Seventh Annual Meeting Of The Organization For The Study Of Sex Differences

OSSD 2013

April 25-27, 2013
Sheraton Lincoln Harbor
Weehawken, NJ
USA

OSSD 2013

SEVENTH ANNUAL MEETING

OF THE

ORGANIZATION FOR THE STUDY OF

SEX DIFFERENCES

APRIL 25-27, 2013

MEETING PROGRAM

OSSD 2013 PRESIDENT'S WELCOME

Welcome to OSSD 2013, the 7th annual meeting of the Organization for the Study of Sex Differences! Under the capable leadership of the chair, Kevin Beck, UMDNJ - New Jersey Medical School, and co-chair, DeLisa Fairweather, Johns Hopkins University, the OSSD Program Committee has put together a spectacular program with an outstanding line-up of basic and clinical scientists. This meeting will also introduce you to a terrific crop of up-and-coming researchers in the field of sex differences, who will present their work in the Elizabeth Young New Investigator Symposium and in the two planned poster sessions. OSSD's mission is to promote research in, and knowledge of, sex and gender differences in biology and medicine. Our first priority is to hold high-quality annual meetings. We fully expect OSSD 2013 to meet that goal and to generate the same level of inspiring cross-discipline interaction as did the previous meetings.

OSSD's official journal, *Biology of Sex Differences* (BSD), celebrated its second anniversary in early November of last year. Under the excellent stewardship of editor-in-chief, Art Arnold, and with the assistance of an internationally acclaimed editorial board, the journal did great last year: the total number of articles published more than doubled, the total number of accessions nearly quadrupled, and the number of articles that got the designation 'highly accessed' climbed five-fold, as did the number of citations. The journal keeps publishing stimulating primary research and review papers in a rich variety of biological and medical sub-disciplines. These papers are freely available on the web and several of them have circulated extensively in news media, drawing a lot of attention. If you haven't done so already, consider BSD for publishing your best work on sex differences in biology and medicine.

Finally, I would like to thank the Society for Women's Health Research for its generous financial as well as administrative support in founding OSSD and in shepherding it through its initial six years. This past year was the first year that OSSD operated independently of SWHR. I would like to express my deep gratitude to the members of OSSD Council and the Executive Board for their tireless efforts that made this all possible.

Geert J. de Vries Ph.D.
President of the OSSD
Professor of Neuroscience
Neuroscience Institute
Georgia State University

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Whitney Room (1st floor)

Thursday, April 25, 2013

7:30 am – 8:30 am		**Breakfast (provided)**
8:00 am – 12:00 pm		**Workshop: "Sex Differences 101": Biological Basics of Biomarkers**
12:00 pm – 1:00 pm	Registration & Exhibits Open	Free Time
1:00 pm – 1:15 pm		**Welcome and Introductions** OSSD President: Geert de Vries PhD OSSD 2013 Program Chair: Kevin Beck PhD
1:15 pm – 2:15 pm		**Keynote Address** **Sex, Stress, and the Brain: From Serendipity to Clinical Relevance** Bruce McEwen PhD
2:15 pm – 3:15 pm		**Elizabeth Young New Investigator Symposium**
3:15 pm – 3:30 pm		Break (provided)
3:30 pm – 5:30 pm		**Presidential Symposium** **Sex Differences in Autism** Chairs: Rosanna Weksberg MD/PhD & Peter Szatmari MD
5:30 pm – 8:00 pm		**Poster Session 1**
8:00 pm – 10:00 pm		**Welcoming Reception**

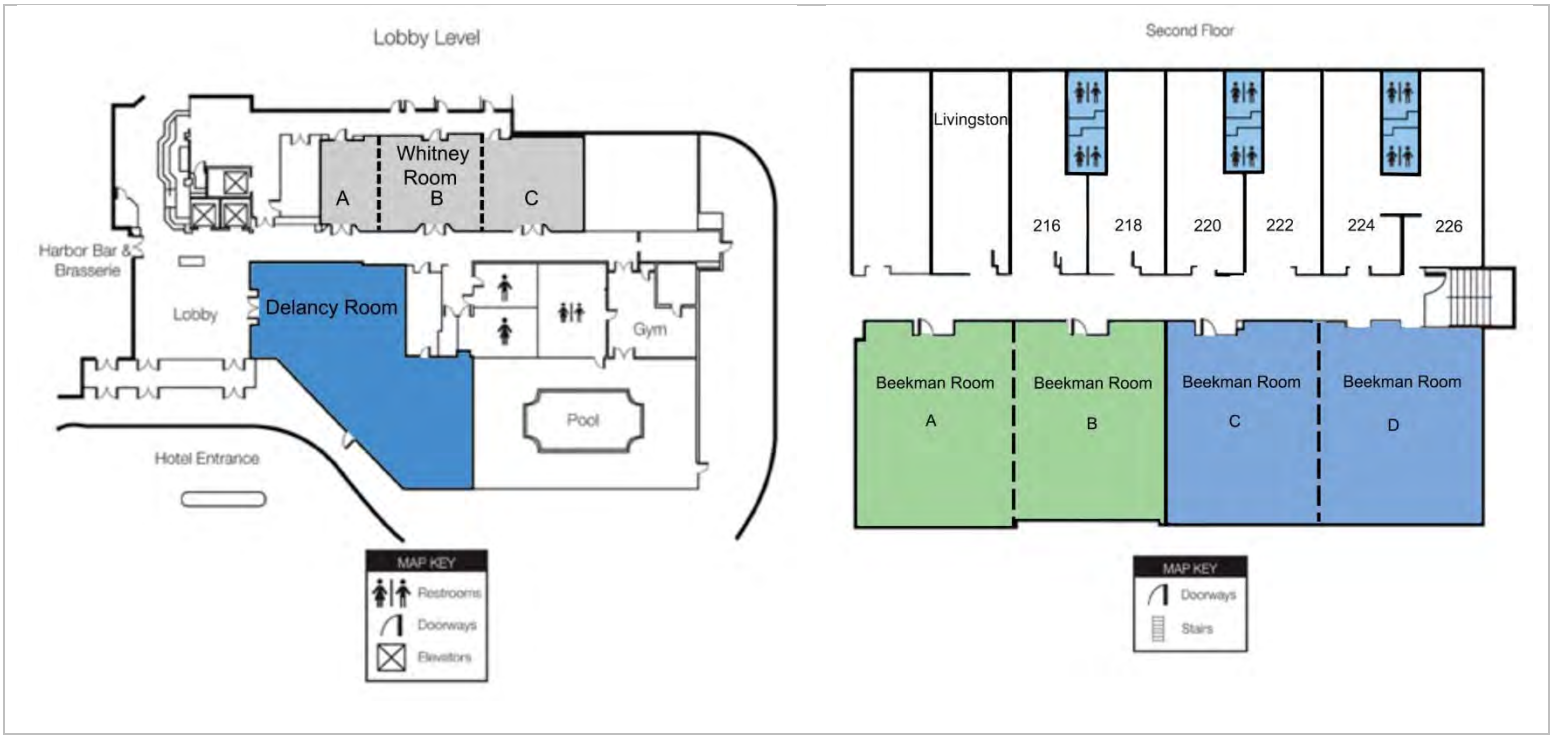
Friday, April 26, 2013

7:30 am – 8:30 am		**Breakfast (provided)**	**Breakfast (provided)**
8:15 am – 10:15 am	Registration & Exhibits Open	Symposium I **Diverse Roles of Gonadal Hormones in the Pathology and Treatment of Epilepsy in Men and Women** Chair: Helen Scharfman PhD	Symposium II **Infections and Heart Disease** Chair: Sally Huber PhD
10:15 am – 10:30 am		Break (provided)	
10:30 am – 12:30 pm		Symposium III **Psychoimmunology of Mental Illness (in memory of S. Zalcman)** Chairs: Kevin Beck PhD & Gretchen Neigh PhD	Symposium IV **Sex Differences in Cardiac Arrhythmias** Chair: Glenna Bett PhD
12:30 pm – 2:30 pm		Free Time	
2:30 pm – 4:30 pm		Symposium V **Clinical Considerations of Sex and Gender in Clinical Practice: Promise, Potential, and Pitfalls** Chair: Marjorie Jenkins MD	Symposium VI **Sex and Gender in Cardiovascular-renal Physiology and Pathology** Chair: Jane Recklehoff PhD

4:30 pm – 5:30 pm		**Special Lecture** **The Use of Prenatal Dexamethasone for Congenital Adrenal Hyperplasia** Alice Dreger PhD
5:30 pm – 8:00 pm		**Poster Session 2**

Saturday, April 27, 2013

7:30 am – 8:30 am	Registration & Exhibits Open	**Breakfast (provided)**	**Breakfast (provided)**
8:15 am – 10:15 am		Symposium VII **Pain Management in Cancer** Chair: Karen Berkley PhD	Symposium VIII **Sex Differences in Gene Expression** Chair: Christine Disteche PhD
10:15 am – 10:30 am		Break (provided)	
10:30 am – 12:30 pm		Symposium IX **Causes and Consequences of Sex Differences in Multiple Sclerosis** Chairs: R. Hal Scofield MD & Sabra Klein PhD	Symposium X **Influence of Sex/Sex Hormones on the Gut's Role as Guardian of Health** Chair: Lisa Kilpatrick PhD
12:30 pm – 2:30 pm		Free Time	
2:30 pm – 4:30 pm		Plenary Symposium XI **Centers for Sex Difference Research** Chair: Janine Clayton MD	
4:30 pm – 5:30 pm		**Capstone Lecture** **Gender and Genetics of Sexual Development** Eric Vilain MD/PhD	
5:30 pm – 6:30 pm		**General OSSD Membership Meeting**	
7:00 pm – 9:00 pm		**OSSD Awards Dinner**	



SEVENTH ANNUAL MEETING of the ORGANIZATION FOR THE STUDY OF SEX DIFFERENCES

PRE-CONFERENCE WORKSHOP: SEX DIFFERENCES 101: FROM BIOLOGICAL BASICS TO BIOMARKERS

APRIL 25, 2013: 8:00 - 12:00

Chair: DeLisa Fairweather PhD (Johns Hopkins University), Co-Chair Virginia Miller PhD (Mayo Clinic)

Introduction and Goals

Virginia Miller PhD (Departments of Surgery and Physiology and Biomedical Engineering, Mayo Clinic)

Animal Models and Experimental Design for Studying Sex Differences

Art Arnold PhD (Department of Integrative Biology & Physiology, University of California – Los Angeles)

Studying Sex Differences in the Clinic: Obstacles and Opportunities

Lori A. Blauwet MD (Department of Medicine, Mayo Clinic)

Experiences with Translational Studies: Human to Animal and Back Again

DeLisa Fairweather PhD (Department of Environmental Health Sciences, Bloomberg School of Public Health, Johns Hopkins University) and Lori Blauwet MD (Department of Medicine, Mayo Clinic)

Policy: a Tool for Translating Research

Michael Coronado PhD (Department of Pediatrics, Stanford University)

KEYNOTE LECTURE

April 25, 2013: 1:15 – 2:15

Sex, Stress and the Brain: From Serendipity to Clinical Relevance

Bruce McEwen PhD (Laboratory of Neuroendocrinology, The Rockefeller University)

Sex and stress hormones act upon on neural targets throughout the brain and influence many aspects of brain function and behavior. Investigations of hormone action in brain have revealed that the adult brain is much more resilient and adaptable than previously believed, and that adaptive structural plasticity involves growth and shrinkage of dendritic trees, turnover of synapses and neurogenesis in the dentate gyrus of the hippocampal formation. Sex and stress hormones mediate adaptive structural plasticity, which has been extensively investigated in hippocampus as well as in prefrontal cortex, amygdala and nigrostriatal and mesolimbic systems. Sex and stress hormones exert their effects on brain structural remodeling through both classical genomic, as well as non-genomic mechanisms and do so in collaboration with neurotransmitters and other intra- and extracellular mediators. This will be illustrated for estrogen actions on synapse formation in the hippocampus and for stress-induced remodelling of dendrites and synapses in the hippocampus, amygdala and prefrontal cortex. The influence of early developmental events such as early life stress and brain sexual differentiation will be noted along with the interactions between sex hormones and the effects of stress on the brain. Because hormones influence so many aspects of brain structure and function and because hormone secretion is governed by the cognitive and emotional brain, the role of brain plasticity and hormone action must be considered in understanding virtually every aspect of brain and body resilience and vulnerability to disease. Supported by NIH Grants MH41256 and 5P01 AG16765.

Elizabeth Young New Investigator Symposium

April 25, 2013: 2:15 – 3:15

Sex Chromosome Complement Affects the CNS Neurodegenerative Response to Injury

Sienmi Du MS (Department of Neurology, Laboratory of Neuroendocrinology, and Department of Integrative Biology and Physiology, University of California at Los Angeles)

Sex Chromosomes and Sexual Dimorphism of Human Transcriptomes

Di K Nguyen PhD (Department of Pathology, University of Washington)

Sex Differences in Stroke-Induced Circulating MicroRNA: A Strategy for Identifying Therapeutic Targets

Amutha Selvamani PhD (Texas A&M Health Science Center, Department of Neuroscience and Experimental Therapeutics, Women's Health in Neuroscience Program)

The Role of Genetic Sex in Affect Regulation and Expression of GABA-Related Genes Across Species

Marianne L. Seney PhD (Department of Psychiatry and Translational Neuroscience Program, University of Pittsburgh)

Elevated Fetal Steroidogenic Activity in Autism

Michael V. Lombardo PhD (Autism Research Centre, Department of Psychiatry, University of Cambridge)

Presidential Symposium: Sex Differences in Autism (Sponsored by Autism Speaks)

April 25, 2013: 3:30 – 5:30

Chairs: Rosanna Weksberg MD/PhD (University of Toronto) & Peter Szatmari MD (McMaster University)

The Genetic Epidemiology of Sex Differences in Autism Spectrum Disorders (ASD)

Peter Szatmari MD (Department of Pediatrics, McMaster University)

It is well known that boys outnumber girls among ASD children by a ratio of about 4 to 1. However, the explanation of this phenomenon is not known. It is possible that girls with ASD are ascertained less frequently than boys due to some kind of ascertainment or diagnostic bias. Another possibility is that there is some factor (genetic, epigenetic or environmental) that protects girls from developing the disorder given the same risk factors as boys. This presentation will bring together data from a variety of family studies suggesting that the "true" sex ratio in ASD is closer to unity than 4 to 1. There is also evidence from high risk families that genetic factors may moderate the phenotype in girls and even protect girls from developing ASD in the first place. Identifying those protective factors should be a high priority for translational studies.

Testing Genetic Etiologies of Sex Differences in Disease Incidence

Arivinda Chakravarti PhD (Departments of Medicine, Pediatrics, and Molecular Biology and Genetics, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University)

Sex-differences in the incidence and prevalence of human disease is ubiquitous and arises from a variety of biological and social factors. The dominant biological hypothesis for sex differences is the action of hormones on host processes. However, this cannot be universally proven since the effects of hormones (androgens, estrogens) and chromosome constitution (XY, XX) are completely confounded. In other words, experimental evidence that disassociates these two effects needs to be considered. Disease incidence from Mendelian X-linked mutations is one compelling example of a non-hormonal sex-difference but there are other genetic arguments. This talk will outline various biological and genetic hypotheses leading to sex-differences in traits and how they can be distinguished using human and animal model studies.

Evidence for Sex Bias Etiologies in Exome and Copy Number Variation (CNV) Data

Stephan Sanders MD (Yale University)

The predominance of male cases is amongst the most striking, consistent, and unexplained observations in autism spectrum disorder (ASD). Epidemiological studies aim to infer differences in the distribution of all genetic risk factors between the sexes by considering the rate of ASD in the population. A complementary approach is to directly assess the distribution of known genetic risk factors between the sexes. Advances in genomics have facilitated the identification of numerous ASD risk factors, including de *novo* copy number variants (CNVs, including 16p11.2) and *de novo* loss of function mutations (e.g. *SCN2A*). This talk will outline how the rate of these ASD risk loci varies between males and females and consider whether these observations support organizational, activational, or sex chromosome theories of sexual dimorphism in ASD prevalence.

Epigenetic Sex Differences from Environmental Exposures Relevant to Autism Spectrum Disorders

Janine LaSalle PhD (Medical Microbiology & Immunology, Genome Center, M.I.N.D. Institute, University of California - Davis)

Epigenetic mechanisms, such as DNA methylation, are responsive to environmental influences and can have long-lasting consequences. Autism spectrum disorders (ASD) have complex neurodevelopmental origins whereby both genetic and environmental factors are implicated. Rett syndrome is an X-linked ASD caused by mutations in the epigenetic factor methyl-CpG binding protein 2 (*MECP2*).

The widespread use of persistent organic polybrominated diphenyl ethers (PBDEs) as commercial flame-retardants has raised concern about potential long-lived effects on human health. This study was designed to reduce the complexity in a controlled experimental system by examining the effects of perinatal exposure to PBDE on both sexes in a genetically and epigenetically susceptible mouse model. A truncation mutant mouse model (*Mecp2*$^{308/y}$) with social behavioral defects is a useful mouse model for examining environmental modifying factors. To test potential genetic, epigenetic, and environmental interactions relevant to social and cognitive behaviors, a daily perinatal low-dose BDE-47 exposure was performed on *Mecp2*$^{308/+}$ dams bred to wild-type C57Bl/6J males. Perinatal BDE-47 exposure negatively impacted fertility of *Mecp2*$^{308/+}$ dams and preweaning weights of female pups.

Global hypomethylation of brain DNA was observed specifically in BDE-47 exposed female offspring and correlated with reduced sociability in a genotype-independent manner. A reversing interaction of *Mecp2* genotype on BDE-47 exposure was observed in a short-term memory test of social novelty that correlated with increased *Dnmt3a* levels specifically in BDE-47 exposed *Mecp2*$^{308/+}$ mice. In contrast, a compounding BDE-47**Mecp2* interaction was observed in a test of spatial learning and long-term memory. These results suggest that genetic and environmental interactions on the developing brain are complex and involve sexual dimorphism, epigenetic dysregulation, compensatory molecular mechanisms, and specific behavioral deficits.

This work was supported by NIH R01ES015171, 2R01HD041462), ARRA stimulus funds 3R01ES015171-04S1, T32002321, and the NIEHS/EPA Center for Children's Environmental Health PO1 ES11269, the U.S. Environmental Protection Agency through the Science to Achieve Results (STAR) program award numbers R833292 and R829388.

Symposium I:

April 26, 2013: 8:15 – 10:15

Diverse Roles of Gonadal Hormones in the Pathology and Treatment of Epilepsy in Men and Women

Chair: Helen Scharfman PhD (NYU Langone Medical Ctr.)

Neurosteroids as Drug Targets in Epilepsy

Michael Rogawski MD PhD (Department of Neurology, University of California, Davis School of Medicine)

Women and men with epilepsy exhibit fluctuations in seizure susceptibility that may be related to alterations in neurosteroid levels. Women often experience seizure clustering that conforms to the menstrual cycle (commonly known as catamenial epilepsy). In women and men, stress or relief from stress may cause clustering, whereas hypogonadism in men may exacerbate seizures. The neurosteroids implicated in these situations are allopregnanolone, a metabolite of progesterone; tetrahydrodeoxycorticosterone, derived from the adrenal steroid deoxycorticosterone; and the

testosterone metabolites 5α-androstanediol, androsterone and etiocholanolone. Neurosteroids are synthesized within the brain, predominantly in principal (excitatory) neurons, and also in peripheral tissues. Their actions on seizures are not believed to be due to interactions with cytosolic steroid hormone receptors. Rather, they enhance the action of GABA on inhibitory $GABA_A$ receptors including nonsynaptic δ subunit-containing $GABA_A$ receptors that mediate tonic inhibition of neurons. $GABA_A$ receptor positive modulatory neurosteroids confer seizure protection in diverse animal models. Withdrawal of endogenous neurosterods may be a key factor in seizure exacerbation, suggest that neurosteroid replacement with natural or synthetic neurosteroids could be a treatment approach. I will discuss promising clinical trials with ganaxolone, the synthetic 3β-methyl analog of allopregnanolone; preliminary human data demonstrate it to be an efficacious and safe treatment for partial seizures in both women and men, although it may be of particular utility in women. Recently, my laboratory has received FDA approval to investigate allopregnanolone in clinical trials. Emerging understanding of the role of neurosteroids in epilepsy and an appreciation of the differences in the physiology of neurosteroids in women and men provide opportunities to optimize therapy for both sexes.

Funding: Research support was received from NINDS (NS002877, NS072094, NS079202) and CDMRP (W81XWH-09-1-0746).

The Role of Gonadal and Brain Synthesis of Estrogen and Androgen in Regulating Brain Structure and Function

Neil MacLusky PhD (Department of Biomedical Sciences, Ontario Veterinary College, University of Guelph)

The fact that circulating gonadal steroids are converted to locally-active metabolites in the brain has been known for more than 40 years. For much of that time, the effects of these metabolites were considered primarily in terms of their potential actions on cell nuclear receptor systems. Over the last decade, it has become clear that androgen synthesis and metabolism in the brain is also involved in directly modulating glial and neuronal plasticity, thereby controlling the activity of sexually differentiated neural pathways. In addition to the role of 5alpha reduction in the generation of active metabolites that affect $GABA_A$ receptor function, local androgen conversion to estrogen can also directly modulate synaptic activity, particularly responses involving glutamate receptor signaling. Thus, in the brain, gonadal steroids play a multifunctional role, acting as both signaling molecules mediating responses to changes in the secretory activity of peripheral endocrine organs, and as neuromodulators rapidly regulating local neurotransmitter function.

Mechanisms Underlying Differences in Brain Excitability in Men and Women and Their Relevance to Epilepsy

Helen Scharfman PhD (Departments of Child and Adolescent Psychiatry, Physiology and Neuroscience, and Psychiatry, NYU Langone Medical Ctr.)

Sex differences in brain excitability have relevance not only to epilepsy, but also many other diseases where hyperexcitability has been suggested to play a critical role. Nevertheless, many aspects of sex differences in excitability are not well understood – and some are even contested. We have used the normal adult male and female rodent to understand sex differences in excitability more clearly, and focused on hippocampus, where the regulation of normal excitability is critical to normal cognitive function, as well as several epilepsy syndromes. Our data suggest that there are robust differences in male and female excitability in normal hippocampus of adult rats. Thus, slices from adult female rats exhibit increased excitability when examined on proestrous or estrous morning of their ovarian cycle whereas adult males do not exhibit increased excitability. However, males exhibit a similar type of altered excitability as female rats, if they are gonadectomized. A primary mechanism underlying

hyperexcitability in both female and males is upregulation of the neurotrophin brain-derived neurotrophic factor (BDNF) in glutamatergic pathways, and actions of BDNF at TrkB receptors on the glutamatergic nerve terminals. BDNF protein levels are increased by 17b-estradiol in the adult female and appear to be tonically suppressed by testosterone in the male. The collective data suggest that normally hippocampal excitability waxes and wanes in adult females and males as BDNF levels rise and fall, but for different reasons that are sex-dependent. These data help explain several aspects about normal sex differences in adult hippocampal function. They also address sex differences in a type of epilepsy that involves the hippocampus, temporal lobe epilepsy.

Symposium II:

April 26, 2013: 8:15 – 10:15

Infections and heart disease

Chair: Sally A. Huber PhD (University of Vermont)

Sex Differences in Viral Myocarditis: The Mouse Model and What It Tells Us

DeLisa Fairweather PhD (Department of Environmental Health Sciences, Bloomberg School of Public Health, Johns Hopkins University)

Cardiovascular disease (CVD) is the leading cause of death in men and women worldwide. Hypertension excluded, CVD occurs more frequently in men than women yet the reasons for this are not well understood. Using an autoimmune mouse model of viral-induced cardiac inflammation, or myocarditis, we have identified serum and cardiac genes/biomarkers that drive disease in males. We have been able to confirm that these biomarkers are elevated in men with myocarditis and dilated cardiomyopathy. Our research indicates that the inflammatory response to viral infection is entirely different when "read" in the context of androgen or estrogen signaling (i.e. androgen or estrogen response elements). We have found that testosterone alters regulation of the inflammatory response resulting in a damaging inflammatory response in males that leads to cardiac remodeling and heart failure. Understanding the mechanistic differences in how men and women develop CVD and heart failure is critical to develop more effective therapies.

Decreased T Regulatory Cells, Increased Th17 Cells and Proinflammatory Cytokine Responses Correlate with Impaired Cardiac Function in Human Myocarditis

Madeleine W. Cunningham PhD (Department of Microbiology and Immunology, University of Oklahoma Health Sciences Center)

Despite many animal models of autoimmune myocarditis and dilated cardiomyopathy, the contribution of T cells in the progression and immunopathogenesis of human myocarditis is not as well defined. Animal models have suggested that reduction of T regulatory (Treg) cells and proinflammatory immune responses may lead to autoimmune myocarditis and subsequent cardiomyopathy. We tested the hypothesis that Treg cells would be decreased and Th17 cells would be increased creating a proinflammatory environment in human myocarditis/DCM (n=23). As detected by FACS analysis, CD4+FOXP3+CD25+ Treg cells were significantly decreased and Th17 cell percentages were increased in myocarditis/DCM compared to healthy subjects. The Th17/Treg ratio was significantly altered ($p=0.04$) in myocarditis/DCM compared to normals. Indicative of a pro-inflammatory response and associated with the Th17 subset, IL-6 ($p=0.0004$) and IL-23 ($p<0.0001$) were elevated in serum in myocarditis/DCM and may account

for significantly altered Th17/Treg cell ratios in disease. Stimulation of PBMCs (CD14+ monocytes) from myocarditis/DCM produced significantly higher pro-inflammatory cytokine levels of TGF-β1 ($p<0.0001$) and IL-6 ($p<0.0001$) compared to normals. In 60% of myocarditis/DCM subjects, reduced Treg cells correlated with increased TGF-β1 and IL-6 responses by PBMCs/monocytes. TGF-β1 was significantly higher in males than in females with myocarditis. In our myocarditis/DCM group, increased serum IL-6 correlated ($r=-0.53$) with decreased left ventricular ejection fraction (LVEF) and decreased heart function. In addition, elevated Th17 cells were associated with left heart failure ($p<0.05$). Our data suggest that reduced T regulatory cells, higher Th17 cells and elevated IL-6/TGFβ1 may play important roles in the pathogenesis of human myocarditis/DCM.

Funding: NIH-R01HL56267; American Heart Association Pre-doctoral Fellowship and NIH-T32AI007633

Sex-Specific Issues in Progression of Cardiovascular Disease: Results from the Kronos Early Estrogen Prevention Study (KEEPS)

Virginia Miller PhD (Departments of Surgery and Physiology and Biomedical Engineering, Mayo Clinic)

Cardiovascular disease remains the number one killer of women. Menopause is a sex-specific shift in the hormonal milieu that increases a women's risk for cardiovascular disease. Data from many observational and epidemiological studies provide evidence that women who use hormone treatments early in menopause have reduced all cause cardiovascular mortality. By implication, these data suggest that use of menopausal hormone treatments (MHT) may slow progression of arterial disease. This hypothesis was tested in the prospective randomized, double blinded trial, the Kronos Early Estrogen Prevention Study (KEEPS). Women who were within 6-12 months of menopause were randomized to either placebo patch and pill, oral conjugated equine estrogen or transdermal 17β-estradiol each with pulsed progesterone for 4 years. The primary outcome was carotid intimal medial thickening with secondary outcomes of coronary calcification, blood inflammatory profile, menopausal symptoms and cognition. Results of this trial as reported at the North American Menopause Society will be summarized as well as potential mechanisms of how MHT alter components of the vascular system that may explain the vascular outcomes.

Symposium III:

April 26, 2013: 10:30 – 12:30

Psychoimmunology of Mental Illness (in Memory of Steve Zalcman)

Chairs: Kevin Beck PhD (University of Medicine & Dentistry of NJ/ VA New Jersey Health Care System) & Gretchen Neigh PhD (Emory University)

Suppression of Sensory Reactivity by Cytokines: An Unexplored Mechanism of Behavioral Depression in Females

Kevin Beck PhD (Stress & Motivated Behavior Institute, Department of Neurology & Neurosciences, UMDNJ – New Jersey Medical School; Neurobehavioral Research Laboratory, VA New Jersey Health Care System)

Stress causes sex-specific behavioral and physiological changes in mammals. Our theory is that the differences in the prevalence of stress-related mental disorders in men versus women can be attributed to these sex differences in how stress affects male and female physiology. Under different stressor models, our laboratory has shown male and female rats exhibit sex-

specific changes in startle reactivity following stressor exposure; males tend to exhibit increased startle reactivity and females decreased startle reactivity. In examining potential mechanisms for this sex-specific effect of stressor exposure on startle reactivity, the peripheral immune response, specifically interleukin (IL)-1β, was found to decrease startle reactivity in a similar manner as certain stressors. This effect of IL-1β is ovarian hormone dependent and is more or less robust in rats strains that exhibit greater stress-induced pro-inflammatory signaling versus anti-inflammatory (glucocorticoid) signaling. Subsequent work has tried to determine if IL-1β reduces startle reactivity in females via subsequent peripheral immune signaling cascades, as well as determine which brain areas are involved in dampening startle reactivity.

Expression of HIV-1 Causes Depressive-Like Behaviors and Decreased Cell Genesis in the Dentate Gyrus of Adolescent Female Rats: Role of Non-Viral Neuroinflammation

Gretchen Neigh PhD (Departments of Psychiatry and Behavioral Sciences and Physiology, Emory University School of Medicine)

The HIV-positive adolescent population experiences an elevated rate of clinical depression, and HIV associated depression accelerates cognitive impairment. Clinical depression has been linked to morphological changes in the brain and increased activity of the inflammatory system. This study used adolescent HIV-1 transgenic rats (HIV-tg), that display related immune-immune response alterations and pathologies, to test the hypothesis that developmental expression of HIV-1-related proteins induces a depressive-like phenotype that parallels a decrease in hippocampal cell proliferation and an increase in pro-inflammatory cytokine activity. Consistent with the hypothesis, HIV-tg rats exhibit depressive-like behaviors, decreased levels of cell proliferation in the hippocampus, and elevated expression of CCl2 in the hippocampus. Importantly, these data support a biological basis for the co-morbid manifestation of depression in HIV-positive patients under conditions devoid of stress or other psychosocial factors which could account for the manifestation of HIV-related depression.

Gender Differences in Stimulated Cytokine Production Following Acute Psychological Stress

Anna Marsland PhD RN (Behavioral Immunology Laboratory, Department of Psychology, University of Pittsburgh)

Individuals differ in the magnitude of inflammatory response to acute psychological stress. Gender may contribute to this variation. We examined lipopolysaccharide-induced production of the pro-inflammatory cytokines interleukin (IL)- 1β, IL-6, and tumor necrosis factor (TNF)- α in response to an evaluative speech task among healthy midlife men (n=28) and women (n=34). Results showed an increase in production of cytokines from pre- to 30 min. post-stress, with no gender differences in the magnitude of this effect. Men showed a significant decrease in cytokine production from pre- to immediately post-stress, whereas women showed no change across this period. These differences were related to menopausal status, with postmenopausal women displaying greater increases in cytokines production across this period than men. Results support increased inflammatory response to acute stress, with gender differences in the patterning of stress-related cytokine activity. Increased immune reactivity among post-menopausal women may contribute to increased susceptibility to inflammatory disease.

Symposium IV:

April 26, 2013: 10:30 – 12:30

Sex Differences in Cardiac Arrhythmias

Chair: Glenna Bett PhD (University of Buffalo)

Sex Differences in Arrhythmia Susceptibility: Drugs, Subunits, and Systems

Glenna Bett PhD (Department of Gynecology – Obstetrics, School of Medicine and Biomedical Sciences, University of Buffalo)

Women have a longer baseline QT_c than men, and are at higher risk for long QT syndrome (LQTS). LQTS is characterized by sudden syncopal attacks, seizures, and even sudden death. LQTS is associated with a particularly dangerous form of abnormal electrical activity, or polymorphic ventricular tachycardia, called Torsade de Pointes (TdP). TdP is a particularly dangerous arrhythmia, and can lead to ventricular fibrillation and sudden death. Both drug-induced and genetically inherited long QT syndrome can result in TdP. Women are at much greater risk (60-75%) than men of suffering the potentially fatal drug-induced side effect of TdP. In addition, sex is an important risk factor in individuals with genetically-based long QT syndromes: Genetic LQTS is present in 1 in 5,000 individuals, with adult women being more susceptible to cardiac events than men. Thus, the problem of arrhythmia susceptibility in women is a major health problem. Progress in addressing this important women's health problem is hampered by a lack of understanding of the basic causes for the differences in the electrical susceptibility to LQTS. The current paradigm maintains that the longer natural QTc of post-pubertal women is the basis for this susceptibility. However, this fails to account for the observation that even though QT_c does not appear to vary during the menstrual cycle, there are cyclical changes in susceptibility to paroxysmal supraventricular tachycardia, and changes in the ability of drugs to prolong QT_C. Although basal QT_c does not change, the balance and kinetics of repolarizing currents does change during the menstrual cycle. This change alters the dynamic properties of repolarization as well as the cardiac pharmacological profile. Understanding the molecular mechanisms for this cycle-dependent change in electrical activity will help improve our understanding of the molecular basis of arrhythmogenesis and the relationship between hormonal signaling and QT prolongation.

Mapping Sex Differences in the Spatial Heterogeneity of Cardiac Electrophysiology

Guy Salama PhD (Department of Medicine, University of Pittsburgh)

Post-pubertal women have longer rate-corrected QTc intervals than men and are two times more likely to be afflicted by a form of polymorphic ventricular arrhythmia known as TdP (torsade de Pointes). TdP caused by the suppression of the fast component of the delayed rectifying K^+ current, I_{Kr} results in repolarization delay and QT prolongation, called Long QT type 2 (LQT2). Congenital forms of LQT2 caused by mutations that result in a 'loss-of-function' of I_{Kr} are rare but drug—induced LQT2 remains a serious public health problem because the channel protein encoded by hERG is highly promiscuous and numerous pharmaceutical agents targeting a broad range of diseases can have lethal off-target cardiac effects. Sex and age differences in the propensity to LQT2 have been attributed to a reduced 'repolarization reserve' in females and is not confined to humans female rabbits, as female rabbits, dogs and guinea pigs have longer action potential durations than males. The molecular basis for this difference has long been attributed to reduced levels of hERG expression but recent studies from our group in female hearts has discovered that estrogen (0.3-1nM) upregulates voltage-gated L-type Ca^{2+} channels and Na/Ca exchanger (NCX) to increase their currents, $I_{Ca,L}$ and I_{NCX}, respectively. In isolated myocytes from the base of female hearts, estrogen acts via a genomic mechanism requiring 24-48

hours to increase levels of message, protein and current densities. Excessive prolongation of the action potential changes the balance of $I_{Ca,L}$ and I_{NCX} and Ca^{2+} fluxes that signal excitation and contraction in the heart. Most importantly action potential prolongation may lead to sarcoplasmic reticulum (SR) Ca^{2+} overload and leakage of Ca^{2+} through the ryanodine receptors, which then reactivates the L-type Ca^{2+} channels out of phase causing ectopic beats. SR Ca^{2+} release during the action potential plateau activated the forward mode of NCX and the consequent Na^{+} influx results in early after-depolarizations (EADs) and TdP. Spatially, EADs originate from the base of the ventricles and may propagate into other regions of the heart, disturbing organized progression of activation and repolarization. This situation can initiate a self-sustaining rapid reentrant excitation with a frequency much greater than the natural heart rate, resulting in tachycardia. We have explored the heterogeneity of cardiac ion channels using proteomics, optical mapping, and electrophysiology. We found heterogeneous expression in currents and exchangers which affect cellular calcium dynamics. Our animal work was confirmed in tissue from healthy adult human hearts. The observed differences were sex-related as it did not occur in the hearts of adult men, as well as age-dependent as it was not manifested in postmenopausal women.

Pregnancy: Sex Dependent Reversible Hypertrophy and Action Potential Prolongation

Randall L. Rasmusson PhD (Center for Cellular and Systems Electrophysiology, University of Buffalo)

Pregnancy is a unique and complex physiological condition that puts numerous stresses on the heart. Cardiac output must adapt to the increased circulating maternal blood mass, changes in fetal demands, and the demands of the uteroplacental circulation. In pregnancy, the heart undergoes reversible physiologic eccentric hypertrophy, secondary to an increased plasma volume and cardiac output. On a short-term basis, the strength and duration of cardiac muscle contraction is modulated by the behavior and relative magnitudes of the currents which underlie the cardiac action potential, and the subsequent ability of the cell to sequester calcium in the sarcoplasmic reticulum or extrude it through sarcolemmal pathways. All of these functions are controlled by the membrane potential and most importantly, the shape and duration of the action potential. Thus, it may not seem surprising that cardiac repolarization is prolonged in pregnancy. However, the adaptation to the increased demands placed on the heart may come with some trade-offs. Action potential prolongation and its clinical phenotype, long QT syndrome, are generally thought to be proarrhythmic. Not surprisingly, PVCs and PACs are more common in pregnancy and the likelihood of having an arrhythmia is higher in pregnancy. The cardiac action potential (AP) arises from the complex interplay of numerous non-linear time-dependent currents. Given the diversity and complexity of the interaction of these currents, mathematical modeling provides a uniquely useful tool to explore the consequence of electrical remodeling on the cellular level. This is particularly true when trying to determine effects and consequences in the intracellular calcium handling dynamics. We have previously developed a comprehensive mathematical model of the mouse cardiac myocyte, in which each current has been assigned a putative molecular basis. This makes the mathematical model suitable for matching with molecular data on changes in expression levels, as was previously done for a neonatal mouse ventricular action potential. We used quantitative analysis of mRNA expression to alter our model of the mouse ventricular myocyte to develop a model of the pregnant mouse myocyte. Understanding the molecular basis and electrophysiological consequences of changes in expression of ion channels in pregnancy is key to understanding characteristic of cardiac repolarization as well as response to pharmacological interventions, and arrhythmogenic potential.

Symposium V:

April 26, 2013: 2:30 – 4:30

Clinical Considerations of Sex and Gender in Clinical Practice: Promise, Potential, and Pitfalls

Chair: Marjorie Jenkins MD (Texas Tech Health Sciences University)

"Sexxing" of Diseases Matters in Caring for the Aging Patient

Marjorie Jenkins MD (Laura W. Bush Institute for Women's Health, Texas Tech Health Sciences University)

Cardiovascular disease is the signature clinical entity for sex and gender differences. However, over the past two decades scientific research in many other areas of aging have revealed pronounced sex and gender differences with resulting clinical implications. This presentation will further clarify the two terms of sex and gender in relation to patient care and provide real-world examples of applying sex and gender evidence within clinical practice to improve the care for both men and women. In addition, there will be a brief review of sex and gender knowledge gaps which provide opportunities for expanding translational and clinical research platforms.

Sex- and Gender-Based Differences in Osteoarthritis

Kim Templeton MD (Department of Orthopedics, University of Kansas Medical Center)

As with most musculoskeletal conditions, sex- and gender-based differences are noted in osteoarthritis. These differences are seen in incidence, joints most commonly affected, risk factors, etiology, and responses to treatment. Factors that have been implicated to explain these differences include differences in anatomic alignment, the influence of sex hormones, risk for and response to injury, ligamentous laxity, and available treatment.

Women and Alzheimer's Disease: What Role does Reproductive Aging Play?

Pauline M. Maki PhD (Departments of Psychiatry and Psychology, University of Illinois at Chicago)

Alzheimer's disease (AD) is the sixth leading cause of death in the U.S., with approximately 5.4 million individuals currently living with the disease. Of the top 10 leading causes of death in the U.S., only AD shows a significant sex difference in the direction of greater risks to women. There is debate about whether this sex/gender difference is due to the greater longevity of women compared to men, or alternatively, whether women have an increased risk of AD, even after accounting for their greater longevity. This presentation will provide an overview of sex- and gender-related risk factors for AD, with a focus on the role of menopause and estrogen. Overall the data suggest that early menopause is a risk factor for dementia and that use of estrogen therapy early in the menopausal transition but not later may reduce the risk of AD.

Symposium VI:

April 26, 2013: 2:30 – 4:30

Sex and Gender in Cardiovascular-Renal Physiology and Pathophysiology

Chair: Jane Recklehoff PhD (University of Mississippi Medical Center)

Relaxin in Renal Physiology and Disease

Jennifer Sasser PhD (Department of Pharmacology and Toxicology, University of Mississippi Medical Center)

Emerging evidence supports a potential therapeutic role of relaxin in fibrotic diseases including chronic kidney disease. Relaxin is a pleiotropic hormone, best characterized for its role in the reproductive system; however, recent studies have demonstrated a role of relaxin in the cardio-renal system. Both relaxin and its receptor, RXFP1, are expressed in the kidney, and relaxin has been shown to play a role in renal vasodilation, in sodium excretion, and as an anti-fibrotic agent. Together, these findings suggest that the kidney is a target organ of relaxin. Various mechanisms have been implicated in the renal effects of relaxin including increased nitric oxide production, stimulation of matrix metalloproteinases, and inhibition of transforming growth factor beta. As clinical studies on relaxin move forward, a better understanding of its mechanisms of action is required, especially with regard to the hormone's effects on renal function. This presentation will discuss the functional and structural impacts of relaxin treatment on the kidney, the evidence that relaxin prevents disease progression in several experimental models of kidney disease, and the potential mechanisms that are involved in the therapeutic actions of relaxin.

Immune Regulation of Blood Pressure in Males and Females

Jennifer Sullivan PhD (Department of Medicine, Georgia Regents University)

There is a growing body of evidence supporting a role for T cells in hypertension in male animal models, yet data in females has been lacking. Pro-inflammatory Th17 cells contribute to hypertension, while anti-inflammatory regulatory T cells (Tregs) maintain immune homeostasis and contribute to cardiovascular health in males. We recently published that immune suppression decreases blood pressure in female SHR implicating a role for lymphocytes in blood pressure control in females, yet there remains a scarcity of data on the role of T cells in hypertension in females. This is particularly alarming when women are more likely to develop autoimmune disorders, including rheumatoid arthritis and systemic lupus erythematosus, both of which have an increased risk of cardiovascular disease. Avaliable data in the literature suggests that females are at greater risk to exhibit a dysfunctional innate immune response, which is mediated by B cells and the production of autoantibodies, however, less is known regarding how females vs. males respond to adaptive immune system activation. We have reported that SHR of both sexes have greater T cell infiltration than normotensive WKY, although female SHR have greater renal Treg infiltration and less Th17 infiltration than males. The differentiation of naïve T cells is dependent in large part, on the local cytokine environment and proximal signals from antigen presenting cells and our data suggests that both of these factors are dependent on sex. My talk will be focused on sex differences in inflammation in hypertension and the implications for blood pressure control.

Mechanisms Responsible for Hypertension and Renal Injury in a Model of Lupus Erythematosus

Michael Ryan PhD (Department of Physiology and Biophysics, University Mississippi Medicine Center)

In contrast to young healthy women, the prevalence of hypertension is markedly increased in young women with the autoimmune disorder systemic lupus erythematosus (SLE). Mortality during SLE is largely due to cardiovascular disease, and hypertension is a major cardiovascular risk factor. Despite this, the underlying mechanisms leading to hypertension during SLE are not well defined. The bias of SLE towards young women, along with evidence that estrogens can promote adaptive immune system activation, suggests a prominent role for estrogens in SLE disease progression. However, the role of estrogens in SLE and SLE associated hypertension remains controversial and unclear. This may be due, in part, to the disparate temporal actions of estrogens on immune system function. For example, estrogens can promote antibody mediated immunity early in disease progression (asymptomatic phase), but have powerful immunosuppressive actions during the symptomatic phase of the disease. These immunosuppressive actions could provide an important protection against the development of hypertension and renal disease in women with SLE. Further complicating our understanding of estrogens role during SLE is clinical data related to the affect of hormone therapy in this patient population. For example, in otherwise healthy postmenopausal women, evidence suggests that hormone therapy increases cardiovascular risk. However, the available clinical data in postmenopausal women with SLE show that hormone therapy does not increase cardiovascular risk, and may even reduce it. This presentation will examine the impact of estrogens on blood pressure control in an experimental model of SLE.

SPECIAL LECTURE

April 26, 2013: 4:30 – 5:30

The Use of Prenatal Dexamethasone for Congenital Adrenal Hyperplasia

Alice Dreger PhD (Medical Humanities & Bioethics Program, Feinberg School of Medicine, Northwestern University)

This talk will review the history of the use of prenatal dexamethasone as it has been aimed at preventing atypical sex development in females affected by congenital adrenal hyperplasia (CAH). As will be shown, this use has been promoted and enacted in scientifically and ethically problematic ways and raises larger issues of how the population of individuals affected with sex anomalies have often been mistreated in research. The talk will conclude with a discussion of why many adults with various disorders of sex development are justifiably wary of participating in sex difference research, and a discussion of what it might take to create an environment of ethical behavior towards and genuine respect for research participants born with atypical forms of sex.

Symposium VII:

April 27, 2013: 8:15 – 10:15

Pain Management in Cancer

Chair: Karen Berkley (Florida State University)

Mechanisms of Bone Cancer: Sex Differences?

Patrick Mantyh PhD (Department of Pharmacology, University of Arizona)

Patrick Mantyh is a Professor in the Pharmacology Department and the Cancer Center at the University of Arizona. He completed his B.S. in molecular biology and botany at the University of Wisconsin, and his Ph.D. at UC, San Francisco, USA and post-doc in Cambridge, England. He also has a JD with a specialty in patent law. His lab developed the first animal models of cancer pain, pancreatic cancer pain and chemotherapy-induced peripheral neuropathy and has translated this work into several ongoing human clinical trials. Several therapies which the lab did the early preclinical work have been approved by the FDA to treat cancer related pain / disease progression. He has received numerous national and international awards for this work. The current focus of his lab is developing an understanding of the mechanisms that drive malignant and non-malignant skeletal disease and pain and translating these findings into human clinical trials.

Cancer Pain, Palliative Care, and Quality of Life: Sex Differences?

Ann O'Mara PhD RN (Community Clinical Oncology Program, Division of Cancer Prevention, National Cancer Institute)

Palliative care is often misunderstood to mean end of life or hospice care. To the contrary, palliative care, within the context of cancer care, is a package of services offered to patients from the time of diagnosis and throughout the course of the illness. Palliative care is also more than cancer pain management because of the array of symptoms and quality of life issues cancer patients experience during and following treatment, as well as at the end of life. Many factors contribute to the prevalence and severity of these symptoms and health related quality of life decrements, among them stage and type of disease, treatment regimens, age, gender, and access to care.

In this presentation, participants will gain an understanding of what constitutes palliative care, the common symptoms and quality of life issues that patients face during and following cancer treatment. During the discussion, gender differences in cancer-related physical symptoms (nausea, vomiting, pain, insomnia) and health related quality of life issues will be highlighted. A review of several recent studies that have examined gender differences will be presented.

Cancer Chemotherapy and Pain: Sex Differences?

Paul Farquhar-Smith PhD (Royal Marsden Hospital)

Chemotherapy induced peripheral neuropathy (CIPN) occurs after many types of anti-cancer therapies and is a major cause of pain and adverse symptoms in cancer survivors. The pattern, severity and natural history of CIPN depend on the causative agent which is in turn dependent upon the type of cancer the patient has. Assessment is problematic and there are few data on effective treatments of CIPN. It is unsurprising that there is little discussion of sex differences in CIPN in the existing literature. However, CIPN is a type of neuropathic pain and there is a growing body of evidence indicating genetic susceptibilities including sex differences that are risk factors for the development and maintenance of certain types of neuropathic pain. This talk will investigate epidemiological, scientific and clinical aspects of CIPN to establish the evidence base or the feasibility that sex differences occur in this under

diagnosed, under recognized yet growing clinical problem.

Symposium VIII:

April 27, 2013: 8:15 – 10:15

Sex Differences in Gene Expression

Chair: Christine Disteche PhD (University of Washington)

X-Chromosome Aneuploidies Explain the Sex-Bias of Lupus and Sjogren's Syndrome

R. Hal Scofield MD (Section of Endocrinology and Diabetes, College of Medicine, University of Oklahoma Health Sciences Center)

Women are at least 8 times more likely to have systemic lupus erythematosus (SLE) and 14 times more likely to have Sjögren's syndrome (SS) when compared to men. We hypothesize that this is a consequence of a gene dose effect from the X chromosome. Chromosome X aneuploidies were found using array based genotyping of single nucleotide polymorphisms (SNP) and confirmed by karyotyping, FISH, and/or quantitative PCR. Among 316 men with SLE, 7 had 47,XXY and 1 had 46,XX. The rate of Klinefelter's syndrome (47,XXY) was statistically different from that found in control men and from the known prevalence in the population. The 46,XX man had an sry gene, which encodes the testes determining factor, on an X chromosome as a result of an abnormal crossover during meiosis. In the case of 46,XX, 1 of 316 was statistically different from the known population prevalence of 1 in ~20,000 live male births. We calculate that the prevalence of SLE among 47,XXY men is the same as among women. 47,XXX was found in 9 of 2,137 SLE and in 6 of 1,483 Sjögren's syndrome patients, but in 2 of the 2,898 control women (OR=6.1, 95% CI 1.3-28.3, P<0.0001; and OR=5.9, 95% CI 1.2-29.1, P<0•0001; respectively). The SLE patients with 47,XXX developed the disease on average ~13 years earlier than other women (23•2 years old vs. 35•5 years old; P=0•044, Mann-Whitney U test). Sex chromosome aneuploidies are found in excess among both men and women with SLE or Sjögren's syndrome. These results support the hypothesis that the X chromosome dose contributes to the sex-bias of SLE and Sjögren's syndrome, independently of circulating sex hormones or phenotypic sex.

Mouse Models for an X-Linked Intellectual Disability Syndrome

Jun Xu PhD (Department of Integrative Physiology and Neuroscience, Washington State University)

Many diseases affect women and men differently due in part to dimorphic gene expression. Kdm5c, an X-linked chromatin modifying enzyme, is expressed more highly in females than males because of incomplete X inactivation. Being a histone demethylase, it regulates chromatin modifications and gene transcription. When mutated, it causes neuropsychiatric symptoms such as intellectual disability, aggression, seizure, and delayed language development.

These symptoms are recapitulated in the Kdm5c knockout mice which, compared to wild type littermates, are more aggressive, less social, and suffer from cognitive deficits such as impaired memory formation in fear conditioning and Morris water maze. Gene mis-regulation is evident: synaptic plasticity genes, for instance, are down-regulated in these mice in the amygdala when fear memory is consolidated.

These phenotypes could be attributed to its role in the developing and/or adult brain. To test, Kdm5c was transiently knocked down in adult mice in the hippocampus using small interference RNA. These mice were then tested for object recognition and they performed poorly. Expression array indicated an up-regulation of GABAergic genes in these mice; at the promoters of these up-regulated genes, higher levels of

histone methylation were detected. By blocking the up-regulation of the GABAergic genes, we were able to rescue the object recognition phenotype, suggesting that the cognitive effect of Kdm5c is possibly mediated by these GABAergic genes.

In sum, Kdm5c and other X-linked chromatin enzymes likely make contributions to the sex differences in mental health and disease.

The X and Y Chromosomes both Contribute to Fundamental Sex Differences in Metabolism and Obesity

Art Arnold PhD (Department of Integrative Biology & Physiology, University of California – Los Angeles)

Men and women differ in the distribution of body fat and susceptibility to cardiometabolic diseases. We have recently used mice with unusual sex chromosomes to discover that the number and type of sex chromosomes has important effects on metabolism, not mediated by gonadal secretions. In general, in adult gonadectomized mice, a second X chromosome dramatically increases body weight and adiposity, so that XX mice are heavier and have greater body fat than mice with one X chromosome. Eating a high fat diet leads to dramatically greater accumulation of triglycerides in the liver of XX mice relative to XY, and hyperinsulinemia. The greater adiposity is associated with higher levels of daytime feeding in XX mice, relative to XY. In some mouse strains, the effect of a second X chromosome is mimicked by the effect of a Y chromosome, so that both XX and XY mice have greater body weight and percent body fat, than mice with one X chromosome. The similar effects of X and Y chromosomes points to a small number of paralogous X-Y genes on the two sex chromosomes, which likely cause the effects. The effects of sex chromosome complement are modified by the effects of gonadal hormones, so that each factor blunts the effect of the other. The effects of sex chromosome complement are surprisingly large, and represent a novel source of sex-biasing factors in the metabolome.

Symposium IX:

April 27, 2013: 10:30 – 12:30

Causes and Consequences of Sex Differences in Multiple Sclerosis

Chairs: R. Hal Scofield MD (University of Oklahoma Health Sciences Center) and Sabra Klein PhD (Bloomberg School of Public Health, Johns Hopkins University)

Molecular Mechanisms of Androgen-Dependent Protection in Rodent Models of Multiple Sclerosis

Shannon Dunn PhD (University Health Network and Women's College Research Institute; Department of Immunology, University of Toronto)

For reasons that remain unclear, the incidence of MS is higher in women as compared to men. A higher female to male sex ratio is also apparent in other autoimmune diseases that have a clear underlying T cell-mediated pathology and manifest during adulthood. Our studies in the mouse model of MS, experimental autoimmune encephalomyelitis (EAE), have suggested that one of the reasons for this sex disparity is because androgens protect males from developing autoimmunity. We found that male T cells that develop in a state associated with low androgen levels are more "feminine" in nature and proliferate more robustly and produce higher levels of Th1 cytokines. We have also discovered that androgens dampen T helper 1 responses through the upregulation of a protective nuclear receptor called peroxisome proliferator-activated receptor (PPAR) alpha in T cells.

In addition to male sex hormones, we have identified that female pubertal factors independently regulate autoimmune risk. Post-pubertal female mice are more susceptible to EAE development than age-matched pre-pubertal controls. This increased EAE susceptibility in post-pubertal females relates to an enhanced ability of antigen presenting cells to prime myelin-reactive T cells. These findings thus shed light on epidemiological evidence that an earlier age of puberty is a risk factor for MS in women, but not men. This talk will provide "our take" on the major factors that are play in the sex-specific regulation of MS risk.

Funding: CIHR and MS Society of Canada

The Y Chromosome as a Regulatory Element Shaping Immune Cell Transcriptomes and Susceptibility to Autoimmune Disease

Cory Teuscher PhD (Departments of Medicine and Pathology, College of Medicine, University of Vermont)

Understanding the DNA elements that constitute and control the regulatory genome is critical for the appropriate therapeutic management of complex diseases. Here, using chromosome Y (ChrY) consomic mouse strains on the C57BL/6J background, we show that susceptibility to two diverse animal models of autoimmune disease, including experimental allergic encephalomyelitis (EAE) and experimental myocarditis, correlates with the natural variation in copy number of Sly and Rbmy1a1 multicopy ChrY genes. In the B6 background, ChrY possesses gene regulatory properties that impact both genome-wide gene expression and the presence of alternative splice variants in pathogenic CD4+ T cells. Using an SJL/J ChrY consomic strain, we discovered an autosome-by-ChrY preference in gene regulation specific to macrophages, the immune cell subset underlying the EAE sexual dimorphism in SJL mice. Importantly, in both genetic backgrounds, an inverse correlation exists between the number of Sly and Rbmy1a1 ChrY gene copies and the number of significantly upregulated genes in immune cells, thereby supporting the copy number variation of Sly and Rbmy1a1 as the ChrY genetic element exerting regulatory properties. Moreover, in humans, an analysis of the CD4+ T cell transcriptome from male multiple sclerosis patients versus healthy controls provides further evidence for an evolutionarily conserved mechanism of gene regulation by ChrY. Thus, these data establish ChrY as a member of the regulatory genome in mammals due to its ability to regulate gene expression and alternative splicing in immune cells linked to disease.

Neuromodulators of Multiple Sclerosis and Psychiatric Illness: The Roles of Sex, Stress, and Hormones

Deborah Walder PhD (Department of Psychology, City University of New York – Brooklyn College).

Multiple Sclerosis (MS; an autoimmune, demyelinating disease) and schizophrenia (a psychiatric disorder) are chronic, debilitating illnesses marked by sex differences with respect to prevalence/incidence and/or symptomatology, which is likely accounted for (in part) by a role of sex hormones. Moreover, there are complex interactions among a range of genetic (e.g., neureglin-1), environmental and neurohormonal susceptibility factors that mutually underlie these illnesses. Interestingly, immunological hypotheses have gained increasing attention in contemporary conceptualizations of schizophrenia, in light of rising prevalence of autoimmune diseases and infections in parents of offspring with schizophrenia. In turn, high prevalence of comorbid psychiatric symptoms (psychosis, depression, mania, anxiety) is well documented in MS. Though speculative, considered together with evidence of shared neuroanatomic features (white matter abnormalities) and the demonstrated role of cytokines in myelination, the aforementioned findings bolster the possibility of (at least some) shared neural mechanisms underlying pathogenesis of schizophrenia and multiple sclerosis. Implications for understanding these illnesses from a neurodevelopmental perspective, with consideration of the modulatory role of sex related factors, will be discussed.

Symposium X:

Influence of Sex/Sex Hormones on the Gut's Role as Guardian of Health

April 27, 2013: 10:30 – 12:30

Chair: Lisa Kilpatrick (Gail and Gerald Oppenheimer Family center for Neurobiology of Stress, University of California – Los Angeles)

Gut Injury and Multiple Organ Dysfunction Syndrome: Modulation by Sex and Sex Hormones

Edwin Deitch MD (Department of Surgery, UMDNJ – New Jersey Medical School)

Today the multiple organ failure syndrome (MODS) is one of the leading causes of ICU deaths and is particular important in younger individuals who have experienced major trauma or have severe sepsis. Yet, due to an incomplete knowledge of the basic biology that initiates or potentiates its development, the mortality rate of these patients remains high and the treatment options remain largely supportive. Thus, basic studies into the biology of MODS is an area of active interest and one of the major hypotheses being experimentally-studied to explain the early development of sepsis and MODS is the gut hypothesis MODS. Our studies in this area have indicated that gut-derived MODS is due to the stressed gut liberating pro-inflammatory and tissue injurious factors into the intestinal lymph which induce a MODS like condition when they reach the systemic circulation. We have termed this phenomenon the 'gut-lymph hypothesis of MODS'. One of the unique aspects of this research has been the observation that the susceptibility to trauma-hemorrhagic shock-induced sepsis and MODS is reduced by female sex hormones and hormonally-intact female animals are largely resistant to trauma-shock-induced MODS. This resistance appears to be at many levels and through several different pathways. While much remains to be learned, these preclinical studies are supported by the majority of studies investigating the role of gender in ICU patients after major trauma or with severe sepsis, where survival is improved in females as opposed to males.

Sex Differences in Gut Microbiome and Risk for Rheumatoid Arthritis

Veena Taneja PhD (Department of Immunology and Rheumatology, Mayo Clinic)

Rheumatoid arthritis (RA) is an autoimmune disease that leads to destruction of joints. Predisposition to RA is associated with the presence of HLA-DRB1*0401 while *0402 provides resistance. An infectious etiology of RA is supported by the presence of certain gut bacterial DNA in synovial fluids of patients. To understand the role of gut bacteria in susceptibility to arthritis, we generated HLA transgenic mice carrying DRB1*0401 and *0402 genes but lacking endogenous class II genes. DRB1*0401 mice develop arthritis that mimics human RA in the presence of autoantibodies and sex-bias. DRB1*0402 mice are resistant to arthritis. We tested if an arthritis-susceptible genotype may be associated with the presence or absence of specific gut bacteria by sequencing the microbiome community structure of HLA transgenic mice. Our data showed dynamic age and sex driven gut microbiome in *0402 mice while *0401 mice lost age and sex differences in their gut microbiome. Dysbiosis in gut microbiome of *0401 mice is associated with an altered age and sex dependent gut permeability with a higher Th17 expression in the guts of *0401 mice compared to *0402 mice. These findings imply that interaction between HLA genes and gut microbiome may influence systemic immune environment in sex-biased manner. We are determining if RA patients show sex-bias in the presence of specific gut bacteria that can be used as biomarker(s). Despite the known sex-bias of RA, current therapeutic guidelines make no distinction based on patient's sex. Modulation of the gut microbiota is an attractive approach to treat autoimmune diseases.

Human Gut Microbiome and Nutrition

Meredith Hullar PhD (J Lampe Studies and Public Health Sciences, Hutchinson Cancer Research Center)

The gut microbial community is tightly associated with host metabolism and provides a mechanistic link to exposures that influence human health. Diet composition is one of the primary determinants of the bacterial community in the human gastrointestinal tract. There is significant interaction between diet and the gut microbiome wherein the composition of the bacterial community can influence the production of specific metabolites from dietary components, and, conversely, the prevailing dietary pattern can encourage dominance of specific bacterial communities. The recent characterization of bacterial enterotypes, based on molecular analyses of the GMC, suggests that networks of microbial species have redundant metabolic pathways which provide about 10% of the host nutrition by the metabolism of diet. In addition, microbial metabolism of dietary constituents provides a myriad of molecules which interact with host pathways during normal homeostasis and/or inflammatory processes. Mechanisms by which the gut microbiome influences human metabolism and subsequent disease risk include: regulation of energy uptake from diet, interaction with signaling molecules involved in host metabolism, modification of gut permeability, and sub-chronic inflammation, a hallmark of obesity-related diseases. These pathways give insight into the multiple ways through which the gut microbiome may influence health and disease risk.

Symposium XI:

April 27, 2013: 2:30 – 4:30

Centers for Sex Difference Research

Chair: Janine Clayton MD (National Institutes of Health: Office of Research on Women's Health)

Sex Hormone Regulation of Bioenergetics

Wendy Kohrt PhD (Division of Geriatric Medicine, University of Colorado School of Medicine)

The newly established Specialized Center of Research (SCOR) on Sex Differences at the University of Colorado School of Medicine is focused on Bioenergetic and Metabolic Consequences of the Loss of Gonadal Function. The lecture will cover the following topics: 1) Existing evidence from preclinical research will be presented to demonstrate that sex hormones influence bioenergetics through the regulation of spontaneous physical activity and metabolic rate. Sex differences in the phenotypic response to the loss of gonadal function will be discussed; 2) Preliminary evidence that sex hormones have similar effects on bioenergetics in humans will be presented; and 3) The approach for investigating the gonadal regulation of bioenergetics in women under the new SCOR will be presented.

Chronic Pain and the Brain – Do Sex Differences Matter?

Emeran A. Mayer, MD (Oppenheimer Family Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA)

The majority of chronic pain conditions, including irritable bowel syndrome, chronic pelvic pain and fibromyalgia are more prevalent in women. Even though differences in health care seeking behavior contribute to this increased

prevalence, population based samples, and results from experimental pain testing support the concept of biological differences in pain perception and modulation. A series of neuroimaging studies performed by our center as part of the SCOR program, have identified both structural and functional sex related differences in patients with irritable bowel syndrome. These differences include greater female responsiveness of emotional arousal circuits during aversive visceral distension, and the expectation of such distension, differences in the dominant frequency of regional intrinsic oscillations of the brain, differences in white matter integrity, and differences in grey matter volume and cortical thickness. When viewed together, these findings suggest that the subjective pain experience may be generated by sex specific brain mechanisms, and that the effectiveness of therapies targeted at these mechanisms may differ between male and female patients.

Sex Differences in Cerebrovascular Function: Are Women Protected?

Jill N. Barnes PhD (Department of Anesthesiology, Department of Physiology and Biomedical Engineering, Mayo Clinic)

Brain blood flow and microvascular responses decrease with aging, and recent data suggests sex differences in cerebrovascular regulation exist. Young women reportedly have higher cerebrovascular function compared with young men; and older women have superior autoregulatory capacity compared with age-matched men. In addition, we have previously shown that age-related differences in cerebrovascular function (or cerebrovascular reactivity) are abolished by cyclooxygenase inhibition, suggesting that these age-associated changes are mediated by prostaglandins. Yet, it is unknown how sex and age interact in response to the stress of cyclooxygenase inhibition. We further examined cerebrovascular function in young men (YM), young women (YW), older men (OM), and older women (OW) before (CON) and during cyclooxygenase (COX) inhibition via indomethacin. There was no age by sex interaction in cerebrovascular function. However, when accounting for the changes in mean arterial pressure during hypercapnia, there was an age by sex interaction in cerebrovascular conductance index (CVCi). During COX inhibition, there was also an age by sex interaction for the ΔCVCi Slope with YM having a greater slope compared with both YW (0.72 ± 0.15 vs. 0.27 ± 0.13 AU; $p<0.01$) and OM (0.26 ± 0.18 AU; $p<0.01$). Our results suggest that sex differences exist in the cerebrovascular response to hypercapnia with and without COX inhibition and that the effect of age is different in women compared to men. Therefore, it is possible that women have a greater risk for cerebrovascular dysfunction. This talk will further discuss these issues and future research questions.

Sex Differences, Metabolomes, and Urinary Tract Infections

Jeffrey Henderson MD PhD (Center for Women's Infectious Disease Research (cWIDR), Washington University)

Urinary tract infections (UTI) are among the most common human bacterial infectious diseases and exhibit well-known sex differences, with a dramatically higher prevalence among adult females than adult males. From adolescence to adulthood, approximately half of U.S. females will have experienced at least one UTI episode; in contrast, male UTI incidence increases in late adulthood. This SCOR uses interdisciplinary approaches to explore UTI pathophysiology across the lifespan and between sexes. The basis for sex differences in UTI susceptibility has classically been attributed to anatomic factors such as urethral length and presence of a colonized vaginal mucosa. However recent advances in metabolomic analyses are now identifying sex-associated biochemical differences that may also contribute to female UTI susceptibility. Combined with microbiological studies, a picture is emerging of key chemical interactions between humans and bacteria with the potential to define new therapeutic and prophylactic strategies for millions of patients each year.

CAPSTONE LECTURE

April 27, 2013: 4:30 – 5:30

Gender and Genetics of Sexual Development

Eric Vilain MD PhD (Departments of Pediatrics, Urology, and Human Genetics, University of California – Los Angeles David Geffen School of Medicine)

Human sexual orientation, one's preference for male or female sexual partners, is the largest sex difference in behavior. It is a largely stable behavioral trait with a strong genetic component. As such it is an interesting model for brain sexual differentiation. Yet its biological mechanisms are poorly understood, and to date traditional linkage studies have not yielded any candidate genes. Furthermore, large scale whole genome linkage studies have failed to identify genes for sexual preference in humans.

We will discuss several scientific approaches to decipher the biological bases of this behavior. We will focus the discussion on the interaction between genes and environment. For instance, we will discuss how twin studies could be used to identify novel genes related to complex human behavior, and how epigenetic variations could influence sex differences in sexual behavior.