PROGRAM

Sixth Annual Meeting of the
Organization for the Study of
Sex Differences

A JOINT MEETING WITH THE

International Society for
Gender Medicine

June 7 – 9, 2012
Sheraton Inner Harbor Hotel
Baltimore, Maryland
USA

CONTENTS

IGM OSSD SWHR

AGENDA

THURSDAY, JUNE 7

8:00 am — **Breakfast Provided** for Workshop Attendees

8:30 – 12:00 pm — **Workshop: Building Sex/Gender-based Competencies into Medical and Graduate Curricula** – CHESAPEAKE III
Chairs: Karin Schenck-Gustafsson, M.D. and Jill Becker, Ph.D.
Speakers:
Jill Becker, Ph.D.– Introduction: key questions and challenges
Karin Schenck-Gustafsson, M.D. and **Ineke Klinge, Ph.D.** – European competencies in sex/gender medicine
Gillian Einstein, Ph.D., Susan Phillips, Ph.D., and **Zena Sharman, Ph.D.** – Canadian strategies for sex/gender approaches in graduate and medical education
Marjorie Jenkins, M.D. and **Joanna Wilson, D.O.**– US approaches to medical curriculum development and methods to track sex and gender competencies within existing curriculum

12:00 – 2:30 pm — **Meeting Registration** – CHESAPEAKE GALLERY

12:00 – 1:00 pm — **Lunch on your own**

1:00 – 1:30 pm — **Opening Ceremony** – CHESAPEAKE I & II
Remarks:
Virginia M. Miller, Ph.D., OSSD President
Marek Glezerman, M.D., IGM President
Margaret McCarthy, Ph.D., OSSD Program Committee Co-Chair
Phyllis Greenberger, M.S.W., SWHR President

1:30 – 3:15 pm — **Presidential Symposium: Sex Differences in Fetal Programming** – CHESAPEAKE I & II
Chairs: Marek Glezerman, M.D. and Virginia M. Miller, Ph.D.
Speakers:
Melissa Hines, Ph.D. – Prenatal testosterone and human neurobehavioral development: outcomes and mechanisms
Tracy Bale, Ph.D. – Prenatal programming of stress dysregulation: epigenetic and placental contributions
Marek Glezerman, M.D. – Fetal programming beyond health and disease

3:15 – 3:30 pm — **Break,** coffee and tea provided

3:30 – 4:30 pm — **Keynote** – CHESAPEAKE I & II
Marianne Legato, M.D. – Gender-Specific Medicine after the Age of Darwin: Achievements and Challenges in 21st Century Science

4:30 – 6:30 pm — **Young Investigator Symposium**

6:30 – 8:30 pm — **Opening Reception** – HARBORVIEW BALLROOM

FRIDAY, JUNE 8

8:00 – 8:30 am **Breakfast provided** – CHESAPEAKE GALLERY

8:30 – 10:30 am **Simultaneous Sessions Begin**

Symposium I – CHESAPEAKE I
Sex Differences and Their Impact on Osteoarthritis
Co-Chairs: Barbara Boyan, Ph.D. and Roger M. Enoka, Ph.D.
Speakers:
Mary O'Connor, M.D. – The knee as an organ: sex differences in incidence and severity of OA
David Hart, Ph.D. – Hormonal modulation contributes to sex differences in OA
Kathleen Sluka, Ph.D. – Central nervous system modulates knee OA pain
Lorena Havill, Ph.D. – Sex differences in naturally occurring knee osteoarthritis in baboons.
— or —
Symposium II – CHESAPEAKE II
Global Assessment of Severe Coronary Artery Disease
Co-Chairs: Pam Ouyang, M.D. and Maria Grazia Modena, M.D.
Speakers:
Pam Ouyang, M.D. – Age and development of ischemic coronary artery disease: does sex matter?
Maria Grazia Modena, M.D. – Coronary artery disease in women: how common "atypical" symptoms reveal different pathophysiological substrates
Karin Schenck-Gustafsson, M.D. – Sex differences in CHD diagnostics
Alexandra Kautzky-Willer, M.D. – Sex differences in cardiometabolic diseases

10:30 – 11:00 am **Break**, coffee and tea provided
Poster Session I Setup and Exhibits Open

11:00 – 1:00 pm **Simultaneous Sessions**

Symposium III – CHESAPEAKE I
Sex Disparities in Cancer
Chair: Michael Cook, Ph.D.
Speakers:
Michael Cook, Ph.D. – Sex disparities in cancer incidence, mortality and survival
Michael Karin, Ph.D. – Inflammation, metabolism, aging and cancer: dangerous liaisons
Svetomir Markovic, Ph.D., M.D. – Sex hormones and immune regulation: implications for cancer therapy
James Fox, D.V.M. – Role of estrogen in *Helicobacter pylori* associated gastric cancer
— or —
Symposium IV – CHESAPEAKE II
Sex Differences in Stem Cells
Chair: Margaret McCarthy, Ph.D.
Speakers:
Johnny Huard, Ph.D. – Effect of donor & host sex in tissue regeneration with muscle derived stem cells
Margaret McCarthy, Ph.D. – Sex differences in neural and glial genesis in the brain
Jaclyn Schwarz, Ph.D. – Sex differences in microglial colonization of the developing brain: implications for health and disease.
Anne Comi, M.D. – Modulation of post-stroke neural and glial progenitor responses is sex-dependent

1:00 – 2:30 pm **Poster Session I** – CHESAPEAKE III

1:00 – 2:00 pm **IGM Assembly** – CHESAPEAKE I

Lunch on your own and free afternoon

SATURDAY, JUNE 9

8:00 – 8:30 am **Breakfast provided** – CHESAPEAKE GALLERY

8:30 – 10:30 am **Simultaneous Sessions Begin**

Symposium V – CHESAPEAKE I
Sex Differences in Mechanistic Pathways of Cardiovascular Disease
Chair: Vera Regitz-Zagrozek, M.D.
Speakers:
Clinton Webb, Ph.D. – Mechanisms of sex difference in vascular function
Noel Bairey-Merz, M.D. – The Yentl Syndrome 2011: Why are there differences in ischemic heart disease in women and men (including genes)?
Vera Regitz-Zagrozek, M.D. – Sex differences in genomics of left ventricular remodeling
Istvan Merchanthaler, Ph.D. –A novel 17-beta-estradiol prodrug for the treatment of menopausal symptoms: hot flushes, depression and sleep disorders in animal models

— or—

Symposium VI – CHESAPEAKE II
Depression and Anxiety Disorders: Novel Targets for Sex Specific Treatments
Co-Chairs: Gretchen N. Neigh, Ph.D. and Kevin D. Beck, Ph.D.
Speakers:
Georgia Hodes, Ph.D. – Epigenetic regulation of sex differences in stress related disorders
Debbie Bangasser, Ph.D. – Sex differences in the stress-response systems: from molecules to mental illness
Kerry Ressler, Ph.D. – Differential sex-specific effects of the PACAP (ADCYAP1R1) and Androgen (SRD5A2) pathways with PTSD in a highly traumatized population
Dov Feldberg, M.D. – Unique characteristics of anxiety and depression among couples undergoing in vitro fertilization treatment

10:30 – 11:00 am **Break,** coffee and tea provided
Poster Session II setup

11:00 – 1:00 pm **Simultaneous Sessions**

Symposium VII – CHESAPEAKE I
Animal Models for Sex Differences Research
Co-Chairs: Margaret McCarthy, Ph.D. and Art Arnold, Ph.D.
Speakers:
Douglas Portman, Ph.D. – Sex differences in the nervous system: Insights from genetic model systems
Susan Fahrbach, Ph.D. – Sex differences in insects: beyond *fru* and haplodiploidy
Daniel Gorelick, Ph.D. – Fishing for sex differences
Gregory F. Ball, Ph.D. – Neural sex differences and similarities in the control of vocal behavior in songbirds

— or—

Symposium VIII – CHESAPEAKE II
Post-traumatic Stress Disorder (PTSD) and One's Sex
Chair: Kathryn Sandberg, Ph.D.
Speakers:
Amy Street, Ph.D. – Experiences of sexual trauma during military service: implications for the gender-specific risk of PTSD
Dawne Vogt, Ph.D. – Gender differences in combat-related stressors and their association with postdeployment mental health among U.S. OEF/OIF veterans
Thomas A. Mellman, M.D. – Sex differences in sleep-related predictors of PTSD
Ann Rasmusson, M.D. – Sex differences in neurobiology with potential relevance to PTSD risk, symptom severity, and chronicity

1:00 – 2:00 pm **Lunch on your own**

— or—

1:30 – 2:30 pm **NIH Workshop** – CHESAPEAKE I
Feel free to bring your lunch to the workshop

1:30 – 3:00 pm **Poster Session II** – CHESAPEAKE III

3:00 – 5:00 pm **Symposium IX** – CHESAPEAKE II
Sex Differences in Global Health
Co-Chairs: Sabra Klein, Ph.D. and Anna Thorson, Ph.D., M.D., M.P.H.
Speakers:
Anna Thorson, Ph.D., M.D., M.P.H. – Sex and gender aspects of tuberculosis: a review
William J. Moss, M.D., M.P.H. – Sex differences in response to measles and measles vaccine
Oralee Branch, Ph.D. – Males, females and children's inflammatory responses during and after malaria infection: sex and sex hormones associated with chronic inflammation
Elizabeth Connick, M.D. – Sex differences in HIV-1 immunopathogenesis

5:00 - 6:00 pm **Capstone** – CHESAPEAKE II
Chris Gregg, Ph.D. – Maternal and paternal gene networks in the male and female brain

6:00 - 7:00 **General OSSD Membership Meeting** – CHESAPEAKE II

7:30 pm **Awards Banquet** (Ticket purchase required) – HARBORVIEW BALLROOM

WELCOME

FROM THE PRESIDENT OF THE ORGANIZATION FOR THE STUDY OF SEX DIFFERENCES

Welcome to the sixth annual meeting of the Organization for the Study of Sex Differences (OSSD) and the first milestone collaboration of theInternational Society for Gender Medicine (IGM)! This joint effort highlights how research into the study of sex differences and gender medicine has permeated all aspects of science and medicine on an international scale. Under the leadership of Margaret McCarthy, PhD of the University of Maryland School of Medicine, Sabra Klein, PhD of Johns Hopkins University and Council of the IGM, this year's program includes an outstanding group of basic and clinical researchers from around the world. My thanks to the Society of Women's Health Research who founded OSSD and continues to provide financial and administrative support for this meeting.

The Official journal for OSSD is the Biology of Sex Differences (BSD) which is published by Biomed Central as an open access, peer-reviewed online journal. Content encompasses all aspects of effects of sex and gender on biology and disease. Thanks to the outstanding dedication of the editor-in-chief, Art Arnold, PhD, and an internationally acclaimed editorial board, the journal is off to a great start with over 2000 accessions/month for abstracts and articles. I encourage all of you to submit your best work to BSD for rapid dissemination of the latest findings in the biology of sex differences to the world.

These are exciting times for the study of sex differences and gender medicine. I am delighted to share them with you. This past year has presented many challenges for OSSD. However, I am optimistic about the Organization's future under the new leadership of our incoming President, Geert de Vries, PhD. I offer him and our members my continued support of the Organizations programs and efforts.

It has been my honor and privilege to serve as your President for these past two years and my heartfelt thanks to the OSSD Council and members for their support and help. OSSD continues to lead the discipline of the study of sex differences. I encourage you to renew your memberships to OSSD and to encourage your colleagues to join so we can continue to be a vital force in directing the future of discovery.

Virginia M. Miller, PhD
President, Organization for the Study of Sex Differences
Professor, Surgery and Physiology
Mayo Clinic

FROM THE EXECUTIVE DIRECTOR

Welcome to all of you and thank you for coming to the Sixth Annual OSSD meeting held in conjunction with the IGM. The Society for Women's Health Research is proud of forming the OSSD almost seven years ago with the help from many of you who have served in a leadership role with the organization. We are especially excited this year that our international colleagues have joined us and we welcome all of them and their students. We all share a common interest: the study of sex and gender differences is crucial in understanding a variety of biological pathways and clinical conditions. We hope you will all enjoy the scientific sessions as well as the beautiful city of Baltimore. Thank you again for attending this important conference.

Christine Carter, Ph.D., M.P.H.
Executive Director, Organization for the Study of Sex Differences
Vice President, Scientific Affairs, Society for Women's Health Research

WELCOME

FROM THE PRESIDENT OF THE INSTITUTE FOR GENDER MEDICINE

It is with great pleasure that I welcome you to the first joint congress on Gender and Sex-Specific Medicine organized by the Organization for the Study of Sex Differences (OSSD) and the International Society for Gender Medicine (IGM). This new collaboration was long overdue. We all need to join forces so that our young discipline continues to develop and to change paradigms. Gender-specific medicine is a new way of looking at the physiologic and pathophysiological differences between men and women and great efforts need to be invested in research and education in order to re-write many chapters in modern medicine. The IGM was founded less than a decade ago as an umbrella organization for national and professional societies dedicated to the study of gender and sex specific differences. Our member societies and organizations are in Austria, Germany, Italy, Israel, and Sweden and in the U.S. Together with individual members from countries without professional societies we have now close to 450 members and we are growing steadily. IGM member societies are sponsoring diversified educational programs and have organized five international congresses and many national workshops and scientific meetings.

During the 5th International Congress on Gender Medicine, which was held in December, 2010 in Tel Aviv, Prof. Virginia Miller, the president of OSSD, and myself agreed that we should have joint meetings of our societies which should take place in alternative years in North America and in countries with member societies of IGM. The respective boards of both societies immediately endorsed this proposal and in June 2012 we will have our first historical joint meeting in Baltimore.

The OSSD and the Society for Women's Health Research (SWHR) have done a great job in taking the lead to put together a program of the highest scientific standard and we at the IGM are proud to be part of it.

I am looking forward with great anticipation to a fruitful, inspiring and scientifically and socially rewarding event.

Marek Glezerman, M.D.
President, The International Society for Gender Medicine (www.isogem.com)
The Emma Najman Professor of Obstetrics and Gynecology, Tel Aviv University
President, The Israel Society for Gender Medicine (www.isragem.org.il)
Director, Research Center for Gender Medicine, Rabin Medical Center, Israel

NEW INVESTIGATOR AWARDS

OSSD 2012 NEW INVESTIGATOR TRAVEL AWARDEES

Michael Coronado

Nafissa Ismail

Deena Kahn

Bharti Manwani

Matia Solomon

OSSD 2012 ELIZABETH YOUNG NEW INVESTIGATOR SYMPOSIUM SPEAKERS

Charlotte Iacobaeus

Georgios Kararigas

Matia Solomon

Kathryn Lenz

Dionne Robinson

Matthew Paul

IGM 2012 NEW INVESTIGATOR AWARDEES

Lena Kosi

Marco Zavatta

SPEAKER BIOGRAPHIES

C. Noel Bairey Merz, M.D., holds the Women's Guild Endowed Chair in Women's Health, and is Director of the Women's Heart Center as well as the Preventive and Rehabilitative Cardiac Center at Cedars-Sinai Medical Center. She also is Professor of Medicine at Cedars-Sinai. Dr. Bairey Merz received her bachelor's degree from the University of Chicago and her medical degree from Harvard University. She completed her residency at the University of California, San Francisco, where she served as Chief Medical Resident. Dr. Bairey Merz also completed fellowships in clinical cardiology and nuclear cardiology at Cedars-Sinai Medical Center. Dr. Bairey Merz's research interests include women and heart disease, mental stress and heart disease, the role of exercise and stress management in reversing disease, and the role of nutrition in heart disease. Currently, she is chair of the National Institutes of Health (NIH)-sponsored WISE (Women's Ischemic Syndrome Evaluation) initiative, which is investigating potential methods for more effective diagnosis and evaluation of coronary artery disease in women. Dr. Bairey Merz has received investigational grants from the NIH-National Heart, Lung and Blood Institute (NHLBI), NIH-National Center for Alternative and Complementary Medicine (NCCAM), the Pfeiffer Foundation, The Eli and Edythe Broad Foundation, The Barbra Streisand Foundation, and the Women's Guild.

Tracy Bale, Ph.D., holds a dual appointment at Penn and is an Associate Professor of Neuroscience in the Department of Animal Biology at Penn Vet as well as Associate Professor of Neuroscience in the Department of Psychiatry at Penn's School of Medicine. Dr. Bale earned her Ph.D. in pharmacology and neurobiology from the University of Washington, and completed her postdoctoral training with Dr. Wylie W. Vale at the Salk Institute in La Jolla, CA. Her research interests are centered on the role of stress dysregulation in disease, and the sex differences that underlie disease vulnerability. Her lab has developed mouse models relevant to neuropsychiatric diseases and obesity, and studies the interaction of genes and the environment, assessing epigenetic mechanisms involved in sex-specific programming of stress pathways in the brain.

Gregory F. Ball, Ph.D., Vice Dean for Science and Research Infrastructure, is a Professor of Psychological and Brain Sciences in the School of Arts and Sciences at Johns Hopkins University. As Vice Dean Ball serves as liaison with the chairs of the school's natural science departments. Ball has been faculty member at Hopkins since 1991. He heads the program committee of the undergraduate neuroscience program. Ball holds joint appointments in the Department of Biochemistry and Molecular Biology, Division of Reproductive Biology, at the Bloomberg School of Public Health, and in the Department of Neuroscience at the School of Medicine. He has amassed more than 200 research publications. His work concerns interrelationships among steroid hormones, the brain, and reproductive behavior. Ball earned a BA in psychology from Columbia University and a PhD in psychobiology from the Institute of Animal Behavior at Rutgers University. He did his postdoctoral work at Rockefeller University.

Debra A. Bangasser, Ph.D., received her B.A. in Psychology from San Diego State University and her Ph.D. in Biopyschology and Behavioral Neuroscience from Rutgers University. Dr. Bangasser is a postdoctoral fellow at the Children's Hospital of Philadelphia and will join Temple University in the fall of 2012 as an Assistant Professor of Psychology and member of the Neuroscience Program. She is the recipient of a number of awards including the Julius Axelrod Travel Award and Young Investigator Awards from the American College of Neuropsychopharmacology, Workshop on Steroid Hormones and Brain Function, and Gordon Research Conference on Catecholamines. Her research focuses on neurobiological mechanisms that mediate vulnerability to stress and stress-related mental illnesses, particularly in females.

Jill B. Becker, Ph.D., received her B. A. and M.A. in Human Development from the University of Kansas, and her Ph.D. in Neuroscience from the University of Illinois. She did Post-Doctoral Research at the University of Michigan before joining the faculty in the Department of Psychology. She is now the Patricia Y. Gurin Collegiate Professor in Psy-

chology and Research Professor in the Molecular and Behavioral Neuroscience Institute at the University of Michigan. Dr. Becker is the recipient of numerous awards including the Louise Hanson Marshall award from the Society of Neuroscience in 2010 and the Sarah Goddard Power Award from the University of Michigan in 2011. Dr. Becker is currently Past-President of the OSSD. Dr. Becker's research focuses on the neural bases for sex differences in motivation and specifically on the role of estradiol in sex differences in drug abuse and female sexual motivation.

OraLee Branch, Ph.D., received her Ph.D. in population biology of infectious disease at Emory University. She did postdoctoral research at NIH, National Center for Biotechnology Information, focusing on epidemiology and computational biology. Now, she is an assistant professor at New York University School of Medicine, and leads the Malaria Immunology and Genetics Amazon project. She developed and continues a longitudinal cohort study in Peru with 8 years of NIH and other grant funding. She studies the development of immunity to malaria, population biology of malaria parasites and host-parasite selection. She has a study on inflammatory infections throughout pregnancy and the impact of inflammation during pregnancy on the delivered infant's birth outcome, and the infant's microbiome, nutrition and growth over the next 24 years of life. Her results suggest that males and females have different responses to and after infection which impacts infection and possibly is associated with longer-term sex-specific outcomes.

Anne M. Comi, M.D., received her B.A. in Biology from the College of the Holy Cross and her M.D. from the State University of New York at Buffalo. She received her pediatric residency training at the Children's Hospital of Buffalo and Pediatric Neurology residency training at Johns Hopkins Hospital. She did postdoctoral research training at Johns Hopkins University and is currently an Associate Professor in the Departments of Neurology and Pediatrics at the Johns Hopkins School of Medicine. Her clinical expertise is in Sturge-Weber syndrome and ischemic injury and seizures in the immature brain. Her laboratory research focuses on post stroke neurogenesis and regeneration; current experiments are determining the differential neurogenic and glial responses to cord blood stem cells in a mouse model of stroke in the immature brain.

Elizabeth Connick, M.D., is a physician-scientist whose research focuses on HIV immunopathogenesis. She graduated from Harvard Medical School in 1988, and performed a medicine residency at Columbia Presbyterian Medical Center and an infectious disease fellowship at University of Colorado. She is currently a Professor of Medicine in the Division of Infectious Diseases at the University of Colorado Denver. She has been involved in clinical trials as well as laboratory-based translational research studies of HIV-1 infection for the past 18 years including studies of immune reconstitution and acute HIV infection. More recently, she has developed an interest in understanding sex differences in HIV pathogenesis. She has served on the Office of AIDS Research advisory committee to identify priorities for the Women and Girls component of the Trans-NIH Plan for HIV-Related Research since 2008 and the Antiviral Drug Advisory Committee for the FDA since 2011.

Michael Blaise Cook, Ph.D., earned his B.Sc. in Genetics at the University of Nottingham, England, and, subsequently, a Ph.D. in Epidemiology at the University of Leeds, England. The focus of his doctoral thesis was sex differences in Barrett's esophagus and esophageal adenocarcinoma, themes still relevant to his current research portfolio in the Hormonal and Reproductive Epidemiology Branch (HREB). Dr. Cook joined the HREB as a Visiting Postdoctoral Fellow in 2007 before becoming a Research Fellow in 2008 and then an Investigator in 2011. He was awarded the Division of Cancer Epidemiology and Genetics (DCEG) Fellowship Achievement Award for research excellence in 2008, the Director's Intramural Innovation Award in 2008, and the DCEG Molecular Epidemiology Course Award for novel research proposals. He is a member of the Barrett's and Esophageal Adenocarcinoma Consortium (BEACON) and a Steering Group Committee member of the Asian Barrett's esophagus Consortium (ABC). Dr. Cook is a strong proponent of high-quality mentorship and he recently completed the NCI Executive Coaching program. Dr. Cook is interested in the epidemiology of esophageal adenocarcinoma and the precursor metaplasia, Barrett's esophagus. In addition, he is interested in the etiology of genitourinary neoplasms (testicular and prostate) and sex differences in cancer pathogenesis.

Gillian Einstein, Ph.D., received her BA in Art History from Harvard University and her PhD in Neuroanatomy from the University of Pennsylvania. After doing research in vision as well as Alzheimer disease at Duke University, and science administration at the National Institutes of Health, she immigrated to Canada where she is currently an Associate Professor of Psychology at the University of Toronto. Her research is on the effects of estrogens and culture on women's biologies. She has edited and annotated a book for MIT Press on foundational papers in Hor-

mones and Behaviour called "Sex and the Brain." She is also the founder and current director of the Collaborative Graduate Program in Women's Health and a founding member of the OSSD. Currently a councilor and the chair of the education committee, she is also an advisory board member of the Institute of Gender and Health of the Canadian Institutes of Health Research.

Susan E. Fahrbach, Ph.D., received her B.A. in Psychology from the University of Pennsylvania, an M.A. in PPP (Psychology, Philosophy, and Physiology) from the University of Oxford, and her Ph.D. in Neurobiology from the Rockefeller University. Dr. Fahrbach did postdoctoral training at the University of Washington and is Reynolds Professor of Developmental Neuroscience in the Department of Biology at Wake Forest University. She is author of numerous articles and reviews, and currently serves on the editorial boards of the journals *Hormones and Behavior, Journal of Comparative Neurology, Arthropod Structure and Function,* and *Apidologie.* Her research focuses on structure-function relationships in the brains of social insects, with an emphasis on the role of nuclear receptors in regulation of adult brain structure by experience and ecdysteroids.

Professor Dov Feldberg, M.D., graduated from the Medical School of Hadassah-Jerusalem University in 1971. He did his fellowship in reproductive medicine in 1984-1985 at the Yale New Haven Hospital with Professor Alan DeCherney and Professor Fred Naftolin. In 1985, he established the fourth IVF Unit in Israel, at the Rabin Medical Center, heading it until 1996. He did his sabbatical in Reproductive Medicine in 1990-1991 at the Center for Reproductive Medicine, Cornell University Hospital, New York, with Professor Zev Rosenwaks. In 1993, he received a Professor degree at the division of OB/GYN Medical School at Tel-Aviv University. In 1994 he was appointed Vice Chairman of OB/GYN Division, Rabin Medical Center. In 2001, Dr. Feldberg was appointed Acting Chairman OB/GYN Division, Rabin Medical Center. He has served as the Executive Vice President of the World Association of Reproductive Medicine (WARM) since 2008. In addition to more than 120 publications in the field of reproductive medicine, Dr. Feldberg has contributed to several chapters in books. He has participated in the organization of many national and international meetings.

James G. Fox, D.V.M., is a Professor and Director of the Division of Comparative Medicine and a Professor in the Department of Biological Engineering at the Massachusetts Institute of Technology. He is also an Adjunct Professor at Tufts University School of Veterinary Medicine and the University of Pennsylvania, School of Veterinary Medicine. Professor Fox is the author of over 530 articles, 80 chapters, 4 patents and has edited and authored 13 texts in the field of *in vivo* model development and comparative medicine. Dr. Fox has received numerous scientific awards, and was elected to the Institute of Medicine of the National Academy of Sciences in 2004. He studies the role of *Helicobacter* sp. induced gastrointestinal cancers. His past and current research has been funded by NIH and NCI, as well as by private industrial sources, for the past 35 years.

Marek Glezerman, M.D., is full professor of obstetrics and gynecology and the Emma Fejman Chair of obstetrics and gynecology at Tel Aviv University. He has chaired the departments of obstetrics and gynecology at three major health care centers in Israel. He has studied medicine in Frankfurt and Paris, has done fellowships and sabbaticals in Munich, Giessen, Chicago, Montreal and at the Weizmann Institute for Science in Israel. He serves on numerous national and international professional and academic committees and editorial boards and is past-president of the Israel Fertility Association. He is president of the International Society for Gender Medicine and founding president of the Israel Society of Gender Medicine and member of two National Councils at the Israel Ministry of and on the FIGO advisory boards for Andrology and Gyne-Oncology. He has written/edited 4 books and published more than 330 chapters in obstetric and gynecologic texts and articles in professional journals.

Daniel A. Gorelick, Ph.D., received his B.A. in music from the University of Pennsylvania and his Ph.D. in cellular and molecular medicine from the Johns Hopkins University School of Medicine. Dr. Gorelick did postdoctoral training in developmental biology and genetics at the Carnegie Institution for Science and was an AAAS Science & Technology Policy Fellow at the U.S. Department of State. His research focuses on differences in estrogen receptor activation in males and females and on how endocrine disrupting compounds influence development.

Maria Grazia Modena, M.D., F.A.C.C., F.E.S.C., is a full Professor of Cardiology at University of Modena Reggio Emilia since 1994. She was president of Italian Society of Echocardiography, President of the Italian Society of Cardiology, Chairman of the Committee of the "Women in Cardiology" European Society of Cardiology and Member of the Steering Committee of XIENCE V SPIRIT WOMEN Study. She received a number of awards, as the "Premio Bellisario" for Medicine, and several research grants. In 1996 she founded the "BenEssere Donna" Center, Women's Clinic, for the study of epidemiology, prevention, diagnosis and treatment of postmenopausal related disorders,

with particular attention to cardiovascular aspects. Her main fields of interest are Cardiovascular Disease in Women and Study of Endothelial Dysfunction. She is well recognized for her researches on the study of the cardiovascular risk factors, especially on the interaction between Diabetes and Hypertension in Postmenopausal Women.

Christopher Gregg, Ph.D., received his BSc. in Biochemistry from the University of Lethbridge and his PhD. in Neuroscience from the University of Calgary. Dr. Gregg did postdoctoral training with Prof. Catherine Dulac at Harvard University and is currently a New York Stem Cell Foundation-Robertson Investigator and Assistant Professor in the Department of Neurobiology & Anatomy at the University of Utah. He is the recipient of several awards, including the Eppendorf & Science Prize in Neurobiology. His work focuses on maternal and paternal effects influencing brain development and function and in the regulation of feeding and motivated behaviors in males and females.

David A. Hart, Ph.D., received his Ph.D. in Biochemistry from Michigan State University, and subsequently post-doctoral research in immunology at the University of Illinois Medical Center. After a number of faculty appointments, he has been most recently a Professor in the McCaig Institute for Bone and Joint Health at the University of Calgary, and the Centre for Hip Health and Mobility at UBC in Vancouver. Dr. Hart's research has focused on sex/gender differences in normal and injured connective tissues, and the healing/repair processes. He has chaired the Institute Advisory Board for the Institute for Gender & Health at the Canadian Institutes for Health Research, and has been a member of the SWHR ISIS Network in MSK. Dr. Hart was elected to the Canadian Academy of Health Sciences in 2008.

Lorena M. Havill, Ph.D., is an Associate Professor in the Department of Genetics at the Texas Biomedical Research Institute. Dr. Havill's research program centers on identification of genetic and other factors that underlie variation in susceptibility to onset and progression of aging-related skeletal diseases (i.e. osteoarthritis and osteoporosis) and changes in bone metabolism. She is particularly interested in sex-based differences in skeletal disease susceptibility. She is the recipient of several Young Investigator Awards from the American Society for Bone and Mineral Research and the Voelcker Fund.

Melissa Hines, Ph.D., received her BA in Psychology from Princeton University and her PhD in Psychology from the University of California, Los Angeles (UCLA). She was a Postdoctoral Fellow in the Laboratory of Neuroendocrinology at UCLA, and a Visiting Scientist at the University of Wisconsin Primate Research Centre, before taking a post as Assistant, then Associate Professor in Psychiatry and Biobehavioral Sciences at UCLA. She is now Professor of Psychology at the University of Cambridge, where she directs the Hormones and Behaviour Research Laboratory. She is past president of the International Academy of Sex Research, and the author of the book *Brain Gender* as well as over 100 other scientific publications. Her research interest is in gender development, and she is currently exploring how inborn predispositions to gender typicality, or atypicality, particularly those caused by testosterone prenatally, act together with postnatal experience to shape gender development.

Georgia E. Hodes, Ph.D., received her B.A. from Bard College and her Ph.D. from Rutgers University in the Behavioral Neuroscience division of the Psychology program. At Rutgers, she trained with Dr. Tracey Shors to examine sex differences in the effects of stress on cognition and hippocampal plasticity across the lifespan. Dr. Hodes began her post-doctoral training with Dr Irwin Lucki at the University of Pennsylvania examining the contribution of neurogenesis and neurotrophin mobilization to strain and sex differences in vulnerability to stress. In 2010, Dr. Hodes joined the laboratory of Dr. Scott Russo as a post-doctoral fellow. Her work in Dr. Russo's laboratory focuses on molecular mechanisms of individual differences in susceptibility and resiliency to stress. Her future interests include examining the molecular substrates directing the functional contribution of hormones and cytokines to the onset, symptoms and generational transmission of depression in both sexes.

Johnny Huard, Ph.D., currently serves as the Director of the Stem Cell Research Center (SCRC). Research at the SCRC includes: 1) Duchene muscular dystrophy (DMD), 2) Critical sized long bone and cranial bone injuries, 3) Acutely injured articular cartilage and articular cartilage damaged by osteoarthritis, 4) Compartment syndrome injured limbs which involve injury to the muscles, nerves, circulatory and lymphatic system vasculature, etc. 5) Infarct injured hearts and cardiomyopathy due to DMD. Dr. Huard's studies have been used clinically for the treatment of urinary incontinence and myocardial infarction. He has authored over 200 peer reviewed articles and 76 review articles, invited papers and book chapters. In 2003, Dr. Huard received the Orthopedic Society's prestigious Kappa Delta Award and the University of Pittsburgh's Chancellor's Distinguished Research Award. Dr. Huard was honored in 2007 with the Prix d'excellence award in recognition of his outstanding scientific achievements, from his alma mater. Dr. Huard's research program is funded by a variety of sources including the National Institutes of Health, the Muscular

Dystrophy Association, the Department of Defense, as well as other private and public foundations. He serves as a standing member of the Skeletal Muscle and Exercise Physiology Study section for the NIH. Dr. Huard currently serves on multiple editorial boards for scientific journals and reviews numerous scientific papers for a wide variety of scientific journals.

Marjorie Jenkins, M.D., transitioned from a private practice to academic medicine in 2001 and is a Professor of Medicine in Texas Tech University Health Sciences Center (TTUHSC) Division of Women's Health and Gender-Specific Medicine. She is the founding executive director and chief scientific officer of the TTUHSC Laura W. Bush Institute for Women's Health and the (former) founding director of the TTUHSC Center for Women's Health and Gender-Based Medicine. She also serves as the Associate Dean for Women in Health and Science and holds the Mrs. Avery "Janie" Rush Endowed Chair of Excellence in Women's Health and Oncology at TTUHSC. Her current research and scholarship efforts are directed toward ovarian cancer, menopause, postmenopausal sexual function and integrating sex and gender differences into medical and pharmacy curricula. She initiated the development and is a lead faculty for the current TTUHSC SOM project, "Development of an Integrated Longitudinal Sex and Gender-Specific Curriculum."

Michael Karin, M.D., received his BSc in Biology in 1975 at Tel Aviv University, Israel and his PhD in Molecular Biology in 1979, at the University of California, Los Angeles. Dr. Karin joined the laboratory of Dr. Beatrice Mintz at the Fox Chase Cancer Center as a postdoctoral fellow. After completing a second, short, postdoctoral fellowship with Dr. John Baxter at the Departments of Medicine and Biochemistry at the University of California San Francisco (UCSF), Dr. Karin undertook his first faculty appointment as an Assistant Professor at the Department of Microbiology at the University of Southern California (USC), School of Medicine, Los Angeles. In 1986, Dr. Karin accepted an Associate Professor position at the Department of Medicine at the University of California San Diego (UCSD), School of Medicine and in 1989 was promoted to a full Professor at the Department of Pharmacology, UCSD School of Medicine, where he has been ever since. Dr. Karin is leading authority on cell signaling, inflammation biology and cancer. His work has been recognized by numerous honors and awards, including the Oppenheimer Award for Excellence in Research from the Endocrine Society (1990), MERIT Award from the NIH/NIEHS (1998), Frank and Else Schilling-American Cancer Society Research Professorship (1999), C.E.R.I.E.S. Research Award for Skin Physiology (2000), Honorary Doctoral Degree, Technical University Munich (2010) and the Harvey Prize in Human Health (2010). In 2005, Dr. Karin was elected to the National Academy of Sciences, USA; in 2007 he became a Foreign Associate of the European Molecular Biology Organization (EMBO); and in 2011 he was elected to the Institute of Medicine.

Alexandra Kautzky-Willer, M.D., is Professor of Gender Medicine at Medical University in Vienna where she heads the Gender Medicine Unit and the University Course of Gender Medicine. She has specialized in Internal Medicine and in Endocrinology and Metabolism. She is board member of numerous medical and scientific associations, among these, the Austrian Associations for Diabetes, Gender Medicine, and Obesity. She is a member of the European (DPSG) and International Diabetes Pregnancy Study Groups and scientific consultant of national and international Medical-Scientific Funds. She serves as reviewer in leading journals and has received several awards such as the Joseph Hoet Research Award 2004. She has published 96 original papers, numerous reviews, book chapters, Guidelines/Practical Recommendations, and Audit Reports. Special research interests are sex- and gender based aspects of obesity, the metabolic syndrome, diabetes and cardiovascular disease including pregnancy and fetal programming.

Ineke Klinge, Ph.D., received her doctoral training in biomedicine (specialization Immunology) from the Free University in Amsterdam and her PhD from Utrecht University, where she also specialized in gender research. She is currently associate professor of Gender Medicine at Maastricht University. Her past and current research for the European Commission focuses on innovation of biomedical and health research by incorporation of sex and gender aspects. The project *GenderBasic* (2005-2008) that she coordinated was elected by the European Commission as a FP6 success story. During winter semester 2008-2009 she was appointed as Maria-Goeppert-Mayer guest professor in Gender Medicine at the Georg-August-University in Göttingen, Germany. In 2010, with Claudia Wiesemann she published the book *Sex and Gender in Biomedicine. Theories, Methodologies, Results.* She is currently co-director of the EU Expert group Innovation through Gender that develops methods of sex and gender analysis for basic and applied research (Gendered Innovations).

Marianne J. Legato, M.D., F.A.C.P., is an internationally known expert in gender-specific medicine, the science of how normal human function and the experience of disease are impacted by biological sex/gender. She is Professor of Clinical Medicine at Columbia University and Adjunct Professor of

Medicine at Johns Hopkins. In 1997 she founded and continues to direct the Partnership for Gender-Specific Medicine at Columbia University. In 2006 she established the Foundation for Gender-Specific Medicine, a nonprofit organization that raises awareness of gender-specific medicine in professional and lay communities world-wide. Grants from both organizations are currently supporting gender-specific research at both Columbia and Johns Hopkins. Dr. Legato founded the indexed journal, Gender Medicine and edited the first medical text of its kind, the Principles of Gender-Specific Medicine (Academic Press, 2004; second edition, 2009). She has written 5 books for the public; most recently, *Why Men Die First* (Palgrave, 2008).

Svetomir N. Markovic, M.D., Ph.D., is a consultant in the Division of Hematology, Department of Internal Medicine, the Division of Medical Oncology, Department of Oncology, and the Department of Immunology at Mayo Clinic Rochester. He holds the academic rank of Professor of Medicine and Oncology and Associate Professor of Immunology. He is recognized with the distinction as the Charles F. Mathy Professor in Melanoma Research. Dr. Markovic is the Chair of the Melanoma Disease Oriented Group of the Mayo Clinic Cancer Center as well as the Chair of the Midwest Melanoma Partnership. His research is focused on understanding opportunities for integration of different systemic treatment modalities into more effective therapy for advanced melanoma.

Margaret (Peg) McCarthy, Ph.D., received a B.A. and an M.A. in Biology from the University of Missouri - Columbia and a Ph.D. from the Institute of Animal Behavior at Rutgers University, Newark NJ. She received postdoctoral training at Rockefeller University from 1989 to 1992 in the Laboratory of Dr. Donald Pfaff and one year at NIH as a National Research Council Fellow. Peg joined the faculty of the University of Maryland School of Medicine in 1993 and is currently a Professor in the Departments of Physiology and Psychiatry and Chair of the Department of Pharmacology. She was the Director of Graduate Education for the Program in Neuroscience for three years and the Associate Dean for Graduate Studies from 2005 – 2011. She has received numerous awards and recognition for her mentoring of graduate students. Dr. McCarthy has a long standing interest in the cellular mechanisms establishing sex differences in the brain. Dr. McCarthy has published over 120 peer-reviewed manuscripts on these topics and her research has been continuously funded by the NIH since 1994. She is currently an Editor at *Endocrinology* and Associate Editor at the *Journal of Neuroscience.* She is former Associate Editor of *Hormones and Behavior*, past Secretary of the Society for Behavioral Neuroendocrinology, current Councilor in the Organization for the Study of Sex Differences and was named one of Maryland's Top 100 Women in 2009.

Thomas A. Mellman, M.D., (Director, Clinical and Translational Research and Stress and Sleep Studies and Professor of Psychiatry at Howard University College of Medicine) Dr. Mellman is the principal investigator at Howard for the CTSA supported Georgetown Howard Universities Center for Clinical Translational Science as well as an RO1 from NHLBI and has been the principal investigator on multiple other research and a Mid-career Investigator Award in Patient Oriented Research. Much of his research and publications have addressed the role of sleep disturbance in the pathogenesis and treatment of PTSD. This included studies that included sleep recordings in the aftermath of traumatic injuries and more recently the impact of PTSD and sleep disturbance on health disparities.

Istvan Merchenthaler, M.D., Ph.D., D.Sc., received his M.D. degree from the University of Pecs, Hungary and his Ph.D. and D.Sc. degrees from the Hungarian Academy of Sciences. His research interests include (i) to develop novel, safe, central nervous system (CNS)-selective estrogen replacement therapy free of side effects in the periphery to alleviate menopausal symptoms (hot flushes, depression, sleep disturbances, and dementia) by utilizing a pro-drug approach and (ii) to improve fertility, prevent chromosomal aneuploidy, and delay neurodegeneration in older women by lowering gonadotropin hormone levels. Currently, he is funded by two RO1 and one R21 grants. He has published 170 peer-reviewed scientific articles. Besides conducting research, he teaches Human Gross Anatomy and Histology to medical students and is the course master of Neuroendocrinology and Biology of Aging in the GPILS program and he is the Director of the BIRCWH K-12 program at UMB.

William Moss, M.D., M.P.H., received his medical degree from Columbia University College of Physicians and Surgeons and his M.P.H. from the Columbia University Mailman School of Public Health. Dr. Moss completed his residency and chief residency in pediatrics at Babies Hospital, Columbia-Presbyterian Medical Center, and his fellowship in Pediatric Infectious Diseases at the Johns Hopkins Hospital. He is an Associate Professor in the Departments of Epidemiology, International Health and Molecular Microbiology and Immunology at the Johns Hopkins Bloomberg School of Public Health. His broad research interests are the epidemiology and control of childhood infections in resource-poor countries, with a primary interest in understanding the impact of the HIV epidemic on measles control and eradication. Areas of current research include the impact of antiretroviral therapy on measles

immunity, the care and treatment of HIV-infected children in rural sub-Saharan Africa, and the epidemiology and control of malaria in southern Africa.

Mary I. O'Connor, M.D., is Chair of the Department of Orthopedic Surgery at the Mayo Clinic in Florida, Associate Professor of Orthopedics at the Mayo Clinic College of Medicine and member of the Florida Executive Operations Team. She is the current President of the Association of Bone and Joint Surgeons and past president of the American Association of Hip and Knee Surgeons and the International Society of Limb Salvage. She has an active clinical practice focusing on surgical treatment of arthritis of the hip and knee joint and salvage of the limb in the treatment of bone and soft tissue sarcoma. She has published on gender differences in outcomes of knee replacement surgery and chaired research and advocacy symposia related to musculoskeletal healthcare disparities. She is a member of the Society for Women's Health ISIS network and was recently awarded a grant by the Society to study potential sex difference in knee osteoarthritis.

Pamela Ouyang, M.B.B.S., received her medical degree from St. Bartholomew's College of Medicine, University of London, UK. She did her residency training in Internal Medicine at Johns Hopkins Hospital, where she also completed Cardiology Fellowship. She has been on the cardiology faculty at Johns Hopkins Bayview Medical Center and is Professor of Medicine at Johns Hopkins University. Dr. Ouyang's research focuses on risk factors for ischemic heart disease, cardiovascular disease in women, and clinical trials in cardiology.

Douglas Portman, Ph.D., received his B.A. in Biochemistry and Ph.D. in Molecular Biology and Genetics, both from the University of Pennsylvania. With a background in molecular cell biology, Dr. Portman began work on *C. elegans* genetics as a postdoc with Scott Emmons, Ph.D., at the Albert Einstein College of Medicine. He joined the faculty of the University of Rochester in 2003 and is currently Associate Professor of Biomedical Genetics in the Center for Neural Development and Disease. His research focuses on the genetic control of sex differences in neural development and behavior in the *C. elegans*, with a particular interest in using this model to gain insight into the biological mechanisms that underlie sex differences in human neuropsychiatric disorders, including autism. More information about his laboratory's research can be found at <wormweb.urmc.rochester.edu>.

Ann M. Rasmusson, M.D., is an affiliate of the Veterans Administration National Center for PTSD Women's Health Science Division, an Associate Professor of Psychiatry at Boston University School of Medicine, and Psychiatry Liaison for PTSD Research and Education at the VA Boston Healthcare System. Her research has focused on the neuroendocrinology of PTSD and PTSD-comorbid medical and other psychiatric disorders such as metabolic syndrome, depression, and nicotine dependence, as well as the development of new PTSD therapeutics. Current funded projects are focused on sex differences in the regulation of neuroactive steroids in PTSD, neurobiological predictors of relapse to tobacco use and response to cognitive processing therapy in PTSD, and the role of deficits in GABAergic neuroactive steroids in the shared risk for PTSD, traumatic brain injury, depression, and chronic pain. She is also Co-Lead for a multisite DOD-sponsored trial of ganaxolone, a synthetic GABAergic neuroactive steroid, for PTSD.

Vera Regitz-Zagrosek, M.D., received her medical degree from Saarland University and undertook post-doctoral training at the Max-Planck-Institute for Experimental Cardiology and University of Madison. She founded the Institute of Gender in Medicine at Charite University Hospital, the Cardiovascular Disease in Women Working Group (German Cardiac Society DGK), the German and International Societies for Gender in Medicine. She coordinates the BMBF-sponsored project "Gender Medicine" and the Berlin site in the German Centre for Cardiovascular Research (DZHK), two DFG-funded collaborative consortia and the ERASMUS project EUGIM. She is Task Force Leader of the Guidelines "Cardiovascular Diseases in Pregnancy" of the European Society of Cardiology.

Kerry Ressler, M.D., Ph.D., received his medical and doctoral degrees from Harvard Medical School, studying the molecular basis of olfaction as Linda Buck's first graduate student. His work at Emory University focuses on mechanisms of fear in mice and humans. He has received numerous awards, including being named an HHMI Investigator, the Freedman Award in Basic Science (NARSAD), the Killiam Award for Translational Research (ACNP), and the Laufer award for Scientific Achievement (ISTSS). He is Principal Investigator (PI) on 2 R01 grants and an RC1 Challenge Grant to understand translational, genetic and psychological risk factors for PTSD. He is a past member of the VA Merit study section for genetics of PTSD and mental health grants, and a current member of the NIH CSR Learning and Memory (LAM) study section. His work in sex differences is relatively recent, after identification of gene pathways which appear to differentially mediate PTSD in a sex- and hormone-specific manner.

Karin Schenck-Gustafsson, M.D., Ph.D., F.E.S.C., is the director and founder of the Centre for Gender Medicine, Department of Medicine, Karolinska Institutet. She is a professor of cardiology and chief consultant of cardiology at the Karolinska University Hospital. From 2007-2009 Dr. Schenck-Gustafsson served as the President of IGM and in 2010 she was the editor in chief of the International Handbook of Gender Medicine. International Awards include Athena Award for M of C btw KI and Columbia (2004) and Florio MAseri Award for Gender in Cardiology (2009).

Jaclyn M. Schwarz, Ph.D., received her B.A. in Psychology from Boston College and her Ph.D. in Neuroscience from the University of Maryland, Baltimore. Her Ph.D. examined the sexual differentiation of the developing rodent brain with a special focus on understanding the estradiol-mediated development of gluamatergic synapses in the neonatal hypothalamus. She is currently a postdoctoral fellow at Duke University studying the early-life factors which influence the development and function of the neuroimmune system, and how this might influence an individual's later life risk or resilience to certain mental health disorders. She has received numerous awards, including the Florence P. Haseltine Award at the first annual meeting for the OSSD in 2007, as well as a pre- and a post-doctoral National Research Service Award from the NIH for her research.

Zena Sharman, Ph.D., is the Vancouver-based Assistant Director of the Institute of Gender and Health (IGH), one of 13 Institutes that comprise the Canadian Institutes of Health Research (CIHR), Canada's national health research funding agency. IGH's mission is to foster research excellence regarding the influence of gender and sex on the health of women and men throughout life and to apply these research findings to identify and address pressing health challenges. Dr. Sharman has a PhD in Interdisciplinary Studies from the University of British Columbia (2010). Her program of research focuses on gender and health care work. She is the co-editor (with Ivan E. Coyote) of *Persistence: All Ways Butch and Femme* (Arsenal Pulp Press, 2011), the first Canadian anthology of its kind on queer sexualities and genders.

Kathleen A. Sluka, Ph.D., P.T., received her physical therapy degree from Georgia State University and her PhD from University of Texas Medical Branch in Anatomy. She did a Postdocotoral fellowship in Neuroscience at the University of Texas in Galveston. She is currently a full professor at the University of Iowa in the Physical Therapy and Rehabilitation Science Graduate Program in the College of Medicine, the Neuroscience Graduate Program, the Pain Research Program and the College of Nursing. Her research focuses on the mechanisms underlying chronic musculoskeletal pain in animal models and translation of these mechanisms to clinical pain populations. She has published over 120 manuscripts, numerous book chapter, and is a regular invited speaker world-wide. She has won numerous awards for her research including the prestigious Frederick W.L. Kerr Basic Science Research Award from the American Pain Society and the Marian Williams Award for research in physical therapy from the American Physical Therapy Association.

Amy E. Street, Ph.D., received her Ph.D. in Clinical Psychology from the University of Georgia in 1998. Dr. Street is clinical psychologist affiliated with the Women's Health Sciences Division of the National Center for PTSD and an Associate Professor of Psychiatry at Boston University School of Medicine. She also serves as the Director of the Education and Training Division of the Department of Veterans Affairs Office of Mental Health Services' National Military Sexual Trauma Support Team, a national policy, education and training resource team focusing on the treatment of Veterans who experienced sexual harassment or sexual assault during their military service. Dr. Street has an active program of research investigating negative health outcomes associated with interpersonal trauma, including sexual harassment, sexual assault and intimate partner violence, in veteran and civilian populations. Her research has received funding from the Department of Veterans Affairs and the National Institutes of Health.

Anna Thorson, M.D., Ph.D., M.P.H., is an Associate Professor and research group leader at the Division of Global Health at Karolinska Institutet, Sweden. She is also a clinical specialist at the Infectious Disease Clinic at the Karolinska University Hospital. She holds a Diploma in Tropical Medicine and Health, a Masters in Public Health and a Ph.D. in International Health, from Karolinska Institutet. Her Ph.D. thesis comprised field studies in Vietnam, of Tuberculosis from a gender perspective. Her current main research focus is HIV/AIDS and TB epidemiology, including health system research (gender, access to care and treatment delivery of TB and HIV/AIDS medication), determinants of sexual HIV transmission and prevention of HIV. She currently works in collaborative research projects in Tanzania, Burkina Faso, Uganda, South Africa, Kenya and Vietnam. She has been an expert consultant to the WHO, comprising work on gender aspects of HIV/AIDS and Tuberculosis in Central Asia and Eastern Europe.

Dawne Vogt, Ph.D., received her Ph.D. in Experimental Psychology from Northeastern University and is currently a Research Psy-

chologist in the Women's Health Sciences Division of the National Center for PTSD, VA Boston Healthcare System, and Associate Professor of Psychiatry at Boston University School of Medicine. Dr. Vogt has published extensively in the deployment stress literature and has focused much of her recent research on gender differences in deployment risk and resilience factors as they relate to mental health. She has received awards including an NIMH research fellowship and the Walter G. Klopfer Award for distinguished contribution to the literature in personality assessment. She is also involved in the research training of predoctoral and postdoctoral trainees and serves on numerous local and national committees in her field. She has additional research interests in stressors unique to women in the military and stigma as a barrier to mental health treatment.

Joanna Wilson, M.D., received her B.S. from the University of Michigan, Ann Arbor and Doctorate of Osteopathy from The University of North Texas, Fort Worth. She completed her residency at UT Southwestern/St. Paul, Dallas in Internal Medicine. She is board-certified in Internal Medicine, and is a Certified Clinical Densitometrist and a NAMS Certified Menopause Practitioner. She is currently an Associate Professor at Texas Tech, Amarillo. She is the Division Chief of Women's Health and Gender-specific Medicine. She is the recipient of a number of awards, including Texas Tech President's Outstanding Clinician Award, Texas Tech Dean's Outstanding Leadership Award, and Haven Health Clinic Community Service Award. Her clinical practice focuses on women's primary care and outpatient gynecology. Dr. Wilson's interest in medical curriculum development to include gender differences is focused on delivery methods of evidence-based medicine to faculty.

PRESIDENTIAL SYMPOSIUM: SEX DIFFERENCES IN FETAL PROGRAMMING

Prenatal testosterone and human neurobehavioral development: Outcomes and mechanisms

Melissa Hines Ph.D., University of Cambridge

Thousands of experiments in non-human species indicate that exposure to testosterone prenatally or neonatally has enduring influences on behavior, increasing male-typical characteristics and decreasing female-typical characteristics. Testosterone also influences the development of the mammalian brain, affecting programmed cell death, anatomical connectivity and neurochemical specification, and these neural changes during early development are thought to explain the behavioural changes.

Testosterone also appears to influence human behavioural development in a manner similar to that documented in other species. Many behaviours that differ on the average for males and females, including childhood toy and activity interests, sexual orientation, gender identification, personality characteristics, and sex-related cognitive abilities, have been linked to levels of testosterone during early development. Much of this evidence has come from studies of individuals exposed to high levels of testosterone and other androgens prenatally, because of the autosomal recessive disorder, congenital adrenal hyperplasia (CAH). For example, numerous studies have found that girls with CAH show increased male-typical, and reduced female-typical, toy and activity preferences. In addition, testosterone measured in maternal blood during pregnancy, or in amniotic fluid during gestation, predicts male-typical childhood play behaviour in typically-developing children. Non-human primates also show sex-typed toy interests, similar to those seen in children, suggesting an inborn, probably hormonal, contribution to these sex differences in object preferences. Although the strongest evidence linking prenatal testosterone exposure to human behaviour has come from studies of children's sex-typed play, substantial evidence also links early testosterone exposure to sexual orientation and to core gender identity, and there is some evidence linking such hormone exposure to aggressive behavior, to empathy, and to targeting ability.

For human behaviors that show sex differences, other factors, including socialization, play a role too, however, and the magnitude of this role appears to vary across behavioral outcomes. In addition, and in contrast to other species, the acquisition of sex-typical behavior in humans involves social-cognitive mechanisms related to gender identification. This presentation will suggest that these social-cognitive mechanisms could be involved in the chain of events linking early testosterone exposure to subsequent sexually differentiated behavior.

Prenatal programming of stress dysregulation: epigenetic and placental contributions

Tracy L. Bale, Ph.D., University of Pennsylvania, Philadelphia, PA

Sex-biased neurodevelopmental disorders, including autism and schizophrenia, have been associated with fetal antecedents such as maternal stress. The mechanisms and transgenerational programming of offspring outcomes through which stress contributes to disease development are not well understood, though likely involve a complex interaction between the maternal environment and effects on the placenta. We have identified a sensitive period of early gestation where maternal stress has sex-dependent epigenetic programming effects on offspring stress pathway neurodevelopment. Male offspring show increased stress sensitivity as adults in behavioral and physiological measures including tests assessing cognitive performance and stress coping strategies. These males also show physiological features of dysmasculinization including reduced testosterone levels, smaller testes, and a shorter anogenital distance suggesting a disruption in normal perinatal masculinization. Second-generation male offspring also show a stress-dysregulation phenotype passed on by the paternal lineage, supporting a

transgenerational epigenetic mode of transmission from father to son. Mechanistically, we have identified dramatic changes in the neonatal brain microRNA environment in response to early prenatal stress. How maternal stress so early in pregnancy can impact the developing brain likely involves changes in placental programming. As the placenta is a sex-specific tissue, we identified a limited set of genes that consistently differ between the sexes across pregnancy, all of which are located on the X or Y chromosomes. Utilizing a proteomics approach, we have found a candidate placental glycosylation enzyme and its biochemical target proteins that are significantly affected by maternal stress. Chromatin immunoprecipitation analyses support a direct mechanism whereby stress experience decreases histone association with this gene, decreasing its expression. As protein glycosylation typically competes with phosphorylation events, such broad changes are likely to yield important outcomes in placenta function and nutrient support of the developing fetus following stress. These results may provide critical insight into the mechanisms contributing to sex biased disease vulnerability to prenatal stress during early pregnancy. Further, as many neurodevelopmental disorders have a sex bias in presentation, these studies may provide novel biomarkers predictive of at-risk pregnancies.

These studies were supported by funding from grants from the NIH MH087597 and MH091258

Fetal Programming

Marek Glezerman, M.D., The Emma Fajman Professor of Obstetrics and Gynecology, Tel Aviv University and Rabin Medical Center

The concept of fetal programming is profoundly changing our perception of the effect of the intrauterine environment for adult health and disease. The obsolete controversy of nature versus nurture is being replaced by the understanding of the importance of exogenous and endogenous effects on the developing fetus which may cause epigenetic changes thus affecting gene expression. As a result one genotype may lead to different phenotypes. Ultimately, this concept has great clinical and public health impact. The definition of maternal-fetal medicine will need to adapt to the new findings related to the intrauterine environment. Indeed, the intrauterine environment is currently regarded by many as the probable most important phase in our life where future health and disease are determined to a large extent. There is of course also a gender aspect to fetal programming. Male and female fetuses may respond differently to exogenous and endogenous stimuli and the different hormonal milieu is of great importance in this aspect. We have looked at pregnancy outcome in relation the sex of the fetus. We have shown that normal singleton pregnancies with a female fetus have a better outcome than those with a male fetus. In twin pregnancies, the best outome is achieved with a female-female pair and in mixed sex twins, the female sibling improves the outcome of her brother while the male twin worsens the outcome of his sister. We have also demonstrated a significantly different growth pattern for female and male fetuses and our results indicate that sonographic weight estimation is more accurate in male fetuses than in female fetuses. There are different types of common birth traumas in male than in female fetuses and male gender is independently associated with adverse pregnancy outcome. Male neonates are twice more likely to die at birth than female neonates but stillbirth is more common in female fetuses. These and other aspects of fetal programming will be discussed.

OPENING KEYNOTE LECTURE

Gender-Specific Medicine after the Age of Darwin: Achievements and Challenges in 21st Century Science

Marianne Legato, M.D., F.A.C.P., Professor of Clinical Medicine, Columbia University; Adjunct Professor of Medicine, Johns Hopkins.

Discoveries build upon themselves and progress in science is exponential. The past 20 years have witnessed astonishingly powerful and profound changes in our medical and technological achievements. The last decade of the twentieth century nullified the idea that the male is normative for all humans and incontrovertibly demonstrated the importance of including both sexes in scientific protocols. The result was the establishment of the new discipline of gender-specific medicine, which has transformed our concept of normal function and the pathophysiology of disease. The first decade of the new century ushered in what is probably the most important phenomenon in human history: the genomic revolution, enabling us not only to read chromosomes, but to create new ones in the just-born age of synthetic biology. We are no longer confined to the Darwinian system in which spontaneous and random mutations in DNA produce life forms that endure- or not- depending on the environment into which the new phenotype emerges. Given the enormous potential of the new science, the role of biological sex not only on naturally occurring but on the synthetically created or altered genome must be explored. Increasingly, we are developing methods

to technically enhance human function: it is inevitable that there will be sex differences in the response to such enhancements. Regrettably and perhaps predictably, thoughtful attempts to consider the legal, moral and economic aspects of our rapidly expanding ability to change the world around us have been uncoordinated and even fragmented. Often, scientists themselves are reluctant to discuss the implications and potential of their work with experts in other disciplines. Rather than resisting such collaborations as irrelevant and even an obstruction to progress, scientists should be leading the discussion of how we should to consider where our spectacular new powers are –and should be – taking us.

NEW INVESTIGATOR SYMPOSIUM

Maternal vascular function in early pregnancy in relation to fetal gender

Abstract Presenter: Charlotte Iacobaeus, M.D., Ph.D.-student[1,2]
Other Authors: Gun Jörneskog M.D.,Ph.D.[2]; Thomas Kahan, M.D.,Ph.D., Prof.[2]; Malin Thorsell, Ph.D.[2]; Ellika Andolf, M.D., Ph.D.[2]
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Background: Fetal gender is independently associated with adverse pregnancy outcome. There is an increased risk for spontaneous abortions, preterm labour and preterm premature rupture of membranes in pregnancies with male fetuses. Women carrying male fetuses are at increased risk for hypertensive disorders during pregnancy, which is a marker for cardiovascular disease later in life, possibly due to a persistent endothelial dysfunction.

Objective: To assess if fetal gender relates to cardiovascular function in women during pregnancy and after delivery.

Materials and Methods: 50 healthy women with singleton viable pregnancies were studied at gestational week 12–14. Supine brachial blood pressure (BP) was measured by a standard oscillometric device. Pulse wave analysis by applanation tonometry was used to calculate central blood pressure and arterial stiffness. Forearm flow mediated dilation (FMD) following ischemia and glyceryl trinitrate, skin microvascular responses (laser Doppler fluxmetry, arbitrary units (AU)) to iontophoretic applications of acetylcholine (Ach) and sodium nitroprusside (SNP), and maximum microvascular hyperaemia (MMH) to local heating were used to assess microvascular function.

Results: At gestational week 12-14, women with a male fetus showed lower microvascular vasodilatation in response to SNP (peak SNP 1.67±0.37 vs 2.17±0.48 AU, p <0.001), and a trend of reduced microvascular response to Ach (peak Ach 1.83±0.35 vs 2.10±0.49 AU, p =0.07x), and MMH (peak MMH 118±33 vs 142±45 AU, p =0.065). There were no differences between the groups in brachial BP (106±7/62±6 vs 107±8/61± Hg central BP (89±7/62±5 vs 92±7/63± Hg), changes in FMD following ischemia (+10.0±3.9 vs +10.2±3.6 % and glyceryl trinitrate (+25.6±4.6 vs +26.1+5.9 %) for male and female gender, respectively, Pulse wave velocity was 5.3 ±0,5 vs 5,6±0.6 m/s p=0,11.Body mass index and age was comparable between the groups.

Conclusion: The results suggest that alterations in maternal skin microvascular function at gestational week 12-14 are related to fetal gender. Women with a male fetus have a lower endothelial-independent vasodilatation. Further analyses at gestational weeks 24 and 34, and at nine month after delivery are in progress and might reveal further differences in cardiovascular function, related to fetal gender.

Sex-specific differences in ventricular gene expression between men and women with aortic stenosis

Abstract Presenter: Georgios Kararigas[1]
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Aortic stenosis (AS) is a major burden for the heart leading to the development of left ventricular hypertrophy (LVH). In severe AS, aortic valve replacement (AVR) is performed resulting in LVH regression. Sex-related differences in the occurrence and prognosis of AS and consequently LVH have been well documented. However, little is known about the underlying molecular mechanisms and how these might differ between men and women. The purpose of this

study was to assess the impact of sex on gene expression in LV of AS patients at the time of AVR whilst aiming at the identification of LVH regression predictors. LV samples of men ($n = 9$; age: 75 ± 8 y) and women ($n = 10$; age: 72 ± 9 y) undergoing AVR were used for RNA isolation. LV geometry/dimension and function were assessed using tissue Doppler echocardiography before surgery and 3 ± 1 days following AVR. Genome-wide expression profiling was performed using the Affymetrix platform and the data were analyzed with R and Bioconductor. Diseased samples were compared with LV samples of men ($n = 10$; age: 56 ± 4 y) and women ($n = 8$; age: 56 ± 5 y) with no apparent cardiovascular disorder. Assessment of single gene differential expression with a false discovery rate-adjusted $P < 0.05$ identified 1491 transcript clusters regulated in male, 2109 in female and 1382 in both male and female samples. Male-specific genes induced in AS included periostin (*POSTN*), nebulin (*NEB*), sarcolipin (*SLN*) and several members of the collagen family, such as collagen type I alpha 2 (*COL1A2*) and type III alpha 1 (*COL3A1*). On the other hand, a number of ribosomal and energy-related genes were repressed in male samples. Female-specific repressed genes in AS included extracellular matrix-related and inflammatory genes, while members of the mitochondrial carrier protein family were induced. Pathway analysis (1000 permutations; $P < 0.05$) revealed that the ECM-receptor interaction, p53 and TGF-beta signaling pathways were induced in male samples, while the oxidative phosphorylation, ribosome and proteasome pathways were repressed. In contrast, several inflammatory pathways, such as the cytokine-cytokine receptor interaction, were repressed in the hearts of women with AS, while the mismatch repair and peroxisome pathways were induced. To identify genes that could potentially predict LVH regression, we tested the association between cardiac gene expression and the difference between pre- and post-operative left ventricular end diastolic diameter (LVEDDd). Among others, we discovered that aquaporin 7 (*AQP7*) is inversely associated with LVEDDd (rho = -0.74; $P < 0.001$). In conclusion, we provide evidence that in patients with AS the genomic response of the heart to LVH differs significantly between men and women. LV gene expression profiling may be useful for the development of a predictive model of LVH regression.

The role of central glucocorticoid receptors in HPA axis regulation in males and females

Abstract Presenter: Matia B. Solomon[1]
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Glucocorticoids are implicated in the pathophysiology of depression. For example, impairments in glucocorticoid signaling due to hypercortisolemia and/or deficient glucocorticoid receptor (GR) mediated feedback are a common feature in depressed individuals. Much of the knowledge regarding GR regulation of the HPA axis and mood relies heavily upon male subjects. This is quite perplexing, given that females are twice as likely to suffer from depression and often exhibit heightened glucocorticoid stress responses. The paraventricular nucleus of the hypothalamus (PVN) is the primary controller of glucocorticoid release, mediated by activation of the hypothalamo-pituitaryadrenocortical axis. Glucocorticoids signaling through GR exert an inhibitory effect on PVN neurons by decreasing excitatory corticotrophin-releasing hormone (CRH) release and down-regulating CRH and arginine vasopressin (AVP) expression. Thus, optimal GR signaling within the PVN appears to be necessary to constrain excessive glucocorticoid secretion. Given the prominent role of the PVN as the "motor arm" of the HPA axis, the present study was designed to test the overarching hypothesis that GR signaling in the PVN is obligatory for normal HPA axis tone. Local PVN GR knockout mice were generated by breeding homozygous GRflox mice with Sim1-cre recombinase transgenic mice. Because Sim1 is primarily expressed in neurosecretory PVN neurons, the resulting Sim1-cre/GRflox mice have a prominent deletion of GR in the PVN, sparing GR expression in other brain regions (e.g.,corticolimbic areas) as well as the pituitary and adrenal. Here, we examined sex differences in the necessity of PVN GR to modulate HPA axis activity. Analysis of HPA axis function revealed no significant differences in nadir and peak corticosterone levels between male PVN GRKO and male control mice. However, when subjected to an acute restraint challenge male PVN GRKO mice had increased adrenocorticotropin hormone (ACTH) and corticosterone responses compared with controls, indicating stress-induced hypersensitivity. Following chronic stress exposure an opposite neuroendocrine profile emerged, with male PVN GRKO mice being hyporesponsive to a novel restraint challenge. Unlike male PVN GRKO mice, female PVN GRKO mice hypersecreted corticosterone under basal conditions (circadian nadir) but had reduced ACTH responses to acute stress, without accompanying changes in corticosterone secretion. In females, PVN GRKO did not affect HPA axis responses to chronic stress. Overall, the data indicate that in males, the PVN GR is required for inhibition of acute stress responses and appears to be in-

volved in maintenance of PVN excitability in the face of chronic drive. In general, the HPA phenotype is considerably more circumspect, findings that are consistent with other studies in our lab that either pharmacological or genetic disruption of GR signaling is relatively inconsequential in intact females. These data suggest that alternative HPA axis regulatory mechanisms exist in females, and raise the possibility that failure of these mechanisms (rather than GR deficit) contribute to the sex differences in behavioral and HPA axis pathology in diseases such as depression.

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Microglia are essential to sexual differentiation of brain and behavior

Abstract Presenter: Kathryn M. Lenz
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Sexual differentiation of the rodent brain largely results from the perinatal androgen surge from the male testis acting to masculinize the male brain. In the preoptic area (POA), neonatal estradiol aromatized from testosterone up regulates the production of the proinflammatory molecule, prostaglandin E2 (PGE2) as a component of sex-specific brain development. PGE2 induces a two-fold greater density of dendritic spines synapses on male POA dendrites compared to females (Amateau & McCarthy, 2002), and also masculinizes adult copulatory behavior (Amateau & McCarthy, 2004). A single neonatal dose of PGE2 is sufficient to masculinize the POA and behavior, suggesting a strong feed-forward process leads to sustained increases in PGE2 during the critical period, yet the mechanisms underlying this feed-forward process were unknown. Microglia, the primary immunocompetent cell in the brain, both produce and respond to prostaglandins, thus we hypothesized that they may be responsible for this feed-forward process. Microglia are in an activated state neonatally and contribute to normal brain development, thus we sought to determine whether there are sex differences in POA microglia and whether they influence brain masculinization. We found that neonatal males have twice as many microglia as females and a more activated morphological profile, and both estradiol and PGE2 masculinize microglial number and morphology in females. Microglial inhibition during the critical period for sexual differentiation prevents estradiol-induced masculinization of dendritic spine density in the POA as well as adult copulatory behavior. Microglial inhibition also prevents the estradiol-induced upregulation of PGE2 in the POA, indicating that microglia are essential to the feed forward process through which estradiol up regulates prostaglandin production. To determine the wider inflammatory signaling profile through which microglia influence sex-specific development, we have measured cytokine levels in the developing POA and found many sex differences, including in IL-1beta and IL-10 (higher in males), and IL-2, IL-4, and TNFalpha (higher in females). These studies demonstrate that immune cells in the brain interact with the nervous and endocrine systems during development, and are crucial for the sexual differentiation of brain and behavior.

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17β-estradiol and signaling through the estrogen receptor-α modulate inflammatory responses to influenza A viruses in females

Abstract Presenter: Dionne P. Robinson[1,2]
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Data from influenza pandemics (i.e. 1918 H1N1, 1957 H3N2, 2009 H1N1) and H5N1 avian influenza outbreaks reveal that sex is a determinant of morbidity and mortality associated with influenza A virus infection of young (15-44 years of age) adults. Compared with males, females are more than twice as likely to die following infection with H5N1 avian influenza. More recently, during the 2009 H1N1 pandemic, females, regardless of pregnancy status, were significantly more likely to be hospitalized than males. While gender roles associated with each sex may influence sex differences in influenza exposure and outcome, we hypothesized that biological differences between males and females impact the immune response to infection. In our rodent model, adult (6-8 weeks of age) male and female C57BL/6 mice are intranasally inoculated with a mouse-adapted H1N1 influenza virus, resulting in females having greater morbidity and mortality than males following infection. My studies reveal that greater influenza severity in females than males correlates not with differences in virus replication, but with greater induction of proinflammatory cytokines and chemokines in the lungs.

Infection with influenza significantly affects reproductive function in both sexes resulting in estrus cycle dysregulation and reduced 17β-estradiol (E2) and progesterone concentrations in females and reduced concentrations of testosterone (T) in males. Removing the testes and ovaries from males and females, respectively, prior to influenza infection eliminates the sex difference in influenza outcome suggesting a role of sex steroid hormones. Exogenous administration of E2 or estrogen receptor-α (ERα) agonist to ovariectomized (ovx) females, but not androgens (e.g. T or 5α- dyhydrotestosterone) to gonadectomized males, protects against influenza infection. Elevated E2 and signaling through ER correlates with altered activity of inflammatory mediators in the lungs, including reduced tumor necrosis factor-α (TNF-α) and monocyte chemoattractant protein-1 (MCP-1), and increased macrophage inflammatory protein 1-α (MIP-1α), compared with placebo treated ovx females. Chemokines are important for immune cell recruitment to the site of infection which can be beneficial for control of influenza, but can promote immunopathology and death if excessive. To test the hypothesis that E2-mediated changes in chemokines, including MCP-1 and MIP-1α, following influenza infection results in altered immune cell influx into the lungs, innate immune cells were enumerated from the lungs of E2-treated and placebo-treated ovx females at several time-points post-inoculation. Following influenza infection, E2-treated females have significantly greater proportions of inflammatory cells, including neutrophils, inflammatory dendritic cells, and plasmacytoid dendritic cells, in their lungs than placebo-treated females during the onset of the adaptive phase of the immune response. Whether E2 treatment and signaling through ERα increases recruitment and activity of influenza-specific cytotoxic CD8 T cells in the lungs is currently under investigation. Collectively these data demonstrate that sex differences in response to influenza are primarily modulated by hormonal regulation of immune responses rather than differential virus replication. Furthermore, E2 treatment protects females against influenza infection by altering inflammatory responses, influencing the recruitment of immune cells into the lungs. Taken together, these data suggest that elevated E2 and use of selective ER modulators may have therapeutic potential against influenza pathogenesis.

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Sex differences in play fighting – now you see them, now you don't: possible role for sexually dimorphic vasopressin expression in the brain

Abstract Presenter: Matthew J. Paul
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Sex differences in behavior are pervasive, including many behavioral disorders characterized by abnormal social development (*e.g.*, autism). Play fighting is the most prominent social behavior in juvenile rats and provides an ideal model to investigate sex differences in the neural control of early social development. Although it is often reported that male juvenile rats play more than females, several studies fail to detect this sex difference. We tested whether the discrepancies in the literature could be explained by a differential influence of context on male and female play. We manipulated residential status of the test cage to determine whether two commonly used play paradigms (Resident-Intruder and Neutral Cage) impact the sex difference in play fighting of Wistar rats. We further investigated the ontogeny and neurobiology of social behavior in males and females by conducting a detailed developmental profile of play fighting and vasopressin mRNA expression in the bed nucleus of the stria terminalis (BNST), a sexually dimorphic neuropeptide system thought to play a role in the regulation of several social behaviors including play. Robust sex differences seen in the Resident-Intruder paradigm (males > females) were absent under Neutral Cage testing conditions. Furthermore, we found that the sex difference was reversed (females > males) around the developmental onset of play (18-19 days of age), with females exhibiting an earlier, more rapid onset than males. At this time, vasopressin mRNA expression in the BNST was high in males but undetectable in females. As levels of play increased with age, male BNST vasopressin expression decreased. A negative correlation between vasopressin and play behavior was also evident when the analysis was restricted to rats of the same age, suggesting an inhibitory role for vasopressin in this nucleus. This agrees with earlier findings in our lab that injections of a vasopressin 1a receptor antagonist into projection areas of the BNST increases play fighting in males (Veenema et al., unpublished results). These data demonstrate that the sex difference in play fighting of rats is context-dependent, implicate more rapid social development in female rats, and suggest vasop-

ressin acts as a neural brake on play. Such differences in the neural control of social behavior may contribute to differences in the incidence and course, and by implication potential treatment, of behavioral disorders.

SYMPOSIUM I: SEX DIFFERENCES AND THEIR IMPACT ON OSTEOARTHRITIS

The knee as an organ: sex differences in Incidence and severity of OA

Mary O'Connor, M.D., Department of Orthopedic Surgery, Mayo Clinic

The purpose of this presentation is to review the knee as an organ including the contribution of different tissues to knee function and the potential influence of sex on such tissues and function. Furthermore, sex and gender differences in the incidence and severity of knee osteoarthritis will be highlighted with an emphasis on clinically relevant differences.

Hormonal nodulation contributes to sex differences in OA

David A. Hart, Ph.D., McCaig Institute for Bone & Joint Health, University of Calgary; SWHR ISIS MSK Network

Introduction: It is clear that sex differences contribute to a higher incidence of anterior cruciate ligament knee injuries (and secondary OA development) in young females and a loss of systemic hormonal regulation in a subset of post-menopausal females contributes to onset of primary OA. Studies of both humans and preclinical models have indicated that hormonal regulation of connective tissue integrity in subsets of females are a relevant factor in defining risk for injury and functioning of the knee. How such hormonal influences are manifest on specific tissues of the knee has been the subject of intense investigation over the past decade and these will be reviewed.
Methodological Approaches: In humans, studies have focused on healthy young females with regular menstrual cycles, twin studies, females with joint hypermobility syndrome, pregnant females, and peri- and post-menopausal females. Such studies have been complemented by experimental preclinical models using in vivo and in vitro approaches.
Results/Outcomes: Studies of young females have shown that knee laxity can vary in some, but not all individuals at different phases of the menstrual cycle. Joint laxity can also vary during pregnancy, and tissues do not return to pre-pregnancy conditions. Following menopause, joint function can change in both humans and following surgical menopause in preclinical models. Twin studies have also supported a role for genetic variables in OA onset in females. Studies to date support the conclusion that hormones influence connective tissues of the knee, but the "how" of such influences at the individual level still remain undefined. While some studies have indicated direct effects of sex hormones on connective tissues and expression of specific genes, how such findings translate into disease risk or injury risk remains.
Conclusions: While hormonal influences contribute to sex differences in risk, it is clear that female populations are comprised of subsets of individuals with different levels of risk and thus are heterogeneous. Significant gaps still exist in our knowledge base in this regard which require addressing.

Central nervous system modulates knee OA pain

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People with osteoarthritis (OA) can have significant pain that interferes with function and quality of life. Women with knee OA have greater pain and greater reductions in function and quality of life than men. In many cases, OA pain is directly related to sensitization and activation of nociceptors in the injured joint and correlates with the degree of joint effusion and synovial thickening. In some patients, however, the pain does not match the degree of injury and continues after removal of the nociceptors with a total joint replacement. While peripheral components could contribute to the underlying pain there is growing awareness that alterations in pain processing in the central nervous system significantly contribute to the ongoing pain of OA. This talk explores the central neural factors that contribute to knee OA pain with an emphasis on differences between the sexes and gaps in knowledge.

Sex differences in naturally occurring knee osteoarthritis in baboons

Lorena M. Havill, Ph.D., Texas Biomedical Research Institute

Osteoarthritis (OA) affects most older and many younger Americans, but the causes of disease onset and of differences between sexes and individuals in susceptibility and progression remain elusive. Non-human primates, such as the baboon (*Papio hamadryas* ssp.), are closely related to humans and, like humans, naturally develop OA with age. Baboons, therefore, can serve as an invaluable model for basic and translational OA research that is directly relevant to humans. We present the results of the first systematic examination of knee OA occurrence and severity in baboons with regard to age and sex. We examined right distal femora ex vivo from 306 adult pedigreed baboons aged 10 to 33 years, equally divided and age-matched between the sexes. Individuals were categorized as "unaffected" or as showing "mild," "moderate," or "advanced" OA based on macroscopic examination of the articular surface of the distal femur. Eighty percent of females and 89% of males show some degree of knee OA (p=0.08). Though this would suggest slightly higher burden of disease in males, a different scenario emerges when patterns of OA severity are considered. Striking sex differences are apparent when the sample is examined with regard to age. Younger male baboons (under the age of 17 years, ~50 years in humans) are affected at a much higher rate (88%) than are females (71%; p=0.003). The most striking difference in the younger animals is the higher percentage of males (57%) relative to females (42%) that show mild cartilage degeneration. Moderate and advanced OA occur at similar rates between sexes in the younger animals (22% v. 23% and 6% v. 9%, respectively). Older male (90%) and female (90%) baboons show no difference in knee OA occurrence, but show very different patterns of severity. Affected older females are equally distributed among the three stages of severity. Males, on the other hand, show much more "moderate" disease (52% v. 33%) and much less "advanced" disease (19% v. 33%) than do females. These results suggest that males tend to develop knee OA earlier in life, but that females progress more rapidly to advanced stages of disease. This work was supported by a grant from the Society for Women's Health Research Isis Network and by a Young Investigator Translational Science Award from the Max and Minnie Tomerilin Voelcker Fund.

SYMPOSIUM II: GLOBAL ASSESSMENT OF SEVERE CORONARY ARTERY DISEASE

Age and development of ischemic coronary disease: does sex matter?

Pamela Ouyang M.B.B.S., Johns Hopkins University School of Medicine

Ischemic heart disease mortality increases with age. An absolute age related increase in mortality that appears to bend upward around the fifth decade of life has led to the hypothesis that menopause associated factors contribute to the increase in ischemic mortality as women age. However, a similar absolute age related increase is seen in men. A proportional mortality model where the logarithm of mortality is plotted against age would be consistent with a constant probability of the failure of tissue reparative cells across a lifetime. We analyzed data from the United Kingdom Office for National Statistics for age and sex specific mortality rates for census years 1950 to 2000 to follow the mortality of three decade-long birth cohorts that included women who reached postmenopausal ages within the 20th century. All-cause mortality and heart disease mortality for men and women, and breast cancer mortality (women only) were studied. Similar US cohorts were also analyzed using data from the US National Center for Health Statistics database. We fitted data using models assuming (i) a linear association between mortality rates and age (absolute mortality) or (ii) a logarithmic association (proportional mortality). For England-Wales data, proportional increases in ischemic heart disease mortality fitted the data better than absolute increases. We identified a deceleration in male mortality after age 45 years (decreasing from 30.3% to 5.2% per age-year, $P = 0.042$), although the corresponding difference in women was non-significant ($P = 0.43$, overall trend 7.9% per age-year, $P<0.001$). By contrast, female breast cancer mortality decelerated significantly after age 45 years (decreasing from 19.3% to 2.6% per age-year, $P<0.001$). We found similar results in US data. Proportional age related changes in ischemic heart disease mortality, consistent with a loss of reparative reserve, fit longitudinal mortality data from England, Wales, and the United States better than absolute age related changes in mortality. The patterns differ by sex. In women, heart disease mortality increased exponentially throughout all ages from the 20's to 70's with no acceleration at menopause. Acceleration in male heart disease mortality at younger ages could explain sex differences rather than menopausal changes in women.

Coronary artery disease in Women: how common "atypical"symptoms reveal different pathophysiological substrates

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Clinical presentation of coronary artery disease (CAD) in women is different, with atypical symptoms, such as back pain, dyspnea, nausea/vomiting and weakness which may be the manifestations of various substrates. We studied coronary microvascular /endothelial dysfunction (ED), in 45 consecutive women (mean age: 57.6 ± 8.7 years) with symptoms and negative traditional tests. Myocardial perfusion at rest and during stress test using magnetic resonance imaging (MRI) revealed "fixed" perfusion defects, probably due to permanent damage of coronary microcirculation; which may precede typical atherosclerotic epicardial CAD as suggested from our follow-up data. Coronary dissection is the most common cause of acute myocardial infarction (AMI) in fertile life and in pregnancy. We have started a registry of such women in Italy, and have enrolled 150 women to date (mean age 30 ± 4. 9 years). In our Registry of 230 post-menopausal hypertensive patients (mean age 68± 6 years), stress-induced AMI with normal CA (Tako-Tsubo cardiomyopathy) was present in 87%, as an example of extreme reversible ED. Finally, the same clinical presentation may characterize older women with epicardial CAD, but still gender differences are described. Pathologic data indicate that women present more often with plaque erosion than rupture and women have more periprocedural complications when undergoing percutaneous coronary interventions (PCI). These findings are confirmed by studies in which we are participating: the ongoing OCTAVIA (Optical Coherence Tomography After Immediately Thrombus Aspiration), and the SPIRIT Women Trial (Evaluation of the safety and efficacy of XIENCE V everolimus-eluting stent system) a prospective, open-label, multicenter study in which 1.572 women were enrolled in 73 sites outside the United State). In the SPIRIT Trial, early postmenopausal women present with more inflammation, and suffer more periprocedural complications due to smaller coronary arteries and presence of palque erosions. In conclusion women differ from men in the clinical presentation of CAD, revealing a spectrum of pathophysological substrates with may have specific impact on treatment and prognosis.

Sex and gender differences in CHD diagnostics

Prof Karin Schenck-Gustafsson M.D., Ph.D., F.E.S.C., Department of Medicine, Karolinska Institutet, Chief Consultant of Cardiology, Karolinska University Hospital

Coronary heart disease (CHD) in women is different from that in men with respect to symptoms, pathophysiology, value of the diagnostic tests and response to treatment. The risk factors have a different impact and women have special hormone-related risk factors. CHD hits women about ten years later than men, but women with risk factors especially with diabetes lose their sex advantage. Women with CHD are less likely to experience chest pain than men and may have less specific symptoms. Non-invasive tests are less sensitive and specific in women compared with men. Women with angina or myocardial infarction have a lower prevalence of significant coronary stenoses and atherosclerosis seems to be more diffuse than in men. In a recent study on all Swedish patients during a year (n=12.200) being investigated because of stable chest pain and referred for a first-time elective diagnostic coronary angiography were included. In the youngest age group (≤59 years), more women than men 78.8 % vs. 42.3% had normal/nonsignificant CAD, whereas more men had either left-main or three-vessel disease (18.2 vs. 4.2%). Was almost 80% of all caths unnecessary in women? Evidently, new techniques are needed to identify coronary heart disease in women.

Sex Differences in cardiometabolic diseases

Alexandra Kautzky-Willer, M.D., Internal Medicine III, Endocrinology & Metabolism, Gender Medicine Unit, Medical University of Vienna, Austria

The dramatic increase in the prevalence of overweight and obesity has resulted in a major burden on healthcare costs in developed countries. Excess fat mass increases the risk of mortality overall and increases individually the risk of chronic diseases like type 2 diabetes, hypertension, cardiovascular disease and many other health problems. Body fat distribution differs between men and women with significant changes during life-time. Obesity and type 2 diabetes are chronic lifestyle-diseases which are dramatically increasing worldwide. Both biological and psychosocial factors, environment and lifestyle are involved in the pathogenesis of these metabolic disorders and thus important sex and gender based differences can be

found. Although obesity causing most cases of type 2 diabetes is classified by the World Health Organisation as one of the principle causes of preventable chronic diseases, prevention strategies and treatment options are limited. Life-long programs including lifestyle (diet, exercise) and behavioural modifications are necessary and there is need of new drug therapies and combination therapies. Bariatric surgery may be an interesting option in subjects with BMI >37kg/m^2 and co-morbidities. Both obesity and diabetes increase the risk of cardiovascular disease (CVD: myocardial infarction and stroke) but also of certain malignancies. Among others women have increased risk of postmenopausal breast cancer and endometrium carcinoma. Obesity (in particular central adiposity) may be associated with even higher risk to develop type 2 diabetes in women than men although various longitudinal studies in middle-aged subjects report higher diabetes incidence rates in men compared to women. Men appear to develop diabetes at lower BMI than women. Diabetes increases the risk of CVD in both sexes but more dramatically in women than men compared to non-diabetic subjects of the same sex. Diabetes may be a more prominent risk factor of stroke in males but obesity may be a more important predictor of stroke in females. Differences in treatment and communication and lack of sex-specific guidelines may further aggravate sex-and gender based outcomes in diabetic subjects.

SYMPOSIUM III: SEX DISPARITIES IN CANCER

Sex disparities in cancer incidence, mortality and survival

Michael B. Cook, Ph.D., Hormonal and Reproductive Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS

Background: Previous research has noted that cancer incidence and mortality rates tend to be higher among males than females, and that males tend to have poorer survival relative to females. However, rarely have these themes been the focus of investigation.
Methods: For analysis of sex differences in cancer incidence, mortality and survival, we used the Surveillance, Epidemiology and End Results (SEER) program data. We computed age-adjusted (2000 U.S. standard population) sex-specific incidence rates and male-to-female incidence rate ratios (IRR). Similarly for mortality, we compared sex-specific mortality rates and examined male-to-female mortality rate ratios (MRR). For assessment of cancer survival, we estimated hazard ratios for death in the 5-year period following cancer diagnosis for males compared with females.
Results: The 5 cancers with the largest male-to-female IRR were Kaposi sarcoma (28.73), lip (7.16), larynx (5.17), mesothelioma (4.88), and hypopharynx (4.13). Only 5 cancers were more incident in females: breast (0.01), peritoneum, omentum, and mesentery (0.18), thyroid (0.39), gallbladder (0.57), and anus, anal canal, and anorectum (0.81). Disparities of cancer mortality largely paralleled those of cancer incidence. In addition, the patterns of sex-specific mortality rates and male-to-female MRRs by age and stratified by decade appeared to be nearly identical to the patterns observed in cancer incidence rates. Cancer survival was generally worse for males than females: the 5 highest hazard ratios were for the cancer sites skin excluding basal and squamous (1.58), endocrine system (1.32), floor of mouth (1.32), anus, anal canal, and anorectum (1.21), and lymphoma (1.20). In contrast, 2 sites were notable for their decreased risk of cause-specific mortality in men relative to women: urinary bladder (0.83) and tongue (0.89).
Conclusions: The results of this analysis supports the idea that sex disparities in cancer mortality arise from the sex differences in cancer incidence. This analysis also shows modestly, but appreciably, worse survival in men for a number of cancers. Future analytic studies should attempt to understand causes of observed sex disparities in cancer.
This work was supported by the Intramural Program of the National Cancer Institute, NIH, Department of Health and Human Services.

Inflammation, metabolism, aging and cancer: dangerous liaisons

Michael Karin, Ph.D., Laboratory of Gene Regulation and Signal Transduction, Department of Pharmacology and Pathology, UCSD School of Medicine, La Jolla, CA.

The most common form of liver cancer, hepatocellular carcinoma (HCC), usually arises in the context of chronic liver disease, such as cirrhosis, viral hepatitis and non alcoholic fatty liver disease (NAFLD). Using chemically induced HCC in mice as an experimental model, we found that inactivation of NF-κB or p38α signaling in hepatocytes results in increased accumulation of reactive oxygen species (ROS) and enhanced hepatocyte death, changes that accelerate HCC development. ROS accumulation and oxidative stress lead to activation of Jun kinases (JNK) and JAK2, resulting in enhanced AP-1 and STAT3 activities. Accordingly, total JNK1 ablation and hepatocyte-specific

deletions of c-Jun or STAT3 inhibit the development of chemically-induced HCC. We also investigated how obesity enhances HCC development using a model of obesity-promoted chemically-induced HCC. Our results indicate that obesity leads to hepatosteatosis which results in metabolic alterations and chronic inflammation. Inhibition of steatohepatitis through ablation of either type 1 TNF receptor (TNFR1) or interleukin 6 (IL-6) abolishes the tumor promoting effect of obesity. Although HCC is one of the most lethal cancers with a 5-year survival rate of 5%, it is very slow growing. Thus, early detection of HCC may provide an opportunity for therapeutic intervention before the cancer becomes too aggressive and refractory to therapy. To this end, we have isolated from livers of mice treated with the chemical carcinogen diethylnitrosamine (DEN) a population of pre-malignant cells that can give rise to HCC when transplanted into a suitable host. These cells, which we named HCC initiating cells (HIC), are not as transformed as HCC cells and display unique properties that should enable both their early detection as well as elimination.

Sex hormones and immune regulation: implications for cancer therapy

Svetomir N. Markovic, M.D., Ph.D., Mayo Clinic-Rochester, MN

Immune-related processes in humans are under temporal regulation. In advanced melanoma, we have showed that systemic immunity is repolarized toward a global state of chronic inflammation and is governed by *infradian* biorhythms of cytokines and immune cell subsets, which extend beyond the 24-hour circadian variability reported in normal volunteers. Our preliminary data also shows that chemotherapy delivery in different "phases" of the *infradian* immune cycle (rhythm) yields dramatically different clinical outcomes, conferring clinical relevance to this early observation. The mechanism of the newly described *infradian* immune biorhythm in advanced melanoma is unknown. Our objective is to identify whether these fluctuations between states of activation and tolerance are an attribute of the host immune response to malignancy, or whether these immune biorhythms may also be manifestation of neuroendocrine regulation of immunity. Published literature offers some supportive evidence towards this supposition: (1) cells of the immune system express receptors for neuroendocrine and sex hormones; (2) the circadian variation of humoral and cellular immunity is hormonally-modulated (3) clinical outcomes in patients with melanoma are influenced by sex and menopausal status; and (4) there appears to be significant overlap between mechanisms of fetomaternal tolerance in normal human pregnancy with those of advanced melanoma. The latter, in conjunction with emerging data on the impact of menopause on normal aging of immunity in women suggest a possible regulatory role of sex hormones in systemic immune homeostasis. Elucidation of these interactions will offer critical insights into as yet unrecognized aspects of personalized cancer therapy particularly relevant in therapeutic modalities that rely on the patients own immune system as a mediator of anti-tumor activity.

Role of estrogen in *Helicobacter pylori* associated gastric cancer

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Helicobacter pylori infection increases lifetime risk of duodenal and gastric ulcers, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric carcinoma (GA). Gastric cancer is the second most frequent cause of cancer-related death worldwide. Age-standardized and cumulative incidence rates of gastric adenocarcinoma are twice as high in males as in females with a 2.5-fold difference around age 60. The age-specific pattern of the M/F gastric cancer incidence curve is a global phenomenon, seen equally in populations with high and low risks for GC. Given the high prevalence of *H. pylori* worldwide, this implies that intrinsic sex differences modulate *H. pylori*-induced carcinogenesis irrespective of other environmental factors. Although estrogen is hypothesized to reduce gastric adenocarcinoma in women due to its myriad of immunomodulatory effects, few studies involving animals with a recognized sexual dimorphism in GC incidence have analyzed the role of 17 -estradiol and H. *pylori* in gastric carcinogenesis. Studies using ovariectomized female *H. pylori* infected INS-GAS mice demonstrated that E2 treatment of chronically infected mice, attenuated the severity of gastritis and reduced the development of gastric cancer. We hypothesized that E2 was protected due to decreases in proinflammatory mediators like *IL-1* and *iNOS* and increases in anti-inflammatory mediators like *IL-10*. E2 administered prophylactically, but not castration, reduced *H. pylori* induced gastric lesions in male INS-GAS mice and was associated with an increase in gastric FoxP3+ regulatory T cells. Infected INS/GAS male mice treated with E2 experienced a significant reduction in gastric lesions with no cancer development compared to more severe lesions and a 40% incidence of gastric carcinoma in infected untreated males. Progressive *H. pylori* gastritis results from chronic inflammatory processes mediated by proinflammatory Th1

and Th17 cells. The attenuation of gastric lesions by E2 treatment was accompanied by a downregulation of proinflammatory cues. Sex differences in gastric cancer incidence, the protective effect of prolonged fertility in females and the reduced risk among women taking postmenopausal hormones, are elements suggesting that sex hormones play a protective role in *H. pylori* associated gastric cancer. Our findings suggest that E2 decreases gastric cancer by decreasing neutrophilic infiltration and attenuating the chronic inflammatory response, and by decreasing expression of Wnt/ß-catenin signaling factors, important in oncogenesis. We believe that the reduction of neutrophilic infiltrate by CXCL1 reduces the exposure of the stomach to oxidative stress, a cause of DNA mutagenesis, decreases proinflammatory cellular infiltrates and delays the progression of gastric cancer.

SYMPOSIUM IV: SEX DIFFERENCES IN STEM CELLS

Effect of donor & host sex in tissue regeneration with muscle derived stem cells

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Members of the Stem Cell Research Center (SCRC) have isolated various populations of myogenic cells from the postnatal skeletal muscle of normal mice by means of the cells' adhesion characteristics, proliferation behavior, and myogenic and stem cell marker expression profiles. Although most of these cell populations have displayed characteristics similar to those of skeletal muscle satellite cells, we also have identified a unique population of muscle-derived stem cells (MDSCs). The MDSCs exhibit long-term proliferation abilities, elevated self-renewal rates, increased resistance to stress, and they are multipotent and can differentiate toward a variety of tissue types including: muscle (skeletal and cardiac), neural, endothelial, osteogenic, and chondrogenic lineages, both in vitro and in vivo. In contrast to other myogenic cell types, MDSCs show very efficient engraftment and regeneration of various musculoskeletal tissues due to their ability to highly survive post-implantation through the high anti-oxydant expression by MDSC. We have recently observed that the gender/sex influenced not only the myogenic, osteogenic and chondrogenic potential of MDSC but also their regeneration index of various tissue of the musculoskeletal system. The gender of the host animal also influenced environmental cues released within the injured tissues which have been found to also impact the regenerative ability of MDSCs. Potential strategies to improve the regenerative potential of MDSCs are being explored to prevent the formation of fibrosis within injured tissues by blocking the action of TGF- 1. Finally, blood vessels contain several cell types, including endothelial cells and pericytes that are likely the place of origin of the murine MDSCs and consequently strategies to improve angiogenesis are being investigated as potential therapeutic options to improve tissue healing. The results outlined above open new avenues by which researchers could use muscle stem cell–based gene therapy and tissue engineering to improve tissue regeneration.

Sex differences in neural and glial genesis in the brain.

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

Ongoing neurogenesis in the mature brain has been a topic of interest and controversy, with evidence for new neurons continuing to be born in the dentate gyrus of the hippocampal formation in humans and the subventricular zone and subgranular layer of the dentate gyrus of the adult rodent. Using the laboratory rat, we have focused on a different developmental phase, the early postnatal sensitive period during which the majority of sex differences in the brain are organized. Using BrdU labeling of proliferating cells combined with neuronal and astrocytic markers, we have found that neural stem cell proliferation occurs at twice the rate in newborn male rats as females. This sex difference is mediated by endogenous estradiol as neural proliferation can be blocked in males by both estrogen receptor antagonists and aromatase inhibitors or stimulated in females by exogenous estradiol administration. The sex difference in stem cell proliferation is transient, occurring only during the first few postnatal days, but reappears in the early juvenile period. Intriguingly, estradiol appears to permanently organize the pattern of stem cell proliferation via epigenetic mechanisms. The amount of global DNA methylation and the activity of DNA methylating enzymes (DNMTs) is significantly higher in neonatal female hippocampus compared to male and decreased in females by exogenous estradiol administration. Inhibition of DNMT activity in females prevents the reappearance of the sex difference in stem cell proliferation in the early juvenile period. Many of the new neurons born during the first few days of life persist until maturity, suggesting an enduring functional

impact of the sex difference in stem cell proliferation, but the behavioral or physiological significance has not yet been identified. This research was supported by NIH R01 NS050525 to MMM.

Sex differences in microglial colonization of the developing brain: implications for health and disease.

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Microglia are the primary immune cells of the brain. Under baseline conditions, microglia survey and maintain homeostasis of the microenvironment. Following insult, injury, or infection, microglia respond with a rapid and robust increase in the synthesis of immune molecules, including cytokines and chemokines. Microglia are first observed within the developing rat brain around embryonic day 14, originating via the infiltration of primitive macrophage precursors from the yolk sac of the developing embryo. At this time, microglia have a large, round, amoeboid morphology and their production of cytokines and chemokines is critical for many processes of normal brain development. Notably, sex differences exist in many processes of neural development; however, it is unknown whether a sex difference concurrently exists in the colonization or morphology of microglia within the developing brain. We analyzed the number and morphology of microglia at multiple points throughout the development of the rat brain, including embryonic day 18, postnatal day (P) 0, P4, P30, and P60. We demonstrate for the first time that the number and morphology of microglia within brain regions important for cognition is dependent upon the sex and age of the individual, as well as the specific brain region of interest. Specifically, males have significantly more microglia than females within the hippocampus, amygdala and cortex at P4; while females have significantly more microglia than males in these same brain regions just prior to adolescence (P30) and into adulthood (P60). Finally, gene expression of a large number of cytokines, chemokines and their receptors shifts dramatically over development of these brain regions, and is also highly dependent upon sex. Taken together, these data warrant further research into the role that sex-dependent mechanisms may play in microglial colonization, number, and function, and their potential contribution to neural development, function, or dysfunction.

Modulation of post-stroke neural and glial progenitor responses is sex-dependent

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Background: Neonatal stroke occurs in 1 in 4000 term births, presents late with seizures, and results in cognitive impairments. Cellular therapy holds promise for a future intervention because of the long time window of efficacy suggested by preclinical studies in adult models. Ongoing safety trials of cord blood in neonates after hypoxic-ischemic injury supports the relevance of preclinical studies with these cells.
Methods: P12 CD1 mice received right common carotid ligation and 48 hours later were injected i.p. with 1x105 CD34+ enriched human cord blood stem cells (CBSC). Behavioral milestones and animal weights were evaluated from P9 to P21. 5-bromo-2'-deoxyuridine (50mg/kg, i.p.) was injected 2h prior to sacrifice on P21; spleen weights were measured. Percent brain atrophy was quantified. Immunohistochemistry was performed and density of BrdU, Iba-1, and GFAP expression or labeled cells in the SGZ and SVZ regions quantified.
Results: Spleen size was reduced and correlated with the severity of the injury and with post-stroke neurogenesis in vehicle treated injured aniamls; CBSC treatment removed these correlations. Severity of injury and animal weight were not impacted by CBSC treatment. Functional tasks were not sensitive to stroke injury, and therefore did not show a CBSC response. In males treated with CBSC, SGZ proliferation was significantly increased bilaterally compared to injured males treated with vehicle, and this was associated with a marginal trend for increased GFAP expression in the contralateral DG; these results were not seen in injured females treated with CBSC. In the contralateral SVZ and SVZ region, there was a trend for increased BrdU associated with significantly increased GFAP expression. Density of Iba-1 labeled cells was increased in the ipsilateral injured DG and SZV but was not altered by the cell treatment in the injured animals, either in the overall group or analyzed by animal sex.
Conclusions: CBSC i.p. after neonatal stroke regulates post-stroke neurogenic niche proliferation and GFAP expression in a sex dependent manner. This suggests a sex-dependent impact of the CBSC upon the radial glial stem cells and astrocytes that likely occurs via cytokine release. Future studies are needed to delineate mechanisms underlying this sex-dependent response.

SYMPOSIUM V: SEX DIFFERENCES IN MECHANISTIC PATHWAYS OF CARDIOVASCULAR DISEASE

The Yentl Syndrome 2011: Why are there differences in ischemic heart disease in women and men (including genes)?

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Women are now more likely to die of ischemic heart disease than men. Explanations suggested include changes in risk factors, menopause, longevity and genes. Women less frequently receive the life-saving medical therapies for ischemic heart disease compared to men. The NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) has documented a high prevalence of coronary vascular dysfunction in women with symptoms and evidence of ischemia with no obstructive CAD. The condition is associated with an adverse prognosis and healthcare costs similar to obstructive CAD, there are an estimated 2-3 million women with existent disease, and a projected 100,000 new cases annually. This places the prevalence, morbidity and costs of coronary vascular dysfunction higher than all female reproductive cancers combined. Study suggests this "female-pattern" of ischemic heart disease is less likely to be recognized and therefore lead to the use of live-saving therapies, suggesting that the "Yentl Syndrome" is alive and well in 2011. Recent data evaluating the impact of guidelines therapy for ischemic heart disease is closing the mortality gap between women and men. Results of many investigators have provided practicing physicians with the ability to translate the findings into clinical care for improved IHD outcomes.

Sex differences in genomics of left ventricular remodeling

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We investigated the influence of Estrogen (E2) and its receptors (ER) on the pathophysiological and molecular mechanisms leading to sex-differences in cardiac remodeling in an animal model of pressure overload (PO) and studied effects of E2 ex vivo in human heart samples. First, we performed transverse aortic constriction (TAC) in male and female wild type mice and mice with genomic deletion of ERß (ERß-/-). Nine weeks after TAC, myocardial hypertrophy was significantly more pronounced in WT males than in females. Male WT TAC animals showed a strong increase in cardiac profibrotic genes and in fibrosis. In contrast, female WT hearts were characterized by preservation of energy metabolism. ER ß was associated with mitochondrial metabolism in females. Only ERß-/- male TAC animals went into the apoptotic gene program. Thus, female sex and ERß contribute to the maintenance of energy homeostasis and limit the development of excentric cardiac hypertrophy, fibrosis and apoptosis. Second, we investigated the effect of E2 in human heart muscle preparations ex vivo. Treatment of muscle strips with estrogen introduced a genomic response that differed in males and females. In males only, the E3 ubiquitin ligase Mylip (MRLC interacting protein) was upregulated and its substrate, the myosin regulatory light chain (MRLC) was downregulated due to increased ubiquitination. Correspondingly, E2 treatment of male mice led to reduced CM contractility, which was characterized by increased expression of MYLIP and decreased MRLC. This indicates that E2 has direct deleterious effects in the male heart. We believe it will be useful to unravel the underlying pathways and to identify novel therapeutic targets for heart failure.

A novel 17-beta-estradiol prodrug for the treatment of menopausal symptoms: hot flushes, depression and sleep disorders in animal models

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The major menopausal symptoms women seek help for include hot flushes, depression/anxiety, and sleep disturbances. Estrogen therapy has been the treatment of choice to alleviate these symptoms; however, many women cannot take estrogens. Therefore, there is an unmet need for novel, efficacious, and safe therapies. Para-quinol of 17ß-estradiol (DHED, based on its chemical structure) is selectively converted to 17ß-estradiol (E2) in the mammalian brain, however, such conversion does not occur in the peripheral tissue including the uterus, breast, or the pituitary gland. Thus, DHED's action is restricted to the brain without causing many of the side effects that can be observed following chronic treatment with estrogens. The current studies were designed to test whether DHED can alleviate hot flushes, exhibit antidepressant and anxiolytic properties, and affect the quality of sleep in animal models. Similarly to E2, DHED reduced naloxone-induced tail skin temperature rise in the rat hot flush model. In the mouse models of depression/anxiety, DHED as

well as E2 resulted in reduced immobility time in the forced swim test and had no effect on locomotor activity in the open field test. However, DHED increased the time animal spent in the center of the field as well as in the open arms of the elevated plus maze. DHED also reduced immobility time in the tail suspension test and reduced despair-like behavior in the learned helplessness test. In OVX rats, DHED, similarly to E2, reduced REM sleep. In all procedures, the efficacious dose of DHED was about 1/5 of E2 and effects of DHED resembled the effects of E2 but while E2 exhibited uterotropic activity, DHED did to stimulate the uterus. *Conclusion:* The use of a CNS-specific DHED may provide a novel and promising treatment for women who suffer from menopausal symptoms. *Supported by:* NIH grants 1RO1AG031535-01A2, 3R01AG031535-01A2S1, and AG031535

SYMPOSIUM VI: DEPRESSION AND ANXIETY DISORDERS: NOVEL TARGETS FOR SEX SPECIFIC TREATMENTS

Epigenetic regulation of sex differences in stress related disorders

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Women have a higher occurrence of mood and anxiety disorders than men, however, little is known about the biological basis of this disparity. The current studies were undertaken to elucidate the genetic and epigenetic mechanisms that contribute to sex differences in a stress-induced behavioral animal model of depression and anxiety. Exposure to a 6 day varied stressor resulted in depression and anxiety associated behaviors only in female mice. Patterns of gene regulation in the nucleus accumbens of male and female mice exposed to the stressor varied between the sexes with only a 3% overlap. Many more genes were regulated in males compared to females suggesting that resiliency to stress in males is an active process. Investigation of a class of enzymes, DNA methyltransferases and methyl binding domain proteins, involved with suppression of gene expression indicated that males and females had different baseline and stress-induced patterns of transcriptional regulation. In addition, we used a combination of viral-mediated gene transfer and conditional knockouts to achieve brain region specific adult regulation of Dnmt 3a and examined its functional relevance to depression and anxiety associated behaviors. These data indicate that Dnmt3a promotes behavioral stress sensitivity differently in males and females. Dnmts and MBDs both contribute to sex specific susceptibility and resilience to stress suggesting that regulators of DNA methylation in the adult brain may be a novel mechanism and potential drug target for sex specific depression and anxiety disorder treatment. Funding source: NIMH 1R01MH090264-01A1 to SJR and NIDA 5TDA07135-28 to GEH.

Sex differences in stress response systems: From molecules to mental illness

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Stress-related psychiatric disorders, such as depression and anxiety, are twice as prevalent in women as in men. Because these disorders are linked to dysregulation of the stress neuropeptide corticotropin-releasing factor (CRF), sex differences in CRF sensitivity could underlie this disparity. Supporting this idea, neurons in the locus coeruleus (LC), a brain arousal center, are more sensitive to CRF in female versus male rats. Recently we related these electrophysiological findings to sex differences in CRF receptor (CRFr) signaling and trafficking. Specifically, the CRFr couples more to the GTP-binding protein, Gs, in females, an effect that can account for elevated responses to acute stress. Additionally, stressor exposure in rats and CRF overexpression in mice causes CRFr internalization in males only, suggesting that females lack this important cellular adaptation. This sex difference was associated with increased LC neuronal firing in female, but not male CRF overexpressing mice. Together, these sex differences in CRFr function can render LC neurons of females more sensitive to low levels of CRF and less adaptable to high levels of CRF. This would translate to hyperarousal, a core feature of stress-related psychiatric disorders. Finally, sex differences in the CRFr could affect the efficacy of CRFr antagonists as therapeutic agents.
This work was supported by USPHS Grant MH084423 and MH092438 to DAB and MH40008 to RJV.

Differential sex-specific effects of the PACAP (ADCYAP1R1) and androgen (SRD5A2) pathways with Posttraumatic Stress Disorder in a highly traumatized population

Kerry Ressler, M.D., Ph.D., Howard Hughes Medical Institute, Emory University

Multiple mechanisms may differentially mediate sex differences in mood and anxiety disorders. This presentation will examine two different genetic studies which demonstrate differential sex-specific associations with posttraumatic stress disorder (PTSD) symptoms. We examined 44 single nucleotide polymorphisms (SNPs) spanning the pituitary adenylate cyclase activating peptide (PACAP, encoded by *ADCYAP1*) and its PAC1 Receptor (encoded by *ADCYAP1R1*) genes in >1200 individuals, demonstrating a sex-specific association with PTSD. A single SNP in a putative estrogen response element within *ADCYAP1R1*, rs2267735, predicts PTSD diagnosis and symptoms in females only. We will present data demonstrating evidence of estrogen dependent expression of *ADCYAP1R1* in mice and humans. We will also present new data examining potential estrogen response element mechanisms regulating *ADCYAP1R1* expression. We also examined a non-synonymous, SNP in the gene coding for steroid 5- -reductase type 2 (SRD5A2), which is associated with reduced conversion of testosterone to dihydrotestosterone (DHT). We found a significant sex-dependent effect of genotype in male but not female subjects on PTSD symptoms (n>1200). We found that the V89L variant of SRD5A2 (rs523349) influences risk for post-traumatic stress disorder (PTSD). We thus demonstrate different examples of sex-specific effects in genetic association studies in which trauma exposure is associated with differential levels of posttraumatic stress or depression symptoms in males vs. females. It is important to appreciate that there are likely many different possible mechanisms which may mediate different sex-specific effects, and that estrogen, testosterone, and their metabolites, along with social and trauma differences may all be processed via different molecular pathways.

Unique characteristics of anxiety and depression among couples undergoing in vitro fertilization treatment

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Objective: Gender-oriented medicine has to do with a broad variety of topics, where there are differences between men and women in etiology, diagnosis, treatment and somatic and psychological responses of patients. Fertility has a special place within the wide range of these subjects.
Psychological effects on the fertility process: The relationship between the physiological and the psychological factors is complex and partly unknown. Yet, enough data has accumulated to show that psychological factors have an important role in fertility treatment. A central psychological factor is stress, whose influence may be critical. For example, it is well known that in infertility treatment the quality and quantity of the sperm as well as the quality and quantity of the ova have a great influence on the success of the treatment.
Gender differences in attitudes and emotional responses to infertility: A fairly large number of studies have found differences between men and women in their responses to infertility and their ways of coping with the problem. Findings show, inter alia, that the drive for parenthood is usually higher among women than among men, and women are generally more willing to make sacrifices for materializing this drive. Findings also show that women tend more than men to express their frustrations and difficulties verbally. There are also gender differences in the psychological modes of coping with the situation.
The importance of understanding gender differences for the success of infertility treatment: The psychological aspects of infertility treatment must be tailored to the characteristics of the specific couple. It was found that in some modes of coping, the husband's coping style affects that of the wife, and vice versa. The treatment must, therefore, take into account the physiological and psychological interaction between the couple. Extensive survey of the relevant literature and the results of our own studies will be presented.

SYMPOSIUM VII: ANIMAL MODELS FOR SEX DIFFERENCES RESEARCH

Sex differences in the nervous system: Insights from genetic model systems

Douglas Portman, Ph.D., Center for Neural Development and Disease, University of Rochester Medical Center

In vertebrates, gonadal steroids have key roles in organizing and activating sex differences in the brain. However, important recent work

has clearly demonstrated that hormone-independent, "genetically driven" mechanisms also have critical roles in the sexual differentiation of the nervous system. Interestingly, this situation is reminiscent of invertebrate sexual differentiation, in which master regulator genes act cell-autonomously to regulate the development and function of the nervous system. I will review our current understanding of sex differences in the nervous system in the fruit fly *Drosophila* and the nematode *C. elegans,* both of which have lent numerous key insights into the genetic control of neural development and behavior. Importantly, recent studies reveal that there may well be genetic conservation of some of the mechanisms used by both vertebrates and invertebrates to translate genetic sex into the modulation of neural development and function.

Sex differences in insects: beyond fru and haplodiploidy

Susan E. Fahrbach, Ph.D., Department of Biology, Wake Forest University, Winston-Salem, NC, USA

Sex differences in insect behavior are well-documented but most of the million+ species of insect of course have not been studied from the essential perspectives of neuroendocrinology and neuroanatomy. This presentation will present case studies of several key species that are exceptions to this rule: the fruit fly, *Drosophila melanogaster* (neural and genetic substrates of male sexual behavior); the hawkmoth, *Manduca sexta* (sex-specific olfactory receptor cells, and how they organize the developing brain); and the honey bee, *Apis mellifera* (brain basis of sex differences in reproductive and non-reproductive behaviors). Major themes include the role of sex-specific cell death and the importance of sexually-dimorphic sense organs during development of the central nervous system plus, relative to vertebrates, the lack of a major role for hormones in promoting the development of sex differences. This material is based in part upon work supported by the National Science Foundation.

Fishing for sex differences

Daniel A. Gorelick, Ph.D. and Marnie E. Halpern, Ph.D., Carnegie Institution for Science, Department of Embryology

The zebrafish (*Danio rerio)* is a useful vertebrate genetic model for the study of sexually dimorphic steroid hormone receptor activity. Estrogens, progestogens and androgens, as well as their receptors, are conserved, and many small molecule endocrine disruptors are effective and easily administered in fish water. The organization of the hypothalamo-pituitary-gonadal axis is similar to that of mammals. Zebrafish embryos and larvae are clear and develop outside of the mother, allowing for live imaging of fluorescent reporters, while the small size and high fecundity of adults enables systematic testing of hundreds of subjects in behavioral assays or in genetic screens. We sought to capitalize on these advantages and establish the zebrafish as a genetic model to investigate sexually dimorphic activity of estrogen receptors. To visualize estrogen receptor activation in vivo, we developed stable, transgenic zebrafish containing five consecutive estrogen response elements (EREs) upstream of green fluorescent protein (GFP). The 5xERE:GFP reporter is specific, sensitive and able to detect exogenous and endogenous estrogens, depending on developmental stage. We identified differences in the number of estrogen responsive cells in the central nervous system between males and females. These transgenic lines will facilitate screens to identify genes and small molecules that regulate estrogen receptor transcriptional activity and the formation of estrogen responsive neurons. We also demonstrate that the reporter lines serve as sentinels for aquatic pollution and as models for studying the effects of endocrine disruptors on embryo development and organ formation.

Neural sex differences and similarities in the control of vocal behavior in songbirds

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One of the most dramatic neural sex differences ever described in the vertebrate brain relates to the brain areas that control the learning and production of song in songbirds. Temperate zone male songbirds tend to form territories in the spring and sing a robust complex vocalization called its song which functions to attract females and repel competitors. This song is learned in a manner akin to human language. A specialized neural circuit was described that regulates the learning, perception and production of song. Nottebohm and Arnold described dramatic male-biased sex differences in the volume of key forebrain nuclei in zebra finches and canaries. Sex differences in the song system have been investigated in about 25 songbird species that exhibit a variety of patterns of sex differences in behavior. Based on an analysis of these species a pattern emerges indicat-

ing that the degree to which there is a sex difference in behavior is reflected in the degree to which there is a sex difference in the volume of the song nuclei. Species that live in the tropics where the male and female produce a single song in a duet are especially illustrative as in these species male/female differences in brain are reduced compared to temperate zone species. One feature of the male songbird brain is the occurrence of song-specific neurons. These are neurons that respond preferentially and specifically to the bird's own song (BOS). Recently Eric Fortune, Melissa Colemen and myself (Science 2011 334: 666-670), studied the plain-tailed wren in Ecuador, a duetting species, and asked whether neurons in the male and female brain responded only to the part of the song they produce, their mate's song or to the joint song. The neural response to playback is clear, cells in HVC are tuned preferentially in both sexes to the joint song as compared to the part of the song produced by the male or the female. Thus in duetting species where males and females cooperate to produce a single song the brain has cells that are similarly tuned in males and females to mediate this complex cooperative behavior.

SYMPOSIUM VIII: POST-TRAUMATIC STRESS DISORDER (PTSD) AND ONE'S SEX

Experiences of sexual trauma during military service: implications for the gender-specific risk of PTSD

Amy E. Street, Ph.D., National Center for PTSD, VA Boston Healthcare System and Department of Psychiatry, Boston University School of Medicine

Despite growing awareness of the changing scope of women's roles in current combat operations, significant questions remain about women's deployment experiences and post-deployment adjustment. Further, combat-exposed women Veterans represent a new and important population for understanding the gender-specific phenomenology of posttraumatic stress disorder (PTSD). Accordingly, the objectives of this investigation were to quantify the gender-specific frequency of deployment stressors (including combat and sexual harassment), the gender-specific frequency of post-deployment mental health conditions, and the gender-specific associations between deployment stressors and PTSD. Data are from a national mail survey of 2,344 female and male Veterans, randomly sampled within gender, deployed in support of the wars in Afghanistan and Iraq. Women were much more likely to report exposure to sexual harassment and less likely to report exposure to combat. Women and men were about equally likely to report symptoms consistent with probable PTSD and symptomatic anxiety, while women were more likely to report probable depression and less likely to report clinically significant alcohol use. Controlling for identified confounders, odds ratios representing the associations between deployment stressors and PTSD were nearly identical for women and men. These findings suggest that the gender-specific risk of PTSD is not absolute, but instead differs substantially by trauma type and must be examined within different trauma type-exposed groups. Most importantly, these results suggest our nation's growing population of female Veterans appear as resilient to deployment stressors as our nation's male Veterans.

Gender differences in combat-related stressors and their association with postdeployment mental health among U.S. OEF/OIF veterans

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Though the broader literature suggests that women may be more vulnerable to the effects of trauma exposure, most available studies on combat trauma have relied on samples in which women's combat exposure is limited and analyses that do not directly address gender differences in associations between combat exposure and postdeployment mental health. Female servicemembers' increased exposure to combat in Afghanistan and Iraq raises the question of whether there are gender differences in the mental health consequences associated with combat-related stress exposure. The current study addressed these research questions in a representative sample of 340 female and 252 male OEF/OIF Veterans who had returned from deployment to Afghanistan or Iraq within the previous year. Participants completed measures of four dimensions of combat-related stress from the Deployment Risk and Resilience Inventory (DRRI), as well as measures of post-deployment mental health including PTSD symptoms (measure by the PCL), depression and substance abuse (measured by the BASIS-24), and mental health functioning (measured by the VR-12). As expected, women reported slightly less exposure than men to most combat-related stressors, but higher exposure to other stressors (i.e., prior life stress, deployment sexual harassment). No gender differences were observed in reports of perceived threat in the war zone. Though it was hypothesized that combat-related stressors would demonstrate stronger negative associations with postdeployment mental health for

women, only one of 16 stressor X gender interactions achieved statistical significance and an evaluation of the clinical significance of these interactions revealed that effects were trivial. The finding that women experience similar levels of combat stress as men highlights the need for increased attention to women's combat experiences in the assessment and treatment of returning OEF/OIF Veterans. The lack of clinical significant differences in associations between combat stressors and postdeployment mental health suggests that female OEF/OIF servicemembers may be as resilient to combat-related stress as men.

Sex differences in sleep-related predictors of PTSD

Thomas A. Mellman, M.D., Department of Psychiatry, Howard University College of Medicine, Washington, DC

Sleep disturbance is a prominent clinical feature of PTSD and appears to may contribute to its onset and maintenance. Abnormal patterns of dreaming have inspired specific interest in REM sleep. Previous studies have suggested that reduced slow wave sleep is found in men with PTSD and impaired sleep maintenance with PTSD has been a more consistent finding of a limited number of studies of women. We recently analyzed data from our prior study of sleep following traumatic injuries and our ongoing with trauma-exposed young adult urban African Americans. The first study indicated associations between impaired sleep maintenance and the development of PTSD in only women. In both studies the mean duration of continuous REM segments was significantly shorter among the participants developing PTSD and those with established PTSD in men and women. These findings support the hypothesis that disrupted REM sleep contributes to PTSD in both sexes.

Sex differences in neurobiology with potential relevance to PTSD risk, symptom severity, and chronicity

Ann M. Rasmusson, M.D., Suzanne Pineles, Ph.D., Erica Scioli, Ph.D., VA National Center for PTSD, Women's Health Science Division, VA Boston Healthcare System, and Boston University School of Medicine

Stress-induced changes in a number of neurobiological factors are associated with acute changes in mood state, brain function, and behavior. Many of these neurobiological factors are influenced by gender; in women, they are also influenced by menstrual cycle phase and reproductive status. Relevant neurobiological factors include: adrenal steroids such as dehydroepiandrosterone (DHEA) and its sulfated derivative, DHEAS, as well as cortisol; other neuroactive steroids such as allopregnanolone and androsterorone, derivatives of progesterone and testosterone, respectively, which potently and positively modulate brain gamma amino butryic acid (GABA) receptor function; peptides such as neuropeptide Y; and classic neurotransmitters such as serotonin, norepinephrine, and GABA. Gonadal hormones, including estrogen, progesterone, and testosterone influence the neurophysiology of these other stress hormone systems and are also influenced by stress. This presentation will review and distill clinical and basic research addressing the potential means by which such sex-related neurobiological factors may influence peritraumatic stress reactions and PTSD symptom severity, as well as the conditional risk for development and maintenance of chronic PTSD, which to date appears to be greater in women.

SYMPOSIUM IX: SEX DIFFERENCES IN GLOBAL HEALTH

Sex and gender aspects of tuberculosis: a review

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Tuberculosis (TB) shows a marked difference between men and women. In 2010 an estimated 800,000 men and 320,000 women died from TB. Based on case notification figures, more men than women are diagnosed with active tuberculosis, although this pattern is not consistent globally. This may be an accurate reflection of a higher incidence of TB among men or it may, in some contexts, reflect gender barriers to accessing national TB programs and health care systems. Differences between men and women have also been demonstrated for detection of TB, progression to disease after infection, and disease outcome, as well as the social consequences of the disease.

Both biological sex and socially constructed gender differences are important determinants of health and interact to produce differences in risks and vulnerability, in health- seeking behavior, and in the ability of individuals to protect their own health. Furthermore, these factors interact with other social determinants of health such as social class, ethnicity, and urban or rural residency. In spite of this, research

addressing the combined effects of sex and gender differences has been a marginalized area, and there are important research gaps, especially in relation to the increasing feminization of the HIV epidemic, where a quarter of all HIV deaths are estimated to be linked directly to TB. While global TB incidence has reversed and there is great progress in relation to the MDGs, there are still important regional variations. The spread of the HIV pandemic has had a profound impact on the epidemiology of TB in sub-Saharan Africa, where HIV rates among young women can be three to six times higher than among men of the same age group. The corresponding high rates of co-infection with HIV and M. tuberculosis is causing important gender specific vulnerability to TB.

Data disaggregated for sex and age need to be examined at national and district levels, in order to reveal dynamic processes such as the interaction with HIV/AIDS and to assess the role of gender-related factors at all stages, while equal efforts are needed to further investigate the sex specific immunological responses to infection and disease progress.

Sex differences in response to measles and measles vaccine

William J. Moss, M.D., M.P.H., Department of Epidemiology, The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Measles provides an intriguing example of sex differences in response to infection. The World Health Organization rescinded the recommendation that young children receive high-titer measles vaccine in 1992 following evidence that, in certain regions of the world, girls receiving this vaccine had increased mortality compared with those receiving standard-titer vaccines. Evidence for increased mortality among girls following wild-type measles virus infection is suggestive but inconclusive. Among persons of different ages and across different regions (primarily in the Americas and Europe), measles mortality in girls was estimated to be 5% higher than in boys. Although older historical data and recent surveillance data did not identify similar sex differences, if true, the higher mortality in girls is in contrast to most other infectious diseases in which disease severity and mortality is higher in males.

Males, females and children's inflammatory responses during and after malaria infection: sex and sex hormones associated with chronic inflammation

OraLee Branch, Ph.D.[1,2], Mario Hoenemann, M.D.[1], Jonathan Merola[1], Jean N. Hernandez, M.D.[2]
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Malaria infections caused by malaria leads to an inflammatory response which is necessary to overcome the infection. The inflammation must be halted soon after infection to limit pathology. An inflammation response can be halted by switching to a Th2 anti-inflammatory response. Earlier studies suggest pubescent boys have a higher inflammatory response and pathology in malaria infections than boys of the same age pre-pubescent. We aimed to study the dynamics of the inflammation response by gender and by the hormone DHEAS levels. In Iquitos, Peru we sampled individuals prospectively regardless of symptoms to obtain blood samples before, during and after malaria infection. We tested 205 malaria-infected infected individuals matched by age, sex and parasite density of infection. We measured pro-inflammatory, CRP, IL-1, IL-6, TNF-α, and IFN-γ, and anti-inflammatory IL-4 and IL-10, cytokines. We also assessed blood marker levels of DHEAS, Leptin, EPO, transferrin, and ferritin. Of 60 individuals who all had a similar level of inflammation response at time of infection (Day 0), we had 16 female adults, 25 male adults and 19 children (<15 years old). We grouped individuals by cytokine responses 30 days after treatment of infection. There were three groups of post-infection levels of cytokines: group-H "halted with negligible levels of inflammatory responses after infection", group-C "chronic inflammation without anti-inflammatory cytokines", and group-M "mixed with anti-inflammatory and medium to high levels of inflammatory cytokines". The males had higher post-infection levels of inflammatory cytokines. Of the 15 with a clear sustained Th1 response without anti-inflammatory cytokines, called group-C, 67% were males. Females and children were more likely to have halted their inflammatory response: of the group-H only 22% were male. The gender difference between group-H and group-C was significantly different ($p<0.05$). Interestingly, the women in group-C ("chronic inflammation") had significantly lower DHEAS levels and higher leptin levels that the average for women overall. Group-M (n=27) was a mix of female and male individuals (not significantly different). We will present how sex and DHEAS levels

might explain variation in the group-M and other groups. We find sex and sex hormone associated differences in the inflammatory response dynamics to malaria infection.

Sex differences in HIV-1 immunopathogenesis

Elizabeth Connick, M.D., Division of Infectious Diseases, Department of Medicine, University of Colorado Denver

Background: HIV-infected women have higher CD4+ T cell counts and lower viral loads than men, but progress at similar rates to AIDS in the absence of treatment. Mechanisms underlying these differences are not understood, nor why better prognostic markers in women fail to confer a survival advantage. Some data suggest that female sex hormones alter HIV-1 replication in vitro and in vivo. Differences in immune activation and HIV chemokine receptor expression have been hypothesized to account for sex differences in HIV pathogenesis.
Methods: We evaluated inguinal lymph nodes from untreated HIV-infected women (n=28) and men (n=27) not on antiviral therapy to determine 1) whether sex differences in CCR5 expression or immune activation account for lower viral loads in women and 2) if women produce fewer virions per infected cell than men. Disaggregated LN cells were analyzed by flow cytometry. Frequencies of virus-producing cells per mm2 of LN (VPC) were determined by in situ hybridization for HIV RNA, and plasma viral load (VL) by COBAS Taqman (Roche). Model estimates (95%CI) are reported from linear and negative binomial generalized linear regressions. Unadjusted results are expressed as medians.
Results: VL (log10 copies/mL) was lower in women (3.85) than men (4.49; p=0.01). In LN, %CCR5+CD4+ T cells and %CCR5+DR+38+CD4+ T cells, but not density of CCR5, were lower in women vs. men (10% vs. 16%, p=0.03; and 40% vs. 44%, p=0.07, respectively). After adjusting for CD4, race, and age, neither CCR5 density nor %CCR5+ on either CD4+ or DR+38+CD4+ T cells was predictive of VL or VPC (p>0.4). %DR+38+CD4+ (p=0.9) and %DR+38+CD8+ T cells (p=0.7) did not differ by sex. VPC were lower in women (0.29) vs. men (0.54; p=0.04). After adjusting for sex, CD4, log10 LN weight, and VPC, women had 0.56 (0.39, 0.73; p=0.002) lower VL than men.
Conclusions: Sex differences in VL cannot be explained by differences in CCR5 expression or immune activation in lymphoid tissues. Sex differences in VL persist even after controlling for VPC suggesting that women produce fewer HIV virions per productively infected cell than men.
These studies were funded by the NIH (R21HD051450, R21HD051450-02S1; and the University of Colorado Center for AIDS Research, AI51550).

CLOSING CAPSTONE LECTURE

Maternal and paternal gene networks in the male and female brain

Christopher Gregg, Ph.D., New York Stem Cell Foundation-Robertson Investigator; Assistant Professor, Neurobiology and Anatomy, University of Utah School of Medicine

Genomic imprinting results in preferential gene expression from paternally versus maternally inherited chromosomes. We used a genome-wide approach to uncover sex-specific parent-of-origin allelic effects in the adult mouse brain. Our approach utilizes RNA-Seq analysis of the transcriptome of mice generated by reciprocal crosses of the distantly related mouse strains CastEiJ and C57BL/6J. We used single nucleotide polymorphisms in the RNA-Seq data to distinguish gene expression from maternally versus paternally inherited alleles. Our study identified preferential selection of the maternally inherited X chromosome in glutamatergic neurons of the female cortex. Moreover, analysis of the cortex and hypothalamus identified 347 candidate autosomal genes with sex-specific parent-of-origin allelic effects influencing gene expression. In the hypothalamus, sex-specific parental effect genes were mostly found in females, suggesting parental influence over the hypothalamic function of daughters. We show that Interleukin 18, a gene linked to diseases with sex-specific prevalence, is subject to complex, regional, and sex-specific parental effects in the brain. We have begun to extend these findings to understand the impact of parental effects on diet-induced obesity in male and female offspring. Our results demonstrate that complex maternal and paternal effects differentially influence the physiology and gene expression of sons versus daughters. Parental effects thus provide new avenues for investigation of sexual dimorphism in brain function and disease.

POSTER SESSION I

Friday June 8, 2012
1:00 – 2:30 pm

POSTER ID: **801**

Sex-differences in pain perception in patients with cardiac syndrome X and patients with obstructive coronary artery disease

Abstract Presenter: Karolina Nowinski[1]
Other Authors: Stefan Grass[2], Hao Jingxia[3], Märta Segerdahl[2], Rolf Hallin[4], Susanna Wiesenfeld-Hallin[3], Karin Schenck-Gustafsson, M.D.[1]
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Introduction: Cardiac syndrome X is a condition characterized by chest pain and signs of ischemia during exercise electrocardiogram (ECG), but with normal coronary angiogram. Two hypotheses have been suggested to explain the chest pain in patients with cardiac syndrome X: 1) the ischemic hypothesis, defined as abnormal coronary microvascular function and 2) the non-ischemic hypothesis, with increased pain perception and myocardial hypersensitivity. Apart from being associated with suffering, disability and health care costs, it is also recognized that the prognosis is not as benign as previously thought. The objective of this study was to investigate if somatosensory thresholds were altered in patients with syndrome X compared to patients with coronary heart disease and healthy controls.

Methods: In total 47 patients 48-71 years of age were included. Coronary heart disease (CHD) was defined as any of the following conditions: previous myocardial infarction, previous coronary artery bypass grafting, percutaneous coronary intervention, symptoms of angina pectoris and a pathological coronary angiography. Syndrome X patients were defined as having angina on exercise-ECG and ST segment depression (at least 1 mm in minimum 2 leads), but normal coronary angiography. Normal controls consisted of age-matched healthy volunteers, non-smokers, without previous history of CHD.

Before the start of the study a general examination by a physician was performed including exercise-ECG. Mechanosensory and pain thresholds in the skin were measured with a series of von Frey filaments exerting pressure of 0.003-152.2 g. The first perception of pressure or pain was recorded and the mean value of three measurements was considered as threshold. Testing was done bilaterally on the thorax, in the area where the patients normally localized their pain. To reduce variability, testing was repeated at a second visit, with at least a one week interval. The sensory data from the first and second visit were pooled and analyzed. Statistical analysis was done with the Mann-Whitney U test after confirming that the parameters were not normally distributed (Shapiro-Wilk test).

Results: The patients, mean age 62, were tested for sensory parameters: 23 healthy, 14 CHD patients, and 10 syndrome X patients. Women (n=32) had significantly lower pain thresholds compared to men ($p<0.05$, n=15). Pressure perception thresholds were not statistically different.
Cardiac syndrome X patients had significantly lower pressure perception and pain thresholds compared to normal controls and CHD patients, $p<0.005$. This difference was still significant ($p<0.05$) when men were excluded from the analysis in order to reduced risk of bias due to the lower pain thresholds in women.

Conclusion: This study showed that patients with cardiac syndrome X had significantly lower mecanical pressure perception and pain thresholds compared with healthy controls and CHD patients. The difference observed could be due to altered sensitivity of peripheral mechanoreceptors and nociceptors and/or central mechanisms. There was also a difference in pain sensitivity between men and women, a phenomenon observed in previous studies.

POSTER ID: **802**

Women's awareness of cardiovascular risk: preliminary results of a northern Italian provincial survey

Presenting Author: F. Buffoli[1]
Other Authors: G. Giannella[2], M.R. Ferrari[1], F. Agostini[1], G. Fornasa[3], M.C. Brunazzi[1], R. Zanini
Author Affiliations: [1]Cardio-thoracic Department, Carlo Poma Hospital; [2]Preventive Medicine Department (ASL); [3]Federfarma (National Federation Pharmacy Holders), Mantova, Italy

Background: Although cardiovascular disease represents the leading cause of death in Europe and accounts for the highest mortality rates in female sex, different studies remark a very poor awareness regarding cardiovascular risk among women.

Aim of the study: prior to the development of a gender oriented local preventive strategy of intervention, we carried out a survey among female population ranging from 40 to 60 years old, in order to evaluate their level of awareness cardiovascular risk.

Methods: in the period 4-27 of May, 2011, a questionnaire including 29 items (6 demographics, 8 about personal history, 8 about awareness of leading causes of death, 8 about knowledge of CV risk factors, 6 about personal risk factors and lifestyle), was delivered to a sample of women ranging from 40 to 60 years old in 131/133 (98.5%) pharmacies of Mantova city and its Province, and web-transmitted to the Provincial Department of Preventive Medicine for analysis.

Results: 2623 questionnaires were filled in and sent for analysis by 94.25% of a sample of 2783 women aged 40-60 years old, representative of the 61039 female population of the same age. Only 28% of surveyed women identified cardiovascular disease as the leading cause of death, being myocardial infarction mentioned by 12% and stroke by 16% of the interviewed. The majority (47%) indicated malignancy as the main threat for their health, (27% indicating breast ,13% lung and 9% ovarian cancer). The awareness of cardiovascular risk among these women proved independent from cultural and educational level and from age. Moreover, in our survey, low perception of cardiovascular risk factors was registered. Although 23.7% of surveyed women declared to suffer from hypercholesterolemia, 22.9% from hypertension, 6% from cardiovascular disease, and 5% from diabetes, in indicating the major CV risk factors, given three possible choices, 61% of interviewed answered hypertension, 54.5% hypercholesterolemia, 51.2% overweight, 51.2% smoke, 32% inactivity, being this perception unaffected by correction for age and educational level.

Conclusion: our data support poor awareness of cardiovascular risk and low level of perception of cardiovascular risk factors, among a sample of 40-60 years old women, representative of the female population in a Northern Italian Province in which cardiovascular disease is the leading cause of morbidity and mortality. Correction for age and educational level unaffected the results, highlighting a question that cross society. In assessing a model of gender-oriented cardiovascular prevention, these data appear unavoidable, with regards to disclosure and application .

POSTER ID: **803**

Hypertension as cardiovascular predictor in post-menopausal women: the long-term follow-up of the "Bene Essere Donna" patients

Presenting Author: Ylenia Bartolacelli, M.D.[1]
Other Authors: Elisa Giubertoni[1], Giorgia Origliani[1], Maria Grazia Modena, M.D.[1]
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Objectives: The aim of this study was to examine the association between cardiovascular events and the major cardiovascular risk factors in a cohort of initially asymptomatic post-menopausal women.

Background: Conventional major cardiovascular risk factors (cigarette smoking, hypercholesterolemia, hypertension, diabetes, and age) fail to explain nearly 50% of cardiovascular events in the general population. This topic was virtually unexplored in the specific population of postmenopausal women. Defining the magnitude of future risk for the development of clinical events is a major focus of effective primary prevention.

Methods: We conducted a prospective study on 603 post-menopausal women, age 62 +/- 6 years, followed-up for a mean period of 82 +/- 28 months (range 57 to, 108 months). The events considered were the onset of hypertension, diabetes and major cardiovascular events intended as myocardial infarction, hospital recovery because of unstable angina, acute pulmonary oedema, acute pulmonary embolism, sudden cardiac death, ictus or transient ischemic attack.

Results: During observation, 59 major adverse events were recorded (9.8% of the entire population). Cox analysis revealed that, between conventional major cardiovascular risk factors, the only independent predictor of prognosis in postmenopausal women resulted the presence of hypertension (odds ratio: 10.22; $p < 0.001$) and particularly the strength of hypertension considered as number of drugs used. In fact a rising number of medicaments used correlates with a higher baseline cardiovascular risk (Person=0,42, p<0,001) and with a largest incidence of events (Odds Ratio: 1,26; C.I. 1-1,6, p=0,04).

Conclusions: In post-menopausal women, only the presence of hypertension and its strength provide independent prognostic information regarding the risk of developing adverse cardiovascular events.

POSTER ID: **804**

Gender differences in characteristics and outcome of unselected implantable cardiac defibrillator receivers: an observational cohort analysis

Abstract Presenter: Marco Zavatta, M.D.[1]
Other Authors: Vincenzo Livio Malavasi, M.D.[1] Maria Grazia Modena, M.D.[1]
Author Affiliations: [1]Modena University Hospital, Modena, Italy

Introduction: The effectiveness of sudden death prevention in patients affected by left ventricular systolic dysfunction (LVSD) with automatic implantable cardioverter/defibrillator (ICD) has been demonstrated in multiple randomized clinical studies. Previous studies have documented important sex differences in ICD use, but there are still limited data regarding the influence of gender on outcome of patients receiving ICDs for primary prevention, although recent trials suggest no gender differences in outcome of patients with underlying heart disease. The majority of patients enrolled in clinical studies regarding ICD therapy were Caucasian males, and women appeared to be largely underrepresented. Moreover female patients showed relevant differences in baseline characteristics, such as age at presentation and weight of coronary artery disease on LVSD. The question may fairly be asked, then, whether women have the same survival benefit and favorable outcomes compared to men.

Materials and Methods: We observed consecutive patients that along 4 years (2008-2011) have been referred to our center to undergo ICD implantation. Our interest have been focused on gender differences regarding baseline characteristics and outcome. Genders were compared with bivariate tests for unadjusted analyses. Then, to adjust for potential confounders, we build a non-parsimonious propensity score for gender using all covariates potentially impacting before or on device implantation.

Results: We studied 154 implanted patients, 131 males and 23 females. Mean follow-up duration was 31±17 months. Women showed a statistically significant higher prevalence of nonischemic cardiomyopathy (69,6%) compared to men (38,9%) (p=0,012) and greater prevalence of left bundle branch block (56,5% vs. 20,6%). Finally a relevant feature of our population was a high prevalence of optimal HF therapy: 86,4% of patients were treated with beta-blocker and 81,2% with renin-angiotensin antagonists. No statistically significant gender difference was shown in major arrhythmic events (42,7% vs. 30,4% p=0,47), appropriate ICD intervention (32,8% vs.17,4% p=0,21) and deaths (13% vs. 14,5% p=0,35). Interestingly, women did not experience any inappropriate ICD intervention, while men received inappropriate shock in 4,6% of cases.

Conclusions: The follow-up observation showed a similar prevalence of deaths and arrhythmic events in men and women, postulating a similar benefit from ICD implant. The relative number of female patients who received ICD in our population is comparable with data from major registries and clinical trials, suggesting that women are more likely to be undertreated than underrepresented in clinical trials (possibly due to unfavorable characteristics), as previously postulated. In our population, women showed a significantly greater prevalence of nonischemic cardiomyopathy. Women showed a significantly higher prevalence of left bundle branch block (LBBB) pattern at surface ECG. The meaning of this feature is uncertain. Previous studies have demonstrated that women develop HF signs and symptoms at a more advanced stage of the disease. Therefore LBBB pattern could be another marker of advanced left ventricular desynchronization. Finally our population data confirmed that the presence of a dedicated HF clinic improves guidelines recommendation adherence in treatment delivery and selection of suitable patients for ICD therapy.

POSTER ID: **805**

Gender differences in heart transplant: how to ameliorating quality of life of men and women

Abstract Presenter: Chiara d'Agostino, M.D., Ph.D.[1,2]
Other Authors: Giuseppe Feltrin[1], Nicola Caretta[3], Antionio Gambino[1], Carlo Foresta[3] and Gino Gerosa[1,2]

Author Affiliations: [1]Department of Cardiac, Thoracic and Vascular Sciences, University of Padova, Padova, Italy; [2]National Research Centre for Gender Health and Medicine, Padova, Italy; [3]Department of Histology, Microbiology and Medical Biotechnologies, Section of Clinical Pathology, Centre for Male Gamete Cryopreservation, University of Padova, Padova, Italy

Gender mismatch in solid organ transplants has been investigated since a long time and it is well known that it is strongly related to immunological problems. However gender issues in clinical transplantation affect outcomes at many levels beyond immunologic concerns: many diseases leading to transplantation are predominantly expressed in one gender, access to transplantation may be affected by gender, women mortality is higher after heart transplant. Moreover the way of accepting transplant can be affected by personal thinking, but also gender differences may determine different approach.

Heart failure and transplanted patients need not only medical support, but also psychological and social help. For this reason, we are strongly convinced that we have to differentiate our approach, in order to improve the quality of life of our patients.

In Padova heart centre, we are leading two projects related to gender issues; the first is concerning male transplanted patients and analyze their higher incidence of erectile dysfunction; the second, in progress, consists in the creation of a "Health centre for medical, psychological and social problems in the heart transplanted women."

I. Vascular erectile dysfunction (ED) is expression of a systemic vascular disease and in particular of endothelial dysfunction. Dysfunctional endothelium plays also a significant role in the onset and progression of coronary artery vasculopathy (CAV). A total of 77 male heart transplanted patients (HTx) (mean age 61,6 + 10,6 years) were enrolled in the study. All subjects underwent medical history, physical examination and biochemical blood tests, penile and vascular echocolordoppler ultrasonography and coronary angiogram. Incidence of ED was 24% before HTX and increased up to 65% after. Post ischemic cardiomiopathy was an indication to HTx in ED group more frequently than non-ED group (45,1% vs 20%). ED patients showed lower peack systolic velocity (PSV), higher cavernosal intima-medial thickness (IMT), higher prevalence of cavernosal plaques (26,7% vs 5.2%, $p<0.05$), higher prevalence of peripheral vascular disease (60.87% vs 26,1%, $p<0.05$) and CAV (45,8% vs 25.8%, $p<0.05$). Presence of CAV was associated with higher prevalence of cavernous disease (71.4% vs 30.4%, $p<0.05$). Cavernous plaque and testosterone plasma levels were statistically associated with CAV. ED HTx patients with cavernous artery disease might be considered at increased risk for developing CAV.

II. The "Centre for medical, social and psychological problems of female heart transplanted patients" is supporting our female patients after transplantation. Too often, they meet problems related to their identity and their family, difficulties to find an appropriate job and can necessitate of a social support to understand their rights. Moreover, women can have problems concerning pregnancy.
For this reason, this centre, in collaboration with different specialists, as gynaecologist, social assistant, legal expert, psychologist and dietist, that can intervene case by case, has the goal of supporting women in their re-borning process. Women underwent to medical history, physical examination, biochemical blood tests and coronary angiography. We have the double purpose to ameliorating women's quality of life and to evaluate role of immunosuppressant drugs on pregnancy and oogenesis.

POSTER ID: **806**

Sex differences in heart failure during acute myocarditis are mediated by testosterone-induced soluble ST2

Abstract Presenter: Michael J Coronado, Ph.D.[1]
Other Authors: Eric W Kostuk[1], Djahida Bedja[1], Madeleine W Cunningham[2], Eric D Abston[1], Adriana Bucek[1], J. Augusto Frisancho[1], Kathleen L Gabrielson[1], Deepti Malhotra[1], Shyam Biswal[1], Leslie T Cooper[3], and DeLisa Fairweather[1]
Author Affiliations: [1]Department of Environmental Health Sciences, Johns Hopkins University Bloomberg School of Public Health, [2]Department of Microbiology and Immunology, University of Oklahoma, [3]Department of Cardiovascular Disease, Mayo Clinic MN

Men who develop acute dilated cardiomyopathy (DCM) from myocarditis have more severe disease and less robust recovery than women. Soluble ST2 (sST2), an interleukin (IL)-1 receptor (R) family member, is associated with greater mortality in patients with acute myocardial infarction or chronic heart failure. In this study we investigated whether alterations in the IL-1R family members sST2, IL-33 or IL-1β could explain gender differences in recovery from acute DCM due to myocarditis. We identified 43 patients from Mayo

Clinic who were diagnosed with acute myocarditis, prospectively enrolled into registries, and had available stored sera. Serum sST2 was higher in men than women with myocarditis ($p = 0.019$). Serum sST2 correlated positively with New York Heart Association class in men ($p = 0.0001$) and negatively with ejection fraction (EF) in all subjects ($p = 0.0001$). To investigate the cause of sST2 elevation we used an autoimmune model of coxsackievirus B3 myocarditis and found that elevated serum sST2 in male BALB/c mice ($p = 0.005$) correlated negatively with EF ($r^2 = 0.19$) and predicted progression to DCM. Gonadectomy with testosterone (Te) replacement in male mice revealed that Te decreased heart function while increasing cardiac inflammation and IL-1β and serum sST2. Treatment of male mice with recombinant IL-1 increased serum sST2 during myocarditis ($p = 9x10^{-5}$). We show for the first time that elevated serum sST2 is associated with progression to DCM and heart failure following myocarditis in males, and we provide evidence that IL-1β can elevate sST2 levels. This study was supported by funding from NIH R01 HL087033 to Dr. Fairweather and NIH R01 HL56267 to Drs. Cooper and Cunningham, and by a Leder Family Foundation Grant to Dr. Cooper.

POSTER ID: **807**

Exploring the sex differences in susceptibility of stress-induced cardiomyopathies: Role of underlying adrenergic-derived myocardium

Abstract Presenter: Steven N. Ebert, Ph.D.[1]
Other authors: Candice Baker[1], Ibrahim Abukenda[1], Chaunhi Van[1], Kingsley Osuala[1]
Author Affiliations: [1]Burnett School of Biomedical Sciences, University of Central Florida College of Medicine, Orlando, FL

Stress-induced cardiomyopathies such as Tako-Tsubo or Broken-Heart Syndrome preferentially affect postmenopausal women following severe emotional trauma. Patients with this type of stress-induced cardiomyopathy typically present with chest pain and other symptoms reminiscent of those associated with myocardial infarction, except without the associated coronary occlusion. Instead, they show profound left ventricular dysfunction, with apical, mid, and sometimes basal regions of left ventricular muscle displaying hypo- or akinesis. These patients typically have high circulating plasma catecholamines when presenting. The biological basis for why postmenopausal women are more susceptible to this type of cardiomyopathy is not clear, though several theories have been proposed. In the present study, we provide a new theory and evidence suggesting that adrenergic-derived myocardium may serve as an anatomical substrate for these syndromes. Using a transgenic knock-in mouse model to map the fate of adrenergic cells in the developing based on expression of the adrenaline biosynthetic enzyme, Phenylethanolamine n-methyltransferase (Pnmt), we show that adrenergic-derived cells within the heart become predominantly (80-90%) localized to the left side of the heart in the adult mouse. In particular, we show that Pnmt-derived cells constitute significant bands of myocardium concentrated in the apical, mid, and basal regions of the left ventricle (LV). Ongoing work in our laboratory is investigating anatomical differences in the distribution of these cells at different ages. We also present preliminary physiological data using echocardiography to measure LV function in adult male and female mice before and after injection of adrenaline (50 ug/kg, i.p.) using high-resolution ultrasound imaging (Vevo2100; Visualsonics, Inc.). This stress test was administered while the mice were anesthetized with isoflurane, and ultrasound data were collected in real time. Our preliminary results show that female mice displayed significantly decreased LV responsiveness to adrenaline compared to males ($p < 0.05$, n=30 per group). Additional tests are underway to determine if menopausal status will alter or influence LV function before or after stress challenges. Development of these models is expected to facilitate evaluation of the underlying biological basis for the observed sex-based differences in the occurrence of Tako-Tsubo and related stress-induced cardiomyopathies in the clinic.

POSTER ID: **808**

Sex differences in vitamin D binding protein are associated with increased myocarditis in men and male mice

Abstract Presenter: Erika J. Douglass, M.P.H.[1]
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Vitamin D (VitD) deficiency has been hypothesized to exacerbate many inflammatory-based diseases including autoimmune disease, cancer, and heart disease. Vitamin D binding protein (DBP) is the primary transporter of VitD and its metabolites in the sera. DBP may increase autoimmune inflammation via its known macrophage activating functions. Macrophages are the primary infiltrate in the autoimmune heart disease, myocarditis. Like other cardiovascular diseases, the incidence of myocarditis is higher in men. In this study, we examined whether sex differences exist in DBP levels in myocarditis patients and in a coxsackievirus B3 (CVB3)-induced model of myocarditis in BALB/c mice. We found that men with myocarditis had significantly higher levels of DBP in the sera (p = 0.03). We verified that DBP mRNA was significantly increased in the heart of male mice with myocarditis, but not in female mice (p = 0.04). Male mice also had significantly increased cardiac mRNA levels of Cyp2R1 (p = 0.03), which is one of the enzymes that converts VitD to its active form resulting in release of DBP. Our results suggest that DPB is protective in females, but not males. Gonadectomy and hormone replacement experiments showed that testosterone is responsible for these DBP increases in the heart (p = 0.03). Our findings suggest that testosterone increases Cyp2R1 (p = 0.03), influences DBP expression (p = 0.03) and may be responsible for the higher incidence of myocarditis in males. To our knowledge, we are the first to report a sex difference in DBP levels in the sera of myocarditis patients. This work was supported by National Institutes of Health Grants HL087033.

POSTER ID: **809**

Sex differences in the effect of vitamin D on inflammatory heart disease: protective in women but damaging in men

Abstract Presenter: Katelyn A. Stafford[1]
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An estimated 1 billion people worldwide have deficient or insufficient levels of vitamin D (VitD), while roughly 25% of individuals in the US are reported to have inadequate VitD levels. Considerable evidence indicates that VitD deficiency is associated with an increased risk of cardiovascular disease (CVD), yet it remains unclear whether low VitD is simply a biomarker of CVD or has a true pathologic role. Myocarditis, an inflammatory heart disease, appears as lymphocytic myocarditis (LM) or giant cell myocarditis (GCM), yet the role of VitD deficiency in the pathogenesis of disease is unknown. We found that 75% of GCM patients had deficient or inadequate levels of VitD (<19ng/mL) whereas only 20% of LM patients had low levels. Following therapy, VitD levels in women but not men with GCM significantly improved (p=0.04). Myocarditis patients are at risk of heart failure, which is reflected by a low ejection fraction (EF). In GCM patients, low EF correlated with low VitD levels in both men and women (r^2 = 0.42). In contrast, poor EF and low VitD was only correlated in women with LM (r^2=0.54), but surprisingly men had an opposite correlation- high VitD correlated with low EF (r^2=0.81). When we examined the role of VitD using VitD receptor (VDR) deficient mice in a model of LM, we found that VDR decreased myocarditis in females (p=0007) but increased inflammation in males (p=0.006). Comparison of microarray data during myocarditis in mice to known VitD response element genes revealed that genes associated with proinflammatory (e.g. caspase-1, p=7.0x10^{-5}) and profibrotic (e.g. TGF- , p=8.6x10^{-6}) immune responses were significantly upregulated in the heart of males, providing a mechanism to explain how VDR increases disease in males. These findings in the mouse model confirm that sex differences exist in the function of VitD/VDR in men and women with LM. A large portion of the population is now taking all sorts of vitamin and mineral supplements including ones for VitD. The role of VitD/VDR has not been extensively investigated based on sex for myocarditis, but it is known that VitD plays a role in many important diseases such as CVD and autoimmune disease such as multiple sclerosis that effect people every day. Therefore, studying the mechanism and effect of VitD is important to a huge number of men and women.

POSTER ID: **810**

Relationship between gender and cardiotoxicity from doxorubicin in spontaneously hypertensive rats

Abstract Presenter: Yanira Gonzalez-Berrios, Ph.D.[1]
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Treatment of cancer with anthracyclines such as doxorubicin (Dox) causes dose-limiting cardiotoxicity, particularly in younger females. Dox metabolites generate excess reactive oxygen species (ROS) using an iron-mediated mechanism in mitochondria of cardiac cells. Since cardiomyocytes have lower levels of antioxidant defense, the cardiac cells are sensitive to ROS; however the exact reason for the gender differences in toxicity is unclear. Currently, an iron chelator, dexrazoxane (Dzr), is used in the clinic to alleviate some of the cardiotoxicity. The aim of our study is to understand gender effects in carditoxicity using a recently-optimized, physiologically-relevant animal model. We used female, male, ovariectomized female, and castrated male adult spontaneously hypertensive rats (SHR). The SHR were implanted with syngeneic breast cancer cell line derived from a spontaneous breast tumor in SHR. After cell implantation, each group of age-matched animals were exposed to either saline, acute high-dose doxorubicin, dexrazoxane, erythropoietin (Epo), or combinations with doxorubicin. Estrogen and testosterone levels were measured to confirm decreased in hormones levels in ovariectomized or castrated rats. Tumor size was used as the marker of anticancer activity. Dox, in combination with either dex or epo showed significant reduction in tumor size after 14 days in each animal group. However, weight loss was more significant in males and castrated males treated with Dox than in females or ovariectomized females. In addition, cardiac troponin T levels were used to assess cardiotoxicity and were higher in males treated with Dox than females, castrate males or ovariectomized females, also treated with Dox. We are currently testing possible links between gender-selective toxicity and oxidant-induced autophagy.

POSTER ID: **811**

Potentially proarrhythmic electrical remodeling in the pregnant heart

Abstract Presenter: Glenna CL Bett[1]
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Although sex differences have been clearly identified in the cardiac EKG for more than a century, the molecular bases of these differences are well not described. Even less well understood is the molecular basis of the adaptation of the female heart to the physiological remodeling associated with pregnancy. We therefore quantified differences in expression level of mRNA of cardiac ion channels between ovariectomized, non-pregnant, and pregnant hearts.

Left ventricular free wall was excised from OVX, non-pregnant (n=18), pregnant (n=6) ovariectomized (n = 8) and mice (C57BL). mRNA was extracted (Trizol, Invitrogen and RNAeasy, Qiagen) and converted to cDNA (First strand synthesis, SABiosicences). We used quantitative real time PCR (SYBR Green in an iQ icycler, Biorad) to determine changes in relative mRNA expression in the mouse left ventricle. Data were analyzed using ANOVA ($p<0.01$ was regarded as significant). The quantified changes in mRNA expression were used to scale current magnitude in a computer model of the mouse cardiac action potential.

Expression of several channels was significantly changed in pregnancy: SCN5A (INa) showed a 1.51 fold increase, $p=0.008$); KCND2 and KCND3 (components of Ito) were reduced 0.48 and 0.35 fold respectively, ($p<0.0001$); the delayed rectifier currents KCNH2 (IKr) and KCNQ1 (IKs) both showed decreased expression (0.26 ($p=0.001$) and 0.59 fold ($p=0.004$) respectively); the sarcoplasmic reticulum uptake pump showed an 0.58 fold decrease ($P=0.005$). Computer simulations were in close agreement with published data. Some of the observed changes in pregnancy (e.g., reduction in the relative expression of repolarizing currents) were potentially pro-arrhythmic.

Our results demonstrate that changes in mRNA expression of sodium and potassium channels during pregnancy are predicted to prolong the cardiac AP and are therefore potentially pro-arrhythmic in a normal heart. However, the pregnant heart has to adapt to a major change in pump load, so these changes may reflect an adaptation to the altered physiology of pregnancy.

POSTER ID: **812**

Maternal vascular function in early pregnancy in relation to fetal gender

Abstract Presenter: Charlotte Iacobaeus, M.D., Ph.D.-student[1,2]
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Background: Fetal gender is independently associated with adverse pregnancy outcome. There is an increased risk for spontaneous abortions, preterm labour and preterm premature rupture of membranes in pregnancies with male fetuses. Women carrying male fetuses are at increased risk for hypertensive disorders during pregnancy, which is a marker for cardiovascular disease later in life, possibly due to a persistent endothelial dysfunction.

Objective: To assess if fetal gender relates to cardiovascular function in women during pregnancy and after delivery.

Materials and Methods: 50 healthy women with singleton viable pregnancies were studied at gestational week 12-14. Supine brachial blood pressure (BP) was measured by a standard oscillometric device. Pulse wave analysis by applanation tonometry was used to calculate central blood pressure and arterial stiffness. Forearm flow mediated dilation (FMD) following ischemia and glyceryl trinitrate, skin microvascular responses (laser Doppler fluxmetry, arbitrary units (AU)) to iontophoretic applications of acetylcholine (Ach) and sodium nitroprusside (SNP), and maximum microvascular hyperaemia (MMH) to local heating were used to assess microvascular function.

Results: At gestational week 12-14, women with a male fetus showed lower microvascular vasodilatation in response to SNP (peak SNP 1.67±0.37 vs 2.17±0.48 AU, p <0.001), and a trend of reduced microvascular response to Ach (peak Ach 1.83±0.35 vs 2.10±0.49 AU, p =0.07x), and MMH (peak MMH 118±33 vs 142±45 AU, p =0.065). There were no differences between the groups in brachial BP (106±7/62±6 vs 107±8/61±7 mm Hg central BP (89±7/62±5 vs 92±7/63±6 mm Hg), changes in FMD following ischemia (+10.0±3.9 vs +10.2±3.6 % and glyceryl trinitrate (+25.6±4.6 vs +26.1+5.9 %) for male and female gender, respectively, Pulse wave velocity was 5.3 ±0,5 vs 5,6±0.6 m/s p=0,11.Body mass index and age was comparable between the groups.

Conclusion: The results suggest that alterations in maternal skin microvascular function at gestational week 12-14 are related to fetal gender. Women with a male fetus have a lower endothelial-independent vasodilatation. Further analyses at gestational weeks 24 and 34, and at nine month after delivery are in progress and might reveal further differences in cardiovascular function, related to fetal gender.

POSTER ID: **813**

Influence of gliptins on endostatin, HbA1c and glucose in 35 NIDDM patients

Abstract Presenter: M. Sponder[1]
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Background: Gliptins are complete inhibitors of dipeptidyl-peptidase-4 (DPP4) and therefore increase the blood levels and bioavailiability of glucagon-like peptide 1 (GLP-1). Consequently, the insulin production and release rises, glucagon release decreases and blood glucose level recede. Endostatin, a potent angiostatic factor, inhibits endothelial cell proliferation and migration and stimulates endothelial nitric oxide synthase (e-NOS).

*Material and Methods:*The study population consisted of 35 NIDDM-patients (15 female, mean age: 60,13±10,80; 20 male, mean age: 58,10±7,32) who could not reach a HbA1c <7% by a metformin monotherapy. The patients obtained 50 mg Vildagliptin +1000 mg Metforminhydrochlorid 2x/d (1-0-1) in tablet-form for 6 months. BMI (kg/m^2), blood glucose (mg/dl), HbA1c (%), endostatin (ng/ml), intima media thickness (IMT; cm) and physical performance (by ergometry; %) were measured before and after treatment for 6 months.

Results: Gliptin treatment was associated with significant decrease in glucose (p<0,01) and HbA1c (p<0,01). HbA1c decreased from 7,70±1,06 to 6,53±0,73% resp. glucose from 140,00±18,78 to 113,47±25,26 mg/dl. Endostatin levels increased significantly from 126,15±35,43 to 145,71±54,67 ng/ml (p<0,04).

Conclusion: A 6 months gliptin treatment is associated with a significant increase in venous endostatin levels in patients suffering from NIDDM. If this gliptin-mediated endostatin up-regulation can be interpreted as an additional vasoprotective property it should be elucidated more closely.

POSTER ID: **814**

Sex matters! Influence of sex and etiology on Endostatin serum levels in patients with chronic heart failure (CHF)

Abstract Presenter: M. Sponder[1]
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Background: Endostatin, a potent angiostatic factor, inhibits endothelial cell proliferation and migration and stimulates endothelial nitric oxide synthase (e-NOS). Chronic heart failure (CHF) is a vasoconstictive state associated with a significant upregulation of neurohumeral factors such as brain-natriuretic peptide (BNP), predicting morbidity and mortality in CHF patients. Therefore, the aim of the present study was to investigate the impact of sex, etiology and functional heart class in CHF on serum endostatin levels.

Material and Methods: Endostatin levels were measured (ng/ml) at rest in 75 individuals, divided into 2 groups: 30 CHF-patients (17dilatative, 13 ischemic; 9 NYHA I, 9 NYHA II, 12 NYHA III) and a control group consisting of 45 "elderly" non smokers (female vs. male). In the CHF group also BNP was measured.

Results: In contrast to the control group, which showed no gender specific difference in mean endostatin levels (female: 112,33±23,59; male: 116,55±16,65), male CHF-patients (263,00±115,39) had much higher endostatin levels compared to female CHF-patients (191,36±52,94). Endostatin levels in dCHF were 192,25+/-44,85 compared to iCHF 260,69+/-116,02. Endostatin also showed a positive correlation to BNP-levels in the CHF group ($p<0,003$).

Conclusion: 1) CHF is associated with upregulation of endostatin levels, especially in female patients. 2) CHF based on ischemic heart disease is associated with higher Endo serum levels compared to DCHF. 3) Furthermore, Endostatin serum levels correlate to BNP levels in CHF patients. Further studies are warranted, to investigate the impact of Endo as prognostic marker in CHF patients.

POSTER ID: **815**

Gender comparison on spontaneously reported adverse bleeding events in Sweden regarding antithrombotic treatment

Abstract Presenter: Diana Rydberg, M.D.[1,2]
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There are conflicting reports on whether there is a gender difference in bleeding events related to antithrombotic treatment. We wanted to explore if there are any gender differences in spontaneously reported adverse bleeding events regarding low-dose aspirin, clopidogrel and warfarin treatment. We therefore performed an exploratory analysis by extracting data on bleeding events from the Spontaneous Adverse drug event Reporting System, Swedis, a Swedish database and data from the Swedish Prescribed Drug register, including all drugs dispensed to the Swedish population (9 million inhabitants). The reported bleeding events from July 1, 2005 to December 31, 2010 were adjusted to the number of unique individuals exposed to the prescribed drug during the same period, for women and men respectively. Bleeding events for the time period 1999-2010 adjusted to the number of prescriptions during the same period were also analyzed. "Serious" bleeding events, which supposedly should not differ in reporting pattern between women and men, were analyzed in the same manner.

The risk for bleeding events with low-dose aspirin (75-320 mg OD) was lower for women (odds ratio (OR) of approximately 0, 80), both when analyzing individual data and the number of prescriptions. The DDD (defined daily dose) per prescription for women was lower compared to men (57 vs. 73 DDD/prescription) for the time period 1999-2010. But the aspirin dose, for both women and men, has decreased when comparing the time period 2005-2010 (51 vs. 68 DDD/prescription). For clopidogrel (standard dose: 75 mg OD) the number of

prescriptions was higher in men. When looking at individual data the bleeding risk is higher for women (OR 1, 43) but when adjusting for the number of prescriptions the bleeding risk is lower for women (OR 0, 87). For warfarin (individualized dosing) no gender difference in bleeding events could be found when adjusting for individual data (OR 1, 01) but women have a higher risk of bleeding events when adjusting for the number of prescriptions (OR 1, 20). The ORs for serious bleeding events are in line with the above mentioned for each drug.

For low-dose aspirin a lower risk of bleeding events was seen in women compared to men and an important factor for this could be lower dosing in women. There was a signal towards an increased risk of bleeding in woman compared to men on clopidogrel treatment. For warfarin, no gender difference was seen regarding adverse bleeding events and it is suggested that individualized dosing is an important factor for this.

POSTER ID: **816**

Ethnic and sex differences in cytokine profile systemic lupus erythematosus

Abstract Presenter: Beverly D. Lyn-Cook, Ph.D.[1]
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Introduction: Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease involving multiple organ systems and is often detected in women in their reproductive years at a ratio of 9:1 compared to men. African American women (AAW) have five times the incidence compared to Caucasian women (CW). Selected cytokines, most specifically interferons (INFs), have demonstrated increased expression in SLE and peripheral blood mononuclear cells from lupus patients. The objective of this study was to determine the relationship of IFNs and related cytokines to African American and Caucasian women with and without lupus. Although the sample size is small, a sex difference was noted in several cytokine levels and expression. These findings could lead to more specific targets in treating this potential life threatening disease, especially in AAW.

Methods: Blood samples were consecutively obtained by informed consent from 270 patients; 137 lupus and 133 none lupus (N-lupus) consecutively seen in the rheumatology clinics at East Carolina University and analyzed using enzyme linked immunoassay (ELISA) for INF-gamma, tumor necrosis factor–alpha (TNF-α), IL-6, IL-10, and IL-6/acting expression. IL-6 expression was also analyzed by real time polymerase chain reaction.

Results: Average levels (pg/mL) of select cytokines showed significant differences. Significant differences were determined by p-value (nonparametric two tail t-test using Graph Pad Prism version 4 software) for female subjects. Lupus patients showed significant higher levels for all cytokines than in Non-Lupus with p-values for INF-gamma, TNF-α, Il-6, IL-10, and IL-6/actin of 0.0118, 0.0034, 0.0001, 0.0033, and 0.0001, respectively. AAW showed higher levels than CW in IL-6/actin expression ($p=0.0010$). AAW had a higher level of expression of IL-6 and IL-10 than white males; however, there was no significant different between AAW and AAM in those selected cytokines ($p<0.095$).

Conclusion: AAW demonstrated a high level of expression for numerous cytokines than N-lupus and CW subjects. These studies should provide targets for treating SLE and further understanding the varied biological and genetic mechanisms of SLE.

POSTER ID: **817**

p38 MAP kinase signaling in myeloid cells controls autoimmune disease of the CNS in a sex-specific manner

Abstract Presenter: Dimitry N. Krementsov, Ph.D.
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Sexual dimorphisms in severity and incidence of autoimmune diseases such as multiple sclerosis (MS) and lupus, are well established, but poorly understood. In fact, over the past 50 years MS incidence has increased dramatically in women. Sex-specific (especially female-specific) disease modifying therapies (DMTs) are clearly warranted, but the mechanistic insight for their design is lacking.

p38 MAP kinase (MAPK) is a key regulator of inflammatory responses in various autoimmune conditions, but its role in MS or MS models remains relatively unexplored. Using an animal model of MS, experimental autoimmune encephalomyelitis (EAE), we have previously shown that pharmacological inhibition of p38 MAPK activity prevents disease in C57BL/6 mice. We also showed that genetic manipulation of p38 MAPK activity in T cells is sufficient to alter disease in a different mouse strain, B10.BR.

We now show that pharmacological inhibition of p38 MAPK only prevented EAE in female, but not male C57BL/6 mice. However, genetic manipulation of p38 activity in T cells in B10.BR mice affected disease in both males and females, suggesting either a strain-specific or a cell type-specific sexual dimorphism. To address these possibilities, we generated C57BL/6 mice lacking p38alpha MAPK in T cells or myeloid cells/macrophages; since both cell types contribute to EAE and MS pathogenesis, and p38alpha signaling in these cells typically plays a pro-inflammatory role. Unexpectedly, T cell-specific deletion of p38alpha in C57BL/6 mice had no significant effect on EAE in either sex. In contrast, deletion of p38alpha in myeloid cells resulted in protection in females, but not males, suggesting that the sexual dimorphism in the EAE response to pharmacological blockade of p38 occurs within the myeloid cell compartment. Analysis of the inflammatory infiltrates in the CNS revealed that female, but not male mice lacking p38 in myeloid cells exhibited reduced immune cell activation compared with controls.

Taken together, our results suggest that p38 MAPK activity in T cells or myeloid cells can control severity of autoimmune disease of the CNS, however the extent of the involvement of either cell type is tightly controlled by genetic factors and sex. These findings reveal important mechanisms underlying sex differences in autoimmune disease, and suggest that the p38 MAPK pathway may present targets for female-specific DMTs for MS.

POSTER ID: **818**

The potential male-specific oncogenic function of Cdca7l in astrocytoma

Abstract Presenter: Min-Hyung Lee, Ph.D. [1]
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The most common types of primary central nervous system (CNS) tumors, astrocytoma and glioblastoma multiforme (GBM), are currently incurable. Both astrocytoma and GBM show male predominance in the population, with a male to female ratio of 1.31:1 for astrocytoma and 1.26:1 for GBM (Kleihues et al., 2000). Previously, our lab has demonstrated that astrocytoma/GBM tumorigenesis in the *Nf1-/+;Trp53-/+cis (NPcis)* mouse model shows gender bias in certain genetic context (Reilly et al, 2009, Walrath et al, 2009). Using the linkage analysis in the *NPcis* mouse, we have recently identified a male-specific genetic modifier on distal chromosome 12 (Chr 12), named *Arlm1* for *Astrocytoma resistance locus in males 1* (Amlin-Van Schaick et al, 2012). *Arlm1* is syntenic to human Chr 7p15, 7p21, 7q36, and 14q32 regions that are frequently altered in human GBM. Furthermore, combinational bioinformatics approaches and cross-species comparisons have identified *Cell division cycle-associated 7-like (Cdca7l)* as a strong candidate for a male-specific susceptibility gene for astrocytoma among 503 candidate genes within this *Arlm1* locus. To investigate the role of *Cdca7l* in astrocytoma/GBM, we analyzed the expression of *Cdca7l* in both human and mouse astrocytoma cell lines in both genders. Our data showed that *Cdca7l* was up-regulated in astrocytoma cells compared to normal brain expression with male-predominant expression. Furthermore, shRNA-mediated silencing of *Cdca7l* in male-derived mouse astrocytoma cells led to the decreased cell growth as well as reduced cell viability suggesting the oncogenic role of *Cdca7l* in astrocytoma/GBM. Future analyses in both male- and female-derived astrocytoma cells will address whether the oncogenic function of *Cdca7l* is indeed male-specific or male-prevalent in astrocytoma/GBM.

POSTER ID: **819**

The extent of US female breast cancer mortality reduction relative to increased incidence of breast cancer diagnoses in the late 20th century

Abstract Presenter: Dhananjay Vaidya, Ph.D.[1]
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Introduction: Changes in practice and screening in the US resulted in large increases in the incidence of clinically diagnosed female breast cancer in the late 20th century. The objective of this study is to determine the extent to which this was matched by changes in breast cancer mortality for premenopausal, perimenopausal and postmenopausal women in different birth cohorts.

Methods: SEER female breast cancer data (1973-1984 and 1995-2006, comprising 88029 records) by stage at diagnosis (in-situ [IS], local [invasive, localized to the breast], regional extension [local nodes or surrounding tissues], distant metastatic) were analyzed by 5-year birth cohort, and national vital statistics female breast-cancer specific data (1981-1984 and 1995-2000, comprising 326752 deaths) were analyzed by annual birth cohort. The 1985-1994 decade was excluded because rates were in flux, though they were stable in the epoch prior and after (Anderson et al. 2007). Incidence and mortality rates for the epoch before 1985-1994 were compared to the epoch after this decade using mixed model Poisson regression with birth cohort as random effect. As breast cancer is hormonally driven, models allowed for different relationships for age<45, 45-55 and >55 years, corresponding to premenopausal, perimenopausal and postmenopausal periods. Mortality rates for age<30 years were excluded. All rates are shown per 100,000 per year.

Results: Between epochs, for premenopausal-age women, the overall rate of breast cancer diagnoses increased from 2.4 to 4.0 with significant increase in the incidence of IS (4.51-fold, p<0.001), local invasive cancer (1.75-fold, p<0.001) and distant metastases (1.50-fold, p<0.001) but not regional extension (0.99-fold, p=0.862). For perimenopausal-age women, the overall rate increased from 18.1 to 28.1 with significant increase in the incidence of IS (4.33-fold, p<0.001) and local invasive cancer (1.74-fold, p<0.001) but a decrease in regional extension (0.83-fold, p<0.001) and no change in distant metastases (1.04-fold, p=0.48). For postmenopausal-age women, the overall rate increased from 26.0 to 44.2 with significant increase in the incidence of f IS (4.57-fold, p<0.001) and local invasive cancer (1.95-fold, p<0.001) but a decrease in regional extension (0.82-fold, p<0.001) and no change in distant metastases (1.02-fold, p=0.58). Breast cancer mortality did not change significantly between the two epochs for premenopausal ages (0.93-fold, p=0.33, from 14.3 to 11.7), but reduced significantly for perimenopausal women (0.79-fold, p<0.001, from 50.0 to 38.8) and postmenopausal women (0.96-fold, p<0.001, from 104.7 to 102.0)

Conclusions: An increased incidence of diagnoses of early stage breast cancer was associated with a concomitant decrease in breast cancer mortality, especially among perimenopausal and postmenopausal women. Though the changes in incidence have similar magnitude for perimenopausal and postmenopausal ages, the relative and absolute mortality reduction was greatest for peri menopausal ages. Because analysis is by birth cohort and age, mortality gains show that the improvement is not merely due to detection of disease at the subclinical stage. Further research into SEER follow-up data may be able to disentangle the benefits of early screening versus new treatment modalities between the two epochs, and cohort differences in the use of oral contraceptives and hormone replacement therapy.

POSTER ID: **820**

Drug treatment in patients with newly diagnosed unprovoked seizures and epilepsy: gender differences

Abstract Presenter: Linnéa Karlsson, Pharm.D[1]
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Introduction: Epilepsy is the most common chronic neurological disorder. Antiepileptic drugs (AEDs) is the mainstay treatment generally initiated in patients after more than one unprovoked seizure. Monotherapy is preferred, but some patients need a multiple AED regimen. Epilepsy is often associated with comorbidities and coadministration of other drugs. Since many AEDs are prone to drug-drug-interactions, patients with epilepsy are at risk to experience such.

Aim: To study the drug treatment in patients with newly diagnosed unprovoked seizures/epilepsy in a population-based cohort in Stockholm County Council.

Materials and methods: Clinical data from the Stockholm Incidence Registry of Epilepsy was cross-linked with drug dispensing data from the Swedish Prescribed Drug Register in order to analyze drug treatment in patients with newly diagnosed unprovoked seizures between 2006 and 2008.

Results: In total 367 patients were prospectively followed. Nearly 50 % had other medications prescribed at index date; women were more likely to have antidepressants, anxiolytics and opioids than men. Within one year, 71.4 % had a dispensed prescription of an AED and 97.9 % were initiated on monotherapy. The most commonly used drugs were lamotrigine and oxcarbazepine in children, carbamazepine and levetiracetam in adults, and carbamazepine and valproate in the elderly. Valproate was more likely to be presribed to male (24.5 %) than female patients (16.8 %). Lamotrigine was more likely to be prescribed to female (17.6 %) than male patients (10.7 %). No gender difference were seen in the proportion of patients prescribed carbamazepine. Clinically important interactions were found in 3.8 %. One year after first dispensed prescription of an AED, 55.3 % of male and 48.9 % of female patients had a dispensed prescription of the same AED as initially prescribed.

Conclusions: A high proportion of patiens received treatment within one year and the choice of first AED were consistent to current treatment guidelines. Many patients used other medications and several of them are related to known comorbidities. No gender differences were seen in the proportion of patients prescribed first AED within one year, nor in the proportion of patients initiated on monotherapy. Valproate was predominately prescribed to male patients and lamotrigine was predominately prescribed to female patients. Drug-drug interactions between the first AED and other prescribed medications were not very common, which indicates that prescribers are well aware of the risk for interactions.

POSTER ID: **821**

Gene expression profiling of rat kidney reveals sex- and age-related differences that may underlie adverse drug reactions and disease

Abstract Presenter: James C. Fuscoe, Ph.D.[1]
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Understanding age- and sex-related susceptibility to adverse drug reactions (ADRs) and diseases is key to protecting public health. The kidney plays a central and complex role in maintaining total body homeostasis, with key functions in excretion of metabolic wastes, blood electrolyte composition, acid-base balance, and hormone synthesis and regulation. In addition, the kidney is involved in the pharmacokinetics and excretion of pharmaceutical drugs via xenobiotic metabolism enzymes and molecular transporters. Developmental and adult aging effects influence predisposition for susceptibility to some ADRs. Studies of renal disease and acute kidney injury (following ischemia-reperfusion injury) suggest sexually dimorphic susceptibilities as well. Thus, we hypothesize that the basal expression levels of genes in the kidney throughout the rat life cycle in both sexes will inform our assessments of ADRs and disease. Untreated male and female F344 rats were sacrificed at 2, 5, 6, 8, 15, 21, 78, and 104 weeks of age, and kidneys were collected for gene expression analysis. Agilent whole-genome rat microarrays were used to query global expression profiles. A 2-way ANOVA ($p < 0.01$) along with >1.5 fold change (from the mean expression level of all ages and sexes) was used to identify 4,061 unique genes that were differentially expressed by sex or age. Principal component analyses revealed notable expression profile differences between age groups with greatest distinction observed between 2 and 5 wks of age. The expression levels of 332 genes were found to differ between the sexes in adult animals of 8 - 21 weeks of age, including Slco1a1 (Oatp1), Slc22a7 (Oat2), Abcb1b (Mdr1), and Abcc8. Pathway analysis of the 332 sexually dimorphic genes revealed gene networks related to xenobiotic and lipid metabolism; molecular transport; and renal tubular injury. Analysis of gene expression in the kidneys of 78 and 104 week old rats, revealed potential sex differences in immune function, and included the genes Cd4, Lat, Lck and Tcrb, which exhibited male-dominance. Furthermore, the gene encoding KIM-1 (an FDA/EMA qualified renal biomarker) showed significant sex (16-fold) and age (140-fold) related differences in expression. These results identify genes that may underlie age- and sex-specific susceptibilities to ADRs or disease states. Understanding these differences should improve personalized medicine both in terms of disease prevention, management, and safer use of drugs. This study was supported by a grant from the FDA Office of Women's Health.

POSTER ID: **822**

Natural variation in the murine Y chromosome influences gene regulation and susceptibility to autoimmune disease

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Sex-specific differences affect many aspects of immune system physiology and although these differences may arise from multiple mechanisms, including differential effects of sex hormones, there is increasing evidence that genetic differences in the Y chromosome can influence immune-mediated diseases. Using a panel of C57BL/6J Y chromosome (B6-ChrY) consomic strains, in which B6 mice inherit the Y chromosome from diverse substrains of mice, we show that natural genetic variation in the mouse Y chromosome directly impacts susceptibility to two sexually dimorphic autoimmune diseases, including coxsackievirus B3-induced myocarditis and experimental allergic encephalomyelitis (EAE), the animal model of multiple sclerosis. The relatively limited genetic diversity in genes encoded on the Y chromosome between substrains of mice suggests that protein-coding genes may not underlie these observed phenotypes. Importantly, recent studies in *Drosophila* show that natural polymorphic variation in tracts of Y chromosome heterochromatin can influence the epigenetic regulation of autosomal and X chromosome gene expression through its interaction with euchromatin, thereby epigenetically regulating phenotypic differences in males. Therefore, we hypothesized that the Y chromosome-regulated differences in disease susceptibility among B6-ChrY consomic strains is the result of an evolutionarily conserved role for the regulation of autosomal and X chromosome gene expression by the Y chromosome. To test this, we examined gene expression differences using Affymetrix Mouse Gene 1.0 ST arrays in naive CD4 T cells from wild-type B6 and B6 mice with an SJL Y chromosome (B6-ChrY^{SJL}), which is the consomic strain combination that exhibits the most dramatic difference in disease susceptibility. Our gene expression analysis using a binary filter ($P<0.05$ and 2X fold change) revealed that natural variation in the Y chromosome results in over 600 genes that are differentially expressed in CD4 T cells. An analysis of these genes using Ingenuity Pathway Analysis identified the top biological functions to be post-transcriptional modifications, including processing and splicing of mRNA. In conformation of this, we discovered over 1700 alternative splice variants that pass a false discovery rate of 0.01, the majority of which are present in B6-ChrY^{SJL} but absent in wild-type B6 cells. We further hypothesized that the Y chromosome may regulate the microRNA transcriptome in CD4 T cells and are currently waiting to receive these data on the complementary Affymetrix microRNA 2.0 arrays. In summary, we have identified an evolutionarily conserved role for the regulation of autosomal and X chromosome gene expression and immune system regulation by the Y chromosome. Future experiments will focus on defining the genetic and molecular basis of gene regulation by the Y chromosome and how this influences susceptibility to autoimmune diseases in males.

POSTER ID: **823**

Genetic models of sex differences in mice: beyond hormones

Abstract Presenter: Sergei G. Tevosian, Ph.D.[1]
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It has been established that numerous pathological conditions in humans are profoundly affected by patient's sex/gender. It is normally presumed that sex is a genetically determined defined binary state (male or female) that has endocrine influence over a pathological condition. However the interaction between sex and the disease could be more complex. While it is possible that in some cases there is no direct genetic connection between the sex of an individual and the pathological condition, notable exceptions do exist. The systematic investigation of the genetic links between the sex of an individual and particular disease is quite difficult in humans who (with notable, but rare exceptions) do not present opportunities for robust linkage analysis. On the contrary, numerous mouse models of sex differences are available for analysis and directed genetic crosses, but insight with respect to the influence of sexual state in these animals on pathological conditions has been insufficient. Transcription factors of the GATA family as well as canonical Wnt pathway play important roles in sex determination and gonadal development; however, proteins involved in these pathways are also prominent in directing the development of various other tissue types. We propose to use animals with mutations in these pathways as representative models for genetic conditions where a mutation has a dual effect: on sex determination and subsequent gonadal development, but also in other organ systems. We believe these models could be useful in understanding

similar relationships between the sexual state and disease in humans.
Supported by grant from the NIH HD042751.

POSTER ID: **824**

Genetic sex may not always correlate with gonadal sex in 46, XX Congenital Adrenal Hyperplasia patients

Abstract Presenter: Eunice Marumudi, Ph.D[1]
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Introduction: Congenital Adrenal Hyperplasia (CAH) is one of the most common autosomal recessively inherited inborn errors of metabolic disorder characterized by loss of activity of steroid 21-hydroxylase (21-OHD) enzyme. In these patients, cortisol production is impaired and 17-OH-progesterone (17 OHP) levels increased. Because of the increased production of androgens, masculinisation occurs in genetically female foetuses. Molecular defects in the *CYP21A2* gene are responsible for manifestation of this disease.

Objective: In the present study we analyzed the genotype of CAH patients who referred to endocrine clinic at AIIMS hospital New Delhi. These patients were subjected to genotype analysis to find out the underlying mutations in the *CYP21A2* gene and to correlate with phenotype.

Methods: Detailed history was taken including the prader staging, genital appearance, and sex of rearing and hirsutism status.

Hormonal Assays: Electrochemiluminiscence method was used for estimating the levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), Dehydroepiandrosterone sulphate (DHEAS), Cortisol Adrenocorticotropic hormone (ACTH) and testosterone (T). Radioimmunoassay (RIA) kit based method was used for estimating the 17 OHP levels. (Diagnostic systems laboratories, Inc., Webster, TX, USA) supplied by Immunotech Marcelle, France).

Cytogenetic analysis: Conventional cytogenetic analysis was carried out on peripheral blood using standard techniques. Karyotyping was carried out on G-banded metaphases obtained from 72-h cultures.

Molecular Analysis: Informed consent to carry out molecular genetic studies was obtained from these patients/parents. DNA was isolated from blood samples of CAH patients by using the Qiagen DNA isolation kit as per the manufacturer's instructions. DNA was quantified and subjected to PCR amplification using specific primers to amply the *CYP21A2* gene (Oriola, 1997).

Results: All these five 46, XX CAH patients were reared as males due to the appearance of their external ambiguous genitalia. Their age at presentation varied from infancy to 34 years. Except one patient, all are from non-consanguineous marriages. USG revealed the presence of uterus and normal bilateral ovaries in these patients. The mean hormone levels were -T: 1.66 ng/ml; 17 OHP: 69.76 ng/ml; Cortisol: 10.92 µg/dl respectively. Two were found to have salt wasting (SW) type and three were found to have simple virilising (SV) type of CAH. Molecular analysis revealed that in SW type, the most severe mutations, I2 and R356W were found when compared to less severe variety of CAH (SV). P30L mutation was observed only in SV type. It is interesting note that one SV patient had ambiguous genitalia, infertility and adrenal adenoma. He was also compound heterozygote for four mutations.

Conclusion: A child born with a disorder of sexual differentiation (DSD) poses a variety of challenges for the treating physician as well as for the parents and family. Hence it is important to provide the molecular diagnosis to parents along with other family members and to assign the most appropriate gender according to the patients'/parents wish and the severity of virilisation. This multilevel approach will be useful for risk assessment as well as to offer genetic counseling.

Reference: Oriola, J. et. al. (1997): "Rapid screening method for detecting mutations in the 21-hydroxylase gene". Clin. Chem, 43:4, pg. 557-561.

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POSTER ID: **825**

Rhox gene expression in female embryonic stem cells and in ovary is regulated by KDM6A, a histone demethylase encoded by a gene that escapes X inactivation with higher female versus male expression

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The *Rhox* genes represent a type of developmentally regulated homeobox (HOX) genes implicated either in male or female reproduction. Within the *Rhox* cluster on the mouse X chromosome *Rhox6* and *9* are expressed higher in ovary compared to testis. KDM6A, a histone demethylase that removes the repressive chromatin mark trimethylation at lysine 27 of histone H3 (H3K27me3), is encoded by a gene that escapes X inactivation, resulting in higher female than male expression levels. Here we report that KDM6A regulates *Rhox6* and *9* expression during early female but not male ES cell differentiation. KDM6A is recruited to *Rhox6* and *9* in female ES cells resulting in removal of H3K27me3 and increased *Rhox* expression, a process inhibited by KDM6A knockdown. In contrast, KDM6A occupancy at *Rhox6* and *9* is low in male ES cells and knockdown has no effect on expression. In adult ovary where *Rhox6 and 9* are highly expressed KDM6A occupancy strongly correlates with expression. Our study implicates for the first time a gene that escapes X inactivation and thus has higher expression in females in the regulation of homeobox genes specifically during early female embryonic stem cell development and in ovary.

POSTER ID: **826**

The role of strain on sex related differences in expression of cytokines and stress gene products in response to gram-negative lipopolysaccharide injection in mice

Abstract Presenter: Ashleigh Everhardt[1]
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The gonadal hormones, estrogen, testosterone and progesterone, have been noted to play a role in the growth and development of certain immune cells, regulating the response of an individual's immune system to bacterial or viral pathogens. It has been observed that females experience a better outcome when infected with certain pathogens as compared to men, whereas the incidence of most autoimmune disorders is higher in women. However, the role of strain in the mouse model used in studies of sexually dimorphic immune responses is not clearly understood. The purpose of this study was to determine the role that strain has on the sexually dimorphic response to gram-negative lipopolysaccharide (LPS), derived from *E. coli*. We hypothesize that in response to LPS, there is a differential immune response that is expressed as a difference in body temperature as well as production of pro-inflammatory cytokines and acute phase stress gene expression specific to sex and strain (CD-1, BALB/c and C57BL/6J). Mice were injected with LPS (5mg/kg) and blood and tissues were collected at 2h, 4h and 7h for analysis of interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β) and macrophage inflammatory protein-1 beta (MIP-1β), Metallothionein-1 (MT-1) and Beta-fibrinogen (β-fib). Because we have demonstrated strain differences in response to LPS over time with respect to specific pro-inflammatory cytokines and acute phase gene products, this must be taken into account when studying sexually dimorphic immune response.

POSTER ID: **827**

Identification of the miR-200 family, a potential mediator of the neurodevelopmental effects of early prenatal stress

Abstract Presenter: Christopher P. Morgan[1]
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Prenatal stress exposure is associated with an increased risk of neurodevelopmental disorders, associations that are often sex-dependent. These diseases often display sex differences in prevalence, presentation, or therapeutic outcomes. While many factors contribute to these differences, sex-specific responses to fetal antecedents are likely involved. We have identified a sensitive period of early gestation when stress has sex-specific programming effects on neurodevelopment. Adult prenatally stressed males show increased stress sensitivity in behavioral and physiological measures. Interestingly, the result of this effect is a reduction in the well-established sex differences in these outcomes. Fitting with this phenotype, these males also appear dysmasculinized, with reduced

testosterone levels, smaller testes, and shorter anogenital distances suggestive of a disruption in normal perinatal masculinization. In an effort to understand the role of miRNAs in mediating the effects of prenatal stress on neurodevelopment we have examined the response of the neonatal brain miRNA environment to both organizational steroids and disruptors of masculinization. Meta analysis of these data has led us to a family of miRNAs, the miR-200 family that is consistently correlated to masculinization. Argonaute HITS-CLIP is allowing us to identify the network of genes regulated by the miR-200 family, furthering our understanding of the sexual differentiation of neural stress pathways, and potentially leading to novel therapeutic targets or biomarkers predictive of neurodevelopmental disease.

POSTER ID: **828**

Sex differences in the effects of adolescent stress on adult brain inflammatory responses

Abstract Presenter: Gretchen N. Neigh[1]
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Clinical and preclinical research supports the hypothesis that females are more susceptible to stress-related affective disorders than males. Additionally, adolescence may be a critical period in which stress modulates long-term mental health outcomes. For example, previous work in our lab has demonstrated that adolescent stress induces sustained depressive-like behavior in female, but not male rats. Here, we tested the hypothesis that adolescent stress primes the female rat brain for subsequent exacerbated neuroinflammatory responses in adulthood more than in males. We first exposed male and female rats to mixed-modality stress (e.g., restraint, isolation, social defeat) during adolescence (PND 37-49). Three weeks later, rats were injected with lipopolysaccaride (LPS; 250 μg/kg; i.p.) or saline and perfused brains and blood were collected 4 hours later. In contrast to the persistent depressive-like behavior observed previously in female rats following this adolescent stress, hippocampal gene expression of inflammatory markers (IL-1beta, TNFalpha, NF-kappaB) after LPS (or saline) was not affected by adolescent stress in females. Conversely, adolescent stress exacerbated hippocampal IL-1beta, TNFalpha, NF-kappaB, and CD11b gene expression following LPS in males. These effects on neuroinflammatory markers in males occurred in the absence of an LPS-induced rise in circulating corticosterone, whereas this corticosterone response was present in females. These data suggest that males are more susceptible to long-term neuroinflammatory consequences of adolescent stress, whereas females are more susceptible to affective behavioral consequences.

POSTER ID: **829**

Sexual differences in oxytocin innervation of the hindbrain

Abstract Presenter: Nafissa Ismail[1]
Other Authors: Benjamin Rood[2], Benjamin Chen[1], Philip Castonguay[1] and Geert J. de Vries[1]
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The presence of oxytocin has been well characterized in the mouse forebrain. In this region, oxytocin is known to modulate autonomic functions and social, sexual, and possibly ingestive behaviors. However, the presence of oxytocin in the mid- and hindbrain is not well characterized in mice. Therefore, in the present study, we examined the distribution of oxytocin in the mid- and hindbrain in sham operated or gonadectomized adult male and female C57Bl/6 mice. The results showed that in both the locus coeruleous and the parabrachial nucleus, the density of oxytocin fibers is sexually dimorphic with males having a lower density of oxytocin fibers than females. Moreover, gonadectomy did not alter this difference, suggesting that these differences were not due to differences in circulating gonadal hormone levels and could be due to organization effects of hormones or directly related to differences in sex chromosomes. We used the four core genotype mice to determine whether sex differences in oxytocin expression depend primarily on the nature of the gonad or sex chromosomal complement. Using in situ hybridization, our results showed that this sex difference does not depend on sex chromosomal complement, which leaves organizational effects of gonadal hormones as the most likely cause. These findings are the first to demonstrate a sex difference in the distribution of oxytocin fibers in the hindbrain and suggest possible mechanisms underlying sex differences in the control of pain, autonomic reflexes, and ingestive behavior. This study is supported by NSF grant IBN 9421658 to GJD.

POSTER ID: **830**

Prenatal testosterone interacts with prenatal stressor exposure differentially based on child sex to predict preschool hyperactivity-impulsivity

Abstract Presenter: Michelle M. Martel, Ph.D.[1]
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Disruptive Behaviors Disorders (DBD), including Oppositional-Defiant Disorder (ODD) and Attention-Deficit/Hyperactivity Disorder (ADHD), are fairly common and highly impairing childhood behavior disorders that are approximately three times as common in boys as girls as early as they can be reliably diagnosed during preschool. Prenatal exposure to testosterone may be particularly relevant to these early-emerging DBD, operating to increase risk by making males (vs. females) more sensitive to environmental conditions during pregnancy. The current study examined associations between preschool DBD symptoms and prenatal testosterone exposure, as well as possible interactions between prenatal testosterone exposure and prenatal environmental stressors, such as alcohol and drug exposure, that might increase risk differentially based on child sex (Beauchaine et al., 2009). The study sample consisted of 109 preschool-age children between ages 3 and 6 (4.34 [1.08]; 61% boys; 18 ODD, 18 ADHD, 43 ODD+ADHD, 30 non-DBD) and their primary caregivers. Primary caregivers completed a semi-structured interview (i.e., Kiddie Disruptive Behavior Disorder Schedule), symptom questionnaires (i.e., Disruptive Behavior Rating Scale [DBRS], Peer Conflict Scale), and a questionnaire on alcohol and nicotine use during pregnancy; teachers and/or daycare providers completed symptom questionnaires (i.e., DBRS); and children provided measures of prenatal testosterone exposure, measured indirectly via finger length ratios (i.e., right 2D:4D) assessed via electronic caliper. Higher prenatal testosterone exposure was associated with increased hyperactivity-impulsivity (r=-.24,p=.04), but not with inattention, ODD, or CD symptoms (r range = -.161-.039, p range = .174-.742). Prenatal testosterone exposure interacted with prenatal nicotine use to predict teacher-rated hyperactivity-impulsivity during preschool, for boys (t=-1.98, p=.048), but not girls (t=-1.45, p=.17), although the three-way interaction was not significant (t=-60, p=.55). As shown in Figure 1, boys exposed to higher prenatal testosterone and increased nicotine use during the prenatal period exhibited higher hyperactivity-impulsivity during preschool, while this effect was largely absent for girls. Prenatal testosterone also interacted with prenatal alcohol exposure to predict teacher-rated hyperactivity-impulsivity differentially based on child sex (three-way interaction t=-2.11, p=.04). As shown in Figures 2 and 3, boys who were exposed to higher levels of prenatal testosterone and alcohol during pregnancy exhibited increased hyperactivity-impulsivity during preschool, but girls did not exhibit this same pattern. Overall, prenatal testosterone exposure seems to interact with prenatal stressors differentially based on child sex, to increase risk for early-emerging sex differences in preschool DBD, particularly hyperactivity-impulsivity.

POSTER ID: **831**

Sexually dimorphic placental responses to maternal air pollutant exposure: the root of sex differences in behavioral and metabolic outcomes of adult offspring?

Abstract Presenter: Jessica L. Bolton[1]
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Sex differences in offspring outcomes following maternal inflammatory insults during pregnancy are gradually gaining recognition in the field of fetal programming. It has been suggested that this is due to the sexually dimorphic strategies male and female placentae employ in a compromised intrauterine environment (Clifton, 2010). We have previously shown that maternal exposure to air pollutants (specifically diesel exhaust particles) during pregnancy markedly increases proinflammatory cytokine expression in the placenta, lung, and brain of E18 mouse offspring (sex undetermined; Auten et al., 2011). Our current research is now revealing that there are marked sex differences in the fetal cytokine and chemokine response to maternal air pollutant exposure in the placenta, but not in the lung or brain. Female offspring of diesel-exposed mothers have higher placental levels of fractalkine, IL-10, eotaxin, and IL-1β compared to

matched male offspring. If female placentae mount a larger immune response to inflammatory challenges than male placentae, then female offspring may have fewer long-term adverse consequences because they can resolve the inflammatory challenge more quickly. In order to explore this hypothesis, we assessed the health of both sexes in adulthood, both at baseline and after exposure to a high-fat diet, which can be considered an inflammatory challenge. We found that male offspring born to diesel-exposed mothers weigh more in adulthood than males born to control mothers. Furthermore, after being placed on a high-fat diet, male offspring born to diesel-exposed mothers develop significantly elevated insulin levels and heightened levels of anxiety, whereas female offspring of diesel-exposed mothers do not show these same adverse effects. Interestingly, we found increased microglial surface antigen (Iba1) expression in the hypothalamus and amygdala of male offspring of diesel-exposed mothers that were placed on a high-fat diet in adulthood. However, these same increases in microglial activation were only observed in the hypothalamus of matched female offspring. These results may be indicative of sexually dimorphic microglial priming in certain brain regions, which may be a consequence of the observed sex differences in placental cytokine response to maternal air pollutant exposure during a critical period of brain development.

This study was supported by a Research Incubator Award to S.D.B. and R.L.A. from the Duke Institute of Brain Sciences.

POSTER ID: **832**

Does exercise have beneficial effects on stress in female rats?

Abstract Presenter: Alexis B. Jones[1]
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Exercise may be beneficial in coping with stress and anxiety. In fact, chronic exercise has been *shown to* alleviate symptoms of stress and anxiety in humans and laboratory animals; however, the mechanisms conferring this protection remain poorly understood. Voluntary physical exercise produces many physiological effects that promote both physical and psychological health. Stress, on the other hand, poses a significant risk factor for many of the same health conditions — e.g. cardiovascular disease, depression, diabetes. The beneficial effect of exercise may be particularly important for women, as anxiety and depression increase after menopause. Therefore, the present experiments were designed to investigate whether voluntary physical exercise, in the form of wheel running, affects circulating levels of the stress hormone corticosterone (CORT) in response to an acute physical stressor. We hypothesized that exercise would blunt the CORT response to restraint stress in female rats and that estradiol plus exercise would further decrease CORT.

Adult female Sprague Dawley rats were ovariectomized (OVX) and given 7 days to recover. OVX rats were given 17-β-estadiol-3-benzoate (EB) or OIL for two consecutive days and were tested during the next two days. Rats were subjected to restraint stress by being placed in a plastic restrainer for 40 min prior to being returned to their home cage or to a novel cage with a voluntary running wheel attached. Software on these latter cages recorded distance, speed, and time spent on wheels for 14 hours, which included the 12-hour period of lights off. The next morning, rats were anesthetized using CO_2 and decapitated. Blood was collected for corticosterone analysis. Additional groups of hormonally intact and OVX rats were sacrificed for CORT analysis after restraint stress without access to running wheels or given 24-hour access to running wheels for 4 weeks prior to restraint stress.

There were no differences in CORT levels between exercised and non-exercised rats that were not subjected to restraint stress. There was, however, a heightened CORT response to restraint in the EB-treated animals. A single bout of exercise blunted the CORT response to restraint, especially in the EB-treated group. Similarly, four weeks of voluntary running reduced the CORT response to restraint in hormonally intact female rats, but not in OVX rats.

Exercise alone does not alter circulating CORT levels in exercise-naïve female rats with or without EB. Stress alone increases CORT and a single bout of exercise may reduce the CORT response in EB-treated rats. Long-term exercise may further blunt the CORT response in hormonally intact female rats. Thus, even a single bout of exercise is effective at reducing circulating stress hormone levels. With increased exercise duration, CORT may be even further reduced. These findings differ from our recent behavioral studies of anxiety-like behaviors after restraint stress and voluntary exercise, in which we found that restraint stress paired with access to voluntary running increased anxiety-like behaviors in both OIL- and EB-treated rats.

Therefore, a single exercise bout or chronic exercise may reduce stress hormones in females with estrogen; nonetheless, either may increase anxiety-like behaviors.

POSTER ID: **833**

Acute restraint stress activates vasopressin and oxytocin cells in the supraoptic nucleus of male and female rats

Abstract Presenter: Joseph I. Terranova, B.S./B.A.[1]
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In this study, we investigated sex differences in the stress-induced activation of the neurotransmitters arginine-vasopressin (AVP) and oxytocin (OXT) using the immediate early gene, c-FOS, as a maker of neural activation. We used an acute restraint stress paradigm, where male and female wistar rats were subjected to a one-time 30-minute restraint test. Following the restraint test, animals were perfused with 4% paraformaldehyde and brain tissue was immunohistochemically processed for c-FOS, vasopressin-neurophysin, and OXT. Neural activation of AVP and OXT was measured in the supraoptic nucleus (SON) using immunoflurosence and confirmed by confocal microscopy. Restraint animals exhibited significantly greater activation of AVP and OXT in the SON than non-restrained controls. There were no significant sex differences in the activation of AVP and OXT in the SON. Our results further elucidate the neurobiological mechanisms of stress and reveal potential therapeutic targets for stress-related disorders.

POSTER ID: **834**

Recent suicidal ideation among female and male university hospital surgeons in Sweden and Italy (the HOUPE study): association with work stressors

Abstract Presenter: A. Fridner, Ph.D. [1,2]
Other Authors: M. Wall, B.Sc.[2], D. Minucci, M.D., Ph.D.[3], M. Marini, Ms.C.[3] and K. Schenck-Gustafsson, M.D., Ph.D.[1]
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Background: Suicide rates for physicians are noted to be higher than for the general population. Surgeons have been reported to admit to more suicidal thoughts than other physicians. Suicide ideation is a recognized precursor of suicide. Surgeons in university hospitals work in a highly demanding work place, with long hours and stressful assignments. Studies have shown that surgeons are at high risk of burnout, and it is likely that work environmental factors are related to suicidal thoughts among surgeons.

Methods: Cross-sectional questionnaire based study including the general Nordic Questionnaire for Psychological and Social Factors at Work (QPS-Nordic), Physician Career Path Questionnaire (PCPQ) and the Mehan Suicidal Ideation Scale. Surgeons working at a university hospital in Stockholm completed the questionnaire. Multiple logistic regression was used to identify independent variables showing the strongest association with suicidal ideation within the last 12 months.

Results: Altogether 19 of 122 (16%) Swedish and Italian female surgeons, and 39 of 233 (17%) Swedish and Italian male surgeons reported having suicidal thoughts within the last 12 months. Among the female physicians, adjusting for non-significant covariates having a partner and number of children, work-related variables associated with recent suicidal ideation were: having been subjected to degrading experiences at work (Odds Ratio (OR)=4.29, 95% Confidence Interval (CI)= 1.52-12.11) and role conflict (OR=2.03, CI=1.14-3.60). Having regular meetings to discuss stressful situations were protective (OR=0.61, CI=0.078-0.61). The same covariates were included for male surgeons, for who having been subjected to degrading experiences at work was significant (OR= 3.43, CI=1.62-7.23) and also sickness presence (OR=1.67, CI=1.19-2.34).

Conclusions: Role conflict was related to suicide ideation among female surgeons, and sickness presence among male surgeons. Recent suicide ideation among both female and male surgeons showed strong association with an important work stressor: having been subjected to harassment at work. For female surgeons, having meeting to discuss work stressor may be protective.

POSTER ID: **835**

Characteristics of female and male academic physicians working while ill (the HOUPE study)

Abstract Presenter: Ann Fridner, Ph.D[1,2]
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Background: In the health care sector sickness presence is common, and especially among physicians. Sickness presence is less studied than sickness absence but might have adverse effects for individual physicians, and for health care of patients. For individual physicians being sick at work decreases the possibilities and time for needed recover, and might lead to future long-term sick leave, and even coronary heart disease.

Methods: Cross-sectional analysis was performed among 677 male and 492 female permanently employed Swedish and Italian physicians from the HOUPE study (Health and Organization among University Hospital Physicians in Europe). The outcome measure was "Have you gone to work with an illness for which you would have recommended a patient to stay at home?".

Results: Altogether 72% of the male and 83% of the female physicians reported affirmative regarding the outcome variable ($p <$ .001). Among the female physicians, one work-related variable associated with working while sick was not being able to decide over work-pace (Odds Ratio (OR)=1.42, 95% Confidence Interval (CI)=1.12-1.80). For male physicians suicide ideation (OR=2.11, CI=1.12-3.90) and role-conflict (OR=1.85, CI=1.51-2.27) increased the risk of going to work while sick. Self-diagnoses and self-treatment were related to sickness presence for both genders (OR=4.35, CI=3.00-6.31) for male physicians and (OR=2.81, CI=1.72-4.60) for female physicians.

Conclusions: A great amount of physicians are working while they are sick, female physicians significantly more often than male physicians. Triggers for females are not being able to decide of working time, and for males role conflict and suicide ideation. Work-place interventions could decrease this maladaptive behaviour.

POSTER ID: **836**

Research – does it block female physicians' career opportunities?

Abstract Presenter: Angelika Bader, M.D.[1]
Other Authors: Barbara Waldenberger-Steidl, M.D.[1], Margarethe Hochleitner, M.D.[1]
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The duties of physicians employed by a university hospital include teaching, research and medical care. The qualifications required for permanent positions and a rise in career level, such as professorships, are almost exclusively achieved in the research field. Is this one-sided focus on research a handicap for female physicians? In 2012 a standardized anonymous questionnaire survey was conducted among the female and male physicians employed at Innsbruck Medical University concerning medical training, job situation, work-life balance, and career opportunities.

At that time the medical university employed 530 female (44.1%) and 672 male (55.9%) doctors. A total of 1202 questionnaires were sent out, of which 22.7% were returned. Of the various motives surveyed as the reason for taking up a career in medicine, the response "very much" was given for: working with people (77.2% of the women, 67.2% of the men), helping others (60% women, 50.8% men), science (15.2% women, 42.2% men). Full-time employment was reported by 75.2% of the women and 96.1% of the men. Attendance at more than five scientific meetings per year was reported by 12.4% of the women and 34.4% of the men. Of the women 15.2% and of the men 43.0% reported having spent a research period abroad. Of the women 14.5% held venia docendi and of the men 53.9%. A willingness to relocate was reported by 54.5% of the women and 71.1% of the men.

All these questionnaire items, which are indispensable for a medical career in Austria, from attending scientific meetings to going abroad for research, acquiring venia docendi and being willing to relocate received a positive reply from far more men than women. One of the reasons is certainly the still almost non-existent compatibility of work and family; it is preached but extremely difficult to practice. Moreover, it is opposed by a patriarchal family image. In addition, several aspects of affirmative action for women, such as the possibility to reduce your working hours, are problematic as long as the entire system is organized around full-time employ-

ment. Changes are conceivable here, but slowly because they would involve sociopolitical issues. In addition, however, the motive for taking up this profession, just as for practically all university degrees, was the desire to work with people and to help others. This was also true of men, but always to a lesser degree. Especially disappointing is the small percentage of women whose interest in research caused them to pursue this profession. In this respect we can ask ourselves whether medical care should have a greater significance on the career ladder, or whether a second, more patient-oriented career ladder should be developed alongside the purely scientific criteria.

POSTER ID: **837**

Women doctors at Innsbruck Medical University – affirmative action for women vs. feminization of medicine

Abstract Presenter: Angelika Bader, M.D.[1]
Other Authors: Barbara Waldenberger-Steidl, M.D.[1], Margarethe Hochleitner, M.D.[1]
Author Affiliations: [1]Innsbruck Medical University, Women's Health Centre, Innsbruck, Austria

The Austrian University Law dictates affirmative action for women and the compatibility of work and family. Numerous affirmative action dictates, quotas and anti-discrimination laws have been enacted. Have the female physicians at the university hospitals benefited from them? Can we see any effects or positive results?

The annual reports of the university hospital were used for data compilation, and in 2002 and 2012 the female physicians at Innsbruck Medical University were surveyed using a standardized anonymous questionnaire.

According to the medical university's staff appointment scheme for 2002, 352 female physicians were employed, or 35.8% of the total physicians. In 2012 the total number of physicians had increased to 1202, of which 530 (44.1%) were women. The number of female physicians thus increased by 50.6%, that of male physicians by only 6.3%. In 2002 and 2012 two university clinics were headed by women alongside a field of 40 male clinic heads. The questionnaires show that the number of permanent positions held by women doubled; in 2002 24.4% of the female physicians held a permanent position and in 2012 already 49.0%. A breakdown for 2002 shows 55.7% of the female physicians to be in training for a specialization, 35.1% to hold a specialization, 8.5% to be training in general medicine and 0.4% of the female physicians to hold a license to practice general medicine; 0.4% did not specify. In 2012 we see 40.7% of the female physicians to be training for a specialization, 47.6% to have a specialization, 5.5% to be training in general medicine and 4.8% to hold a license to practice general medicine, while 1.4% did not specify.

At first glance affirmative action for women can be called a success. In these 10 years the number of female physicians rose by 50.6%, and that alone would already be a success. More than that can not be derived from the annual reports. The questionnaires also largely show good figures. The fact that the number of women in permanent positions doubled can also be viewed as a positive outcome of affirmative action for women. However, a closer look at the breakdown shows the for 10 years logical but nevertheless aimed-for rise by women from training positions to fully qualified specialist positions. On the other hand, the percentage of women training to practice general medicine has meanwhile declined, because this job category has largely been downscaled and is now almost exclusively for women. We find an increase in the number of women licensed to practice general medicine and holding a permanent position; meanwhile this is a purely female domain. These last two job categories are those with the lowest salary, the least prestige and the fewest opportunities for advancement at the university hospital. Part of this very gratifying increase in the percentage of women doctors stems from these two job categories, which prompts us to ask ourselves whether this is the beginning of a feminization of medicine. Evidence for a trend to feminization is also given by the fact that in 10 years the number of female clinic heads has remained at two vs. 40 male clinic heads, despite changes in personnel. The opportunity for promotion to management positions has apparently not visibly changed for female physicians despite all dictates and affirmative action efforts.

POSTER ID: **838**

Gender medicine education to healthcare professionals through e-learning. The experience of Karolinska Institutet Center for Gender Medicine

Abstract Presenter: Birgitta Hübinette, R.N.[1]
Other Authors: Juan Jesús Carrero, Ph.D.[1], Karin Schenck-Gustafsson, M.D., Ph.D.[1]

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Gender-specific aspects of medical care are not yet integrated in the curricula for undergraduate education of healthcare professionals in Sweden or in most other countries. Computer assisted learning can represent an important asset in this process.

Since 2011 Karolinska Institutet implements an e-learning course on gender medicine (credited with 7.5 points of higher education), on the basis of constructive teaching alignment and problem-based learning. The aim of the course is to increase awareness of the social, psychological and biological similarities and differences between men and women, and how these impact on health care. Intended learning outcomes (ILOs) are:
1. To describe the basic principles of gender-based medicine and the concepts of sex and gender.
2. To reflect on how biological and socio-cultural aspects influence health and disease from a gender perspective.
3. To critically evaluate clinical evidence from a gender perspective identifying gender gaps and gender bias.
4. Using given principles, to solve a clinical case that involves gender-oriented critical thinking.

Teaching and learning activities aligned to these ILOs include group discussions (chat) about the participant's professional experiences on gender medicine, team work with peer-feedback on consensus definitions on gender medicine, weekly journal clubs and power point presentations on gender-specific aspects of selected disease domains, and individual resolution (using the "Gender Lens tool" http://www.genderandhealth.ca/) with peer-feedback on pre-selected medical cases. An examination task includes the design and resolution of a clinical case by the participants, placed within their field of work/interest and/or their personal experience. Evaluation criteria for this examination task includes taking into consideration and reflecting upon the whole dimension of gender medicine (biological differences, treatment considerations and sociological/psychological aspects in both patient and healthcare providers) when solving such case.

So far 60 individuals from distant locations within the Nordic countries have completed this course and evaluated it as "a positive and eye-opening experience", "a self-realization on unconscious stereotypes", "a new tool for facing patients" or a "a useful learning for both professional and private life". Most appreciated aspects were the flexibility of online working, the broadness of topics discussed and the multidisciplinary nature (medical doctors, nurses, psychologists, dentists, physiotherapists…) as well as the varied working experience of the participants (from last-year university students to 20 year professional experience), which allowed inter-generational and experience-based learning.

To conclude, e-learning can represent effective teaching and learning tool for gender medicine for both undergraduate and postgraduate education. Each learner can progress at his/her preferred pace and according to his/her professional background, linking people into learning communities without the need of physical encounters.

POSTER ID: **839**

How to get gender medicine into medical universities

Abstract Presenter: Margarethe Hochleitner, M.D.
Author Affiliation: Innsbruck Medical University, Women's Health Centre, Innsbruck, Austria

In Austria, we have a national and an international society for Gender Medicine and also national and international meetings every year. At all our medical universities we offer Gender Medicine as an elective. But how do we get Gender Medicine into the heads of our researchers? How do we incorporate Gender issues into all our lectures and all our research projects? We attempted to develop a method that would establish Gender Medicine as a regular subject, just as any other field of medicine.

Innsbruck Medical University offers two degree programs: Human Medicine and Dental Medicine. In both we introduced Gender Medicine as an elective, but at the same time we felt it was not enough to only teach volunteers. We wanted Gender Medicine to be a regular core subject, just like all other medical disciplines. So we included Gender Medicine in the compulsory curriculum twice. We started by teaching basics and then repeated the basics in the last year of medical training and discussed clinical experience with the students. Like all other subjects, Gender Medicine is included in the compulsory examinations. In the new degree program in Molecular Medicine Gender Medicine is incorporated as a Master Module that was developed in an EU project. Moreover, it is compulsory in the clinical PhD program, where the students also have to include gender questions and a gender project in their PhD thesis. Here, too,

we strive to have young researchers practice including Gender Medicine questions in all their projects as a matter of course. The next step in an Austrian scientific career is to be granted venia docendi. The criteria for venia docendi also include a compulsory Gender Medicine course. Here again we try to discuss the inclusion of Gender questions in all subject lectures and all research projects.

We have always seen Gender Medicine as a cross-cutting subject and thus from the beginning we aimed to cross-link Gender Medicine as a means of incorporating it in all medical disciplines. Moreover, we have also been successful in teaming up with Innsbruck University, where our ring lecture series is currently recognized as an elective for Gender Competence. Gender Medicine is also accepted as an elective in the PhD programs of all faculties, which gives rise to very interesting questions on Gender Medicine from completely different disciplines.

We started five years ago. In the beginning there were a lot of discussions and it was a controversial subject. Today it feels normal. So it looks like we were able to integrate Gender Medicine into the curriculum and into the research projects, at least those of our students. We hope that by including a Gender aspect in the scientific work for their PhD they will continue to do so in future.

POSTER SESSION II
Saturday June 9, 2012
1:30 – 3:00 pm

POSTER ID: **901**

Steroid concentrations in antepartum and postpartum saliva: normative values in women and correlations with serum

Abstract Presenter: Elizabeth Hampson, Ph.D.[1]
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Saliva has been advocated as an alternative to serum or plasma for steroid monitoring. Little normative information is available concerning expected concentrations of the major reproductive steroids in saliva during pregnancy and the extended postpartum. Matched serum and saliva specimens were collected in 28 women with normal singleton pregnancies between 32 and 38 weeks gestation and in 43 women during the first six months postpartum. Concentrations of six steroids (estriol, estradiol, progesterone, testosterone, cortisol, DHEA) were quantified in saliva by enzyme immunoassay. We found that steroid concentrations in antepartum saliva showed linear increases near end of term, suggesting an increase in the bioavailable hormone, for most of the major steroids examined. Observed concentrations were in agreement with the limited data available from previous reports. Modal concentrations of the ovarian steroids were undetectable in postpartum saliva and, where detectable in individual women, approximated early follicular phase values. Only low to moderate correlations between the serum and salivary concentrations were found, suggesting that during the peripartum saliva provides information that is not redundant to serum. This may be due, in part, to differential rates of change in the total and bioavailable fractions of the circulating steroid in the terminal weeks of the third trimester as a result of dynamic changes in carrier proteins such as corticosteroid binding globulin.

POSTER ID: **902**

Investigating the timing of estradiol treatment on cocaine-induced conditioned place preference

Abstract Presenter: Linda I. Perrotti, Ph.D.[1]
Other Authors: Samara A. Morris Bobzean[1], Torry S. Dennis[1], Alexandra Schiller, Aspen Samuel[1]
Author Affiliations: [1]Department of Psychology, University of Texas at Arlington, Arlington, TX

Women and female rodents are more responsive to the stimuli that trigger drug use and craving than males. Previous work in our lab has demonstrated that female rats develop display higher levels of cocaine-primed reinstatement to conditioned place preference (CPP) than males. These data indicate that females form stronger associations between cocaine and the environment in which it was administered. Current evidence suggests that increases in levels of estradiol increase the responsiveness of females to drug cues. However, our knowledge of the timing of the effects of elevated levels of estradiol during the different phases of drug use and learning is limited. In other words, are elevated levels of estradiol more influential in the processes of learning to associate cues/environments with the positive effects of drug *or* is estradiol more important in mediating the previously conditioned response. The aim of the present study was to compare the effects of estradiol administration given during the conditioning or testing phases of a CPP paradigm on the magnitude of cocaine-induced CPP. Ovariectomized adult rats received subcutaneous (s.c.) injections of 5ug of 17β-estradiol dissolved in 0.1mL of peanut oil (EB) or peanut oil (PO) during either the conditioning phase of CPP (COND) or the Testing (TEST) phase of CPP. On each of the three saline and three cocaine conditioning days, animals in the COND groups received s.c. EB or PO treatments 30 minutes prior to receiving interperitoneal (i.p.) injections of either 0.9% saline or 15mg/kg of cocaine and were then confined to the corresponding previously assigned saline/cocaine chamber for 30 minutes. On the day of the Preference Test, EB or PO treatments were withheld for animals in the COND groups while rats in the TEST groups were given EB or PO injections 30 minutes prior to the CPP acquisition test. During the Acquisition Test, all rats were allowed free access to all chambers for 15 minutes. While all rats acquired cocaine-induced CPP, the magnitude of CPP was significantly higher for all EB-treated animals compared with all PO-treated females. At this time, data comparing EB/COND and EB/TEST animals are inconclusive. Data analysis for these groups

is currently underway in addition to experiments examining a wider range of cocaine and estradiol doses.

This study is supported by a NARSAD award to LIP

POSTER ID: **903**

Suppression of estrogen receptor alpha (ERα) in the mouse bed nucleus of the stria terminalis by testicular hormones is absent in neonates and reverses rapidly in adults

Abstract Presenter: D.A. Kelly, Ph.D.[1]
Other Authors: A.A. Krentzel[1], N.G. Forger, Ph.D.[1]
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The principal nucleus of the bed nucleus of the stria terminalis (BNSTp) is a sexually dimorphic region of the mammalian forebrain linked to male sexual behavior and the regulation of stress and anxiety. The BNSTp is larger in volume and cell number in males than females of several species including rats, mice, guinea pigs, and humans, and contains neurons that express both androgen and estrogen receptors. We have observed that the expression of ERα in the BNSTp is sexually dimorphic: the area of ERα immunoreactivity (IR) in male mice is less than 5% of that seen in females. We also demonstrated that this sex difference is due to the suppression of ERα by testicular steroids: three weeks after gonadectomy expression remains high in females and is elevated to female levels in males. Here we examined how quickly testicular steroids can suppress ERα in the adult BNSTp and when testicular hormones begin to suppress ERα during postnatal development. In adult males, ERα suppression is rapidly reversed after testicular hormones are removed: males show significant upregulation of ERα IR 24 hours after gonadectomy. ERα expression in the BNSTp could therefore be highly sensitive to changes in circulating testosterone, providing a potential mechanism for sex-specific regulation of functions linked to the BNST. During perinatal life, ERα plays an important role in the sexual differentiation of the BNSTp, reducing cell death in newborn males in response to estrogens derived from aromatized testosterone. We therefore examined the area positive for ERα IR in the BNSTp of male and female mice at birth (P1), the peak of neuronal cell death (P6), before puberty (P20), and in adulthood (P60). We found abundant ERα expression and no sex differences in BNSTp ERα IR at birth. Thus, prenatal androgens do not reduce ERα protein in males. In females, the area of ERα IR is stable through postnatal development when normalized for the size of the BNSTp. In males, the normalized area of ERα IR decreased about 50% between P1 and P6, but the marked reduction of ERα IR was only evident in adults, suggesting that the rise in circulating testicular hormones at puberty suppresses ERα in the male BNSTp.

Supported by NIMH R01MH068482.

POSTER ID: **904**

Effects of estrogen on food intake, weight gain and c-Fos labeling in the NTS in ovariectomized rats on a restricted feeding schedule

Abstract Presenter: Rebecca J. Naukam, M.T.S.[1]
Other Authors: Zoey Miranda[2], Amie Francis[3], Liming Fan, M.S.[1], and Kathleen S. Curtis, Ph.D.[1]
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It is well known that treatment with 17-β-estradiol-3-benzoate (EB) decreases *ad libitum* food intake and body weight gain in ovariectomized female rats. However, effects of EB on food intake and body weight gain have not been studied when access to food is limited. Therefore, the goal of this study was to determine whether EB affects food intake and body weight gain in ovariectomized rats on a restricted feeding schedule. We first monitored food intake for a two hour period during the day, as well as overnight each day for two weeks. Then the overnight feeding was omitted and the rats had food only during the two hour period each day, for an additional two weeks. EB-treated rats ate less and gained less weight compared to oil vehicle-treated controls (OIL) during the first week when feeding was restricted to the two hour period, but ate as much as did OIL-treated rats on the subsequent week. EB-treated rats maintained a lower body weight throughout the study. We also videotaped animals during the first week of the restricted feeding schedule to determine latency to eat. We did not find any difference in the latency to eat between EB- and OIL-treated rats, suggesting that there was no difference in learning the feeding routine. The mechanism for the transient difference in food intake during the first week of the restricted feeding schedule has not been elucidated, but one possibility involves inhibitory peripheral signals. We hypothesize that this transient effect of EB on food intake and weight gain is due to differences in sensitivity to signals

of gastric distention which are carried by vagal afferents to the hindbrain nucleus of the solitary tract (NTS). Accordingly, we examined c-fos labeling, a marker of neural activation, in the NTS of OIL- and EB-treated rats. There were few c-fos labeled neurons in the NTS of *ad lib* fed controls or in animals on the restricted feeding schedule that were not permitted to eat. In contrast, both OIL- and EB-treated animals that were on the restricted feeding schedule and allowed to eat had significantly greater levels of c-fos labeling in the NTS, as expected in rats that consume large amounts of food. The number of c-fos labeled neurons was comparable in the middle NTS; however, EB-treated rats had a somewhat greater number of c-fos labeled neurons in the caudal NTS compared to OIL-treated animals. The small difference between the OIL- and EB-treated animals in c-fos labeling in the caudal NTS is consistent with our hypothesis and suggests that the transient differences in food intake and weight gain during the first week of a restricted feeding schedule may be due to differences in sensitivity to signals of gastric distention carried by vagal afferents to the NTS. In particular, there may be greater responsiveness to such signals in the caudal NTS, where we also have found EB-dependent differences in estrogen receptor numbers.

POSTER ID: **905**

Estrogen markedly upregulates neutrophil serine proteases: implications for estrogen-mediated proinflammatory and autoimmune responses

Abstract Presenter: Rujuan Dai, Ph.D.[1]
Other Authors: Bettina Heid[1], Catharine Cowan, M.S.[1], Deena Khan[1] and S. Ansar Ahmed, Ph.D., D.V.M.[1]
Author Affiliations: [1]Department of Biomedical Sciences and Pathology, Virginia-Maryland Regional College of Veterinary Medicine, Virginia Tech, Blacksburg, VA

Female sex hormone, estrogen plays a profound role in the development and function of the immune system. Although the molecular and cellular mechanisms remain elusive, estrogen has been suggested to play a role in the gender bias of autoimmune disease incidence. In this study, we investigated the potential implication of neutrophil serine proteases in estrogen-mediated inflammation.

Our laboratory has extensive experience in a murine model of estrogen-induced pre-inflammatory state. Briefly, four to five week-old wild type C57BL/6 male mice were orchiectomized and surgically implanted with estrogen or placebo implants for 6-8 weeks, and subsequently splenocytes were utilized for molecular immunological analysis. We have recently reported that estrogen treatment induced serine protease-mediated proteolysis of nuclear STAT-1 and NF-κB in splenocytes, and increased the production of STAT-1 and NF-κB-regulated inflammatory molecules including IFNγ and nitric oxide. In the previous report, the type of serine protease regulated by estrogen was not investigated, and is thus the subject of present study.

In this study, we found that *in vivo* estrogen exposure significantly upregulated the expression and activity of neutrophil serine proteases including neutrophil elastase, proteinase 3, and cathepsin G. The Real-time RT-PCR analysis revealed that estrogen treatment increased neutrophil elastase mRNA level over 10 folds, and proteinase 3 and cathepsin G mRNA levels over 80 folds in splenocytes when compared to placebo. The Western blot analysis also indicated that neutrophil elastase protein level was remarkably enhanced in splenocytes from estrogen-treated mice. In accordance with increased mRNA/protein expression, the specific activities of neutrophil elastase, proteinase 3, and cathepsin G were increased in splenocytes from estrogen-treated mice when compared to control. Further flow analysis revealed that there was a substantial increase of neutrophils in both peripheral blood cells and splenocytes from estrogen-treated mice, suggesting that *in vivo* estrogen exposure promotes neutrophils development and differentiation. Interestingly, we found that nuclear STAT-1 and NF-κB protein were also proteolyzed in splenocytes from MRL-lpr mice, which accompanied with the increased neutrophil serine proteases expression and activity in splenocytes from MRL-lpr mice when compare to MRL controls. Also, selective inhibition of serine protease activity with 4-(2-Aminoethyl) benzenesulfonyl fluoride hydrochloride (AEBSF) abolished the truncation of nuclear STAT-1 and NF-κB protein, and decreased the inflammatory IFNγ and nitric oxide production in activated splenocytes from MRL-lpr mice.

In addition to their critical roles in neutrophils mediated immune defense against microorganisms, neutrophil serine proteases also play an important role in the regulation of non-infectious inflammatory responses, innate and adaptive immunity. The contribution of neutrophils and neutrophil serine proteases in the pathogenesis of autoimmune lupus is emphasized in recent studies with the finding of *neutrophil extracellular traps (NETs)* in activating plasmacytoid dendritic cells to produce high level of type I IFN. Therefore, our novel finding of estrogen upregulation neutrophil serine proteases expression/activity provides a new insight into the un-

derstanding of estrogen promotion of inflammation and certain type of autoimmune disease such as lupus. This study is supported by National Institutes of Health (5 RO1 AI051880-05) and inter-departmental fund.

POSTER ID: **906**

Estrogen upregulates IL-17 induction by regulating transcription factors and by epigenetic miRNA regulation

Abstract Presenter: Deena Khan[1]
Other Authors: Rujuan Dai[1], Bettina Heid[1], and S. Ansar Ahmed[1]
Author Affiliations: [1]Department of Biomedical Sciences and Pathobiology, Virginia-Maryland Regional College of Veterinary Medicine, Virginia Tech, Blacksburg, Virginia

It is well documented that the majority of autoimmune diseases predominantly afflict females both in animal models and in humans. The precise underlying mechanism for this pathological sex differences in the immune system needs further investigations. The potential reasons for this gender disparity are sex hormones, sex chromosomes and epigenetic and environmental influences. Female sex hormone particularly estrogen plays an important role in modulating immune responses. We have recently reported that IL-17 levels are markedly induced in activated splenocytes by estrogen, an immunomodulatory hormone known to influence many female-predominant autoimmune/inflammatory diseases. It is now evident that IL-17 plays a major role in inflammation by regulating the induction of various proinflammatory genes, which aid in recruitment and activation of neutrophils. Although considered to be protective in infections, overproduction of IL-17 has been associated with aggravated tissue injury in many autoimmune diseases. However, the molecular basis of estrogen promotion of IL-17 is still unclear. Given that estrogen promotes IL-17 induction, and is involved in regulation of different transcription factors, we hypothesize that multiple transcription factors are involved in estrogen-mediated IL-17 induction. To test this hypothesis, we determined key transcription factors and microRNA (miRNA, which target transcription factors) that regulate IL-17 induction. Splenocytes from estrogen- and placebo-treated C57Bl/6 orchiectomised male mice were activated by known IL-17 stimulants (IL-6+TGFβ+antiCD3) and transcription factors and miRNA determined by Western blotting or Real-time PCR. IL-17 synthesis by activated splenocytes was markedly decreased following inhibition of Jak-2-STAT3 (by AG490) and of NF-κB (by A77 1726), suggesting their role in IL-17 induction. We also found that ROR T was increased in estrogen-treated mice and tended to correlate with IL-17 levels. Interestingly, IL-17 repressor protein Ets-1 was markedly decreased in estrogen-treated mice. Since Ets-1 is downregulated by miR-326, we investigated whether miR-326 is increased in estrogen-treated mice. We found that, miR-326 levels were upregulated in cells from estrogen-treated mice when compared with cells from placebo-treated mice, indicating possible miR-326-mediated downregulation of Ets-1 in estrogen-treated mice. These findings suggest that estrogen-upregulates IL-17 induction by increasing responsiveness to cytokines and by regulating multiple signaling pathways (JAK-2-STAT3; NF-κB and ROR T), and also by epigenetic miR-326 regulation of Ets-1. These novel studies may have far-reaching implications that could clarify our understanding of the mechanism of estrogen-mediated proinflammatory responses. Future studies are being conducted to study in detail the signaling events, which favor IL-17 induction in estrogen treated mice. This study is supported by NIH 5R01 A1051880-05, Lupus Foundation and Intramural funds.

POSTER ID: **907**

LPS induction of PGE2 synthesis, aromatase activity, and estradiol content is limited to the second week of life in the developing cerebellum

Abstract Presenter: Christopher L. Wright
Other Authors: Jessica F. Knutson, Kathy Kight, Katrina Williams, Margaret M. McCarthy

Given that autism spectrum disorder is strongly associated with not only pathologies in cerebellar morphology but also exposure to inflammatory stressors in utero and during early childhood, we hope to identify novel regulatory pathways for cerebellar development which can be perturbed by inflammatory responses during limited periods of development. We have recently shown the inflammatory mediator prostaglandin E2 (PGE2) increases aromatase activity and estradiol content to reduce the size of the dendritic arbor of Purkinje cells in both sexes and negatively impact social play behavior in male rats. PGE2 also mediates the febrile response because the preoptic area and hypothalamus tightly regulate production of PGE2 to control body temperature in response to indicators of infection, such as the cell wall components of gram negative bacteria, lipopolysaccharides (LPS). Despite the fact that the febrile circuit is discretely localized to the diencephalon, administration of LPS nonetheless floods the whole brain with PGE2. This raises the possibility that LPS

exposure could stimulate PGE2 production, activate aromatase, increase estradiol content and blunt the dendritic development of Purkinje cells. Here, we will show LPS exposure increases PGE2 but not estradiol levels in the posterior vermis of the cerebellum six to eight hours after treatment during the second week of life on post natal day (PN) 10 in both males and females. In contrast, LPS administration during the first and third weeks of life, PN4 and PN17 respectively, do not increase PGE2 levels in the posterior vermis even though LPS does increase levels in the preoptic area during the third week. LPS administration also increases the activity of aromatase 16 hours after treatment and the levels of estradiol 20 hours after treatment in both sexes. Co-administration of LPS plus nimesulide, an inhibitor of PGE2 synthesis, prevents the induction of aromatase activity. When interpreted, the results suggest that there is not only a critical period for LPS-induced PGE2 production during second week of life but also the loss of the sensitive window may be caused by the loss of ability of LPS exposure to induce PGE2 synthesis. Thus it may be moot to determine whether there is also a lost ability of LPS or PGE2 to induce aromatase synthesis of estradiol, or a lost ability of LPS, PGE2 or estradiol to influence Purkinje cell morphology during the first and third weeks of life. Given that no sex differences were found in the increases in either PGE2 or estradiol or the activation of aromatase, it still remains to be determined how manipulations of PGE2 signaling in the cerebellum affects social play behavior in males but not females.

POSTER ID: **908**

Sex difference in microRNA Let-7f mediated neuroprotection following focal cerebral ischemia in rats

Abstract Presenter: A. Selvamani[1]
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Age- and gender-related differences were observed in infarct volume in rats following focal cerebral ischemia. Previous work from our lab indicated that older females sustain a larger infarct as compared to younger females (Selvamani and Sohrabji, 2008), however this difference is not observed in age-matched males. Significant neuronal damage observed specifically in the older females may be due to the loss of ovarian hormones observed in this group, and also suggests that neuroprotective factors may be influenced by the endocrine environment. MicroRNA (miRNA) are an emerging class of therapeutic molecules for inflammatory diseases such as cardiovascular disease, cancer and stroke. MicroRNAs (miRNAs) are small, non-coding RNA molecules of 18-25 nucleotides that function as translational repressors by binding to complementary messenger RNAs (mRNAs), thus inhibiting translation and/or degradation of mRNA. In fact, miR-181 and miR124a have been implemented in neuroprotection and stroke-induced-neurogenesis respectively, following ischemia. We focused on Let7f, a member of a highly conserved family of miRNA and because of its known role in regulating angiogenesis. Let7f also has a consensus binding sequence on the IGF-1 gene, which we recently showed is critical for estrogen-mediated neuroprotection in older females (Selvamani and Sohrabji, 2010b). Thus antagomirs (inhibitors) to Let7f should elevate IGF-1 and promote neuroprotection. In adult females, ICV infusions of Let7f antagomirs 4h post stroke significantly reduced cortical and striatal infarct volume as compared to animals infused with scrambled oligos. Furthermore, females treated with Let7f showed improved performance on sensory motor tasks. Surprisingly, infusions of anti-Let7f to age-matched males did not reduce cortical or striatal infarct volume and their performance on sensory motor tasks was no improvement from controls. In order to determine the impact of the gonadal hormonal environment, we performed an additional study using ovariectomized females. In ovariectomized females subject to MCA occlusion, anti-Let7f infusion had no effect on infarct volume and were similar to controls. To further determine whether the sex difference in Let7f action on infarct volume was associated with ovarian hormones such as estrogen, we evaluated several validated target genes for Let-7f that are also regulated by estrogen. These include the neurotrophin BDNF, the water channel Aquaporin-4 (AQP4), the tumor suppressor gene PTEN, the vesicular glutamate transporter SLC17A7 and the sterol reductase DHCR24 which also functions as a H2O2 scavenger. All of these genes were significantly upregulated by anti-Let7f in the ischemic cortex of intact females, while none of these genes were upregulated in the the ischemic cortex of males. Collectively these data suggest that post-stroke anti-Let7f treatment has therapeutic potential and that there is a sex difference in the role of anti-let7f in stroke recovery, which may be related to the gonadal steroid environment.

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POSTER ID: **909**

Differential effects of sex and aging on stroke induced inflammation

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Stroke is the third leading cause of death in the U.S and the leading cause of disability. Women enjoy a lower stroke incidence than men; however, this stroke risk is modified with age so that elderly women bear the major brunt of this disease. Inflammation plays a critical role in the response to stroke, and post-ischemic inflammatory responses strongly contribute to the extent of ischemic brain injury. Although much is known about the post stroke inflammatory cascade in brain; the contribution of age and sex to post ischemic inflammation has been understudied. Aging is a non-modifiable risk factor for stroke and is a critical determinant to stroke outcome in the two sexes. Since 75-89% of strokes occur in the elderly, it is important to determine if the inflammatory response to ischemic stroke differs with age and biological sex before translation of immunomodulatory therapeutic strategies into the clinic. Therefore, the objective of this study was *to characterize the differential effects of sex and age on post stroke inflammatory milieu of brain.* Young(6 months), aging(15 months) and aged(20-22 months) male and female C57BL6 mice were subjected to 60 minutes of transient middle cerebral artery occlusion (MCAO). Twenty four hours after MCAO surgery, Brain mononuclear cells(BMNC's) were harvested from ischemic hemisphere by using a 60 and 30% percoll gradient after collagenase and DNAse enzymatic digestion. BMNC suspension was stained with fluorophore conjugated antibodies for CD45, CD3, CD11b, CD11c and Gr1 and the cells were counted using LSRII (BD Biosciences). We found that CD45hiCD3+T cell percentage was 13.6+/-3 in young male vs. 6.7+/-1.9 in young females; 29.8+/-6.8 in aging males vs. 9.6+/-3.27 in aging females, and 28.6+/-4.5 in aged males vs. 32.7+/-6.2 in aged females. We found a significant main effect of age $F(2,33)=10.4, p<0.05,$ sex $F(1,33)=4.04, p<0.05,$ and a significant age by sex interaction $F(2,33)=3.25, p<0.05$ in the percentage of T cells(CD45hiCD3+). The CD45hiCD3-CD11b+ CD11c+ dendritic cell percentages were 5.6+/-2.3 in young males vs. 20.6+/-5.4 in young females; 9+/-3 in aging males vs. 25+/-6.4 in aging females, and 20.4+/-4 in aged males vs. 20+/-3 in aged females. We saw a significant main of sex in the percentage of dendritic cells (CD45hiCD3-CD11b+ CD11c+), $F(1, 33) =7.794, p<0.05$. There was no significant difference in the number of microglia(CD45 intermediateCD11b+) after stroke across age in both males and females. We conclude that T cell percentages in the brain significantly increase with age and are higher in young and aging males vs. females after ischemic stroke. Dendritic cell percentages are higher in the young and aging female vs. male brains after stroke. Our study suggests heterogeneity in inflammatory response to ischemic stroke in the two sexes across the lifespan. This work is funded by NS055215-06A1 and 11PRE7440068.

POSTER ID: **910**

Anti-phospholipid antibodies and parathyroid hormone: a study of gender in Huges Syndrome

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The Anti-phospholipid Syndrome (APS), also known as Hughes syndrome, is a systemic autoimmune disease characterized by recurrent thromboembolic events (venous and / or arterial), abortion and the presence of antiphospholipid antibodies. The APS can occur during the course of other autoimmune diseases (secondary APS) or in primitive form. The APS is generally considered a gender disease, which mainly affects women with a ratio four to one to men (4:1). The purpose of this research project is to investigate the association between APS and higt value of PTH. The aim of the study is also to assess whether this association is influenced by gender. The sera of 119 patients, including 59 with APS (48 women and 11 men) and 60 control subjects (50 women and 10 men), was subjected to the search of anti-phospholipid antibodies (aPL), antibodies cardiolipin and anti- 2 glycoprotein I by enzyme immunoassay technique (ELISA), and intact PTH with tecnique of Electrochemiluminescence Immunoassay (ECLIA). 34% of the patients tested presents the Anti-Phospholipid Syndrome type I (APS I) while the remaining 66% is affected by the shape of type II (APS II). PTH levels were above the reference values in 44% of patients with APS (35% APS I, 65% APS II), while only 13% of the comparison group presents an increased secretion of parathyroid hormone. Analyzing data from a gender perspective, it was found that in 46% of women with APS

there is association between an increased PTH secretion versus 36% of men tested. In the control group, negative for the aPL, an altered secretion of PTH was only observed in women. The data obtained were subjected to statistical analysis. The 2 test has confirmed that the correlation between APS and hyperparathyroidism is significant with a probability of 99% .The calculation of odds ratio was greater than 1 (5.12), indicating the existence of a positive association. Finally the AUC (p<0,0006), has revealed the usefulness of the PTH assay as a diagnostic test associated with the APS. The results obtained show the usefulness of the determination of PTH in suspected APS, a high degree of association between abnormal secretion of PTH and the onset of APS affects more females than males. The hypersecretion of PTH is associated more APS type II to APS type I, regardless of gender, given that a study aimed to understand the mechanisms involved, could clarify.

POSTER ID: **911**

Regional variation in cerebral glucose transport and insulin signaling across the estrous cycle

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Glucose is the primary fuel of the brain and alterations in glucose availability directly impact neuronal function [1, 2]. Disease states such as diabetes affect cerebral glucose metabolism [3-5], and have been linked to neurodegeneration [6-10]. Variation in glucose transport is influenced by hormonal state, yet models of cerebral glucose transportfocus on the male and ovariectomized female. Female sex steroids impact glucose metabolism in contrasting ways; estradiol enhances glucose uptake and insulin sensitivity, while progesterone decreases glucose uptake and promotes insulin resistance [11, 12]. Prior studies fail to explore how physiological fluctuations in sex steroids influence glucose transporters and insulin signaling. **Our hypothesis is that natural variation in sex steroids across the estrous cycle co-occur with changes in glucose transporter and insulin receptor expression and function.** Our research furthers understanding ofcellular mechanisms whereby sex steroids modulate glucose metabolism, and are critical toward future studies examining glucose-dependent neurological diseases in the female.

Cerebral glucose uptake varies during the estrous cycle. Uptake is highest during proestrus in the rat, when estradiol levels peak[13]. Glucose uptake is mediated by facilitative glucose transporters (GLUTs), as outlined below [16]. The insulin receptor (IR) is a tyrosine kinase receptor that undergoes autophosphorylation to activate downstream cascades and produce insulin's effects[17].

Cerebral Glucose Transporters[16]

Transporter	Location	Function
GLUT1	Endothelial cells; astrocytes	Transport across blood brain barrier (BBB); regulation of metabolic fuel to neurons
GLUT3	Widespread; Neurona (somatodendritic)	Primary transporter for uptake into neurons
GLUT4	Cortex, Hypothalamus, Hippocampus, Cerebellum; Neuronal (somatodendritic)	Insulin-sensitive; IR activation induces GLUT4 trafficking to plasma membrane for uptake

Several experiments have demonstrated that sex steroids alter glucose metabolism. Treatment with 17β-estradiol increasesexpression of GLUT1 in ovariectomized rat BBB endothelium [18, 19] and GLUT3 and GLUT4 in ovariectomized rhesus macaque frontal cortex [20]. Estrogen receptor activation also increases IR activation and GLUT4 trafficking [21, 22].Current research fails to explore the simultaneous influence of progesterone in cerebral glucose metabolism, which we do mechanistically across the estrous cycle.

Adult female rats (n=26) are swabbed to determine cycle stage, and 6-8 rats from each stage are selected along with six age-matched males. Rats are decapitated and uterine weights collected. Plasma estradiol, progesterone, and insulin are measured by ELISA. The hypothalamus, prefrontal cortex, and hippocampus are dissected, homogenized, and separated into total protein, plasma membrane, cytosolic, and microsomal fractions. GLUT1, GLUT3, GLUT4, and IR expression are examined by immunoblot. Microsomal and membrane fractions are compared for GLUT4 trafficking. IR activation is examined by blotting for phosphorylated IRβ subunit in plasma membrane.

We anticipate an increase in GLUT1, GLUT3, GLUT4 and IR expression, as well as enhanced GLUT4 trafficking and IR activation, dur-

ing proestrus, when estradiol peaks, and a decrease during estrus after the progesterone spike. We expect that GLUT4 will undergo the most pronounced changes due to the roles of estradiol and progesterone in insulin signaling. These experiments improve the understanding of mechanisms whereby sex steroids modulate cerebral glucose metabolism, and are essential to future studies of neurological diseases in females.

POSTER ID: **912**

Ovulation is associated with increased neural network connectivity and reduced gray matter volume in the healthy female brain

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Introduction: Recent studies have come to conflicting conclusions regarding the effect of gender on human brain connectivity using resting state fMRI (Biswal, et al 2010, Tomasi and Volkow 2011 and Weissman-Fogel, et al 2010). It is possible this is in part caused by variability in functional connectivity (FC) introduced by normal physiological variation across the menstrual cycle. We demonstrate consistent variation in functional connectivity across the menstrual cycle using a seed-based analysis of resting state fMRI data. Core regions of the default mode network (DMN) and the dorsal attentional network (DAN) were evaluated as to FC intensity and extent across the menstrual cycle. Additionally, we conducted voxel -based morphometry to analyze the variation in gray matter volume across the menstrual cycle.

Methods: fMRI sessions of thirteen normally cycling healthy women were analyzed for this study. Participants underwent four fMRI sessions during their menstrual, follicular, ovulation and luteal phase. Menstrual cycle phases were verified by serum hormone analysis. For VBM analysis we obtained T1 MPRAGE volumes. Resting state fMRI scans consisted of 171 volumes collected with a TR of 2 seconds using echo planar imaging with a 3.594 x 3.594 x 6 mm resolution. fMRI data were analyzed using AFNI. To perform seed-based FC analysis we defined seeds, extracted the mean time series and regressed that time series to the whole brain on a voxel-wise basis. Within-subject analyses were performed on whole brain correlation coefficients for each seed using one-way RM-ANOVA for phase. We controlled for multiple comparisons using a Monte Carlo simulation to determine minimum cluster size.

Results: Menstrual cycle phase had a significant effect on seed-based FC in the DMN, left and right DANs. In the DMN, RM-ANOVA revealed regions of significant phase effect including bilateral dorsolateral prefrontal cortex, right hippocampus, bilateral middle temporal gyri and right parietal lobule. In the left and right DANs, widespread phase effect was discovered including bilateral thalamus, periaqueductal gray and bilateral dorsolateral prefrontal cortex. Almost exclusively, DMN and DAN FC was strongest during the ovulation phase. Menstrual cycle phase also had a significant effect on brain gray matter volume with a peak effect in the left and right parietal lobes, left and right middle temporal gyrus and right fusiform gyrus. Gray matter volume was greatest during the menstrual phase and reached its nadir during luteal or ovulation phase.

Conclusions: We found that in the DMN and right- and left-seeded DANs, FC varied significantly across the menstrual cycle in healthy females, and peaked during ovulation. These findings support the notion that higher variation in connectivity in females when compared to males is at least partly due to menstrual cycle effects (Tomasi and Volkow, 2011). In contrast, while gray matter volume also varied significantly across the menstrual cycle, it was greatest in menstrual phase and lowest during the ovulation or luteal phases. These complex alterations in the neural architecture across the menstrual cycle reinforce the concept that acute alterations in hormone levels as experienced by a normally cycling woman have significant effects on neural processes (Hampson and Young 2008).

POSTER ID: **913**

Influence of patient sex and gender on medication use, adherence and prescribing alignment with guidelines

Abstract Presenter: Amy Steinkellner, Pharm.D.[1]
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Background: Studies have demonstrated significant physiological differences in drug absorption, distribution, metabolism and excretion in women. To date, this knowledge has not been broadly translated into sex-specific dose and guideline development. Although poor adherence to therapies and clinical guidelines is known to be widespread and influenced by many factors, the influence of patient sex and gender is not well documented.

Objectives: This study investigated differences between men and women in medication use, adherence, and prescribing alignment with evidence-based guidelines.

Methods: A national pharmacy claims database was used to describe medication use, adherence and prescribing alignment with evidence based guidelines in nearly 30 million eligible members, age 18 to 65, between 1/1/2010 and 12/31/2010. Medication Possession Ratio (MPR) was calculated among utilizing members to measure adherence.

Results: Women were prescribed more medications across all age bands, an average of 5.0 drugs, compared to 3.7 drugs per eligible male member. During the study timeframe, 68% of female members were prescribed a chronic or acute medication compared with 59% of eligible males. The higher female average persists, even after accounting for prescription contraceptives. In addition to higher medication utilization, itself a risk factor for increased non-adherence, in 25 of 25 clinical measures relating to cardiovascular disease and/or diabetes, women were less adherent to medications and not prescribed medications in alignment with recommended clinical guidelines as often as men.

Conclusions: Sex-neutral prescribing may result in women being mis-dosed, potentially leading to suboptimal therapeutic outcomes and avoidable adverse events or side effects. Differences noted between the sexes in medication use, adherence, and prescribing alignment may indicate a need for more personalized dosing and therapeutic management to improve outcomes. These results warrant additional study and reporting of sex-based differences at all levels of basic and clinical research, as well as subsequent translation into more personalized and gender specific treatments, recommended dosing levels, and clinical guidelines.

POSTER ID: **914**

Representation of females and racial/ethnic subgroups in FDA approved orthopedic medical devices: a ten year review

Abstract Presenter: Dipali Davé, M.D.[1]
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Introduction: Sex differences found in males and females lead to variations in prevalence, progression of diseases and health outcomes. Factors such as physiology, genetics, body size, and hormones often elicit different responses to certain diseases and medical conditions. Although differences in efficacy and safety have been well documented in certain drugs, less information is available for medical devices. The purpose of this study was to review the US FDA approved orthopedic Premarket Applications (PMA) for demographic data including racial/ethnic subgroups.

Methods: All orthopedic clinical device studies submitted to the FDA in support of PMAs approved from January 2002 to December 2011 were reviewed. Descriptive analyses of demographic features of study participants were conducted to note trends in 12 month intervals in participation of females and racial/ethnic subgroups.

Results: Of the 32 submitted PMAs reviewed, 30 PMAs included participation percentages of males and females and 9 PMAs included racial/ethnic subgroup participation. Female participation was 50% in 2002, 36.5% in 2003, 46.8% in 2004, 50.2% in 2005, 38.5% in 2006, 35.9% in 2007, 46.4% in 2009, 49% in 2010, and 51.3% in 2011. Over the 10 year period an average of 45% of the clinical device studies participants were female. The average racial/ethnic subgroup participations over the ten years were White: 90.1%, Black/African American: 3.3%, Hispanic/Latino: 5.1%, Asian: 1.4%, Native Hawaiian or Other Pacific Islander: 0%, American Indian/Alaskan Native: 0.4%, and Other: 2%.

Conclusions: This ten year review indicates that with the exception of a two year decline (2005-2006) there has been a positive trend in female participation. However lower participation of females in hip replacement device studies was seen despite a higher prevalence of hip fractures in this population. Trend analysis in racial/ethnic subgroups over the past ten years proved difficult due to the low numbers reported in the clinical studies. The representation within these clinical device studies was 90% White and all other

subgroups were lower than the current demographic stratification of the US population. To conduct clinically meaningful analysis researchers should be encouraged to collect sex and racial/ethnic data in orthopedic clinical devices. FDA recently issued a Draft Guidance titled "Evaluation of Sex Differences in Medical Device Clinical Studies" which when finalized will provide guidance for the design and conduct of clinical studies to improve information about the safety and effectiveness of new medical devices in females.

POSTER ID: **915**

Population pharmacokinetics of alcohol in Korean healthy subjects: effect of gender, AST on the pharmacokinetics of alcohol

Abstract Presenter: Byungjeong Song, M.S.[1]
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Alcohol is a psychoactive substance that has a very large cariability on pharmacokinetics and effect according to individuals conditions such as race, gender, weight, etc. This study was performed to elucidate gender difference of alcohol pharmacokinetics in Korean healthy subjects using modelling skills. We administered alcohol (55.39 g alcohol, 19.5 v/v% alcohol 360 mL as Korean spirit) to Korean health human (male 22, female 7) over 40 minutes. Blood alcohol concentrations (BACs) were measured using breath alcohol analyser. Nonlinear mixed effect modelling with NONMEN(version IV) were used for analysing pharmacokinetics of alcohol and effect of gender. One-compartment model with zero-order elimination kinetics was used to explain time versus BACs. Forward selection and backward elimination were performed to find out covariate of alcohol pharmacokinetics. Visual predictive check (VPC) and bootstrap were performed to evaluate the model. Estimate of apparent volume of distribution (V_d/F) was 82.1 L. Absorption rate constant (k_a) and elimination constant (K_0) were 0.0655 min^{-1} and 0.0559 g/min, respectively. Gender, AST were confirmed as significant covariates in alcohol pharmacokinetics ($p < 0.05$). The pharmacokinetic models developed in this study was well established to describe absorption and elimination of alcohol in Korean healthy subjects. In addition, Gender determined as a significant covariates and AST is determined also. Bootstrap and VPC evaluated robustness of the developed model. The final pharmacokinetic model which contained significant covariates described the variability of alcohol pharmacokinetics. Thus, Gender is a significantly affected to alcohol pharmacokinetics in Korean subjects.

POSTER ID: **916**

Gender differences in pharmacotherapy: a population based study

Abstract Presenter*:* Julia Daragjati, Ph.D. student[1]
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Introduction: It has been clearly evidenced that physiologic differences between men and women are numerous regarding every organ and apparatus as for cardio-vascular system, nervous system and immune system. These differences affect drug efficacy and safety including pharmacokinetic and pharmacodynamic aspects. Worldwide, efforts have been made to disseminate the relevance of taking sex and gender into account in different researches and clinical trials. Epidemiology is a great help in answering these questions by offering several measures to describe therapies outcome as predictors to health/disease patterns.

Objective: The purpose of this analysis was to explore, by using an administrative database, gender and age differences in drug prescriptions chargeable to the Local Health Service of the assisted population.

Methods: All residents of the Local Health Area 16 of the Veneto Region (Italy) ages 15-44, 45-64, 65-79 and >=80 years in the period 1st of January until 31st of December 2010, were included in the study. The Public Health Service system, covering this area, keeps record of all drug prescriptions from public or private Pharmacies. All medications dispensed during 2010 were considered and classified by ATC, Anatomical Therapeutic Chemical Classification System. Results were reported as odds ratios of prescriptions dispensed to males and females with 95% confidence intervals to screen the number of subjects that received at least one medication. A detailed analysis was conducted for Cardiovascular and Anti-diabetic drugs.

Results: Of the 491,261 included subjects, 255,026 were females and 236,235 males. Females were more treated in most of Chemical therapeutic subgroups as antiulcer drugs (OR=0.80, 95% confidence interval [CI] 0.74-0.86), antibiotics as for tetracyclines (OR=0.91 95% CI 0.85-0.93), penicillins (OR=0.90 in the 95% CI 0.83-0.94), anti migraine products (OR 0.34 95% CI 0.0.31-0.36), antipsychotics (OR=0.86, 95% CI 0.81-0.90), antidepressants (OR=0.44, 95% CI 0.40-0.52) diuretics (OR=0.72, 95% CI 0.66-0.80). Instead, males were more treated with antidiabetic drugs, insulin therapy (OR= 1.24 95% CI 1.21-1.30) and with oral hypoglycaemic (OR=1.37 95% CI 1.33-1.40), more treated also for cardiovascular disease with antithrombotic agents (OR=1.16 95% CI 1.14-1.20), betablockers (OR=1.15 95% CI 1.10-1.20), ACE-inhibitors (OR=1.25 95% CI 1.20-1.30). Males were generally more treated with cardiovascular medications. A more obvious gender difference was noticed between males and females of 15-44 years old, decreasing with aging, but still the difference remained statistically significant.

Conclusions: Our results support the hypothesis that in general females are more treated than males, consequently more exposed to chronic and acute conditions, especially in the reproductive years 15 to 44 and in pre- and post-menopausal age, according to the literature. Regarding to Cardiovascular drugs, on the contrary, men were more exposed than women.

POSTER ID: **917**

Medical documentation for assessment of work ability in long-term sickness absence cases – the significance of patients gender and psychosocial conditions

Abstract Presenter: Anny Larsson
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There have been and still are differences in long-term sickness absence between different groups in Sweden. One of the most apparent difference can be found between women and men where women represent the majority of long-term sickness absences. In an agreement between the State, Local Authorities and Regions in Sweden, action against women long-term sickness and work absenteeism is being prioritized. This present study has been a part of the mentioned measure and investigates medical reports on health status used when assessing patients' work ability. The aim was to determine if psychosocial aspects that are irrelevant to the medical condition are stated in medical reports on health status and if so are causing gender differences. To obtain information as to whether psychosocial aspects were described in the study base, 247 medical reports on health status were analysed using content analysis. The qualitative content analysis resulted in five categories with a total of 16 identified factors that were all of psychosocial nature and irrelevant to the patients medical condition. The identified factors became the basis for an assessment form that was later used on the survey data previously analysed. The analyses of the data from the review of the assessment form showed a correlation between the stated degree of reduced work ability and the presence of medically irrelevant psychosocial aspects. Thus our study reveals a gender bias in the assessment of long-term sickness absence, where women's reduced work ability is to a bigger extent motivated by irrelevant psychosocial factors.

POSTER ID: **918**

Epidemiology of gender prevalence in Korean population

Abstract Presenter: Byung-yo Lee, B.S.[1]
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Women have different relationships with drugs than do men, with the differences based in gender at least as much as in biology. In addition, gender-specific influences can also play a significant role in drug effect. Disease such as angina pectoris, thyroid cancer, rheumatism and osteoporosis affect women more frequently than men. Women are also more likely to live longer and, in consequence, experience more chronic diseases needing treatment with a range of medications, opening the door to an increased risk of harmful drug interactions than men. As well, the marketing of often geared primarily to women and girls, so they may be preferentially exposed to misleading information. In guidelines of FDA, EMEA, and ICH, women are adequately represented in pivotal trial populations, typically reflecting the approximate extent one would predict from the gender prevalence of the disease or condition in the target population. The

aim of this study was to determine the phenomenology, gender prevalence of frequently diagnosed disease in Korea. Surveys conducted by the Health Insurance Review & Assessment Service (HIRA) of Korea between 2007 and 2011. Ages of subjects on this data, 0 to 80years, are divided into 10 classes. Based on these classes, gender prevalence of frequently diagnosed diseases are analyzed in this study. Gender difference analyzed by epidemiology study can be a standard for gender ratio of subjects. It is expected that adverse reaction of medication by gender difference is reduced.

POSTER ID: **919**

Gender and drug utilization – a systematic analysis of gender differences in prevalence of drug therapy in Sweden

Abstract Presenter: Desirée Loikas, M.Sc. Pharm.[1,2]
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A majority of the Swedish population purchases prescription drugs and most medical consultations result in a prescription. Gender differences in drug utilization have been demonstrated in several therapeutic areas. However, there is a lack of both comprehensive overviews on gender differences in entire populations and studies analyzing the rational of the differences.

In 2010, 2.8 million men and 3.6 million women (60% and 76% of all men and women in Sweden, respectively) purchased at least one prescribed drug. Data from the Swedish Prescribed Drug register, including all drugs dispensed to the Swedish population (9 million inhabitants), have been used to systematically describe and analyze gender differences in prevalence of drug treatment in the Swedish population 2010. All ATC 2nd level groups with ambulatory care prescribing accounting for >75% of the total volume in DDDs and a prevalence of >1% were included in the analysis. Some ATC 2nd level groups were subdivided into 3rd or 4th level to attain better description of the usage. Period prevalence was measured in number of patients per 1000 individuals (PAT/TIN) and differences between the sexes were calculated in both absolute and relative values (with 95 CI).

Fifty pharmacological groups were included in the study. Groups with large gender difference in absolute values with higher prevalence in women were e.g. antibiotics (264 vs. 195 PAT/TIN), hypnotics and sedatives (98 vs. 63 PAT/TIN) and drugs for acid related disorders (98 vs. 75 PAT/TIN). Groups with higher prevalence in men were e.g. antithrombotic agents (89 vs. 123 PAT/TIN), lipid modifying agents (77 vs. 105 PAT/TIN) and ACE inhibitors (57 vs. 84 PAT/TIN). Large relative differences with higher prevalence in women were seen for e.g. antimycotics (RR=6.6 (6.4-6.7)), thyroid therapy (RR=4.5 (4.4-4.5)) and antiobesity preparations (RR= 2.6 (2.6-2.7)). Large relative differences with higher prevalence in men were seen for e.g. psychostimulants (RR=0.62 (0.61-0.64)), antidiabetics (RR=0.68 (0.68-0.69)) and antithrombotic agents (RR=0.72 (0.72-0.73).

There are differences in drug utilization between men and women in Sweden. Varying morbidity may explain some differences whereas other differences may indicate under- or over use of certain drugs in one of the sexes.

POSTER ID: **920**

Minor gender differences in the introduction of new medicines in the Swedish population: a cross sectional population database analysis

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Drug prescribing is one of the most important processes in healthcare with more than two thirds of all consultations in primary care resulting in drug prescriptions. Prior studies have shown that women have more healthcare consultations and higher drug utiliza-

tion than men. However some studies suggest that men receive newer and more expensive drugs.

We used data from the Swedish Prescribed Drug register, including all drugs dispensed to the Swedish population (9.4 million inhabitants), to study if there were differences in use of new drugs between men and women in Sweden. The analysis included eighteen new substances in ambulatory care launched in Sweden 2004-2005. Period prevalence (patients per 1000 inhabitants) and the ratio of each substance to other drugs in the same drug class (ATC) were calculated two and four years after registration. Results were presented as relative ratios (men/women).

The results showed no gender difference overall; about as many new substances were used more by men as by women. Minor gender differeces were seen for individual substances such as eplerenone, rasagilin and atazanavir, with higher use among men, and erlotinib, solifenacin and insulin glulisin, with higher use among women. However, these differences could potentially be explained by gender differences in morbidity and they did also decrease over time.

POSTER ID: **921**

Binge drinking decreases density of myelinated fibers in the medial prefrontal cortex of male, but not female, adolescent rats

Abstract Presenter: Wanette Vargas[1]
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Binge drinking is highly prevalent in teenagers and associated with an increased risk of addiction, cognitive impairments, and dysregulation of emotions, all of which are strongly dependent on the integrity of white matter in the prefrontal cortex. The present study tested the hypotheses that (1) binge drinking during adolescence will interfere with myelination of axons in the prefrontal cortex during development and that (2) there will be a sex difference in vulnerability to the toxic effects of alcohol on the prefrontal cortex, with increased toxicity in females. A voluntary operant binge drinking model was used to elicit high alcohol intake during early adolescence (postnatal days 28-42) in male and female Wistar rats. Brains were collected following intracardial perfusion 4-6 hours after the last session. Brains were sectioned coronally and Black Gold II (a gold phosphate complex) was used to label myelinated fibers in sections from the prefrontal cortex. Microscopic analyses were conducted to determine fiber density and index alterations in myelinization patterns in layers II, III, and V of the anterior cingulate, prelimbic, and infralimbic subdivisions of the medial prefrontal cortex. Results indicate that binge drinking is associated with decreased myelinated fiber density in the cingulate cortex of male (but not female) adolescent rats. This unexpected finding indicates that males may to be more vulnerable to the effects of binge drinking on myelin on axons within this brain region. The functional consequence of the observed changes in myelin and neurobiological mechanisms by which in the males and females differ in these effects remains to be determined.

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POSTER ID: **922**

Social interaction as a predictive measure for alcohol intake in male and female Wistar rats

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Alcohol is one of the most common drugs of choice among teenagers. Normally, the method of consumption is drinking large quantities of alcohol in short periods of time, otherwise known as "binge drinking." Elevated anxiety has been shown to be an outcome of high levels of alcohol exposure. However, preexisting anxiety may play a significant role in the onset of binge drinking. The present study tested the hypothesis that higher baseline levels of behaviors that have been previously used as indices of social anxiety would serve to predict alcohol intake during early adolescence. To test this hypothesis, male and female adolescent Wistar rats underwent a social interaction test as a measure of anxiety before exposure to high levels of alcohol throughout early adolescence (postnatal days 28-42). To measure voluntary binge drinking behavior, we used an operant self-administration model of intermittent access to sweetened alcohol, in which food and water was available ad libitum. Although

males and females differ in social interaction behavioral measures no clear relationship was evident between these behavioral measures and binge drinking during adolescence. Future analyses will utilize principal component analyses to determine whether multiple measures cluster to form more informative constructs that are predictive of adolescent drinking in male and female rats.

POSTER ID: **923**

Differences between men and women with non-alcoholic fatty liver disease (NAFLD) in parameters of liver fibrosis, metabolism and lifestyle factors

Abstract Presenter: Miriam K. Leitner, Dr.[1]
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Aim: Although non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in adults and children worldwide, there are only a few studies focusing on gender specific differences in pathology, characteristics and treatment strategy of this disease. The aim of the current study is to detect differences and correlations in metabolic parameters, scores of liver fibrosis and lifestyle factors between men and women with and without non-alcoholic fatty liver disease (NAFLD), thus providing the basis for a sex- and gender-specific analysis of the risk profile „NAFLD".

Materials and Methods: 21 male and 18 female overweight, non-diabetic participants were selected from a highly homogenous (according to age, lifestyle –eating habits, physical activity, smoking- and drinking- behaviour, BMI and education) sample. NAFLD was diagnosed with MRT (liverfat > 5%). Participants were divided into two groups (FLD= liver fat > 5%; CON= liver fat < 5%). All participants performed a 2h-oral glucose tolerance test (OGTT) and answered questionnaires (IPAQ, EPIC) regarding lifestyle (eating habit, MET minutes, socioeconomic status); anthropometric data (BMI, W/Hratio) and blood parameters (liver enzymes, inflammatory markers, nutritional parameters) were measured additionally.

Results: FLD showed sex-differences in Waist-Hip-Ratio, whereas no differences in anthropometric parameters was detected in CON. Among FLD, women had significantly higher glucose load and C-peptide levels during the OGTT than their male counterparts, while there were no sex-differences in CON. Furthermore parameters of insulin-sensitivity (OGIS) and the Disposition Index were higher in men than in women in FLD. In FLD liver-fat highly correlated with liver enzymes ALT and AST in women but not in men. Two liver fibrosis scores (NAFLD-fibrosis-score and BARD-Score) showed significant differences between men and women with FLD.

Conclusion: Sex-specific differences in metabolic parameters are more pronounced among FLD when compared to CON. If the results of the current study prove valid in a larger cohort, insulin-sensitivity, parameters of OGTT, the liver enzymes ALT and AST, and Waist-Hip- Ratio should be considered when suggesting the implementation of a sex-specific score for NAFLD patients.

POSTER ID: **924**

Gender differences in liver fibrosis progression in hepatitis C

Abstract Presenter: S. Piovesan[1]
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Chronic infection with the hepatitis C virus (HCV) affects more than 150 million subjects worldwide and is a major cause of cirrhosis and of end-stage complications. Disease progression is quite variable being influenced by several virus and host factors.
Aim of this study was to asses sex differences in liver fibrosis progression in patients with chronic HVC infection.

A first analysis was conducted in 267 patients (146 males and 121 females), mean age at inclusion: 48±10.7. All patients had presented with a mild histological form of chronic hepatitis and had been followed up for 7 to 10 years without any therapeutical intervention. Rate of fibrosis progression, was calculated by the annual changes in F Metavir score, using data from sequential liver biopsies and was 0,0153/year for females and 0,0173/year for males patients

(p=0,041) and this difference was maintained after adjustment for covariables (age, BMI and HCV-genotype).

All patients were also analyzed for a 7 genes signatures (CRS) recently described to correlate with the risk of developing cirrhosis. In this analysis male patients showed a significantly higher CRS score (0,6828±0.12) compared to female patients (0,5276 ± 0.14; p<0,00001) and the percentages of patients with higher risk CRS was 52% for males and 20,5% for females (p<0,001). Interestingly, the 7 SNPs signature and several genetics aplotypes related to TLR4 gene showed a statistically significant correlation with liver fibrosis progression in male but not in female patients.

In a second analysis we evaluated the relationship between liver stiffness (measured by FIBROSCAN) and hemodynamic parameters of portal flow in 96 HCV patients (45 males, 51 females).

After stratification by age and cofactors, males had significant higher liver stiffness compared to females (<40 yrs 10,95 vs. 5,74 KPa; 40-60 yrs 14,42 vs. 10,66 KPa; >60 yrs 15,47 vs. 11,16 KPa; p=0,027). The mean maximum portal velocity showed a better correlation with liver stiffness in females compared to males.

These results provided evidence of a significant gender difference in development and patophysiology of liver fibrosis in hepatitis C.

POSTER ID: **925**

Type 2 diabetes impairs exercise induced reductions in abdominal fat independent of gender

Abstract Presenter: Devon A. Dobrosielski, Ph.D.[1]
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Purpose: Men have more visceral abdominal fat and women more subcutaneous fat. Visceral fat is associated with cardiometabolic abnormalities such as diabetes. Exercise training has been shown to reduce total and abdominal fat in men, whereas few studies examining regional fat loss have included women or have evaluated whether diabetes affects the exercise-induced loss of abdominal fat. To study this, combined data from two randomized trials of exercise was analyzed. All subjects had milder forms of hypertension; subjects in one of the trials also had non-insulin requiring type 2 diabetes (T2DM).

Methods: In the combined dataset, 140 subjects had T2DM, whereas 115 subjects did not. In both trials, subjects, aged 40 to 75 years, were randomized to the same supervised exercise 3 times per week (EX) following American College of Sports Medicine guidelines or to a usual care (UC) control group for 6 months. Besides mild hypertension or T2DM, subjects were free of clinical cardiovascular disease or other major illnesses that would preclude exercise training. Both trials measured the same key outcomes including body weight, abdominal fat depots (total, subcutaneous, visceral) by magnetic resonance imaging and peak oxygen uptake (peak VO_2) on a treadmill.

Results: There were 217 subjects (aged 60.0 ± 6.9 yrs; n=96 women) who completed the trials (n=44 women and n=70 men had T2DM). At baseline, women had lower peak VO_2: 20.0 ± 4.6 ml/kg/min vs. 26.2 ± 4.0 ml/kg/min; more abdominal total fat: 524 ± 183 cm^2 vs. 505 ± 149 cm^2 and subcutaneous fat: 389 ± 147 vs. 309 ± 113 cm^2 and less visceral fat: 123.7 ± 58.6 cm^2 vs. 178 ± 69 cm^2; all p's<0.01. Subjects with T2DM had greater total abdominal fat: 588.8 ± 153.4 vs. 439.7 ± 139.3 cm^2 and subcutaneous fat: 402.3 ± 132.3 vs. 296.0 ± 116.2 cm^2, but a similar amount of abdominal visceral fat. Across the entire sample, EX resulted in increased peak VO_2 (+3.6 ± 2.9 ml/kg/min), and decreased abdominal total (-37 ± 64 cm^2), subcutaneous (-22 ± 38 cm^2) and visceral fat (-17 ± 33 cm^2); all p's<0.01. There were no gender differences in these responses. When examined by diabetes status, the exercise training reduced total abdominal fat (-52.5 ± 49.2 cm^2), subcutaneous fat (-25.6 ± 32.5 cm^2), and visceral fat (-26.7 ± 30.8 cm^2), all p's<0.01, in those without T2DM, whereas these outcomes did not change in subjects with T2DM.

Conclusion: Though men and women differ in abdominal fat distribution at baseline, exercise training decreased abdominal fat similarly in both genders. However, having T2DM impairs fat loss in abdominal compartments. Whether this failure to reduce abdominal fat in T2DM is due to impaired fat mobilization or use of medications for diabetes management is yet to be determined.

POSTER ID: **926**

Integration of a longitudinal gender-specific women's health curriculum: translating sex and gender-specific science into medical education

Abstract Presenter: Marjorie R. Jenkins, M.D.[1,2]
Other Authors: Joanna Wilson, D.O.[1,2], Leigh Johnson, Ph.D.[1,2], Betsy Jones, Ed.D.[1,2], Robert Casanova, M.D.[1], Richard Dickerson, Ph.D.[1], Bradley Miller, M.D.[1] and Simon Williams, Ph.D.[1], Brittany Chan[1,2], Michelle Devine[1,2], Skyler Mclaurin[1,2], Shamini Parameswaran[1,2], Michael Song[1,2], Curtis Stennett[1,2], Vera Von-Bergen[1,2]
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There is a growing body of scientific knowledge on sex and gender differences as it relates to all levels of human function. Medical students must be prepared to provide healthcare that incorporates the question and application of answer of the question "Does Sex/Gender Matter?" at the earliest stages of clinical evaluation. With support from the Dean and collaboration with the Laura W. Bush Institute for Women's Health at Texas Tech University Health Sciences Center, the TTUHSC School of Medicine is developing a longitudinal 4-year curriculum in Gender-Specific Women's Health (GSWH).
Sex and gender are basic human variables which all humans have without exemption. While the GSWH curriculum content will focus on sex and gender differences across the lifecycle including differences in manifestations and processes of pathology and treatment; it is the goal of this project to assimilate sex and gender awareness throughout the entire medical school curriculum through the creation of an ongoing gendered learning environment for both faculty and students. Innovations such as a longitudinal "family" case series in problem-based learning cases will be utilized throughout the 4-year curriculum. A web-based monthly CME module for faculty, residents and students, will focus on sex and gender differences across the "Top 20 Health Topic" addressing gender issues in patient communication, diagnosis, prognosis, and treatment of major common health issues. Our current curriculum has been assessed for sex and gender content of YR1 and YR2 through a model Student Scholars real-time audit as well as cross-referencing content with the textbook of Gender-Specific Medicine (Legato 2nd ed.)

This poster outlines accomplishments in years 1 and 2 of the TTUHSC School of Medicine GSWH Longitudinal Curriculum development including curriculum audit results, and ongoing plans for Years 3-5 including curricular initiatives, learning activities, and evaluation strategies, while providing opportunities for peer institutions to collaborate.

POSTER ID: **927**

Rhetoric to action: national initiatives to integrate evidence-based sex and gender differences into medical education

Presenting Author: Jan Werbinski, M.D.[1,2]
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Background: Despite significant scientific evidence on sex- and gender differences in health at all levels of function; gaps remain in incorporating this critically important dimension in teaching, research and practice. Suboptimal health outcomes for women stem from barriers at multiple levels. The recent Institute of Medicine report *Women's Health Research: Progress, Pitfalls, and Promise* notes that although strides have been made in research on women's health issues, challenges remain in translating research into practice.

Objectives: The *Women's Health Working Group* (WHWG), conceived in 2009 by the American Medical Women's Association and collaborating with the American College of Women's Health Physicians, has a mission to integrate sex- and gender-specific data in medical education and facilitate translation of sex and gender-specific women's health into clinical practice.

Methods: The WHWG is raising awareness of the need for sex- and gender-specific medical education, as well as facilitate this education, initially by disseminating sex- and gender-specific educational and research resources through an online, free-of-charge repository of resources – the *Advancing Women's Health Initiative* (AWHI). This digital library, housed at advancing womenshealth.com, has an accompanying blog. The group is working with the National Board of Medical Examiners (NBME) to assess the presence of sex- and gender-specific competencies in testing materials and to identify any potential gaps.

Results: To date, the AWHI has 160 contributing members and 14 official collaborating organizations. The oversight committee for this

initiative includes a multidisciplinary group of 40 national experts in women's health and gender-specific medicine. The digital library has 49 folders, more than 300 documents, including journal articles, curricula, PowerPoint presentations, and other teaching materials. The blog has had over 22,500 visitors, both national and international. This work will also highlight national climate in this area through reporting of student awareness and interest in sex and gender differences curricula and student knowledge of sex and gender in specific disease processes.

Conclusions: The efforts of the AWHI are building the infrastructure that is vital to addressing gaps at all levels - research, education and clinical practice - to advance the integration of sex- and gender-specific medicine from the bench to the bedside.

POSTER ID: **928**

Gender-specific women's health longitudinal curriculum project: curriculum analysis and competencies

Abstract Presenter: Brittany Chan, M.S.3
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Introduction: Texas Tech University Health Sciences Center School of Medicine and the Laura W. Bush Institute for Women's Health are currently in year 2 of a 5-year curriculum project to integrate Gender-Specific Women's Health (GSWH) information across the 4-year curriculum.

Methods: Three MS1s and three MS2s were selected to audit their coursework for sex and gender-based content. Students attended lectures/small groups and documented relevant content on a WebCT forum. Issues unique to women (e.g., pregnancy, menopause, etc) were not included in the final audit. To measure coverage of gender-based health issues, we used a leading text in gender-based medicine, *The Principles of Gender-Specific Medicine* (2nd ed. Legato). A separate medical student investigator and a faculty investigator independently compared a list of competencies formulated from Legato's textbook to the 2010-2011 MS1 curriculum. The MS2 curriculum comparison is in progress.

Results: Analysis indicated that the current curriculum adequately covers gender differences in disease prevalence and normal anatomy/physiology. There was relatively little coverage of pathology, diagnosis, treatment, outcomes, or prognosis.
Audits of four MS1 courses found that Structure and Function of Major Organ Systems and Host Defense contained the majority of gender-related content. Out of four MS2 courses, the most gender content was found in System Disorders 1 and Multisystem Disorders and Cancer. The least was found in General Principles and Integrated Neurosciences. Analysis of the MS1 courses showed that Biology of Cells and Tissues covered the greatest percentage of competencies from Legato's textbook (91%). On average, the MS1 curriculum included 53% of the target competencies.

Conclusions: Though our curriculum provides adequate coverage in some areas, we have several strategies for improvement. Integration of GSWH content throughout the 4-year curriculum with pre- and post- integration assessments of students' knowledge and attitudes toward gender-specific women's health issues will be conducted.

POSTER ID: **929**

Assessment of the consistency of pregnancy labeling across therapeutic classes

Abstract Presenter: Onyeka Otugo, B.S.[1]
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Background: Pregnancy labeling is an essential source of information for addressing the potential risks that pregnant women and their developing fetus may face while taking prescription medication. The current pregnancy labeling system uses five letter categories: A, B, C, D and X. The current system often does not adequately reflect the potential reproductive and developmental risks associated with medication use during pregnancy and has been criticized for being simplistic because of an implied representation of hierarchy of risk. Another concern about the current pregnancy labeling system is that drugs within the same category may have similar potential to cause toxicity.

Objective: The objective of this study is to evaluate the consistency of pregnancy labeling across different therapeutic drug classes for the top 20 therapeutic classes by pharmaceutical sales in 2010.

Methods: The top 24 drugs were obtained from Drugs.com's listing of the top 200 drugs by sales in 2010 and were classified into 20 therapeutic classes. The Clinical Pharmacology website (http://clinicalpharmacology-ip.com/) was used to identify the drugs' therapeutic classes and the corresponding drugs that shared these classes as well. The current approved US-FDA labels for these drugs were then obtained from the archived label section on Daily Med (dailymed.nlm.nih.gov). Each subgroup was evaluated for the consistency of labeling based on the letter categories and other available pregnancy label information including the presence of animal and human data for a particular drug.

Results: Advair® (Fluticasone/Salmeterol) and Diovan HCT® (Valsartan and Hydrochlorothiazide) were excluded from this study because these drugs were combination products. For the remaining 22 drugs, 20 therapeutic classes were analyzed. Nine classes were found to be consistently labeled with one pregnancy category across class. For example, all statins were consistently labeled category X. For the drugs surveyed in the study, none were classified as pregnancy category A, and the majority was classified as C (66%). For drugs with the same pregnancy category for all 3 trimesters, the presentation of animal studies ranged from 75% to 92%. The drugs that had more than one pregnancy category had a presentation of animal studies in 57%. Human studies reported in pregnancy labeling were rare across all categories; category D and X had the greatest amount of human data (25%).

Conclusions: Some differences exist with pregnancy labeling across therapeutic classes, which should be improved by the implementation of FDA's new proposed rule for Pregnancy and Lactation labeling. The new labeling will eliminate the letter category and emphasize the need to make updates as new data on drug use by pregnant women become available.

POSTER ID: **930**

Gender differences in Sardinian Centenarians from the AKEA-2 Study: the importance of genes-environment interaction

Abstract Presenter: G. Baggio[1]

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Sex-specific ageing of men and women follow different trajectories. The AKEA 2 Study focussed the attention on Sardinian centenarians because of their higher frequency (Koeing, 2001, Poulain et al. 2004) and the magnitude of the sex ratio with respect to that observed both elsewhere in Italy and worldwide (Deiana et al., 1999). As the number of male centenarians in Sardinia is exceptionally high, this generates a particularly low female sex ratio (FSR). At the 2011 census this ratio was 2.6 women for men compared with 4.2 for the rest of Italy. FSR differences also exist within Sardinia and are linked to the geography of elderly mortality for men. Some areas have the lowest FSR mainly due to lower mortality (higher survival) among men aged 80 and over.

Comparing geography distribution of male survival with male survival sex ratio it is immediately clear that the two geographies are similar. This means that where the survival after 80 years is particularly higher for men, the survival sex ratio is favourable to men. In other words in these areas the FSR is lower than elsewhere.

Moreover there is a fairly high correlation between the geography of the male sex ratio and the geography of mortality for cancers. The advantage enjoyed by men in high longevity zones can be traced to their relatively low mortality for these causes. In addition geography of mortality for cancers does show an overlap with geography of "polluted areas".

Thus the high male sex ratio in Sardinia (low FSR) is the outcome of lower mortality (higher survival) among over 80-year men and of lower mortality from cancers in a wide pollution-free area of the island.

For speculating on the importance of genes factors it needs to move from macro to micro data analysis. The AKeA2 demographic survey collected preliminary data concerning family genealogies of the Sardinian centenarians (100 men and 100 women) and control groups. A first analysis of the main characteristics of the survey data has demonstrate that centenarian women have on average fewer children than the controls, and at an older age, particularly for their last child. They seem to have been favoured both by a lower fertility, and by the

young age of their parents at the moment of their own procreation. The mothers of centenarians, particularly female centenarians, lived longer on average than those of deceased control groups. The most interesting result concerns the significantly lower number of deaths in the first year of life among the children of the people who survived to become centenarians. Women and men that live longer may have genes or behaviours that enhance the survival of their children in the first year of life.

Longevity is a match between genes and environment and Centenarians are a fantastic model for studying these two fundamental components of life.

POSTER ID: **932**

Male reproductive behaviors are affected by 3 -Diol, the androgen metabolite

Abstract Presenter: Mario Oyola[1,2]
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The reproductive hormone, testosterone, and its metabolites play an important role in inducing organizational effects on the developing brain and other sexual behaviors. It has been well recognized that testosterone can be intracellularly converted in brain tissue to 17-estradiol by the aromatase enzyme or to DHT by 5 reductase. However, DHT is further metabolized to 5α - androstane-3α, 17β -diol (3α-Diol) and to 5α - androstane-3β, 17β-diol (3β - Diol). Moreover, the conversion of DHT to 3β-Diol is unidirectional and recent studies indicate that 3β-Diol preferentially binds to estrogen receptor β (ERβ) and activates transcriptional processes. In contrast, 3α-Diol has little affinity for ERβ or ERα. Ultimately, 3β-Diol is converted to inactive 6α- or 7α-triols (5α androstan-3b, 6α, 17β-triol; 5α -androstan-3β, 7α, 17β-triol) by the actions of the enzyme CYP7B1. Thus, CYP7B1 may be an important pre-receptor regulator of estrogenic functions mediated by 3β-Diol in the brain. While CYP7B1 has been found in high levels in the brain, its significance in regulating 3β-Diol-mediated functions remains unknown. In this study, we investigated the role of 3β-Diol on the behavioral phenotype using CYP7B1 null mutant mice (CYP7B1-/-).

Our results indicate that male sexual behaviors were significantly reduced in CYP7B1-/-compared to their wild type littermates (CYP7B1+/+). This could to be due to a defective vomeronasal olfactory system, since the male CYP7B1-/- mice demonstrated no preference to the female estrous bedding in the olfactory preference test even though testosterone levels were not different. In comparison to the wild type littermates, androgen receptor mRNA was decreased in the olfactory bulb of the CYP7B1-/- mice, while those in the medial amygdala remained unchanged. Consistent with this, testosterone administration to gonadectomized animals down-regulated ARmRNA in the olfactory bulb of CYP7B1+/+, but not in the CYP7B1-/- males. Moreover, the levels of ERβ mRNA in the olfactory bulb were significantly lower in the CYP7B1-/- mice when compared to the CYP7B1+/+ mice. Interestingly, no genotype effect was observed in stress-induced anxiety behaviors and stress-responsive hormone levels. Furthermore, sexual differentiation of the brain appears normal in the CYP7B1-/- mice based on the presence of the sexually dimorphic distribution of calbindin-immunoreactity in the preoptic area. Ongoing studies are aimed at examining the role of 3β-Diol and ERβ on organizational and activational effects of steroid hormones on the brain.

POSTER ID: **933**

Sex differences in the effects of testosterone on vocal development and song system morphology in adult male and female canaries

Abstract Presenter: Melvin L. Rouse Jr., M.A., Ph.D., M.D.
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The crystallization of song is the endpoint of sensorimotor song learning and is dependent on testosterone. In some seasonal breeding species such as canaries, males go through the sensorimotor stage every year. Female canaries usually sing a simpler song than male canaries but the treatment of females with testosterone (T) can induce a song development process that results in song that is more male-like. In the present study we investigated T-induced song development in male and female canaries. Males were castrated and all birds were placed on short days (8L:16D) for 8 weeks. Male and female cohorts were implanted either with a low (2mm), medium (6mm), high (12mm) silastic implant filled with crystalline T or an empty "blank" control implant (12mm). Immediately after the capsules were surgically implanted subcutaneously,

birds were housed individually in sound attenuated chambers and behavior was recorded three times per day (0800, 1200, and 1630) for 30 minute sampling periods. Brains were collected after 1 week or 3 weeks of treatment. Our results indicate that males are more sensitive to the activational effects of T as noted by shorter response latencies in the induction of song. Furthermore, early in T-treatment males sang songs with greater energy, however, by the end of treatment males and females did not differ in vocalization energy. Despite shorter response latencies in the induction of song, males did not differ from females in the rate of syllable matching across days. We also measured the volume of song nuclei such as HVC (used as its proper name) and there are significant differences in the volume of this song control nucleus despite a similar treatment with T. We also examined the immunoreactivity of tyrosine hydroxylase (TH) the rate limiting enzyme for catecholamines in HVC. Though males generally exhibited greater expression of TH immunoreactivity in HVC, females displayed a distinct dose effect in relation to T-treatment and TH immunoreactivity. However, after 3-weeks of T-treatment, there was a strong correlation of TH immunoreactivity and vocalization energy in males only. These data indicate that though T takes longer to remodel the neural system of females making it more male-like, the pattern of behavioral development in response to T as measured by syllable matching occurs at a similar rate in the two sexes.

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POSTER ID: **935**

Sex differences in emotional reactivity in Irritable Bowel Syndrome (IBS) and Human Controls (HC) – an fMRI Study

Abstract Presenter: Kristen Coveleskie[1,2]
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Background: Differences in the relative engagement of cortical (greater in male patients) and affective brain regions (greater in female patients) have been demonstrated between female and male IBS patients, during rectal distension and during an abdominal pain expectation task. However, it is not known if such sex related differences are specific to abdominal pain related task, or if they are only seen in IBS patients.

Aims: To investigate sex differences as well as IBS specific differences in emotional-arousal circuitry during an emotional reactivity task, unrelated to IBS symptoms. Based on our previous work with this task and in assessment of sex differences in autonomic reactivity, we hypothesized greater brain responses to the task would be seen in brain networks related to prefrontal and to central autonomic control (insula cortex [INS], amygdala) in both IBS and HC males.

Methods: Brain response was measured in 72 female (38 HC, 34 IBS) and 46 male (26 HC, 20 IBS) subjects using a Siemens Allegra 3T MRI scanner. Subjects were asked to view and match negatively valenced faces (Face) or geometric forms(Form). The contrast between these two viewing conditions (Face-Form) is considered an index of "emotional reactivity". Analyses were restricted to a homogenous group of individuals demonstrating emotional reactivity in the right amygdala at a liberal criteria of $p<.20$. Sex differences during emotional reactivity were tested in apriori specified regions comprising emotional-arousal, cortico-modulatory and homeostatic afferent circuitry by applying a second-level random effects general linear model controlling for subject and using an implicit baseline. Each region of interest was tested using small volume correction specifying a family-wise error rate of $p<.05$.

Results: 32 HC (7 male) and 27 IBS (10 males) who met criteria for high emotional reactivity were included. In all subjects significant BOLD responses were observed in a wide range of brain regions, including anterior INS, amygdala, hippocampus, anterior mid cingulate cortex (aMCC), and dorsal and ventral lateral prefrontal cortices (PFC). As hypothesized, males, both IBS and HC, showed greater brain activity in response to the task. More specifically, IBS males showed greater activation in several INS subregions, several PFC subregions (left dorsal medial PFC, left dorsal and ventral lateral PFC) and right amygdala compared to IBS females. HC Males showed greater response than HC females in the posterior INS, and the right hippocampus. No regions tested showed greater reactivity in female IBS or HC subjects.

Discussion: In this group of emotional responders, a GI symptom unrelated emotional reactivity task was associated with greater engagement of prefrontal modulatory regions and INS cortex in male subjects, regardless of disease group. These findings are consistent with previous findings using abdominal pain related tasks in both human subjects and rodents, and suggest a generalized sex difference in the response to the brain to a variety of emotionally salient stimuli.

POSTER ID: **936**

Female gender associated with less use of reperfusion in ST-elevation myocardial infarction: a study from the RIKS-HIA registry

Abstract Presenter: Nina Johnston[1,2]
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Background: Less use of reperfusion therapy in women has been shown in previous studies in patients with ST-elevation myocardial infarction (STEMI). Reasons for refraining include older age and associated comorbidities associated with high risk of net harm, diagnostic difficulties due to atypical symptoms or left bundle branch block (LBBB), or patient delay. We studied the use of reperfusion therapy (i.e. fibrinolysis, percutaneous coronary intervention, or coronary angiography only) in men and women with STEMI and also examined variables accountable for any differential use.

Methods: Patients with a discharge diagnosis of ST-elevation myocardial infarction in Sweden (N=33931 from the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions [RIKS-HIA]) during 2004-2008 were included. Multiple regression analysis was performed to evaluate the association of clinical characteristics (*see table*) with acute reperfusion therapy.

Results: Rates of reperfusion were lower in women than men. LBBB, atypical symptoms, and delayed presentation were found to have the strongest association with use of less reperfusion. However, even after adjusting for these factors female gender retained its independent association.

Multivariate Model (OR 95% CI)

	18–59 years N=7375			**60–74 years** N=12096			**75–89 years** N=12845		
Female	1.33	1.12	1.57	1.16	1.03	1.30	1.22	1.11	1.34
Left bundle branch block	7.29	5.73	9.29	8.38	7.22	9.73	10.41	8.93	12.13
Atypical symptoms	4.87	3.68	6.44	5.37	4.52	6.37	5.71	4.97	6.56
Symptom to ECG>12h	3.69	3.19	4.28	3.93	3.52	4.38	3.39	3.05	3.77
Renal dysfunction*									
Moderate (eGFR 40-60ml/min)	1.19	0.89	1.58	1.10	0.96	1.25	1.24	1.13	1.36
Severe (eGFR<40 ml/min)	2.68	1.57	4.57	1.95	1.46	2.59	1.59	1.33	1.91
Warfarin treatment	*too few*			2.00	1.55	2.58	1.74	1.44	2.10
Known diabetes	1.25	1.05	1.48	1.35	1.21	1.51	1.17	1.06	1.30
Known prior myocardial infarction	1.82	1.48	2.23	1.82	1.60	2.07	1.99	1.80	2.20
Known prior cardiovascular lesion	*too few*			1.29	1.05	1.58	1.30	1.13	1.50
c statistic	0.732			0.797			0.822		

*eGFRestimated glomerular filtration rate using Cockroft-Gault

Conclusion: We found less use of reperfusion therapy in women compared to men with STEMI. Commonly cited reasons for refraining from therapy did not explain this gender difference.

POSTER ID: **937**

Higher myocardial lipid content in female diabetics compared to male with similar diabetes duration correlates with GDF15 serum concentrations

Abstract Presenter: Kosi L[1],
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Background: Type II diabetes is associated with a diastolic dysfunction of the heart. The reason possibly being the increased myocardial lipid content due to cardiac glucolipotoxicity common in diabetic and obese subjects. GDF15 is an inflammatory and apoptotic protein up-regulated in the injury of the heart. Female diabetics have a 4-6-fold increased risk for cardiovascular events possibly due to lac of the protective estrogen effect compared to non-diabetic subjects.

Methods: 60 Patients, 30 male and 30 female, treated at our diabetes metabolic unit of the Medical University of Vienna underwent magnetic resonance spectroscopy performed with 3 Tesla Siemens MRT. GDF-15 was measured in serum of the patients by Quantikine ELISA assays.

Results: The mean age was 55,9±7,2, weight 88,3±17, BMI 31,6± 5,1kg/m^2 and duration of diabetes 6±2 years. Female patients had significantly higher myocardial lipid content than male diabetics (1,9±0,5 vs 0,9±0,3, p=0.003). Ejection fraction was decreased similarly in both sexes (51,4±2,3 vs 49,2±0,9, p_ns). GDF15 levels were increased in both sexes and did not differ significantly (2358 ±180 pg/ml). However GDF15 serum concentrations strongly correlated with cardiac lipid content (r_S=0.33; p=0.015, r_S=0.35; p=0.009) especially in female patients (r_S=0.35; p=0.009) pointing toward the fact that female diabetics suffer from severe cardiac injury after even 6 years diabetes duration compared to the male patients.

Conclusion: To conclude type II diabetes per se is a risk factor for cardiovascular events, especially in women, perhaps due to increased myocardial fat resulting in dyastolic dysfunction, strongly correlating with increased GDF15 levels. GDF-15 can be seen as a possible early marker for cardiac injury in type II diabetic patients, with a special focus on women being at higher risk.

POSTER ID: **938**

Papillary thyroid cancer (PTC) gender disparity: a multicentric study

Abstract Presenter: Isabella Merante Boschin[1]
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Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer, accounting for approximately 80% of cases. Our intention is to consider the patients underwent surgery for PTC in different southern European endocrine-surgery centers and to compare females (F) vs males (M) as regards a series of clinical, histopathologic, genetic and molecular variables.
We considered 658 patients underwent surgery for PTC from 2007 to 2011 at Surgical Pathology, University of Padova, and General Surgery Department, University of Trieste. We revised clinical and histopathologic documents and we compared F vs M as regards the following variables: age, extention of surgery, node dissection, TNM, mono/plurifocality, BRAF mutations, out come. A p value less than 0.05 was considered statistically significant.

Comparing F vs M we observed: the F was 489 (74%) vs 169 M (26%) (p<0.015), the mean age was 46 years (range 11-86) in F vs 46 years (range 11-83) in M (p<0.44), total thyroidectomy was realized in 474 F (97%) vs 161 M (95%) (p<0.72), node dissection was realized in 387 (79%) F vs 132 (78%) M (p<0.99), central node dissection in 340 (88%) F vs 94 (71%) M (p<0.75), laterocervical node dissection in 47 (12%) F vs 38 (29%) M (p<0.011), stage I was in 315 (64%) F vs 87 (51.5%) M (p<0.19), stage II in 15 (3%) F vs 4 (2.5%) M (p<0.51), stage III in 126 (26%) F vs 54 (32%)M (p<0.24), stage IV in 33 (7%) F vs 24 (14%) M (p<0.22),

monofocality was in 279 (57%)F vs 89 (52.7%) M (p<0.64), plurifocality was in 210 (43%) F vs 80 (47.3%) M (p<0.76), the association with thyroiditis was in 132 F (27%) and in 25 M (15%) (p<0.001)(BRAF – V600E mutation was identified in 143 (29%) F vs 52 (30.7%) M (p<0.84).

We revised the follow up in 395 cases. The mean time of follow up was 37 months (range 1-343) in F vs 45 months (range 4-156) in M, 251 (88%) F underwent I131radioiodinetherapy vs 91 (83%) M (p<0.74), the median dose was 132.63 mCi (range 50-500) in F vs 139.42 mCi (range 50-350) in M (p<0.27), the median time of follow up was 37 months in F and 45 months in M (p<0.24), the median value of Tireoglobulin (Tg) was 7 mU/L (range 0.1-485.3) in F vs 19.83 (range 0.1-593) in M (p<0.11), F was free of disease in 274 (96%) vs 102 (93.5%) M (p<0.64). The differences statistically significant regarded the number of patients, the laterocervical node dissection, the association with thyroiditis.

POSTER ID: **939**

Neonatal disruption of the PGE2-E2 signaling pathway in the cerebellum affects normal Purkinje cell development and sex-specific behaviors relevant to Autism Spectrum Disorder

Abstract Presenter: Jessica Knutson[1]
Other Authors: Margaret McCarthy, PhD[1,2]
Author Affiliations: [1]Program in Neuroscience, [2]Department of Physiology, University of Maryland School of Medicine, Baltimore, Maryland

Autism spectrum disorder (ASD) is defined by inappropriate social interactions, impairments in social communication, repetitive or stereotyped behaviors, and abnormal responses to sensory stimuli. The exact cause is unknown, but ASD is considered a neurodevelopmental disorder with complex genetic and environmental origins and a well-known higher incidence in males versus females. Cerebellar pathology is strongly associated with ASD, such as reduced cerebellar volume, particularly in the posterior vermis (Courchesne *et al*, 1988), as well as a reduced number of Purkinje and granule cells (Palman et al, 2004). Inflammation during the developmental period between *in utero* and early childhood is also strongly associated with ASD - the same time period during which the most significant cytoarchitectural changes occur in the cerebellum. Prostaglandin E2 (PGE2) is the principle mediator of inflammation, ultimately responsible for inducing fever, while its receptor EP3 is the primary receptor driving the fever response (Kauffmann *et al*, 1997). Prostaglandins are lipid-derived molecules ubiquitous in mammalian tissues that function as paracrine, endocrine, and autocrine signaling molecules as part of a wide variety of physiological functions.

We have discovered a signaling pathway in the cerebellum where PGE2 stimulates aromatase activity, increasing the conversion of testosterone into estradiol (E2). Increased PGE2 results in increased estradiol production and a decrease in spinophilin, a marker for dendritic spines. This decrease in spinophilin correlates with a decrease in Purkinje cell dendritic length with no change in spine density, as determined by morphological analysis with Golgi-COX staining. If the pathway is shifted in the other direction, where PGE2 synthesis is decreased by inhibition of the COX1/2 enzyme, spinophilin (and Purkinje cell dendritic length) increases, suggesting this signaling pathway is carefully balanced to control the appropriate development of the Purkinje cell dendritic tree.

Previously we have shown that treatment with the anti-inflammatory drug Nimesulide, a COX-2 inhibitor that decreases PGE2 production, during postnatal week 2 disrupts not only normal cerebellar development, but also behaviors relevant to Autism Spectrum Disorder. Specifically, males show a decrease in social play behavior, an increase in pain sensitivity, and an increase in object fixation. Here we show that the opposite manipulation, increasing PGE2 levels directly, results in the same reduced social play behavior in males, with similar abnormalities in other behaviors. No changes are seen in basic motor tasks or olfactory responses, thus we conclude that disrupting the PGE2-E2 signaling pathway in the cerebellum during the second postnatal week interferes with normal cerebellar development and correlates with abnormal behaviors also seen in children with ASD. This suggests that during this developmental period, fever and inflammation may increase the risk for development of ASD by altering cerebellar development.
This study was supported by grant R01-MH091424 from the National Institute of Mental Health.
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Saturday, June 9, 2012
6:00 – 7:00 p.m.

AGENDA

Call to Order by OSSD President

Executive Director Report

Council Reports

BSD Journal Updates

New Business

Introduce and turn meeting over to incoming President.

Open Forum

Adjourn

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