, Ethiopia

---

89. Title: Sex differences in activation and regulation of cytokines in the brain after systemic immune challenge

Authors List: Natalie C. Tronson Ph.D. & Ian Speirs B.S.

Author Affiliations: Department of Psychology, University of Michigan, Ann Arbor, MI, USA.

Abstract: Immune responses show. Females typically show stronger responses than males to a variety of immune challenges including lipopolysaccharide (LPS) and vaccines. These differences in males and females seen to correlate with In contrast, there are less clear patterns of sex differences in behavioral changes mediated by cytokine signaling. Males show enhanced febrile responses to systemic LPS challenge, whereas females but not males show decreased sexual behaviors. This suggests that not only is the magnitude of immune response in the brain different in males and females, but the patterns of cytokine activation may also show substantial sexual dimorphism. Several studies have examined the early response of IL-1β, TNFα, IL-6 in the brain in both males and females, however little data exists on the persistence of these responses, brain region specific changes, or the broad network of cytokine activation and resolution after systemic immune challenge. Here, we used a multiplexed approach to determine the activation and resolution of cytokine network in hippocampus, hypothalamus, and blood of male and female mice up to 7 days after a single LPS (250μg/kg, i.p.) injection. We found (1) brain region specific changes in cytokines, with hippocampus more responsive compared with hypothalamus, (2) greater overall activation and persistence of cytokines in hippocampus of male compared with female mice, and (3) sex-specific patterns of cytokine activity, with males and females showed distinctive regulation of a subset of cytokines. These findings demonstrate qualitative and quantitative differences in patterns of inflammatory signaling and its regulation in the brain after systemic immune challenge in males and females. Delineating neuroimmune responses and their regulation in males and females will be critical for determining the contributions of systemic inflammatory markers to development of neuropsychiatric disorders.

Funding: This study was funded by NIH Grant R00MH093459 to NCT.

Contact Information: Natalie C. Tronson, Department of Psychology, East Hall, 530 Church Street, Ann Arbor, MI, 48109; 734-936-1495; ntronson@umich.edu

90. Title: Endocannabinoids and microglia modulate sex differences in brain and behavior

Authors List: Kathryn J Argue, Ph.D.[1], **Jonathan W VanRyzin, B.S.**[2], Margaret M McCarthy, Ph.D.[1]

Author Affiliations: [1]Department of Pharmacology, University of Maryland, Baltimore, School of Medicine, Baltimore, MD, USA; [2]Program in Neuroscience, University of Maryland, Baltimore, School of Medicine, Baltimore, MD, USA.

Abstract: Juvenile males of most species display higher levels of social play behavior compared to females. We have been exploring the mechanistic basis of this sex difference and found it negatively correlates with the number of newly proliferated cells in the developing amygdala Moreover, the sex differences in play behavior and cell proliferation are mediated by the endocannabinoid system. Further investigation into involvement of the endocannabinoid receptor types revealed surprising evidence of cooperation between the two receptors. Neonatal activation of either CB1 or CB2 alone was not sufficient to increase female play behavior, however dual-agonist treated newborn females displayed increased levels of social play when tested as juveniles (ANOVA $p < 0.05$). Conversely, dual-antagonist treated females had reduced play behavior (ANOVA $p < 0.05$). Further investigation revealed that activation of either CB1 or CB2 is sufficient to decrease the number of BrdU+ cells in the female developing amygdala. One potential mechanism through which the endocannabinoid system could mediate the number of newly born cells and hence play behavior is through microglia-mediated phagoptosis. Microglia are the innate immune cells of the brain and phagoptosis is the engulfment of living cells. There are more phagocytic microglia in the neonatal male amygdala than the female. Activation of CB1 increased the number of phagocytic microglia in females to levels observed in males. Treatment with minocycline, an inhibitor of microglial activation, increased male BrdU+ cell counts to female levels, but did not alter the number of female BrdU+ cells. These results are consistent with the interpretation that the lower number of proliferating cells in the male amygdala is due to higher rates of primary phagocytosis by microglia.

Funding: This study was funded by RO1MH52716-018 to MMM.

Contact Information: Kathryn J Argue, Department of Pharmacology, University of Maryland, Baltimore, School of Medicine, 655 W Baltimore St., Baltimore, MD 21201; 1-410-706-2654; kargue@som.umaryland.edu

---

91. Title: Flow cytometry: A novel application for detecting sex differences in cell proliferation in the developing brain

Authors List: Jonathan W VanRyzin, B.S.[1], **Kathryn J Argue, Ph.D.**[2], Margaret M McCarthy, Ph.D.[2]

Author Affiliations: [1]Program in Neuroscience, University of Maryland, Baltimore, School of Medicine, Baltimore, MD, USA. [2]Department of Pharmacology, University of Maryland, Baltimore, School of Medicine, Baltimore, MD, USA

Abstract: One of the most common ways for sex differences in brain development to manifest is through regulation of cell numbers via differential rates of cell genesis. Sex differences in cell proliferation have been detected in the developing hippocampus and amygdala of the laboratory rat. Understanding the mechanistic origins of these sex differences is fundamental, but quantification requires labor-intensive immunohistochemistry followed by microscopy and stereological counting methods. This methodology is time consuming, expensive and subject to both the vagaries of each immunohistochemical staining run and individual interpretation of the signal. Here we describe the novel application of flow cytometry to brain region-specific analysis of postnatal cell proliferation, as a method for high throughput and unbiased quantification for sex differences in the brain. Flow cytometry offers the unique advantage of highly sensitive quantification of single cells within a population, based on fluorescent signal intensity. This method allows for recovery and detection of all the predominant cell types in the brain, with the ability to detect small changes in rare populations. Using the thymidine analog 5-ehtynyl-2'-deoxyuridine (EdU) as a marker for cell proliferation, we validated our previous findings in the amygdala, showing that neonatal females have more EdU+ cells than males ($p < 0.05$). Furthermore, this method is able to

quantify proliferation of specific cell types in the neonatal brain and will greatly accelerate our understanding of the origins and impact of sex differences in cell proliferation.

Funding: This study was funded by RO1MH52716-018 to MMM.

Contact Information: Jonathan W VanRyzin, Department of Pharmacology, University of Maryland, Baltimore, School of Medicine, 655 W Baltimore St., Baltimore, MD 21201; 1-410-706-2654; jvanryzin@umaryland.edu

---

92. Title: Sex differences in extracellular matrix gene expression and protein activity in fibroblasts derived from embryonic stem cells

Author Affiliations: Zhe Wang[1, 2], Yan Wen[1,] Song Quan[2], Bertha Chen[1]

Author Affiliations: [1]Department of Ob/Gyn, Stanford University School of Medicine, Stanford, CA. [2]Center for Reproductive Medicine, Department of Ob/Gyn, Nanfang Hospital, Southern Medical University, Guangzhou, China

Abstract: Stem cells (SC) are widely studied for soft tissue regeneration. Both genetic and epigenetic mechanisms are essential in SC maintenance and differentiation. Little is known about sex differences in the genetic and epigenetic regulation of SC differentiation into fibroblasts, a key cell type in soft tissues. Fibroblasts help maintain tissue integrity by regulating extracellular matrix (ECM) proteins. This function is modulated by reproductive hormones. We sought to examine sex differences in ECM genes expression and protein activity in fibroblasts differentiated from human embryonic SC (hESCs). We compare these to fibroblasts derived from adult induced pluripotent SC line (iPSC) to examine the effect of epigenetic changes. Fibroblasts are differentiated from male (H1) and female (H9) hESCs and female iPSCs. These are then cultured with 17β-estradiol and analyzed by RT-PCR (gene expression) and zymography (protein activity). Collagen I and III, TIMP-1, MMP-9, and MMP-2 gene expressions were higher in H1-derived fibroblasts compared to those from female H9. Most ECM gene expressions were higher in iPSC-derived compared to H9 fibroblasts. Estrogen had no impact on ECM gene expression in both H1 and H9 derived fibroblasts. In contrast, iPSC-derived fibroblasts had a significant decrease in TIMP-3 gene expression with estrogen stimulation. As for protein activity, H1 and H9-derived fibroblasts differed in MMP response profile with estrogen stimulation. iPSC fibroblasts only showed an increase in MMP 9 expression. Fibroblasts derived from male and female hESCs exhibit different profiles in ECM gene expression. Estrogen stimulation is associated with different MMP activities in hESC-derived fibroblasts compared to iPSC-derived fibroblasts, suggesting that epigenetic changes affect MMP activity. Future studies will examine whether reproductive hormone exposure during SC differentiation can modulate epigenetic mechanisms in male and female hESC differentiation.

Funding: WSDM seed grant 2014.

Contact information: Bertha Chen, MD, Professor, Department of Ob/Gyn, Stanford University, School of Medicine, 300 Pasteur Dr., HH-333, Stanford, CA 94305, Tel: 650-725-5986, Email: bchen@stanford.edu

---

93. Title: Extreme natural biology: Sex-specific analysis of exceptional longevity and predictors of life expectancy in advanced age in the first systematic study of canine centenarians and supercentenarians

Authors List: David J. Waters PhD, DVM, Emily C. Chiang PhD, Aimee H. Maras DVM, Cheri L. Suckow RN, and Seema S. Kengeri MD, PhD.

Author Affiliations: The Center for Exceptional Longevity Studies, Gerald P. Murphy Cancer Foundation, West Lafayette, Indiana, USA

Abstract: Pet dogs living in the same households as humans offer an outbred mammalian population to study the genetic and environmental determinants of longevity. To move closer to understanding the mechanistic underpinnings of sex differences in human longevity, we analyzed data from the first systematic study of more than 300 canine centenarians–exceptionally long-lived Rottweiler dogs that lived more than 30% longer than average life expectancy for the breed. In this analysis of extreme longevity in pet dogs, we discovered a female longevity advantage (female : male ratio of 2:1); the female advantage was accentuated in canine supercentenarians (female : male ratio of 5:1). Like in humans, exceptional longevity in both female and male dogs is accompanied by morbidity compression–63% of canine centenarians and 76% of canine supercentenarians are escapers, i.e. free of all major diseases for a duration equivalent to the first 100 human years of life. Of particular importance is the observation that canine centenarians and supercentenarians display profound resistance to cancer, with a cancer mortality rate of only 8% in dogs with the most extreme longevity compared to a cancer mortality rate of more than 70% in dogs with usual longevity. The research points to two sex-specific predictors of exceptional longevity in Rottweiler dogs: duration of lifetime ovary exposure in females; and height (short stature) in males. Interestingly, neither of these factors have value in predicting life expectancy in advanced age, i.e. after the equivalent of 100 human years. Instead, in canine centenarians, Kaplan-Meier survival analysis revealed being female or an escaper favors longer life expectancy in advanced age. Studying the extreme natural biology of the oldest-old pet dogs provides an underutilized opportunity to gather clues to understanding sex-specific mechanisms underlying the phenotypes of highly successful aging and cancer resistance.

Contact Information: David J. Waters, Center for Exceptional Longevity Studies, Gerald P. Murphy Cancer Foundation, 3000 Kent Avenue, Suite E2-400, West Lafayette, Indiana 47906; 765-775-1005; dwaters@gpmcf.org

---

94. Title: Sex differences in well being as a function of adaptation to macro-economic and political changes

Author: **Barbara Wejnert, Ph.D.**

Author Affiliations: Global Gender Studies Program, University at Buffalo, State University of New York.

Abstract: Women, who have more complex societal roles than men and whose employment is more tenuous, are more vulnerable to the rapid restructuring in macro-political and economic systems, bearing more costs of changes. Using multilevel longitudinal models I assessed data on men and women well-being during economic and political changes in countries across the world. My world-scale analyses show that women and men benefit from growth of democracy and global economy, but the regional analyses indicate that women benefit only in the most economically-developed and highly-democratized core countries and to some degree in semi-peripheries. Contrastingly, in transitional democracies of underdeveloped countries men well-being improves with growth of democracy, but the level of women's well-being declines. Only after two decades the declining access of women to education, participation in a labor force and decline in health, women's well being slowly improves. In the low developed transitional democracies of the former communist bloc the situation is more difficult. The effects of democratic growth on the level of women's well-being are negative and no expected improvement within the two decades is predicted. Women's employment becomes more fragile, primary schooling becomes less attainable, female illiteracy increases, medical care either declines or does not improve, contrasting relatively high women well-being achieved during the communist era. These findings suggest that prior research finding of a positive impact of democracy and global economy on people's well-being is bias being affected by the situation in well-established democracies of the Western states while lacking specific consideration for less-developed countries. Also the outcomes of democracy and global economy should underscore differential impact of macro-transitions on men versus women, suggesting gender and regional specific investigations on people adaptation to democratization and globalization.

Funding: This study was funded by the Civil Engagement and Public Policy Research Fellowship, University at Buffalo and Program Grant from the Institute for International Education.

Contact Information: Barbara Wejnert, Department of Transnational Studies, Global Gender Studies Program, University at Buffalo, State University of New York, 703 Clemens Hall, Buffalo NY 14260

---

95. Title: Altered reward response and reversal learning in a mouse model of Klinefelter syndrome

Authors List: Shayna M. Williams-Burris[1,2,3], Jessy D. Martinez[3], Haley Hrncir[3], Dorothy Yu[3], Yilei Zhang[3], Arthur P. Arnold Ph.D.[2,3]*, J. David Jentsch Ph.D.[4,5]*

Author Affiliations: Neuroscience Interdepartmental Program[1], Laboratory of Neuroendocrinology of the Brain Research Institute[2], Department of Integrative Biology and Physiology[3], Department of Psychology[4], and Department of Psychiatry and Bio-behavioral Sciences[5], University of California, Los Angeles, Los Angeles CA. *equal contribution

Abstract: The karyotype XXY, which causes Klinefelter syndrome (KS), is the most common sex chromosome trisomy in humans. KS is characterized by low testosterone and infertility, increased rates of some health problems, and specific cognitive deficits such as in executive function. Here we used the XY* mouse model to measure reward response and reversal learning, which is a measure of executive function. The XY* model produces in 2 different male genotypes: XY*, similar to XY, and XXY*, similar to XXY. We studied both groups either gonadectomized (GDX) or gonadally intact (sham surgery only). This design allows for an analysis of whether genotype or activational effects of hormones contribute to the KS phenotype. For the reward response test, mice were presented with two bottles containing sweetened condensed milk (SCM) or water for 2 hours per day, and the amount of each liquid consumed was recorded. In both intact and GDX mice, the XY* males preferred the 3% SCM more than the XXY* mice, but both genotypes preferred the 10% SCM equally. Next, the 10% SCM solution was used as a reinforcer in the reversal learning task. Here, the mice were tested in an operant conditioning chamber containing an array of 5 nose poke apertures on one side and a reinforcer delivery magazine on the opposite side. Mice were trained to respond to one of two apertures (left or right of center) across trials and sessions. Once the mouse successfully poked the correct hole at performance criterion, the task was reversed such that a poke to the opposite side was correct, and trials to criterion were measured. We found that the XXY* mice required significantly more trials to reverse than the XY* mice indicating an executive function deficit that models that seen in KS men. Studies to test reversal learning in GDX mice are underway and will shed light on whether this phenotype is related to differing testosterone levels, or to genotype.

Funding: This study was supported by 1R01HD076125 and HD007228.-

Contact Information: Shayna M. Williams-Burris, Neuroscience Interdepartmental Program, Terasaki Life Science Building Room 1146, 610 Charles E. Young Drive South, University of California, Los Angeles, Los Angeles, CA 90095; 1-310-825-9340; shayna.williams@ucla.edu

---

96. Title: Dopaminergic innervation of the medial prefrontal cortex in male and female rats across adolescence

Authors List: Jari Willing PhD[1,2], Joseph M. Brodsky B.S.[1,2], Laura Cortes[1], Taehyeon Kim B.S[1]., & Janice M. Juraska PhD[1,2]

Author Affiliations: [1]Department of Psychology, [2]Neuroscience Program, University of Illinois, Champaign-Urbana IL

Abstract: Adolescence is a critical period for brain maturation, characterized by the reorganization of many interacting neural networks. The medial prefrontal cortex (mPFC), a region highly involved in executive function, is particularly known to undergo anatomical changes between preadolescence and adulthood that may have implications for the dysfunctions of the prefrontal cortex (addiction, mental illness) that often originate during adolescence. We have previously shown sex differences in the loss of neurons in the mPFC between adolescence and early adulthood. Females lose a significant number of neurons in the 10 days following the onset of puberty, while males did not have any clearly timed loses. It is not known whether this pattern of sex differences in pruning also applies to the neurotransmitter input to the mPFC during adolescence. In the present study, we track changes in the volume of TH immunoreactive axons in the layers of the male and female mPFC at multiple time points from preadolescence to adulthood (P25, P35, P45, P60 and P90) in the same animals in which neuronal pruning was examined. In layers 2/3, females had a significant increase in the volume of fibers across age ($p<.03$) which was due to an increase from P25 to P35 ($p< .04$) before puberty. Males also had significant effect of age ($p< .02$) which was similarly due to an increase between P 25 and P35 ($p<.02$) which is clearly prepubertal. The similarity of the timing of these changes between the sexes makes it unlikely that pubertal hormones are the basis for the increase. Preliminary analysis also reveals similar trends for layer 1 of the mPFC, and layers 5/6 are also being quantified.

Funding: NIH MH099625 to JMJ

Contact information: Jari Willing, 603 E Daniel, Department of Psychology, Champaign IL 61820, 518-253-0086, jwilling

---

97. Title: Bipolar disorder and risk of rapid cycling by sex: genome-wide investigation of genetic differences

Authors List: Stacey J. Winham, PhD[1], Almila Erol, MD[2,3], Susan L. McElroy, MD[4], Mark A. Frye, MD[2], Miguel L. Prieto, MD, MSc[5], Alfredo B. Cuellar-Barboza, MD[6], Jennifer R. Geske, MS[1], Colin L. Colby, BA[1], William V. Bobo, MD, MPH[2], Joanna M. Biernacka, PhD[1,2]

Author Affiliations: [1]Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA; [2]Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, USA; [3]Department of Psychiatry, Ataturk Education and Research Hospital, Izmir, Turkey; [4]Lindner Center of HOPE, Mason, OH, USA; University of Cincinnati, Cincinnati, OH, USA; [5]Universidad de los Andes, Facultad de Medicina, Departamento de Psiquiatría, Santiago, Chile; [6]Department of Psychiatry, Universidad Autonoma de Nuevo Leon, Monterrey, Mexico.

Abstract: Bipolar disorder (BD) is highly heritable, and BD course of illness differs by sex; e.g., women experience more frequent episodes of rapid cycling (RC) between depression and mania than men. However, few studies have considered sex differences in the genetic etiology of risk for BD. In this study, we investigate genome-wide SNP*sex interaction effects on BD risk and risk for RC in two genome-wide association studies of BD. The Mayo Clinic Bipolar Disorder Biobank Study included 896 BD cases and 764 healthy controls and the Genetic Association and Information Network Bipolar Study included 1001 BD cases and 1034 healthy controls, genotyped on two separate genome-wide SNP arrays. We examined evidence for SNP*sex interactions on BD risk (case-control analysis; N=3695) and risk of rapid cycling (case-only analysis; N=1211) at 193,849 loci genotyped in both studies. Pooled analyses were performed using logistic regression adjusted for study. Presence of BD ($p=0.001$) and RC ($p=0.06$) were more common in females. The top ranking SNP*sex interaction on BD risk was rs11677059, an intergenic variant upstream of the LRRTM4 promoter (OR=1.5, P=2.0E-5), an important regulator of synapse development and function previously associated with suicide attempts in BD females; rs11677059 is a binding site for transcription factor CEBPB, which regulates genes related to inflammatory response, an important process in BD disease etiology. The top-ranking SNP*sex effect on RC was rs4912515 in an intron of ABCC5 (OR=2.2, P=6.9E-6), a gene involved in multi-drug resistance; rs4912515 is a

binding site for transcription factor FOXA1, which regulates tissue-specific gene expression. No genetic variants reached significance after multiple testing correction (p>2.6E-7). This is the first study to investigate genome-wide SNP*sex interaction effects on RC risk. Results suggest new risk variants for BD that differ by sex, although replication is necessary.

Funding: This study was supported by the National Institutes of Health Office of Research on Women's Health (Building Interdisciplinary Careers in Women's Health award K12HD065987) and the Marriot Family Foundation.

Contact Information: Stacey J. Winham, Health Sciences Research, Mayo Clinic, 200 First Street SW, Rochester, MN 55905; (507) 266-3662; winham.stacey@mayo.edu

---

98. Title: Antagonizing peroxisome proliferator-activated receptor-alpha (PPARα) activity abrogates sex differences in T helper 1 (Th1) immunity in mice

Authors List: Monan Angela Zhang[1], Jeeyoon Jennifer Ahn[1], Fei Linda Zhao[1], Thirumahal Selvanantham, Ph.D.[1], Thierry Mallevaey, Ph.D.[1], David Spaner, M.D.[1,2], Shannon E. Dunn, Ph.D.[1,3,4],*

Author Affiliations: [1]Department of Immunology, University of Toronto, Toronto, ON, Canada, M5S 1A8; [2]Sunnybrook Health Sciences Centre, Toronto, ON, Canada, M4N 3M5; [3]Toronto General Research Institute, University Health Network, Toronto, ON, M5G 2M1; [4]Women's College Research Institute, Toronto, ON, Canada, M5G 1N8

Abstract: Females exhibit more robust Th1 immune responses than males. This sex difference is thought to underlie why women generate enhanced cellular immune responses. Our previous work suggested that this sex disparity is a consequence of higher activity of the androgen-induced gene PPARα in males. The objective of this study was to determine the underlying mechanism of how PPARα regulates Th1 immunity in male murine T cells and to determine the utility of a novel small molecule antagonist of PPARα, NXT-1120, to boost cellular immunity in male mice. In comparing the expressions of Th-associated genes between activated male wild type and PPARá-/- CD4+ T cells, we observed higher expressions of the Th1 regulators T-bet and Eomes as well as the Th1 cytokine IFN-ã in PPARá-/- cells. However, IFN-ã was the only gene that was elevated in PPARá-/- T cells cells after knock-down of T-bet activity or IFN-ã receptor signaling. This result indicated that *Ifng* is the gene target of PPARα repression. We further showed using chromatin immunoprecipitation assay that treatment of male CD4+ cells with the PPARα ligandactivator fenofibrate induced the recruitment of PPARα to specific *cis* regulatory elements in the *Ifng* locus that associated with the enhanced presence of the nuclear receptor co-repressor 1 (NCOR)-containing corepressor complex and reduced histone acetylation at these same sites. Conversely, treatment with the small molecule PPARα antagonist NXT-1120 increased histone acetylation across the *Ifng* locus and IFN-γ mRNAs selectively in male T cells. Finally, we found that treatment of mice *in vivo* with NXT-1120 abrogated the sex difference in IFN-γ production by NKT, CD4+ and CD8+ T cells and improved the survival of male, but not female mice during infection with the classic Th1-associated pathogen *Listeria monocytogenes*. Our studies thus uncover a mechanism for sex differences in cellular immunity and introduce a novel drug that can boost cellular immune responses in males.

Funding: This study was funded by a CIHR grant (MOP-97807) to SED. MAZ, JJA, and FLZ were supported by studentships and SED by a Don Paty award from the MS Society of Canada. MAZ was also supported by an Ontario Women's Health Scholars Award.

Contact Information: Shannon Dunn, 67 College St. Rm 4-421, Toronto, ON M5G 2M1, Canada, Ph: 416-340-4423, Email: sdunn@uhnresearch.ca

99. Title: Sex differences in Ventricular Adaptation and Recovery in Patients with Aortic Stenosis undergoing Transcatheter Aortic Valve Replacement (TAVR)

Authors List: Juyong Brian Kim, MD, MPH[1,2], Ryan G. O'Malley, MD[1,2], Francois Haddad, MD[1,2], Catherine Dao, MD[1,2], Dominik Fleischmann, MD[2,3], Joseph C. Wu, MD, PhD[1,2], David Liang, MD, PhD[1,2], William F. Fearon, MD[1,2]

Author Affiliations: [1]Division of Cardiovascular Medicine, Stanford University, Stanford, CA; [2]Cardiovascular Institute, Stanford University, Stanford, CA; [3]Department of Radiology, Stanford University, Stanford, CA.

Abstract: Background: Female patients with aortic stenosis (AS) have been suggested to develop a greater degree of concentric left ventricular (LV) hypertrophy and better preservation of systolic function and ventricular recovery following aortic valve replacement (AVR) compared to their male counterparts. We propose to define the sex differences in LV remodeling in AS using detailed imaging and blood biomarkers and their correlation to clinical outcomes. **Methods and Results**: Accordingly, we propose 3 specific aims. 1) Determine sex-related differences in ventricular adaptation and recovery by measuring traditional echocardiographic parameters and novel metrics of ventricular strain estimation; *2)* Determine the sex-related differences in biomarkers of fibrosis and ventricular stress in patients undergoing TAVR. We will use the ongoing *Stanford TAVR Biobanking Repository* which has collected to date 100 participants with a proportion of 34% female; and *3)* Define the sex-related difference in fibrosis and recovery using magnetic resonance based post-contrast myocardial T1 time imaging sequence. For this objective, we will prospectively recruit patients undergoing TAVR and plan to recruit 15 female and 15 male. **Conclusions**: The proposed study will improve our understanding of sex differences in myocardial response to pressure overloaded state and their subsequent response to treatment. The findings from this study will help to identify the high-risk patients early and also establish sex specific recommendations for monitoring patients with severe aortic stenosis, and timing for intervention with aortic valve replacement.

Funding: *Translational Research Applied Medicine Grant,* Department of Medicine, Stanford University awarded to JBK; Stanford *Cardiovascular Institute Seed Grant* to the Biomarker and Phenotypic Core Laboratory (Director: FH); and the Stanford *Women and Sex Differences in Medicine (WSDM) Center Seed Grant* Award to WFF.

Contact Information: William Fearon, Division of Interventional Cardiology, 300 Pasteur Drive, Stanford, CA 94305. 650-723-6459. wfearon@stanford.edu.


SSD
ORGANIZATION FOR THE
STUDY OF SEX DIFFERENCES
Founded by the Society for Women's Health Research


SSD
ORGANIZATION FOR THE
STUDY OF SEX DIFFERENCES
Founded by the Society for Women's Health Research

ATTENDEES CONTACT INFORMATION as of April 1, 2015

First Name	Last Name	E-Mail	Organization
J. Jennifer	Ahn	jy.ahn@mail.utoronto.ca	University of Toronto
Farjana	Akther	f_akther@u.pacific.edu	University of the Pacific
Elizabeth	Alexandre	ergalexandre@uol.com.br	Institute Dante Pazzanese of Cardiology, Brazilian Association of Medical Women, MWIA Medical Women International Assoc.
Yasir	Alsiraj	yaal223@g.uky.edu	University of Kentucky
Yasir	Alsiraj	yaal223@g.uky.edu	University of Kentucky
Andre	Altmann	altmann@stanford.edu	Stanford University
Charlotte	Anderson	charlotteanderson@students.federation.edu.au	Federation University Australia
Lauren	Anderson	laurencanderson8@gmail.com	Boston College
Kathryn	Argue	kargue@som.umaryland.edu	University of Maryland School of Medicine
Arthur	Arnold	arnold@ucla.edu	University of California, Los Angeles
Kathryn	Arthur	kcorbe@midwestern.edu	Midwestern University
April	Au	april.au@mail.utoronto.ca	University of Toronto
Eric	Austin	eric.austin@vanderbilt.edu	Vanderbilt University
Angelika	Bader	angelika.bader@tilak.at	Medizinische Universitat Innsbruck
C Noel	Bairey Merz	merz@cshs.org	Cedars-Sinai Medical Center
Fiona	Baker	fiona.baker@sri.com	SRI International
May	Bakir	maybakir@gmail.com	Cedars-Sinai Medical Center
Tracy	Bale	tbale@vet.upenn.edu	University of Pennsylvania
Jill	Barnes	barnes.jill@mayo.edu	Mayo Clinic
Mariam	Barseghyan	barseghyanmariam@gmail.com	University of California, Los Angeles
Jill	Becker	jbbecker@umich.edu	University of Michigan
Eric	Belin de Chantemele	ebelindechanteme@gru.edu	Medical College of Georgia
Marla	Berry	mberry@hawaii.edu	University of Hawaii
Jessica	Bolton	jlb74@duke.edu	Duke University
Carolyn	Brown	carolyn.brown@ubc.ca	University of British Columbia
Katelyn	Bruno	kbruno@jhu.edu	Johns Hopkins University
Sarah	Burke	s.burke@vumc.nl	VU University Medical Center Amsterdam
Blanche	Capel	blanche.capel@duke.edu	Duke University
Lori	Capozzi	capozzi@uchc.edu	University of Connecticut Health Center
Fadi	Charchar	f.charchar@federation.edu.au	Federation University Australia
Emily	Chiang	emilychiang1225@gmail.com	Gerald P. Murphy Cancer Foundation
China	Chien	chinac@stanford.edu	Stanford University
Joe	Cho	cho@morganclaypool.com	Morgan and Claypool
Janine	Clayton	claytonja@mail.nih.gov	National Institutes of Health
Sarah	Conway	sec399@nyumc.org	NYU Medical Center
Michael	Coronado	mcoronad@stanford.edu	Stanford University
Stephanie	Correa	stephanie.vanveen@ucsf.edu	University of California, San Francisco
Alex	Dang	alexdang530@gmail.com	California State University, Long Beach

First Name	Last Name	E-Mail	Organization
William	Davies	daviesw4@cardiff.ac.uk	Cardiff University
Geert	de Vries	devries@gsu.edu	Georgia State University
Tyler	Demarest	tgdemarest@gmail.com	University of Maryland School of Medicine
Xinxian	Deng	dengx2@uw.edu	University of Washington
Leslie	Devaud	devaudl@pacificu.edu	Pacific University
Sharon	DiMauro	dimauro@uchc.edu	University of Connecticut Health Center
Christine	Disteche	cdistech@u.washington.edu	University of Washington
Maja	Djurisic	djurisic@stanford.edu	Stanford University
Erika	Douglass	edouglas@jhsph.edu	Johns Hopkins University
Karen	Drexler	karen@drexler.com	Emory University
Annie	Duchesne	aduchesn@ubishops.ca	Bishop's University
Shannon	Dunn	dunn.shannon14@gmail.com	University of Toronto
Gillian	Einstein	gillian.einstein@utoronto.ca	University of Toronto
Renata	Engler	renata.engler@gmail.com	University of the Health Sciences
C. Neill	Epperson	cepp@mail.med.upenn.edu	University of Pennsylvania Medical School
Emmanuel	Fadiran	emmanuel.fadiran@fda.hhs.gov	US Food and Drug Administration
DeLisa	Fairweather	dfairweather@jhu.edu	Johns Hopkins University
Jamie	Feusner	jfeusner@mednet.ucla.edu	University of California, Los Angeles
Abigail	Forson	abigail.forson@cihr-irsc.gc.ca	Canadian Institute of Health Research
Susan	Fried	skfried@bu.edu	Boston University
Andrea	Frump	anfrump@iu.edu	Indiana University
David	Furman	furmand@stanford.edu	Stanford University
James	Fuscoe	james.fuscoe@fda.hhs.gov	US Food and Drug Administration
Liisa	Galea	lgalea@psych.ubc.ca	University of British Columbia
Mary	Gamble	mvg7@columbia.edu	Columbia University
David	Garbe	davidgarbe@mac.com	University of Pennsylvania, HHMI
Rona	Giffard	rona.giffard@stanford.edu	Stanford University
Tamar	Green	tgreen2@stanford.edu	Stanford University
Xiaoyuan	Han	xyhan@stanford.edu	Stanford University
Vincent	Harley	vincent.harley@princehenrys.org	Monash University, University of Melbourne
Katherine	Hastings	khasting@usc.edu	University of Southern California
Candice	Herber	candice.herber@ucsf.edu	University of California, San Francisco
Margarethe	Hochleitner	margarethe.hochleitner@i-med.ac.at	Medizinische Universitat Innsbruck
Melissa	Holmes	melissa.holmes@utoronto.ca	University of Toronto
Caitlin	Howe	cgh2121@columbia.edu	Columbia University
Leyla	Innala	leyla@mail.ubc.ca	University of British Columbia
Sabra	Inslicht	sabra.inslicht@va.gov	San Francisco VA Medical Center
Nafissa	Ismail	nafissa.ismail@uottawa.ca	University of Ottawa
Anula	Jayasuriya	anula@gilmour.net	Gilmour Academy
Marjorie	Jenkins	marjorie.jenkins@ttuhsc.edu	Texas Tech University Health Sciences Center
Wei	Jiang	jianw@musc.edu	Medical University of South Carolina
Daphna	Joel	djoel@post.tau.ac.il	Tel Aviv University
Martin	Johansson	martin.johansson@ebc.uu.se	Uppsala University

First Name	Last Name	E-Mail	Organization
Erika	Jones	erika.jones@cshs.org	Cedars-Sinai Medical Center
Tanja	Jovanovic	tjovano@emory.edu	Emory University
Janice	Juraska	jjuraska@illinois.edu	University of Illinois
Robert Paul	Juster	robert.juster@mail.mcgill.ca	McGill University
Georgios	Kararigas	george.kararigas@charite.de	Charite Hospital Berlin
Tatsuo	Kido	tatsuo.kido@ucsf.edu	University of California, San Francisco
Lisa	Kilpatrick	lisa@lisakilpatrick.com	University of California, Los Angeles
Roy	Kim	roykim81@ucla.edu	University of California, Los Angeles
Sabra	Klein	saklein@jhsph.edu	Johns Hopkins University School of Public Health
Rebecca C.	Knickmeyer	rebecca_knickmeyer@med.unc.edu	University of North Carolina Medical School
Sabrina	Kolker	skolker@gmail.com	University of Toronto
Daria	Kolmogorova	dkolm072@gmail.com	University of Ottawa
Martina	Koniger	mkoniger@wellesley.edu	Wellesley College
Peter	Koopman	p.koopman@imb.uq.edu.au	University of Queensland
Milka	Koupenova (Zamor)	milka.koupenova@umassmed.edu	University of Massachusetts Med School
Dimitry	Krementsov	dkrement@uvm.edu	University of Vermont
Agnes	Lacreuse	alacreuse@psych.umass.edu	University of Massachusetts, Amherst
Tim	Lahm	tlahm@iu.edu	Indiana University
Muriel	Larauche	mlarauche@mednet.ucla.edu	University of California, Los Angeles
Yun-Fai Chris	Lau	chris.lau@ucsf.edu	University of California, San Francisco
Emily	Lawrence	ellawren@usc.edu	University of Southern California
Leslie	Leinwand	leslie.leinwand@colorado.edu	University of Colorado, Boulder
Kathryn	Lenz	lenz.56@osu.edu	Ohio State University
Lana	Leung	lleung@midwestern.edu	Midwestern University
Tamara	Lewis Johnson	lewisjohnsont@niaid.nih.gov	National Institutes of Health, NIAID
Yunmin	Li	yunmin.li@ucsf.edu	University of California, San Francisco
Fudong	Liu	fliu@uchc.edu	University of Connecticut Health Center
Naomi	Lowy	naomi.lowy@fda.hhs.gov	US Food and Drug Administration
David	Lyons	dmlyons@stanford.edu	Stanford University
Devon	Magliozzi	dmaglioz@stanford.edu	Stanford University
Amanda	Mahnke	mahnke@medicine.tamhsc.edu	Texas A&M University
Dolores	Malaspina	dolores.malaspina@nyumc.org	NYU Medical Center
Monica	Mallampalli	monica@swhr.org	Society for Women's Health Research
Anna Maria	Martits	annamartits@terra.com.br	Brazilian Association of Medical Women, MWIA Medical Women International Assoc.
Stacy	Masucci	s.masucci@elsevier.com	Elsevier
Franck	Mauvais-Jarvis	fmauvais@tulane.edu	Tulane University
Margaret	McCarthy	mmccarthy@som.umaryland.edu	University of Maryland School of Medicine
Louise	McCullough	lmccullough@uchc.edu	University of Connecticut Health Center
John	Meitzen	jmeitzen@gmail.com	NC State University
Marilene	Melo	marilenermelo@uol.com.br	Brazilian Association of Medical Women, MWIA Medical Women International Assoc.
Virginia	Miller	miller.virginia@mayo.edu	Mayo Clinic

First Name	Last Name	E-Mail	Organization
Morgana	Mongraw-Chaffin	mmongrawchaffin@ucsd.edu	University of California, San Diego
Kathleen	Morrison	kmorr@vet.upenn.edu	University of Pennsylvania
Claire	Murphy	cmurphy@mail.sdsu.edu	San Diego State University
Naomi	Nagaya	nagaya@tamu.edu	Texas A&M University
Sahin	Naqvi	naqvi@wi.mit.edu	MIT
Gretchen	Neigh	gmccand@emory.edu	Emory University
Patricia	Nguyen	patricia.k.nguyen@gmail.com	Stanford University
Martha	Nolan	martha@swhr.org	Society for Women's Health Research
Colleen	Norris	colleen.norris@ualberta.ca	University of Alberta
Mariko	Ogawa	ogawam@tdc.ac.jp	Tokyo Dental College
Janet	Okogbaa	jokogbaa@stanford.edu	Stanford University
David	Page	page_admin@wi.mit.edu	MIT
Min Jung	Park	mpark33@gmail.com	Texas A&M University
Heather	Patel	heather.patel@ttuhsc.edu	Texas Tech University Health Sciences Center
Andrew	Pekosz	apekosz1@jhu.edu	Johns Hopkins University
Sanne	Peters	sanne.peters@georgeinstitute.ox.ac.uk	Oxford University
Lindsay	Pickett	lindsaypick46@umaryland.edu	University of Maryland School of Medicine
Kristen	Pleil	kpleil@email.unc.edu	University of North Carolina, Chapel Hill
Minolfa	Prieto	mprieto@tulane.edu	Tulane University
Nancy	Raymond	raymo002@umn.edu	University of Minnesota
Naftali	Raz	nraz@wayne.edu	Wayne State University
Abbas	Raza	araza2@uvm.edu	University of Vermont
Armin	Raznahan	raznahana@mail.nih.gov	National Institutes of Health
Vera	Regitz-Zagrosek	vera.regitz-zagrosek@charite.de	Charite Hospital Berlin
Paul	Reisberg	preisberg@wellesley.edu	Wellesley College
Allan	Reiss	areiss1@stanford.edu	Stanford University
Karen	Reue	reuek@ucla.edu	University of California, Los Angeles
Anne	Richards	anne.richards@ucsf.edu	University of California, San Francisco
Thalia	Robakis	trobakis@stanford.edu	Stanford University
Meaghan	Roy-O'Reilly	royoreilly@uchc.edu	University of Connecticut Health Center
Kathryn	Sandberg	sandberg@georgetown.edu	Georgetown University
Londa	Schiebinger	schieb@stanford.edu	Stanford University
Ashley	Schmeling	aschmeli@umich.edu	University of Michigan
Jaclyn	Schwarz	jschwarz@psych.udel.edu	University of Delaware
Ashley	Scott	ashley31@umbc.edu	University of Maryland, Baltimore County
Pamela	Scott	pamela.scott@fda.hhs.gov	US Food and Drug Administration
Amutha	Selvamani	aselvamani@medicine.tamhsc.edu	Texas A&M University
Marianne	Seney	seneyml@upmc.edu	University of Pittsburgh Medical Center
Nirao	Shah	nms@ucsf.edu	University of California, San Francisco
Sonali	Shaligram	sshaligram@pacific.edu	Pacific University
Rebecca	Shansky	r.shansky@neu.edu	Northeastern University
Rupali	Sharma	rshar069@uottawa.ca	University of Ottawa
Mingxin	Shi	mingxinshi1988@siu.edu	Southern Illinois University

First Name	Last Name	E-Mail	Organization
Linda	Shortliffe	lindashortliffe@stanford.edu	Stanford University
Farida	Sohrabji	sohrabji@medicine.tamhsc.edu	Texas A&M University
John	Stallone	jstallone@cvm.tamu.edu	Texas A&M University
Marcia	Stefanick	marcias@stanford.edu	Stanford University
Harise	Stein	harise@stanford.edu	Stanford University
Meir	Steiner	mst@mcmaster.ca	McMaster University
Sara	Stockman	sara.stockman@som.umaryland.edu	University of Maryland School of Medicine
Casey	Sullivan	casey.sullivan@nih.gov	National Institutes of Health
Maral	Tajerian	maral@stanford.edu	Stanford University
Joshua	Talboom	joshua.talboom@bannerhealth.com	Banner Sun Health Research Institute, ASU
Amanuel	Tesfay-Gebremedhin	amanuelpraise@gmail.com	Jimma University Ethiopia
Cory	Teuscher	c.teuscher@uvm.edu	University of Vermont
Ayse	Tezcan	aztezcan@ucdavis.edu	UC Davis
Brian	Trainor	bctrainor@ucdavis.edu	UC Davis
Jennifer	Tremmel	jtremmel@stanford.edu	Stanford University
Natalie	Tronson	ntronson@umich.edu	University of Michigan
Houng-Wei	Tsai	houng-wei.tsai@csulb.edu	California State University, Long Beach
Soban	Umar	sumar@mednet.ucla.edu	University of California, Los Angeles
Henryk	Urbanski	urbanski@ohsu.edu	Oregon Health & Science University
Jonathan	VanRyzin	jvanryzin@umaryland.edu	University of Maryland School of Medicine
Victor	Viau	viau@mail.ubc.ca	University of British Columbia
Zhe	Wang	wangz031@stanford.edu	Stanford University
David	Waters	dwaters@gpmcf.org	Gerald P. Murphy Cancer Foundation
David	Waxman	djw@bu.edu	Boston University
Donna	Werling	donna.werling@ucsf.edu	University of California, San Francisco
Shayna	Williams-Burris	shayna.williams@ucla.edu	University of California, Los Angeles
Stacey	Winham	winham.stacey@mayo.edu	Mayo Clinic
Xueyan	Yang	xueyan@stanford.edu	Stanford University
Julia	Zehr	zehrj@mail.nih.gov	National Institutes of Health
Monan Angela	Zhang	monanangela.zhang@mail.utoronto.ca	University of Toronto
Zhengui	Zheng	zzheng@siu.edu	Southern Illinois University
Anna	Zychlinsky Scharff	ankazychlinsky@hotmail.com	Hannover Medical School

SPONSORS AND DONORS

MORGAN & CLAYPOOL PUBLISHERS

COLLOQUIUM

DIGITAL LIBRARY OF LIFE SCIENCES

Time-saving Expert Reviews for Researchers and Trainees

www.morganclaypool.com

Selected e-Books of Interest for OSSD 2015 attendees:

Sex and the Developing Brain

Margaret M. McCarthy, *University of Maryland School of Medicine, Baltimore*
November 2010, 110 pages, (doi:10.4199/C00018ED1V01Y201010DBR001)

Brain Development and Sexual Orientation

Jacques Balthazart, *University of Liege, Belgium*
August 2012, 134 pages, (doi:10.4199/C00064ED1V01Y201208DBR008)

The Immune System and the Developing Brain

Jaclyn M. Schwarz, *University of Delaware* and **Staci D. Bilbo**, *Duke University*
October 2011, 128 pages, (doi:10.4199/C00045ED1V01Y201110DBR004)

Sex and Gender Differences in CV-Renal Diseases and Hypertension

Jane F. Reckelhoff, *University of Mississippi Medical Center*
November 2014, 97 pages, (doi:10.4199/C00118ED1V01Y201409ISP057)

Developmental Programming of Cardiovascular Disease

Barbara T. Alexander, *University of Mississippi Medical Center*
June 2013, 77 pages, (doi:10.4199/C00084ED1V01Y201305ISP038)

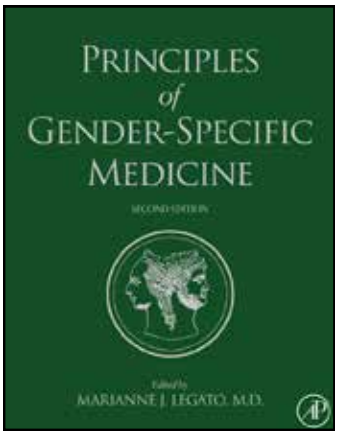
Free Access to these eBooks is available for researchers at institutions that license **Colloquium**. *Visit our website to see if you have free access, or to request a free trial, email cho@morganclaypool.com.*

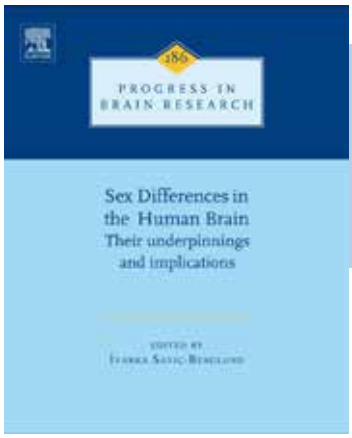
AVAILABLE FROM ELSEVIER

Enter code **BIOMED215** at checkout for **25%** off plus free shipping!

Human Physiology in Extreme Environments
By **Hanns-Christian Gunga**
December 2014 / ISBN: 9780123869470
Price: $99.95

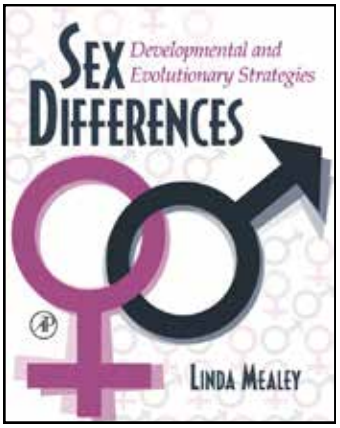
Principles of Gender-Specific Medicine
2nd Edition
Edited by **Marianne J. Legato**
November 2009 / ISBN: 9780123742711
Price: $144.00





Sex Difference in the Human Brain
Their Underpinnings and Implications
Edited by **Ivanka Savic-Berglund**
January 2011 / ISBN 9780444536303
Price: $305.00

Sex Differences
Developmental and Evolutionary Strategies
By **Linda Mealey**
April 2000 / ISBN: 9780124874602
Price: $103.00



ELSEVIER

FORTHCOMING!

Sex Differences in Physiology — 9780128023884 — February 2016
By Gretchen Neigh and Megan Mitzelfelt

An all-encompassing reference that details basic science research into sex differences in all physiological fields. It includes scientific discoveries concerning sex differences in cardiovascular, respiratory, renal, gastrointestinal, and musculoskeletal physiology. Also included is coverage of development, endocrinology, neurophysiology, immunity, and metabolism. This important reference will meet the resource needs of investigators interested in incorporating sex differences into their research programs and provide clinicians with the basis for providing the best, sex-based medical treatment options.

Visit store.elsevier.com for more information!

See you next year!

Apri1 2016
Philadelphia

SSD
ORGANIZATION FOR THE STUDY OF SEX DIFFERENCES
Founded by the Society for Women's Health Research