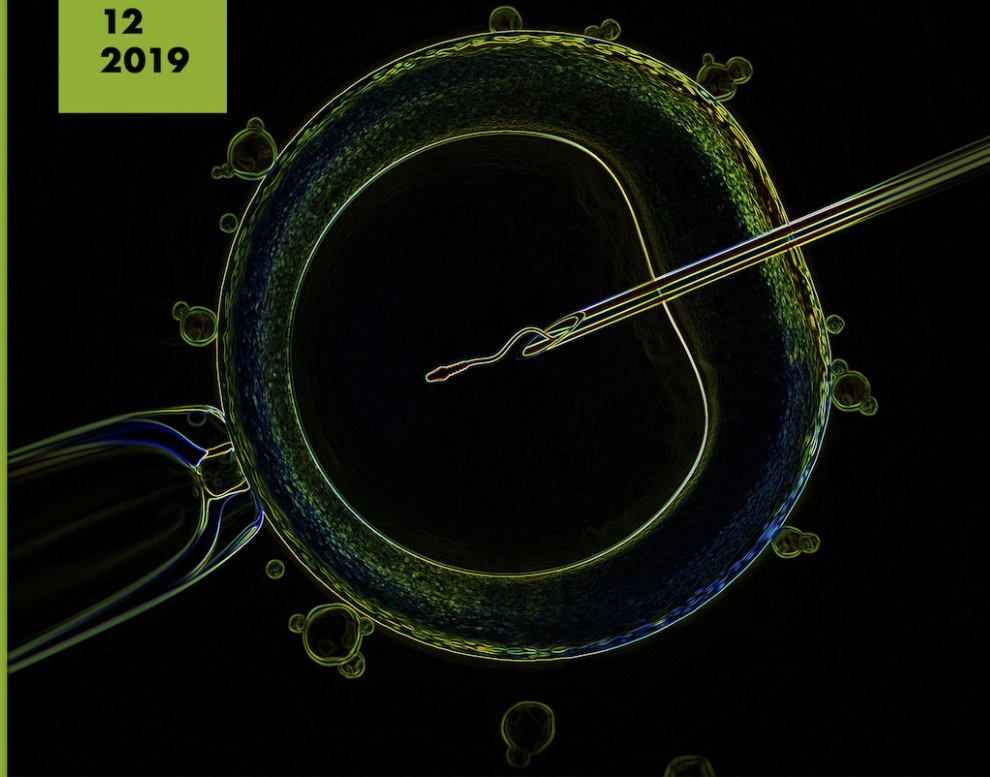


**June
12
2019**



Natural and Assisted Reproduction: Science and Outcomes Symposium

Presented by the Center for Research on Reproduction and Women's Health & The P50-Penn Center for Epigenetics in Reproduction at the University of Pennsylvania



Dmitry Kissin
CDC



Jacquetta Trasler
McGill University



Kotaro Sasaki
University of Penn



Patricia Hunt
Washington State Univ



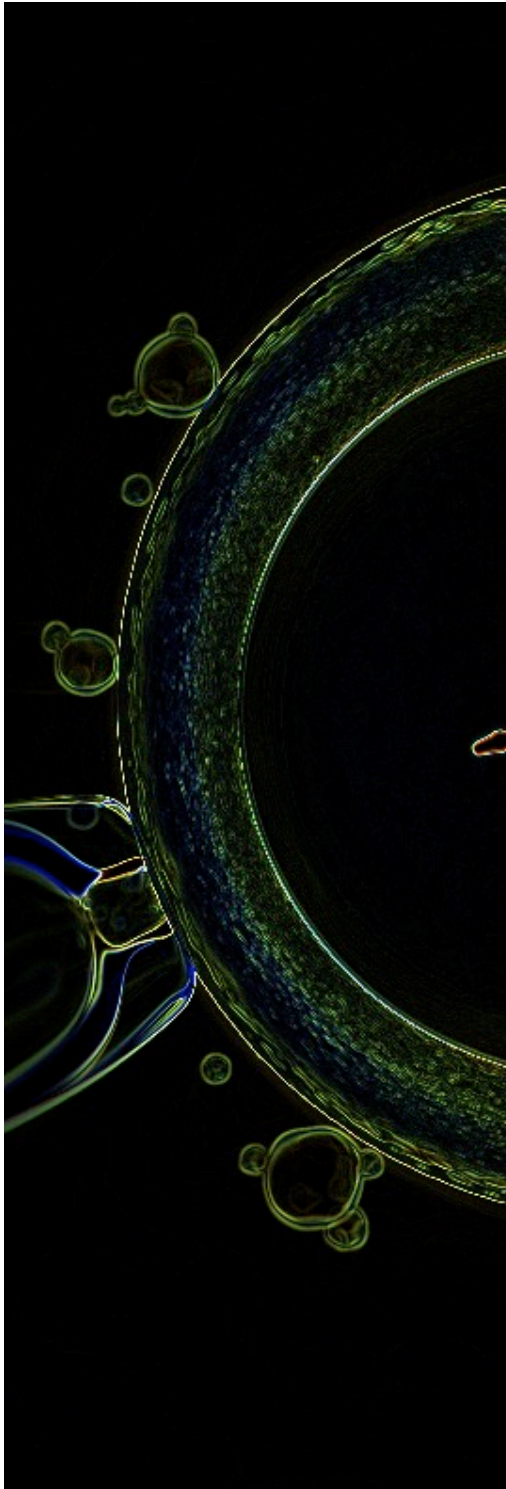
Paolo Rinaudo
UCSF

Wed, June 12, 2019 • 9:00am - 6:00pm • BRB Auditorium

421 Curie Blvd, Philadelphia, PA 19104 • To register or submit an abstract visit:
<https://www.med.upenn.edu/crrwh/events.html>



SUBMIT YOUR ABSTRACT BY MAY 8TH || || || || REGISTRATION DEADLINE MAY 22ND



SCHEDULE

NATURAL AND ASSISTED
REPRODUCTION: SCIENCE
AND OUTCOMES
SYMPOSIUM

.....

9:15AM

DMITRY KISSIN, MD, MPH

*Child health outcomes after in vitro
fertilization*

9:45AM

PAOLO RINAUDO, MD, PHD

MASTROIANNI LECTURE

*Health from the beginning of life: The
Developmental Origin of Health and Disease
hypothesis and the preimplantation embryo*

AFTERNOON

1:00PM

JACQUETTA TRASLER, MD, PHD

*Inducing and correcting epigenetic defects
associated with infertility and ART: Are folic
acid supplements the answer?*

3:00PM

KOTARO SASAKI, MD, PHD

*Germline specification in primates
and its reconstitution in vitro*

4:00PM

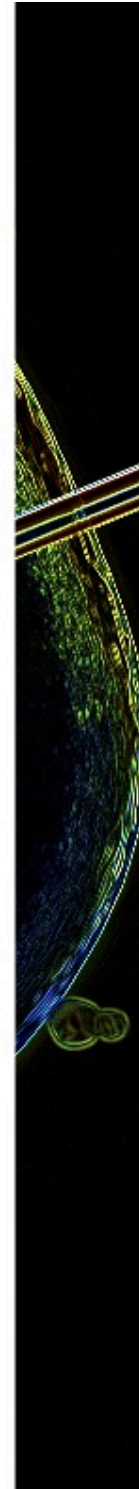
PATRICIA HUNT, PHD

CUOZZO MEMORIAL LECTURE

The germline and the environment

JUNE 12, 2019

BRB Auditorium



**Natural and Assisted Reproduction: Science and Outcomes Symposium
Luigi Mastroianni Jr., M.D. Memorial Lecture
and James M. Cuzzo Memorial Lecture**

**June 12, 2019
Biomedical Research Building II/III
421 Curie Boulevard
Philadelphia, PA 19104**

Table of Contents

	Page
Program	5-10
Luigi Mastroianni, Jr., M.D. (1925-2008)	11
James M. Cuzzo (1915-1976)	12
Dimitry Kissin, MD, MPH Team Lead, Assisted Reproductive Technology Team, Maternal and Infant Health Branch, Division of Reproductive Health, Centers for Disease Control and Prevention	13
Mastroianni Memorial lecturer Paolo Rinaudo, MD, PhD Professor of Obstetrics Gynecology & Reproductive Sciences, University of California San Francisco, Reproductive Endocrinology and Fertility Specialist, UCSF Center for Reproductive Health	14
Jacquetta Trasler, MD, PhD James McGill Professor, Departments of Pediatrics, Human Genetics and Pharmacology & Therapeutics, McGill University Senior Scientist, Research Institute of the McGill University Health Centre	15
Kotaro Sasaki, MD, PhD Assistant Professor, School Of Veterinary Medicine University of Pennsylvania	16
Cuzzo Memorial Lecturer Patricia Hunt, PhD Meyer Distinguished Professor, School of Molecular Biosciences Center for Reproductive Biology, Washington State University	17

**Natural and Assisted Reproduction: Science and Outcomes Symposium
Luigi Mastroianni Jr., M.D. Memorial Lecture
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**June 12, 2019
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421 Curie Boulevard
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Table of Contents (cont.)

Abstracts - Oral Presentations	18-23
1:30 PM – Laren Reische	18
1:45 PM – Hayley Richardson	19
2:00 PM – Yongjuan Guan	20
2:15 PM – Paul Kroeger	21
2:30 PM – Emma Lewis	22
2:45 PM – Lacey Luense	23
Abstracts – Interactive Posterboard Presentations	24-46
Group 1 – IUE	24-29
Group 2 – Male Reproduction	30-34
Group 3 – Reproductive	35-38
Group 4 – ART	39-43
Group 5 – Cancer	44-47
Past Luigi Mastroianni, Jr., M.D. Memorial lecturers	48
Past James M. Cuzzo Memorial lecturers	49

**Natural and Assisted Reproduction: Science and Outcomes Symposium
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**June 12, 2019
Biomedical Research Building II/III
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8:00 – 9:00 Registration, Poster Assignments, Continental Breakfast

**9:00 am Welcoming Remarks - BRB II/III Auditorium
Deborah Driscoll, MD**
Luigi Mastroianni Professor and Chair, Department of Obstetrics
and Gynecology; Director, Center for Research on Reproduction
and Women's Health

Morning Session – Moderator: Monica Mainigi, MD

9:15 am Dmitry Kissin, MD, MPH
Team Lead, Assisted Reproductive Technology Team, Maternal
and Infant Health Branch, Division of Reproductive Health,
Centers for Disease Control and Prevention

Child health outcomes after in vitro fertilization

30 min (25 min + 5 min for questions)

9:45 am Mastroianni Memorial Lecture

Introduced by Christos Coutifaris, MD., PhD, Celso-Ramon Garcia
Professor, Division of Reproductive Endocrinology and Infertility,
Department of Obstetrics and Gynecology

Paolo Rinaudo, MD, PhD
Professor of Obstetrics Gynecology & Reproductive Sciences, University
of California San Francisco, Reproductive Endocrinology and Fertility
Specialist, UCSF Center for Reproductive Health

**Health from the beginning of life: The Developmental Origin of
Health and Disease hypothesis and the preimplantation embryo**

10:45 am Coffee Break

Natural and Assisted Reproduction: Science and Outcomes Symposium
Luigi Mastroianni Jr., M.D. Memorial Lecture
and James M. Cuzzo Memorial Lecture

June 12, 2019
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11:00 am **Interactive Poster Session** - BRB II/III Lobby

CRRWH Affiliated Posters (see pages 23 to 46)

12:00 pm **Luncheon - Invited Speakers and Registrants** - BRB II/III Lobby -
Seating for lunch is available in the BRB lobby, 252 BRB, 1201 BRB,
1301 BRB, and the 14th Fl Faculty Lounge

Afternoon Session - Moderator: Dr. Marisa Bartolomei, PhD

1:00 pm **Jacquetta Trasler, MD, PhD**

James McGill Professor of Pediatrics, Human Genetics, and
Pharmacology and Therapeutics McGill University Senior Scientist,
Montreal Children's Hospital and Research Institute McGill University
Health Centre

30-minute talk (25 min + 5 min for questions)

**Inducing and correcting epigenetic defects associated with infertility and ART:
Are folic acid supplements the answer?**

Trainee Talks (10 min + 5 min for questions)

1:30 pm Laren Reische
**Altered metabolic outcomes in IVF-conceived offspring and abnormal placental
epigenetic profiles**

1:45 pm Hayley Richardson
**Impact of Mode of Conception on Early Pregnancy Human Chorionic
Gonadotropin Rise and Birthweight**

2:00 pm Yongjuan Guan
The SCF ubiquitin E3 ligase drives the meiotic G2 to MI phase transition

2:15 pm Paul Kroeger
Evaluating the potential to repurpose statins for ovarian cancer therapy

Natural and Assisted Reproduction: Science and Outcomes Symposium
Luigi Mastroianni Jr., M.D. Memorial Lecture
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2:30pm Emma Lewis
Regulatory T cell dysfunction in a mouse model of pregnancy loss

2:45 pm Lacey Luense
Gcn5-mediated histone acetylation governs nucleosome dynamics in spermiogenesis

3:00 pm **Kotaro Sasaki, MD, PhD**
Assistant Professor, Department of Biomedical Sciences,
University of Pennsylvania School of Veterinary Medicine

Germline specification in primates and its reconstitution in vitro
30-minute talk (25 min + 5 min for questions)

3:30 pm **Awards**

Three research awards were established in honor of Professors Susan Heyner, Ph.D., Bayard T. Storey, Ph.D. and Joseph Touchstone, Ph.D. These three individuals served the Division of Reproductive Biology, the CRRWH, the Department of Obstetrics and Gynecology and the University of Pennsylvania with distinction over the course of their careers as faculty. The awards are given on an annual basis to non-faculty trainees and staff who have distinguished themselves through their research contribution during the past calendar year.

3:45 pm **Snack Break**

4:00 pm **Cuzzo Memorial Lecture**
Introduced by Dr. George Gerton, PhD
Executive Committee Member, Center for Research on Reproduction
and Women's Health, University of Pennsylvania Perelman School of
Medicine

Patricia Hunt, PhD
Meyer Distinguished Professor, School of Molecular Biosciences
Center for Reproductive Biology, Washington State University
The germline and the environment

5:00 pm **Cocktail Hour**

Poster Session 11:00 AM – 12:00 PM

Group 1 IUE: Moderator Becky Simmons – 6 Posters

11:00 Apoorva Joshi IUE/placenta

In utero exposure to gestational diabetes alters the transcriptome and methylome of human fetal stem cells revealing an enrichment of interferon pathways

11:10 Apoorva Joshi IUE/placenta

Maternal obesity and perfluorooctanoic acid synergize to alter lipid metabolism in human fetal hepatocytes predisposing the offspring to NAFLD

11:20 Yu-Chin Lien IUE

Altered Transcription Factor Binding and Gene Bivalency May Contribute to Long-term Gene Dysregulation in Intrauterine Growth Retarded Rat Islets

11:30 Thea Golden IUE

IUGR Causes Pancreatic Inflammation in the Neonatal Rat

11:40 Tammy Ying IUE

Neonatal IL-4 administration decreases body fat content and weight and also improves glucose tolerance in adulthood.

11:50 Sneha Mani IUE/placenta

Maternal Decidual Cells Regulate Trophoblast Invasion: Studies from a Novel Organ-on-a-Chip Device

Group 2 Male Reproduction: Moderator George Gerton – 5 Posters

11:00 Jacob D. Herford Male Reproduction

Non-steroidal anti-inflammatory drugs reduce vas deferens epithelial MRP4 expression and prostaglandin export

11:10 Cetewayo Rashid Male Reproduction

Paternal bisphenol A exposure alters offspring glucose tolerance in a time and sex specific manner

11:20 Fang Yang Male Reproduction

TEX15 is required for epigenetic silencing of transposable elements in the germline

Group 2 Male Reproduction: Moderator George Gerton – 5 Posters (cont.)

11:30 Rui Guo Male Reproduction

MORC2A is essential for male fertility and epigenetic silencing of transposable elements

11:40 Lei Zhang Male Reproduction

Pilot screening of male contraceptive drugs by targeting the meiosis specific proteins MEIOB and SPATA22

Group 3 Reproduction : Moderator Monica Mainigi – 4 Posters

11:00 Arunika Das Reproduction

Mechanisms of epigenetic centromere inheritance through the mammalian germline

11:10 Jessica Y. Chotiner Embryo

Cyclin B3 is a maternal factor essential for embryogenesis

11:20 REXXI Prasasya Epigenetics

TET1 is required for maternal imprint erasure during primordial germ cell development

11:30 PARS Alummi Poster

Fueling the pipeline: Educating Young Women in the Reproductive Sciences

Group 4 ART: Moderator Christos Coutifaris – 5 Posters

11:00 Eric A. Rhon-Calderon ART

Altered reproductive epigenetic profiles in mature IVF-conceived offspring

11:10 Jayashri Ghosh ART

Effect of fresh vs frozen embryo transfer technology on the placental epigenome

11:20 Kelly A. Duffy ART

Clinical Phenotype of Beckwith-Wiedemann Syndrome in Natural versus Assisted Reproductive Technology Conceived Pregnancies

11:30 Marissa S. Weiss ART

Stress and Success: Data from a Prospective Cohort Study Investigating the Impact of Early Life Stress on IVF Outcomes

Group 4 ART: Moderator Christos Coutifaris – 5 Posters (cont.)

11:40 Lisa A. Vrooman ART

Compromised fetal growth and abnormal placental development in a mouse model of Assisted Reproductive Technologies (ART)

Group 5 Cancer: Moderator Lin Zhang – 4 Posters

11:00 Haineng Xu Cancer

Combination inhibition of WEE1 and ATR causes tumor regression in a Cyclin E level dependent manner

11:10 Yasuto Kinose Cancer

Comprehensive molecular and experimental characterization of ovarian clear cell carcinoma cell lines for in vivo drug development

11:20 Guannan Zhang Cancer

Elucidating the roles of estrogens in the development and prognosis of malignant pleural mesothelioma

11:30 Jiao Yuan Cancer

Integrated Analysis of Genetic Ancestry and Genomic Alteration Across Cancers

**2019 Natural and Assisted Reproduction:
Science and Outcomes Symposium**
Center for Research on Reproduction and Women's Health
Perelman School of Medicine at the University of Pennsylvania
and
The P50-Penn Center for Epigenetics in Reproduction

Luigi Mastroianni, Jr., M.D. Memorial Lectureship

Luigi Mastroianni, Jr., M.D.
(1925-2008)

The Luigi Mastroianni, Jr., M.D. Memorial Lectureship was established in honor of Dr. Mastroianni, former Chairman of the Department of Obstetrics and Gynecology of the University of Pennsylvania.

Dr. Mastroianni was an internationally recognized pioneer in reproductive biology and committed to translational basic knowledge into clinical care.

Through the training and recruitment of promising young physicians, Dr. Mastroianni built one of the best research programs in women's health in the nation.

To commemorate his vision and leadership in academic medicine, we have created a lectureship that supports one of his greatest passions – training investigators in the field of reproductive medicine.



Luigi Mastroianni

**2019 Natural and Assisted Reproduction:
Science and Outcomes Symposium
Center for Research on Reproduction and Women's Health
Perelman School of Medicine at the University of Pennsylvania
and
The P50-Penn Center for Epigenetics in Reproduction
40th James M. Cuozzo Memorial Lecture**

**James M. Cuozzo
(1915-1976)**

This lecture series honors the outstanding contributions of James M. Cuozzo to the Department of Obstetrics and Gynecology. Mr. Cuozzo was the Business Administrator from 1963-1976. During his tenure, he was instrumental in establishing a firm financial footing for the department.

In recognition of his efforts, this annual memorial lecture brings internationally recognized scientists to the University of Pennsylvania so that they may convey their research findings in the fields related to reproductive biology.



Dmitry Kissin, MD, MPH

Team Lead, Assisted Reproductive Technology Team
Maternal and Infant Health Branch
Division of Reproductive Health
Centers for Disease Control and Prevention



Title of talk: Child health outcomes after in vitro fertilization

Dr. Dmitry Kissin is Epidemiologist and Health Scientist in the area of reproductive health. He received his Doctor of Medicine degree with specialization in Obstetrics and Gynecology from the St. Petersburg State Medical University and did his residency training in Ott Research Institute of Obstetrics and Gynecology in St. Petersburg, Russia. Dr. Kissin also received Master of Public Health degree with specialization in Epidemiology from the State University of New York in the United States. He worked on a variety of projects, both domestically and internationally, in the areas of women's health and maternal and child health, ranging from Sudden Infant Death Syndrome (SIDS), family planning, prevention of mother-to-child HIV transmission, prevention of influenza among pregnant women, and most recently – infertility and Assisted Reproductive Technology (ART). Currently, he is leading ART Surveillance and Research Team in Maternal and Infant Health Branch, Division of Reproductive Health. His team maintains the National ART Surveillance System and monitors effectiveness and safety of ART in the United States and conducts wide-ranging epidemiological and clinical research on many aspects of infertility and ART. In addition, Dr. Kissin is Adjunct Assistant Professor of Gynecology and Obstetrics at Emory University School of Medicine, where he mentors students, residents and fellows in the area of reproductive health, infertility, obstetrics and gynecology. Dr. Kissin published over 100 manuscripts in peer-reviewed journals and 2 book chapters on various topics in reproductive health.

Paolo Rinaudo, MD, PhD

Luigi Mastroianni Jr., M.D. Memorial Lecturer

Professor, Reproductive Endocrinology and Infertility
University of California San Francisco



Title of talk: Health from the beginning of life: The Developmental Origin of Health and Disease hypothesis and the preimplantation embryo

The focus of our research is to understand how *in vitro* fertilization and *in vitro* culture during the pre-implantation period affect fetal and adult development. This has particular relevance in light of the widespread use of artificial reproductive techniques (ART). In fact, fetal adaptations in utero to adverse conditions can lead to specific diseases in the adult, including diabetes, high blood pressure and coronary heart disease. This phenomenon, termed the developmental origin of adult health and disease or the Barker hypothesis, has been extrapolated back to preimplantation development.

Our laboratory is creating a mouse model of IVF for better analyzing long term outcome. One avenue of research analyzes glucose tolerance, fat content and growth in adult animals generated *in vitro* or *in vivo*. The goal of this study is to understand if animals generated *in vitro* have a different phenotype that could lead to disease in later life.

A second avenue of research analyzes if placentation is different in animal generated *in vivo* or *in vitro*. Finally, we evaluate how different culture conditions determine gene expression changes and modify DNA methylation pattern or histone code in preimplantation embryos or adult animals generated *in vivo* or *in vitro*.

Jacquetta Trasler MD, PhD

James McGill Professor

Departments of Pediatrics, Human Genetics and Pharmacology & Therapeutics

McGill University

Senior Scientist, Research Institute of the McGill University Health Centre



Title of talk: Inducing and correcting epigenetic defects associated with infertility and ART: Are folic acid supplements the answer

Summary of Research

My main research interest and expertise is the field of epigenetics, as it pertains to normal development in children and the prevention of birth defects. The epigenome provides a way for the environment to interact with our genomes to modify gene expression in ways both adaptive and maladaptive and undergoes its most dramatic remodeling in germ cells and early embryos. Our clinical focus is the 10-20% of couples who suffer from infertility or delay child-bearing and increasingly (1-6% of pregnancies) resort to the use of assisted reproductive technologies (ARTs). Both infertility and the use of ARTs are associated with epigenetic (DNA methylation) defects and adverse outcomes in children.

We are currently carrying out fundamental and translational research on two main themes, one on infertility/subfertility and the second on ARTs. In Theme 1, we examine infertility, sex-specific susceptibilities and germ cell exposures resulting in abnormal epigenomic patterning and health outcomes. In Theme 2, we determine roles of ARTs in perturbing epigenomic programs and inducing birth defects and then devise approaches to counselling and prevention. For our research in these two themes we: 1) use gene-targeted under- and over-expression mouse models to determine sex-specific timing and roles of DNA methylation patterning at times of genome-wide epigenomic reprogramming in germ cells and embryos, 2) study environmental manipulations such as ARTs and folic acid diets to test how perturbing key epigenetic programs interferes with normal development and, 3) exploit state-of-the-art epigenomic technologies to track epigenetic perturbations that result in abnormal development in our mouse and human studies. With basic mouse models we can separate genetic factors such as those resulting in infertility from environmental factors to determine how techniques used in assisted reproduction or environmental factors interfere with normal epigenomic patterning in the germline and embryo. Epigenomic profiling and outcome studies can then be compared across mouse and human studies. With our research we expect to gain a fundamental understanding of how parents' exposure to environmental stressors or diet can predispose their children to developmental defects, metabolic disease, obesity and neurodevelopmental disorders.

Kotaro Sasaki, M.D., Ph.D.

Assistant Professor, School of Veterinary Medicine
University of Pennsylvania



Title of talk: Germline specification in primates and its reconstitution in vitro

Dr. Kotaro Sasaki is Assistant Professor at the University of Pennsylvania School of Veterinary Medicine and a member of Institute for Regenerative Medicine.

Dr. Sasaki received his MD and PhD from Hokkaido University in 2005 and Kyoto University in 2017, respectively. He is a board-certified anatomic pathologist, completed anatomic pathology residency at the University of Pittsburgh in 2011 and renal pathology fellowship at the University of Washington in 2012. Prior to joining the University of Pennsylvania, he completed a postdoc training at Mitinori Saitou Lab at Kyoto University, Japan.

His major research interest involves the understanding the molecular mechanisms of human germ cell and gonadal development using single cell genomics and their in vitro reconstitution using pluripotent stem cells.

Patricia Hunt, Ph.D.

40th James M. Cuzzo Memorial Lecturer

Meyer Distinguished Professor, School of Molecular Biosciences Center for Reproductive Biology, Washington State University



Research in the Hunt laboratory focuses on mammalian germ cells, with a major emphasis on meiosis, the specialized cell division that gives rise to the haploid germ cells. In the human female the incidence of pregnancy loss due to chromosome abnormalities is extraordinarily high. This is a reflection of the fact that the meiotic process is highly error-prone and the incidence of errors in women is strongly influenced by age. Thus, a major research focus is on understanding the control of the normal meiotic process in the mammalian female, the mechanisms(s) by which errors occur, and the way in which age influences female meiosis. In addition, a serendipitous finding that resulted from an accidental exposure in our animal facility, has led to a new avenue of research for the Hunt laboratory. The inadvertent exposure of our mice to the estrogen mimic, bisphenol A (BPA) from damaged caging materials (polycarbonate cages and water bottles) led to the realization that environmentally relevant doses of BPA cause meiotic disruption and aneuploidy in the mouse. Current studies focus on determining the reproductive effects of exposure to chemicals with estrogenic activity during different developmental time points.

1:30 PM – Oral Presentation – Laren Reische

Altered metabolic outcomes in IVF-conceived offspring and abnormal placental epigenetic profiles

Riesche, Laren, Rhon-Calderon, Eric, Vrooman, Lisa, Bartolomei, Marisa

Institutional Affiliation: Perelman School of Medicine, University of Pennsylvania

Abstract: Objective: IVF is associated with adverse placental-mediated pregnancy outcomes as well as increased risk of cardiometabolic abnormalities. Using our advanced IVF mouse model, the objective of this study was to investigate the long-term cardiometabolic outcomes of IVF-conceived offspring and determine whether term placental epigenetic profiles predict offspring outcomes.

Materials and Methods: For the IVF group, CF1 female mice were superovulated with PMSG and hCG administered 48 h apart. Fourteen hours later, cumulus-egg complexes were collected and IVF was performed with capacitated mature spermatozoa collected from B6SJL male mice. The fertilized eggs were cultured to the blastocyst stage and then non-surgically transferred into pseudo-pregnant CF1 females. For the natural control group (Nat), CF1 females were mated overnight with B6SJL males. At term, pups were delivered via c-section and placentas were collected. Longitudinal metabolic phenotyping at 16-, 20-, 24- and 28-weeks consisted of weight, glucose tolerance testing and fasting serum measures of total cholesterol, triglycerides and insulin. At 39-weeks of age, offspring were sacrificed, and all cardiometabolic tissues were collected. Global DNA methylation (DNAm) and DNAm of imprinted genes was assessed with luminometric methylation assay (LUMA) and pyrosequencing, respectively. Student's t-test were used to evaluate differences between groups.

Results: Placental efficiency was significantly lower in IVF compared to Natural ($p=0.002$). For IVF males, weight was significantly higher at 0–5 weeks of age ($p<0.05$). IVF males also demonstrate significantly higher triglycerides at four timepoints: 12 weeks ($p=0.01$), 16 weeks ($p=0.0189$), 20 weeks ($p=0.0011$) and 28 weeks ($p=0.0416$). In addition, IVF males demonstrated a significant elevation in cholesterol at 28 weeks compared to Natural males ($p=0.0345$) and significantly higher insulin at three timepoints: 20-weeks ($p=0.0477$), 24-weeks ($p=0.0001$), and 28-weeks ($p=0.0129$). For IVF females, weight was significantly higher than Natural females at 2–3w ($p<0.05$). IVF females also demonstrated significantly higher cholesterol at four time points: 12 weeks ($p=0.0187$), 16-weeks ($p=0.0034$), 20-weeks ($p=0.0022$), and 24-weeks ($p=0.115$). Global DNAm was significantly lower in placentas from IVF-conceived females ($p=0.011$). Percent methylation detected at the H19/Igf2 ICR was also significantly lower in IVF-conceived females compared to naturally conceived females ($p<0.00001$). Those females with the lowest global placental DNAm demonstrated cardiometabolic abnormalities later in life (i.e. highest weight, triglycerides and cholesterol and lowest mean arterial pressure and heart rate).

Conclusions: Our findings demonstrate that while both male and female offspring demonstrate altered metabolic outcomes, the specific metabolic domains that are affected may be quite different based on sex. Additionally, the placental epigenetic profile may provide predictive value for altered metabolic outcomes of females.

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1:45 PM – Oral Presentation – Hayley Richardson

Impact of Mode of Conception on Early Pregnancy Human Chorionic Gonadotropin Rise and Birthweight

Richardson, Hayley M., Kalliora, Charikleia, Mainigi, Monica A., Coutifaris, Christos, Sammel, Mary D., Senapati, Suneeta

Institutional Affiliation: University of Pennsylvania

Abstract: Altered hCG kinetics have been observed in conceptions after fresh vs. frozen/thawed embryo transfers and following blastomere biopsies in cleavage stage embryos. While preimplantation genetic testing has improved pregnancy rates in some populations, the impact of trophoctoderm biopsy on hCG kinetics and subsequent birthweight is unknown. The aim of this study was to determine differences in first trimester hCG kinetics by mode of conception and subsequent risk of small and large for gestational age infants (SGA and LGA). Groups examined include unassisted natural conceptions, pregnancies after fresh embryo transfer (ET), frozen ET, and trophoctoderm preimplantation genetic testing for aneuploidy (PGT-A) followed by frozen ET. Serial serum hCG measurements were assessed for 598 singleton pregnancies between 10 and 28 days post-conception. A joint random effects and logistic model was used to evaluate the effect of mode of conception on hCG slope (per day increase in log-transformed hCG) and incidence of SGA/LGA. Models were adjusted for maternal age, body mass index, and parity as appropriate. Odds ratios illustrate the change in risk associated with a one standard deviation increase in hCG slope. Fresh ET had the highest incidence of SGA (12%) and frozen ET had the highest incidence of LGA (16%). PGT-A had the lowest incidence of each event (4% SGA and 8% LGA). Estimated hCG rise was fastest among PGT-A, followed by frozen ET, unassisted, and fresh ET. Significant differences in hCG slope were found for all five pairwise group comparisons tested: PGT-A/unassisted ($p < 0.01$), PGT-A/fresh ET ($p < 0.01$), PGT-A/frozen ET ($p = 0.02$), fresh ET/frozen ET ($p < 0.01$), fresh ET/unassisted ($p = 0.03$). hCG rise is associated with a higher risk of SGA ($OR = 0.64$, $p < 0.01$), yet hCG rise does not impact LGA risk ($OR = 1.16$, $p = 0.33$). Notably, PGT-A is not associated with abnormal fetal growth phenotypes, supporting the safety of this technology. These findings suggest the superovulated environment in fresh ET may predispose to abnormal trophoblast differentiation and early placentation resulting in altered hCG kinetics and fetal growth; yet the mechanisms of LGA in frozen ET may be mediated by other mechanisms beyond trophoblast function.

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2:00 PM – Oral Presentation – Yongjuan Guan

The SCF ubiquitin E3 ligase drives the meiotic G2 to MI phase transition

Guan, Yongjuan, YG Leu, N. Adrian, AL, Ruthel, Gordon, GR, Luo, Mengcheng, ML Wang, P. Jeremy, PJW

Institutional Affiliation: Department of Biomedical Sciences, University of Pennsylvania School of Veterinary Medicine, Philadelphia, Pennsylvania 19104, USA

Abstract: The meiotic prophase I to metaphase I (G2/MI) transition requires chromosome desynapsis and metaphase competence acquisition. Control of these major meiotic events is poorly understood. S-phase kinase-associated protein 1 (SKP1), a core component of a Skp/Cullin/F-box (SCF)-type E3 ubiquitin ligase complex, was reported to be a putative meiotic chromatin-associated protein. Here we report that SKP1 was highly expressed in pachytene to metaphase I spermatocytes and post-meiotic round spermatids. SKP1 localizes to lateral elements of the synaptonemal complex, but only in the synapsed regions of meiotic chromosomes. To elucidate the function of Skp1 in meiosis, we generated Skp1^{f/f} mice, in which exons 3 – 5 are flanked by loxP sites. Germ cell-specific inactivation of Skp1 using the constitutive Ddx4-Cre caused a complete loss of germ cells in males. To circumvent the pre-meiotic germ cell loss, we carried out tamoxifen-inducible inactivation of Skp1 specifically in germ cells using the Ddx4-CreERT2 (referred to as Skp1 cKO). Histological analyses showed that post-meiotic spermatids and metaphase spermatocytes were absent in Skp1 cKO testes. Nuclear spread analysis showed that in Skp1 cKO testes, diplonema increased to over 50% compared to 18% in untreated testes. Three homologous recombination markers, MLH1, γ H2AX and RPA2, which were absent in WT diplotene cells, persist in around 50% of Skp1 cKO diplotene spermatocytes. These results suggest that loss of SKP1 causes premature desynapsis and precocious pachytene exit in spermatocytes. HORMAD proteins are associated with unsynapsed chromosome axes, however, HORMAD1 and HORMAD2 were highly enriched on both synapsed and unsynapsed regions of all chromosomes in Skp1-deficient pachynema and diplonema. These results demonstrate that SKP1 is required for removal of HORMAD proteins from synapsed chromosome axes in pachynema and reduces their return to autosomal axes in diplonema. Phosphorylation of histone H3 at serine 10 and EMI2, two markers of metaphase, were significantly decreased in Skp1 cKO testes. Failure of metaphase transition in Skp1 cKO spermatocytes was resistant to okadaic acid treatment. Metaphase promoting factor activity was sharply reduced in Skp1 cKO testes evidenced by decreased histone H1 kinase activity. Overall, we conclude that SKP1 functions as an intrinsic competence factor that orchestrates chromosome desynapsis and metaphase entry.

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2:15 PM – Oral Presentation – Paul Kroeger

Evaluating the potential to repurpose statins for ovarian cancer therapy

Kroeger Jr., Paul T., Drapkin, Ronny

Institutional Affiliation: University of Pennsylvania, Perelman School of Medicine

Abstract: The recent exciting results using primary PARP inhibitor maintenance after upfront treatment for advanced ovarian cancer in BRCA1/2 mutation carriers highlight the importance of identifying druggable vulnerabilities in this disease. The fact that not all ovarian cancer patients will benefit from PARP inhibitors or experience durable responses, places great emphasis on the need to identify additional therapies. Repurposing existing FDA-approved drugs offers an opportunity to accelerate progress in this area.

Statins are drugs primarily prescribed for hypercholesterolemia and have been intensely researched for decades. Some of this work has demonstrated, through epidemiologic approaches and limited experimental studies, that statins have anticancer properties. We hypothesized that statins can be repositioned as part of a therapeutic regimen for HGSOC.

Here, we demonstrate that certain ovarian cancer cell lines are exquisitely sensitive to treatment with statins. Our ongoing studies reveal that HGSOC cells that are sensitive to statin treatment manifest an amplification of chromosome 1q21. Within this genomic region are the S100 proteins, previously identified as potential biomarkers in several cancer types, as well as the anti-apoptotic protein MCL1. We performed a Reverse Phase Protein Array (RPPA) analysis on higher dose/short exposure, and low dose/longer exposure statin-treated cells. In both conditions, MCL1 levels were altered in statin-sensitive cell lines, while there was no such change in non-sensitive lines. After identifying MCL1 as a potential marker of response, Western blot analysis demonstrated a dose-dependent decrease in protein level of MCL1 with increasing statin concentration. Additionally, a short pro-apoptotic splice variant of MCL1 was produced upon statin treatment, but only in the sensitive lines.

Mechanistically, we find that phospho-YAP (inactive) is upregulated after statin treatment. This data corroborated previous research that suggested that multiple different statins decrease nuclear YAP. Given its role as an oncogene, the apparent ability of statins to deactivate YAP and downregulate MCL1 steers statins in a promising direction for their repositioning for future therapeutic use.

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2:30 PM – Oral Presentation – Emma Lewis

Regulatory T cell dysfunction in a mouse model of pregnancy loss

Lewis, Emma L., Barila, Guillermo O., Porrett, Paige M., Elovitz, Michal A.

Institutional Affiliation: University of Pennsylvania

Abstract: Background: One of the proposed mechanisms of unexplained pregnancy loss is maternal immunologic rejection of the fetus. However, the specific immune mechanisms causing rejection have not been described. Regulatory T cells (Tregs) are necessary to maintain maternal–fetal tolerance, and systemic Treg depletion leads to fetal demise. We hypothesize that mechanisms of fetal rejection involve qualitative Treg dysfunction, in addition to quantitative defects.

Objective: To investigate a more mechanistic understanding of Treg function in CBA pregnancies, an established model of immune-mediated fetal loss.

Methods: Pregnant CBA and C57BL/6 mice, mated with DBA/2 males, were sacrificed at embryonic day 14 (E14) and assessed for fetal resorption. Maternal spleen, blood, decidua and placenta were collected for analysis by flow cytometry and ELISA. In subsequent experiments, T cells from the spleens of virgin and pregnant CBA and C57BL/6 mice were sorted and used for in vitro assays.

Results: The resorption rate of CBA pregnancies is 18-fold higher than that of C57BL/6 pregnancies (CBA: 21.1%, C57BL/6: 1.14%, $p=0.0005$). Virgin CBA and C57BL/6 female mice have equivalent splenic Treg population sizes. During pregnancy, C57BL/6 splenic Tregs increase from 8.0% to 20.5% of CD4+ T cells ($p=0.0003$), while CBA mice show no Treg expansion. Similarly, virgin CBA and C57BL/6 female mice have equivalent levels of splenic CD8+ T cells, but C57BL/6 mice have decreased levels of splenic CD8+ T cells during pregnancy ($p=0.0003$), while CBA CD8+ T cell levels do not change. Specific to the maternal–fetal interface, placentae from CBA pregnancies have fewer Tregs ($p=0.023$) and more IFN γ protein expression ($p=0.0005$) than placentae from C57BL/6 pregnancies. Tregs from virgin C57BL/6 and CBA mice have equivalent suppressive activity, but Tregs from pregnant CBA mice have less suppressive activity than those from pregnant C57BL/6 mice ($p=0.004$).

Conclusion: Collectively, these results indicate that CBA mice have an altered immune state that is further changed by pregnancy. The functional deficiencies in CBA Tregs likely contribute to the high rate of fetal loss. Correlating these immunological changes in CBA mice to humans with recurrent pregnancy loss may lead to new understanding of this adverse reproductive outcome.

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2:45 PM – Oral Presentation – Lacey Luense

Gcn5-mediated histone acetylation governs nucleosome dynamics in spermiogenesis

Luense, Lacey, J., Donahue, Greg, Lin-Shiao, Enrique, Rangel, Richard, V., Bartolomei, Marisa, S., Berger, Shelley, L.

Institutional Affiliation: University of Pennsylvania

Abstract: During spermatogenesis, male germ cells undergo a dramatic reorganization of chromatin structure, whereby nearly all histones are replaced by protamines. Approximately 90–95% of histones are evicted during this process and abnormal protamine incorporation or histone retention has been linked to reduced fertility in mice and humans. This process begins with a profound increase in histone acetylation in round and elongating spermatids, which promotes relaxation and increased accessibility of chromatin to facilitate nucleosome eviction and protamine incorporation. The genomic location of retained nucleosomes is of great interest, given their potential role in fertility and early embryo development. To investigate nucleosome eviction/retention we generated pre-meiotic, germ cell specific, conditional knockout mice for the histone acetyltransferase Gcn5. Expression of Gcn5 was greatest in meiotic spermatocytes and round spermatids, corresponding with H3K9/K14ac, thus making it an ideal candidate to investigate the functional and mechanistic role of HATs in spermiogenesis. Mice lacking Gcn5 exhibited a severe reproductive phenotype resulting in abnormal testis weight, sperm production, sperm morphology, and reduced male fertility. Furthermore, Gcn5cKO germ cells exhibited abnormal chromatin dynamics during spermiogenesis. We found notable failures of chromatin accessibility, thus preventing proper nucleosome eviction and ultimately leading to increased nucleosome retention in sperm. Overall our findings provide detailed physiological and genomic evidence of the consequences of acetylation loss during spermiogenesis. Establishment of this mouse model for altered acetylation will provide important insights into mechanisms underlying the paternal epigenome and its contribution to male fertility and embryonic development. We are currently utilizing our Gcn5cKO mouse model to introduce an abnormal complement of sperm nucleosomes into embryos to determine the effect of excess paternal nucleosomes on pre-implantation embryonic development. Together, the proposed research will provide important insight into the mechanisms governing early embryonic development, including the effects of the paternal epigenome on chromatin dynamics and zygotic genome activation.

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Interactive Poster Session

Group 1 – IUE: Moderator, Becky Simmons, MD, PhD – 6 Posters

11:00 AM – Apoorva Joshi

In utero exposure to gestational diabetes alters the transcriptome and methylome of human fetal stem cells revealing an enrichment of interferon pathways

Pinney, Sara. E., Joshi, Apoorva, Yin, Victoria, Min, So Won, Condon, David, Wang, Paul

Institutional Affiliation: Children's Hospital of Philadelphia

Abstract: Gestational diabetes (GDM) has profound effects on the intrauterine metabolic milieu, induces marked abnormalities in fetal glucose and insulin secretion and is linked to obesity and diabetes in the offspring, but the mechanisms remain largely unknown. In order to gain a better understanding of the mechanisms responsible for fetal programming of obesity and diabetes after in utero exposure to GDM exposure, we sought to measure changes in gene expression and genome wide DNA methylation in human amniocytes, a fetal stem cell, exposed to GDM in utero. For this study we used a nested case control design from which cases and controls were selected from an established biospecimen repository of amniocytes and amniotic fluid samples. Cases affected by GDM were identified by post-delivery questionnaire and confirmed by measuring amniotic fluid c-peptide (fetal derived). Matching criteria for the nested case control design included maternal age, gestational age at amniocentesis and gestational age at birth. All samples were from uncomplicated, healthy singleton term pregnancies without maternal complications other than GDM or known fetal abnormalities. RNA was isolated from amniocytes and used for creation of RNA-Sequencing libraries. EdgeR was used to identify differentially expressed genes from RNA sequencing data via fold change, p-values, and q-values calculated after Bonferroni correction (n=8; 4 per sex). Selected RNA-Seq results were confirmed via QPCR. Ingenuity Pathway Analysis (IPA) identified enriched biological pathways. Differentially methylated regions (DMRs) were determined from Enhanced Reduced Representation Bisulfite Sequencing (ERRBS) (n=16; 8 per sex) by identifying sequential CpGs with significant changes in DNA methylation >5%, and with $p < 0.05$ over the entire DMR. We identified 20 differentially expressed genes ($q < 0.10$) analyzing data from male and female amniocytes together, but only 4 genes in male only and 2 in female only analyses. Using a significance threshold of $p < 0.01$, we identified 65 differentially expressed genes when grouping male and female samples together, 46 genes in the male only analysis and 68 in the female only analysis. QPCR confirmed increases in IFI44, ULBP1 and SAMD9L. Differentially expressed genes were strongly enriched for interferon inducible proteins, a novel fetal programming pathway after in utero GDM exposure. IPA showed enrichment in molecular mechanisms regulating growth, oxidative stress metabolism and GPCR signaling pathways. Offspring sex-specific analysis greatly enhanced DMR identification. Nine DMRs were identified in all, 41 in male and 20 in female samples. These experiments suggested that early exposure to GDM in utero leads changes in gene expression and DNA methylation in amniocytes showing strong enrichment in interferon related pathways. These results provide insight into the mechanisms by which GDM exposure leads to metabolic health effects in the offspring by highlighting a novel role for interferon related pathways.

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Interactive Poster Session

Group 1 – IUE: Moderator, Becky Simmons, MD, PhD

11:10 AM – Apoorva Joshi

Maternal obesity and perfluorooctanoic acid synergize to alter lipid metabolism in human fetal hepatocytes predisposing the offspring to NAFLD

Joshi, Apoorva, Golden, Thea, Saraf, Namita, Doulias, Paschalis–Thoma, Ischiropoulos, Haralambos, Pinney, Sara. E.

Institutional Affiliation: Children's Hospital of Philadelphia

Abstract: Per- and polyfluoralkyl substances (PFAS), including the frequently used compound perfluorooctanoic acid (PFOA) are persistent non-biodegradable pollutants that are wide spread environmental contaminants (including drinking water) in the US including the Philadelphia area. PFOA is a surfactant used in fire-fighting foams, non-stick cookware, waterproof clothing, carpets and food packaging due to its water repelling properties. Human have persistent and chronic exposure to PFOA due to its half life of 3–5 years which has been linked to altered immune responses, abnormal cholesterol and lipid levels hepatomegaly, abnormal liver enzymes and fatty liver disease, obesity and insulin resistance. There is limited information regarding early life exposure to PFOA and later development of obesity, metabolic disease and hepatic toxicity. However, maternal obesity has profound effects on the intrauterine metabolic milieu, induces abnormalities in glucose homeostasis and insulin secretion in the fetus and is linked to obesity, diabetes and non-alcoholic fatty liver disease (NAFLD) in the offspring, although the molecular mechanisms are not well defined. Multiple studies support the concept that there is a critical developmental window of programming in which in utero exposures can make an individual more susceptible to adult diseases such as NAFLD. We hypothesize that gestational exposure to PFOA in the setting of maternal obesity leads to increased lipotoxicity in the fetal liver resulting in steatohepatitis and an exacerbated immune response and ultimately to NAFLD later in life. We created an in vitro system to study the potential combined effects of PFOA and maternal obesity (with palmitic acid as a surrogate) on the development of NAFLD using HepaRg cells, a human derived fetal-like hepatocyte cell line. Here we report that exposure to PFOA combined with palmitic acid leads to increased expression of critical genes regulating de novo lipogenesis (SCD1, SREBP f1, FASN). In addition, combined exposure to PFOA and palmitic acid results in suppression of fatty acid oxidation as measured by ³H labeled palmitate. Furthermore, PFOA and palmitic acid reduce the mitochondrial content and superoxide generation and increase activation of NF kappa beta and production of IL1 beta. We are expanding these experiments to a mouse model of gestational exposure to PFOA and maternal obesity to better characterize the molecular mechanisms involved in fetal programming of NAFLD.

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Interactive Poster Session

Group 1- IUE: Moderator, Becky Simmons, MD, PhD

11:20 AM - Yu-Chin Lien

Altered Transcription Factor Binding and Gene Bivalency May Contribute to Long-term Gene Dysregulation in Intrauterine Growth Retardated Rat Islets

Yu-Chin Lien, Xueqing Maggie Lu, Paul Zhiping Wang, and Rebecca A. Simmons

Intrauterine growth retardation (IUGR), which induces epigenetic modifications and permanent changes in gene expression, has been associated with the development of type 2 diabetes. Using a rat model of IUGR induced by bilateral uterine artery ligation, we performed ChIP-Seq and RNA-Seq to assess the association of genome-wide histone modifications and gene dysregulation in islets from 2 and 10 week rats. IUGR induced significant changes in enrichment of H3K4me3 and H3K27me3 marks in both 2-wk and 10-wk islets, which were correlated with expression changes of multiple genes critical for normal islet function in IUGR islets. HOMER analysis showed that IUGR-induced histone mark changes were enriched at transcription factor binding motifs, such as Nkx2-1, Nkx2-5, FoxL2, Pax7, Sox4, Mitf, and Oct4-Sox2-Nanog. These transcription factors were also identified by Ingenuity Pathway Analysis of islet transcriptomes as top upstream regulators that regulate the changes in gene expression and biological activities. In addition, our ChIP-seq data revealed more than 1,000 potential bivalent genes as identified by enrichment of both H3K4me3 and H3K27me3. No expression or very low expression of these genes was consistent with a poised state of transcription. The poised state of many potential bivalent genes was altered by IUGR. Interestingly, 3 genes important for islet function, *Acod1*, *Fgf21*, and *Serpina11*, which were poised in 2-wk control islets, lost their poised state in 10-wk control islets, but gained bivalency in 10-wk IUGR islets. In contrast, another 3 genes, *Cdh16*, *Lrrc27*, and *Lrrc66*, which were not poised in control 2-wk islets, gained *de novo* bivalency in 10-wk control islets, but lost their poised state in 10-wk IUGR islets. Collectively, our findings suggest alterations of histone modification in key transcription factors and genes which may contribute to long-term gene dysregulation and an abnormal islet phenotype in IUGR rats.

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Interactive Poster Session

Group 1 – IUE: Moderator, Becky Simmons, MD, PhD

11:30 AM – Thea N. Golden

IUGR Causes Pancreatic Inflammation in the Neonatal Rat

Thea N. Golden¹, Cheyenne Williams¹, G. Scott Worthen² and Rebecca A. Simmons^{1,2}

Institutional Affiliation: ¹Center for Research on Reproduction and Women's Health, Perelman School of Medicine, University of Pennsylvania, ² Division of Neonatology The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

Abstract: The intrauterine milieu influences fetal development and perturbations can have lifelong effects on the offspring. Intrauterine growth restriction (IUGR) is a common complication of pregnancy and increases the risk of type 2 diabetes (T2D) in the offspring. Using a rat model of IUGR, bilateral uterine artery ligation, we identified immune pathways that are causal to beta cell failure. Previously we have shown that Th2 cytokines are transiently elevated at day 19 in islet lysates of IUGR fetuses. Postnatal administration of interleukin 4 (IL4) neutralizing antibody to IUGR pups on days 1-6 of life reduced postnatal day 14 (PD14) cytokine expression and ameliorated the IUGR phenotype in adult IUGR rats. The aim of this study was to identify immune cells in the pancreas, spleen, and lymph nodes during the postnatal period. At PD7, the number of T cells and macrophages increases in the non-islet portion of the pancreas of male IUGR pups. Finally, at PD14 immune cell population numbers normalize in the non-islet or islet portion of the pancreas. However, RNAseq and immunohistochemistry demonstrate a change in immune cell activation as evidenced by an increase in TNF, IL1B, CXCL9 and CCL3 gene expression and COX2 protein expression in the islets of IUGR pups at PD14. Overall, this work demonstrates a complex and transiently altered immune cell response to IUGR in the postnatal period. Further investigation of altered immune cell populations and pathways will further our understanding of IUGR caused T2D.

Supported by to DK55704 (RAS, GSW) and T32ES09851 (TNG).

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Interactive Poster Session

Group 1 – IUE: Moderator, Becky Simmons, MD, PhD

11:40 AM – Tammy Ying

Neonatal IL-4 administration decreases body fat content and weight and also improves glucose tolerance in adulthood.

Tammy Ying and Rebecca A. Simmons

Intrauterine growth restriction (**IUGR**) due to uteroplacental insufficiency is a common complication of pregnancy and leads to an increased risk for type 2 diabetes (**T2D**) in adulthood. We model IUGR by performing bilateral uterine artery ligation in pregnant rats at d18 of gestation (term 22 days). Offspring are growth restricted and newborn males, but not females have decreased β -cell proliferation and impaired insulin secretion which is associated with inflammation and increased IL-4 levels. IUGR males develop obesity and insulin resistance in adulthood. Neutralizing IL-4 antibody given on postnatal days 1-6 normalizes hyperglycemia in adult IUGR animals. The aim of this study was to determine whether IL-4 is sufficient to recapitulate the IUGR phenotype. IL-4 (50ng or 100ng) or PBS was injected subcutaneously to normal newborn rat pups on postnatal days 1-6. IL-4 had no adverse effects on newborn rat pups and weights did not differ between the IL-4 and PBS injected pups (n=15). At 2 weeks and 10 weeks of age IL-4 injection had no effect on glucose stimulated insulin secretion as measured by both static incubation experiments and perfusion studies (n=6, n.s.). Surprisingly, neonatally IL-4 injected rats had decreased fasting blood glucose levels at 10 weeks of age (n=6-7; p=0.0055) suggesting improved glucose homeostasis. Thus, the fat of the neonatally IL-4 injected animals was analyzed. At P14, animals treated with IL-4 in the newborn period had decreased body fat content (p=0.0173) compared to control (n=6). Further, at 7 weeks of age IL-4 injected rats weighed less than controls (n=7; p=0.00017) and that difference increased with age. These results suggest that IL-4 is not sufficient to recapitulate the IUGR metabolic phenotype. However, IL-4 administered transiently during the neonatal period has lasting effects in adulthood, decreasing fat content and improving glucose tolerance.

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Interactive Poster Session

Group 1 – IUE: Moderator, Becky Simmons, MD, PhD

11:50 AM – Sneha Mani

Maternal Decidual Cells Regulate Trophoblast Invasion: Studies from a Novel Organ-on-a-Chip Device

Mani,Sneha, Blundell,Cassidy, Park, Ju Young, Rachel, Huh, Dongeun, Mainigi,Monica

Institutional Affiliation: University of Pennsylvania

Abstract: Introduction: Early in pregnancy, fetal extravillous trophoblasts (EVTs) migrate into the maternal decidua and remodel spiral arteries (SA). Abnormal EVT invasion has been linked to many adverse pregnancy outcomes including miscarriage and preeclampsia. These disorders remain poorly understood because of the difficulty in studying early placentation in vivo and in modeling fetal-maternal crosstalk in vitro. Here we demonstrate a novel organ-on-chip platform, Implantation-On-A-Chip (IOC), which incorporates fetal and maternal cells in a physiologically relevant system and reveals the critical role(s) of maternal cells in early placentation.

Methods: The small IOC device uses a compartmentalized design and an optically transparent elastomer to incorporate relevant cell types. This enables precise control of the cellular microenvironment and advanced analytic capabilities. Primary EVT from first trimester placenta are co-cultured with uterine endothelial cells (ECs) in perfusable microchannels separated by an extra-cellular matrix (ECM) hydrogel composed of a mixture of collagen and Matrigel and uterine fibroblasts. Confocal microscopy and maximum projection images are used to quantify invasion and examine protein expression.

Results: In the IOC, ECs proliferate to form an endothelial tube covering each surface of the microchannel, mimicking a spiral artery. When EVTs are seeded on the device alone, EVTs remain primarily in their channel. In the presence of the ECs, EVTs invade through the ECM and reach the EC compartment in 72 hours. Adding uterine fibroblast cells to the ECM compartment significantly reduces EVT invasion as compared to culture of EVTs with ECs, though more than with EVTs alone. Once EVTs reach the ECs, EVTs induce EC apoptosis, as detected by a caspase marker and TUNEL staining, recapitulating spiral artery remodeling.

Conclusions: Our novel IOC device is able to model the 3D microarchitecture of the maternal-fetal interface during implantation to study EVT invasion and SA remodeling. Our studies demonstrate that ECs alone stimulate EVT invasion, and this process can be modulated by uterine fibroblasts. We believe that this platform can significantly help us understand the cells and factors regulating human implantation and allow for mechanistic investigation that could lead to significant advances in our understanding and treatment of adverse pregnancy outcomes.

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Interactive Poster Session

Group 2 – Male Reproduction:: Moderator, George Gerton, PhD – 5 Posters

11:00 AM – Jacob Herford

Non-steroidal anti-inflammatory drugs reduce vas deferens epithelial MRP4 expression and prostaglandin export

Herford, Jacob, D., Lillich, James, Schultz, Bruce, D

Institutional Affiliation: Kansas State University College of Veterinary Medicine

Abstract: Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin (PG) synthesis and can compromise epithelial barriers. The present study attempted to characterize whether NSAID-induced alterations occurred in the male reproductive tract, which typically expresses high levels of PG synthase 2 (PTGS2). Immortalized porcine vas deferens epithelial cells (PVD9902) were grown on Snapwell® permeable supports in the absence or presence of NSAIDs (Ibuprofen, Celecoxib, Indomethacin) and transepithelial electrical resistance (Rte) was measured daily. On day 14, NSAIDs were withdrawn, and tests were performed on days 14, 16 and 18. Mucosal and serosal media were harvested to determine PGE2 concentrations. Electrophysiological assessments were conducted followed by harvesting total cell protein and RNA. Monolayers in all conditions developed a 'tight' epithelial barrier with Rte > 4000 Ω cm². NSAID exposure increased time to half-maximal barrier formation by 13–35 hours, and reduced the overall barrier development rate. Absent stimulation, PG accumulates preferentially in the mucosal medium, although serosal accumulation can be detected. NSAIDs reduced PGE2 in both mucosal and serosal media to undetectable levels. We speculated whether PG export from the cell was due to the multidrug resistance-like protein (MRP4). Immunoblot and RT-PCR confirmed MRP4 expression, which was reversibly reduced by NSAID exposure. Our results show that NSAID exposed male reproductive duct epithelia exhibit decreased PG secretion (> 95%), delayed barrier formation and reduced expression of a major PG export protein. These results suggest that therapeutic NSAID treatments may have a negative effect on male reproductive tracts, thus affecting fertility.

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Interactive Poster Session

Group 2 – Male Reproduction:: Moderator, George Gerton, PhD – 5 Posters

11:10 AM – Cetewayo Rashid

Paternal bisphenol A exposure alters offspring glucose tolerance in a time and sex specific manner

Cetewayo Rashid, PhD^{1,2,3}, Amita Bansal, PhD^{1,2,3}, and Rebecca A. Simmons, MD^{1,2,3}

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ABSTRACT

It is becoming increasingly accepted that maternal exposure to the ubiquitous environmental pollutant bisphenol A (BPA) predisposes offspring to metabolic impairments, but paternal contribution in this context remains unresolved. To investigate a relationship between paternal BPA exposure and offspring obesity and glucose tolerance, a mouse model was developed using dietary BPA exposure at doses comparable to human exposure levels (7% Corn Oil diet (Control), 10 µg/mg/day (Lower BPA), and 10 mg/kg/day (Upper BPA)). Two exposure windows were investigated, the first being direct exposure of sires beginning at 5 weeks of age and continuing for 12 weeks prior to mating, and the second being *in utero* exposure, in which sires were exposed during gestation and lactation. In both exposure models, dams and F1 offspring were maintained on control diet. At 16 weeks of age, offspring underwent body composition analysis measured by NMR and glucose tolerance testing. Statistical analysis was performed using Oneway-ANOVA with Dunnett's correction. Paternal BPA exposure during adulthood did not affect offspring metabolic health. *In utero*-exposed sires produced glucose intolerant female offspring. Insulin tolerance testing found insulin sensitivity to be unaltered and *ex vivo* islet perfusion showed Lower BPA females had enhanced glucose-stimulated insulin secretion compared to controls. These data demonstrate that, while paternal BPA exposure after sexual maturity may be metabolically innocuous, paternal BPA exposure during development precipitates sex-specific impairments in glucose tolerance likely mediated by diminished glucose effectiveness. Finally, as a possible mechanism of phenotypic inheritance, spermatozoa RNA from *in utero*-exposed sires were sequenced. Transfer RNA fragments and miRNAs were differentially expressed and many of the tRNA fragments were also differentially expressed in other paternal dietary models of offspring glucose intolerance. Further studies are required to describe precisely the glucose homeostatic impairment and determine if these changes in small non-coding RNAs confer phenotypic inheritance.

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Interactive Poster Session

Group 2 – Male Reproduction:: Moderator, George Gerton, PhD – 5 Posters

11:20 AM – Fang Yang

TEX15 is required for epigenetic silencing of transposable elements in the germline

Yang, Fang, Lan, Yemin, Bartolomei, Marisa, Wang, P. Jeremy

Institutional Affiliation: 1Department of Biomedical Sciences, 2Department of Cell and Developmental Biology, University of Pennsylvania, Philadelphia, Pennsylvania

Abstract: Germ cells undergo extensive epigenetic reprogramming during development. During this critical period, retrotransposons are reactivated due to genome-wide erasure of DNA methylation and are re-silenced by de novo DNA methylation. Retrotransposons, mainly LINEs, SINEs, and endogenous retroviruses (collectively referred to as junk DNA), occupy 40% of the mammalian genome. Although retrotransposons play an important role in genome evolution, their mobilization could be detrimental to genome integrity. Multiple epigenetic mechanisms are responsible for silencing retrotransposons in the germline: DNA methylation, repressive histone modification, small RNAs, and heterochromatinization. Here we report that TEX15, a germ cell-specific protein, is required for silencing of transposable elements in germ cells. Inactivation of *Tex15* leads to male sterility, due to meiotic arrest, but knockout females are fertile. In the adult *Tex15*-deficient testis, LINE1 is de-silenced in spermatocytes, while IAP LTR-retrotransposons are upregulated in spermatogonia. We performed RNA-seq analysis of *Tex15*^{+/−} and *Tex15*^{−/−} gonocytes at E16.5, E18.5, and PND2.5. Germ cells are flow-sorted using Oct4-GFP. RNA-seq analysis revealed de-silencing of some families of LINE1, ERVK (LTR), and ERV1 (LTR) in *Tex15*^{−/−} gonocytes at E18.5 and PND2.5. To determine whether the de-silencing of retrotransposons is due to defects in piRNA biogenesis, we investigated piRNA production by IP of MILI and MIWI2 and found that both MILI and MIWI2 proteins are associated with piRNAs, suggesting that TEX15 functions either downstream or independent of the piRNA pathway. Next, we performed whole genome bisulfite sequencing (WGBS) using FACS-sorted PND2.5 gonocytes. The genome-wide DNA methylation level is comparable between *Tex15*^{+/−} and *Tex15*^{−/−} gonocytes. Strikingly, some families of retrotransposons are hypomethylated in *Tex15*^{−/−} gonocytes. There are two features of this hypomethylation: hypomethylation occurs in evolutionarily young (thus active) LINE1s and in the 5'UTR of LINE1s but not in the ORFs and 3'UTRs. The 5'UTR of LINE1 is its promoter. Thus, hypomethylation at LINE1 5'UTR leads to transcription. In *Tex15*^{−/−} gonocytes, there is a failure in de novo re-methylation specifically at transposable elements after genome-wide demethylation in PGCs. Here we demonstrate that TEX15 is a novel epigenetic regulator of transposable elements in male germ cells. In future experiments, we plan to examine histone modifications by ChIP-seq and identify TEX15-interacting proteins by IP/mass spectrometry.

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Interactive Poster Session

Group 2 – Male Reproduction:: Moderator, George Gerton, PhD – 5 Posters

11:30 AM – Rui Guo

MORC2A is essential for male fertility and epigenetic silencing of transposable elements

Guo, Rui

Institutional Affiliation: Department of Biomedical Sciences, University of Pennsylvania School of Veterinary Medicine; State Key laboratory for Reproductive Medicine, Nanjing Medical University, China

Abstract: MORC (microorchidia) proteins are chromatin remodeling factors. MORC proteins contain GHKL-type (Gyrase, Hsp90, histidine kinase, MutL) ATPase domain and PHD zinc finger domain, implying functions in DNA metabolism and epigenetic regulation. MORC2A is a member of the MORC protein family (MORC1-4) in mice. Dominant mutations in MORC2 cause axonal Charcot-Marie-Tooth disease (CMT) in humans. Morc2b is a retrotransposed homologue of Morc2a in mice and is essential for chromosomal synapsis, meiotic recombination and fertility in both sexes. A genome-wide CRISPR screen identified MORC2A as a retroelement silencing factor in repressive epigenetic modifications in mouse ES cells. Here we show that MORC2A is essential for meiosis in males. Morc2a-deficient males are infertile and have grossly reduced testicular mass. Immunofluorescence of the synaptonemal complex demonstrated that Morc2a-deficient germ cells fail to undergo homologue pairing during the zygotene stage of meiosis, resulting in meiotic arrest. MORC2A is highly expressed in mouse testis and localized in the nucleus of spermatogonia, spermatocytes, and round spermatids. Especially, MORC2A is enriched in the heterochromatin. We find that LINE1 retrotransposons are highly up-regulated in the Morc2a-deficient spermatocytes. Through co-immunoprecipitation, we detected the association of MPP8, a subunit of HUSH silencing complex, with MORC2A. Our results have shown that MORC2A is essential for epigenetic silencing of transposable elements in male germ cells and thus male fertility.

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Interactive Poster Session

Group 2 – Male Reproduction:: Moderator, George Gerton, PhD – 5 Posters

11:40 AM – Lei Zhang

Pilot screening of male contraceptive drugs by targeting the meiosis specific proteins MEIOB and SPATA22

Zhang, Lei, Xu, Yang, Schultz, David C, Cherry, Sara, Wang, P. Jeremy

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Abstract: Although explosive information have been revealed about spermatogenesis from both genomic and proteomic researches, the progression of male contraceptive drug development is still limited. It partially contributes to a series of ethical and social problems. Currently, testosterone analogs are the only category in clinical trials for male contraceptive drugs. Novel alternatives begin to appear, such as JQ1, which prevents chromatin remodeling through inhibiting testis specific protein BRDT, in turn causes a reversible infertility in male mice. The success of JQ1 indicates that targeting the proteins involved in spermatogenesis may provide the possible male contraceptive drug candidates. Our laboratory and others have found that the meiosis specific proteins, MEIOB and SPATA22, are essential for spermatogenesis. The knockout mice of either Meiob or Spata22 are infertile in both sexes. Meanwhile, MEIOB binds to SPATA22 and the stability of the two proteins depends on the interaction. Based on that, we have developed a cell-based fluorescence assay for the MEIOB–SPATA22 interaction. The pilot screening with 4,000 chemical compounds identifies several candidates which reveal less fluorescent signal. Further western blot results indicate that the selected chemical compounds promote the degradation of MEIOB and SPATA22. We find that one of the compounds, Compound 244 (C244), decreases the protein levels of MEIOB and SPATA22 in cultured mouse spermatocytes. The following animal experiments show that high dose of C244 may reduce the ratio of testis/body weight after double injection per day for 7 days in juvenile mice. The animal results also show that C244 may arrest the development of spermatocytes at the zygotene-like stage and may induce apoptosis. The mechanism of C244 is still unclear and further experiments are still needed. In conclusion, our findings indicate that C244 may cause sterility in mice through dysregulation of the meiosis process. A larger library of more chemical compounds will be used for further screening in order to identify stronger and more specific male contraceptive lead compounds that target the MEIOB and SPATA22.

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Interactive Poster Session

Group 3 –Reproduction: Moderator, Monica Mainigi, MD – 5 Posters

11:00 AM – Arunika Das

Mechanisms of epigenetic centromere inheritance through the mammalian germline

Das, Arunika, Fu, Valencia, Black, Ben E., Lampson, Michael A.

Institutional Affiliation: University of Pennsylvania

Abstract: Centromeres direct genetic inheritance but are not themselves genetically inherited. Instead, centromeres are defined epigenetically by the presence of a histone H3 variant, CENP-A. According to existing models for centromere inheritance, preexisting CENP-A nucleosomes serve as templates to direct new assembly, which quantitatively maintains centromere chromatin through every cell cycle. We find differences between maternal and paternal centromeres in the zygote, suggesting differential centromere inheritance through the male and female germlines. To test the dependence on the preexisting template, we created CENP-A hemizygous mice with reduced levels of centromere chromatin in the gametes. We show that genetically wild-type progeny from hemizygous parents have partially reduced centromere chromatin in somatic tissue and in the male germline but wild-type levels in the female germline. Furthermore, we find no detectable differences between maternal and paternal centromeres in the germline when only one parent is hemizygous. We conclude that quantitative germline inheritance is only partially determined by pre-existing CENP-A nucleosomes. Centromere chromatin equilibrates between maternal and paternal centromeres after fertilization and resets in the female germline, independent of the inherited template.

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Interactive Poster Session

Group 3 –Reproduction:: Moderator, Monica Mainigi, MD – 5 Posters

11:10 AM – Jessica Chotiner

Cyclin B3 is a maternal factor essential for embryogenesis

Chotiner, Jessica, Y., Wang, Jeremy

Institutional Affiliation: University of Pennsylvania School of Veterinary Medicine

Abstract: Cyclins and cyclin-dependent kinases (CDKs) regulate progression through both the mitotic and meiotic cell cycles. Though there is great functional redundancy in the cyclin family, some are required for viability. Cyclin B3 (Ccnb3) is an X-linked germ cell specific cyclin. CCNB3 is essential for female fertility, but not for male fertility or general viability. Recent characterization of Ccnb3 suggests that it is important for female meiosis. However, here we demonstrate that Ccnb3 has a meiosis-independent role in female fertility. To uncover the role of Ccnb3 in female fertility, we created a knockout model using CRISPR/Cas9 to delete one half of the coding region, resulting in a truncated transcript with a premature stop codon that lacks the conserved C-terminal cyclin domain. Ccnb3^{-/-} ovaries are morphologically normal and contain follicles in all stages of development. Oocytes are ovulated in comparable numbers to that of Ccnb3^{+/-} controls. Furthermore, ovulated Ccnb3^{-/-} oocytes appear to be able to complete meiosis. In vivo fertilization assays show that Ccnb3^{-/-} oocytes can be fertilized, producing 2-cell embryos in comparable numbers to that of heterozygous oocytes. These embryos can be cultured ex vivo to produce blastocyst stage embryos. In vivo, these embryos ultimately undergo implantation and persist until roughly embryonic day 7.5. Preliminary data supports that Ccnb3 is a maternal factor essential for embryogenesis. CCNB3 is also X-linked in humans. Based on our mouse study, mutations in human CCNB3 are expected to cause recurrent pregnancy loss (RPL).

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Interactive Poster Session

Group 3 –Reproduction:: Moderator, Monica Mainigi, MD – 5 Posters

11:20 AM – REXXI PRASASYA

TET1 is required for maternal imprint erasure during primordial germ cell development

Prasasya, REXXI

Institutional Affiliation: Cell and Developmental Biology Department, Epigenetics Institute, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.

Abstract: In mammals, a subset of developmentally critical genes is expressed from a single parental allele. The monoallelic expression of these imprinted genes is regulated by differential DNA methylation between the two parental alleles on cis-acting elements known as imprinting control regions (ICRs). Parentally inherited, somatic methylation patterns of ICRs are reprogrammed in the primordial germ cells (PGCs) to allow for the acquisition of sex-specific imprinting marks during gametogenesis. Recent work supported the involvement of Tet-Eleven Translocation (TET) family of methylcytosine dioxygenases in the proper establishment of germline imprinting. We previously observed abnormal hypermethylation of ICRs in mature gametes and progeny of Tet1^{-/-} male and female mice and hypothesized that TET1 is required for methylation erasure of ICRs in PGC development. Through incorporation of Oct4-GFP reporter line, we isolated PGCs from Tet1^{-/-} and Tet1^{+/+} mutant mice at embryonic day (E)12.5, E13.5, and E14.5 and characterized methylation levels of representative ICRs using bisulfite mutagenesis, followed by pyrosequencing. Several maternally methylated ICRs fail to fully demethylate in male and female Tet1^{-/-} PGCs by E14.5. This directly correlates with hypermethylation of maternally methylated ICRs in Tet1^{-/-} sperm. In contrast, two paternally methylated ICRs, H19/Igf2 and IG-DMR, achieved hypomethylation in Tet1^{-/-} female and male PGCs. As H19/Igf2 and IG-DMR were previously found to be stochastically hypermethylated in Tet1^{-/-} oocytes, our result suggests that the lack of TET1 may render paternally methylated ICRs susceptible to ectopic remethylation in growing oocytes irrespective of the completion of methylation erasure in PGCs. As TET2 is concurrently expressed in demethylating PGCs along with TET1, we are currently generating Tet1^{-/-};Tet2^{-/-} embryos to characterize the contribution of TET2 in ICR methylation erasure. Overall, this study demonstrates the differential requirement for TET1 in demethylation of maternal and paternal imprints during PGC development.

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Interactive Poster Session

Group 3 –Reproduction:: Moderator, Monica Mainigi, MD – 5 Posters

11:30 AM – PARS Alumni Poster

Fueling the pipeline: Educating Young Women in the Reproductive Sciences

Jamie Shuda· Christos Coutifaris, Marisa S. Bartolomei, Monica Mainigi

Since women account for a minority of those employed in STEM careers, recruiting the next generation into the fields of science and medicine is critical for continued innovation and progress. In this poster we describe the Penn Academy for Reproductive Sciences (PARS), a NIH-sponsored outreach program that is designed to attract young women to the biological sciences, by providing them with hands-on research experiences in a university environment. Here, we outline the foundation of PARS, its impact on educating young women about the science behind their bodies, and its influence on developing an overall interest in reproductive biology. We encourage you to hear from PARS alumnae about their experience in the program and the impact it has made on their college and career paths.

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Interactive Poster Session

Group 4 –ART: Moderator, Christos Coutifaris, MD, PhD – 5 Posters

11:00 AM – Eric A. Rhon–Calderon

Altered reproductive epigenetic profiles in mature IVF–conceived offspring

Rhon–Calderon, Eric A., Riesche, Laren, Vrooman, Lisa, Bartolomei, Marisa

Institutional Affiliation: Epigenetics Institute, Department of Cell and Developmental Biology, Perelman School of Medicine, University of Pennsylvania, Smilow Center for Translational Research, Philadelphia, PA, USA. bDepartment of Family and Community Health, Claire M. Fagin School of Nursing, University of Pennsylvania. Philadelphia, PA, USA.

Abstract: Assisted Reproductive Technologies (ART) have helped many couples to overcome infertility problems. In vitro fertilization (IVF) is the most common technique used as ART and has recently been refined in order to increase success rate of pregnancies. However, laboratories have shown that IVF is related to health risks for mothers and fetuses including, stillbirth, preterm birth, intrauterine growth restriction, abnormal placentation, and other pregnancy complications. Using our IVF mouse model, we aimed to investigate morphological and epigenetic outcomes of reproductive tissues. For the IVF group, female mice were superovulated, cumulus–egg complexes were collected and IVF was performed with capacitated mature sperm. Fertilized eggs were cultured to the blastocyst stage and transferred into pseudo–pregnant females. For the natural group (Nat), females were naturally mated overnight. All pups were delivered via c–section. At 39–weeks of age, the offspring were euthanized and reproductive tissues were fixed and frozen. Global DNA methylation (DNAm) and DNAm of imprinted genes was assessed with luminometric methylation assay (LUMA) and pyrosequencing, respectively. Student's t–test was used to evaluate differences between groups. IVF females presented a lower ovarian/body weight ratio ($p=0.0075$) [Nat: 4.50 ± 3.13 ; IVF: 0.50 ± 0.17], ovaries presented lower global DNAm ($p=0.0124$) [Nat: $67.2\%\pm 3.5$; IVF: $57.4\%\pm 7.9$], lower DNAm at IG–DMR ($p=0.005$) [Nat: $42.3\%\pm 1.6$; IVF: $36.6\%\pm 2.9$]; decreased expression of *Dlk1* ($p=0.0044$) [Nat: 1.0 ± 0.3 ; IVF: 0.2 ± 0.1] and *Esr1* ($p=0.0012$) [Nat: 0.8 ± 0.5 ; IVF: 0.2 ± 0.1]. While IVF males did not show difference in testes/body weight ratio, their testes and sperm showed higher global DNAm ($p=0.0234$) [Nat: $64.9\%\pm 6.0$; IVF: $70.6\%\pm 2.3$] ($p=0.0484$) [Nat: $66.5\%\pm 5.5$; IVF: $74.3\%\pm 3.1$] respectively, higher DNAm at IG–DMR ($p=0.0458$) [Nat: $90.8\%\pm 1.6$; IVF: $88.0\%\pm 2.7$] and decreased expression of *AR* ($p=0.0368$) [Nat: 1.00 ± 0.15 ; IVF: 0.70 ± 0.20]. Taken together, our results suggest that IVF procedures alter the epigenetic profiles of reproductive tissues in a manner that likely compromises the reproductive function of offspring in both sexes.

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Interactive Poster Session

Group 4 –ART:: Moderator, Christos Coutifaris, MD, PhD – 5 Posters

11:10 AM – Jayashir Ghosh

Effect of fresh vs frozen embryo transfer technology on the placental epigenome

Ghosh, Jayashri, Mainigi, Monica A., Coutifaris, Christos, Barnhart, Kurt T., Sapienza, Carmen, Senapati, Suneeta

Institutional Affiliation: Temple University

Abstract: Background: In vitro fertilization involves the transfer of fresh embryos into a superovulated in-utero hormonal environment or the transfer of frozen embryos into a physiologic in-utero hormonal environment. We hypothesized that type of embryo transfer might influence the maintenance of epigenetic marks after preimplantation epigenetic reprogramming, thereby causing methylation differences at birth. Our group and others have shown that fresh embryo transfers result in placental global hypomethylation of LINE1 elements; yet the differential impact of the in-utero hormonal milieu on gene-specific methylation remains unknown.

Objective: To identify genes and potential pathways involved in observed epigenetic differences in pregnancies conceived after fresh and frozen embryo transfers.

Methods: We used Illumina Infinium MethylationEPIC BeadChip featuring >850,000 CpGs. In discovery cohort, we assayed 68 placental samples (20fresh, 24frozen and 24controls) to identify differentially methylated positions (DMPs) between fresh and frozen embryo transfers. In validation cohort, we assayed 96samples (52fresh and 44frozen). CpG sites with two-tailed t-test p-values<0.05 and a mean difference >5% were considered to be significantly different.

Results: In discovery cohort, 16,412CpGs were significantly different between the two groups. We identified significant genes with minimum 2DMPs, resulting in 6501CpGs. Among these, 381CpGs were significant in validation cohort. Nearly 96% (367CpGs) were in the same direction in both cohorts. Among these, 365CpGs were hypomethylated in the fresh embryo transfer group compared to the frozen transfer group. Pathway analysis identified multiple genes in the thyrotropin releasing hormone receptor (TRHR) signaling pathway (PLCB4, CACNA1E, PLCB1, TRHR, CACNA1A, CACNB2) to be hypomethylated in fresh embryo transfers. We also observed that fresh embryo transfers resulted in more than three times the number of methylation differences (93DMPs) than frozen embryo transfers (27DMPs) compared with natural conceptions. Furthermore, all of the significant CpGs were hypomethylated in fresh transfers and hypermethylated in frozen embryo transfers compared to controls. All the significant CpGs were hypomethylated in fresh and hypermethylated in frozen embryo transfers compared to controls.

Conclusion: Our study indicates that hypomethylation of genes in fresh embryo transfers may result in a dysregulated thyrotropin releasing hormone receptor signaling pathway.

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Interactive Poster Session

Group 4 –ART:: Moderator, Christos Coutifaris, MD, PhD – 5 Posters

11:20 AM – Kelly Duffy

Clinical Phenotype of Beckwith–Wiedemann Syndrome in Natural versus Assisted Reproductive Technology Conceived Pregnancies

Duffy, Kelly A., Hathaway, Evan R., Deardorff, Matthew A., Kalish, Jennifer M.

Institutional Affiliation: Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania

Abstract: Background: Beckwith–Wiedemann syndrome (BWS) is the most common epigenetic growth disorder, affecting approximately 1 in 10,000 patients. However, the incidence of BWS in pregnancies conceived by assisted reproductive technology (ART) is increased to 1 in 1,200. The most common epigenetic alteration in BWS in both ART– and naturally conceived pregnancies is loss of methylation at imprinting control center 2 (IC2 LOM) on chromosome 11p15. Epigenotype–phenotype correlations have demonstrated that patients with IC2 LOM have higher frequencies of omphalocele, macroglossia, ear creases/pits, facial nevus simplex, and prematurity and lower frequencies of organomegaly/nephromegaly, macrosomia, lateralized overgrowth, and tumors compared to patients with other molecular defects. While the phenotype of IC2 LOM patients has been described, no previous analyses have evaluated whether specific phenotype features of IC2 LOM conceived via ART exist.

Objective: In this study, we evaluate the clinical features of a cohort of IC2 LOM patients to determine whether the incidence of features differ between naturally and ART–conceived patients.

Methods: Patients were identified from the BWS Registry and grouped according to their conception type (natural conception or ART, which included IVF and/or ICSI). Clinical features and methylation results were recorded and BWS clinical score was calculated according to international consensus criteria. Data were analyzed using SPSS Statistics (version 25). Fisher's exact test was used to compare the frequency of clinical features. Independent t–tests were used to compare the BWS clinical score, number of features, and methylation percentage. Significance was set at $p < 0.05$.

Results: A total of 113 patients with IC2 LOM were included. No significant differences were found between the natural ($n=76$) and ART ($n=37$) groups in regard to BWS clinical score, number of cardinal and suggestive features, or methylation percentage in blood. The only significant clinical feature identified to be different between the groups was macrosomia, which was more common in the naturally conceived patients. Predictably, multiple gestation pregnancies were more common in the ART group.

Conclusion: While ART has been shown to increase the incidence of BWS, the specific phenotype of children with BWS conceived by ART does not significantly differ from that of naturally conceived children with BWS.

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Interactive Poster Session

Group 4 –ART:: Moderator, Christos Coutifaris, MD, PhD – 5 Posters

11:30 AM – Marissa S. Weiss

Stress and Success: Data from a Prospective Cohort Study Investigating the Impact of Early Life Stress on IVF Outcomes

Weiss, Marissa S., Walter, Jessica R., Koelper, Nathaneal C., Kalliora, Charikleia, Brooks, Rachel B, Stentz, Natalie C.; Barnhart, Kurt; Epperson, C. Neill; Senapati, Suneeta

Institutional Affiliation: University of Pennsylvania, Division of Reproductive Endocrinology and Infertility

Abstract: Objective: Women who experienced early life stress (ELS) have aberrant hypothalamic-pituitary-adrenal responses as well as an increased inflammatory response to induced stress when compared to ELS naïve women. The impact of ELS on infertile women is largely unknown. We sought to determine the prevalence of ELS in the infertile population and the impact of this dysregulated stress reactivity on IVF cycle characteristics and outcomes.

Design: Prospective cohort study

Materials and Methods: Women aged 18-42 were recruited for enrollment prior to initiating an autologous IVF cycle. Consenting participants completed the CDC-Kaiser Adverse Childhood Experience Questionnaire. Those who indicated 2+/10 positive responses were considered to be ELS positive. A power analysis indicated that a sample size of 277 subjects would provide at least 80% power with an alpha of 0.05 to detect a 40% relative difference in live birth rates between groups. Continuous variables were compared using Student's t-test or Mann-Whitney U test based on normality, while χ^2 or Fisher's exact tests were used to compare categorical variables by ELS status. Logistic regression was used to assess for predictors of live birth and early pregnancy failure adjusting for confounders as appropriate

Results: The prevalence of ELS positivity in this infertile cohort was 29.2% (n=83/284). ELS positive women and controls were similar in age, race/ethnicity, and history of anxiety/depression, however higher BMIs were observed in the ELS positive group (mean BMI 27.4 vs 25.6 kg/m², p=.02). While live birth rates were similar in the two groups (37% vs 35%; aOR 1.13, 95% CI 0.65-1.95, p=0.658), ELS positive women had significantly higher rates of early pregnancy loss (EPL) per transfer (28% vs 17%, p=.04). This association persisted when the analysis was restricted to patients undergoing their first IVF cycle and excluding cycles in which preimplantation genetic testing was performed. After controlling for BMI and parity, ELS positivity remained significantly associated with EPL (aOR 1.95, 95% CI 1.05-3.62, p=0.03). However, when EPL rates were considered only among those who achieved a pregnancy, no difference was observed between groups.

Conclusions: Early life stress has a longstanding impact on adult health. While IVF cycle parameters and pregnancy rates do not seem to be impacted, infertile women who experienced ELS have significantly higher rates of early pregnancy loss per transfer. Further studies are needed to elucidate the precise mechanisms of these findings to identify risk reduction methods in this unique, potentially vulnerable, subpopulation of patients pursuing fertility services.

Supported By: Penn Presbyterian George L. and Emily McMichael Harrison Fund for Research in Obstetrics and Gynecology; NIH T32HD007440-21

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Interactive Poster Session

Group 4 –ART:: Moderator, Christos Coutifaris, MD, PhD – 5 Posters

11:40 AM – Lisa Vrooman

Compromised fetal growth and abnormal placental development in a mouse model of Assisted Reproductive Technologies (ART)

Vrooman, Lisa A., Rhon-Calderon, Eric A., Chao, Olivia Y., Nguyen, Duy, Riesche, Laren, Schultz, Richard M., Bartolomei, Marisa S.

Institutional Affiliation: University of Pennsylvania

Abstract: Assisted reproductive technologies (ART), which include in vitro fertilization (IVF), account for up to 10% of births in some countries. Unfortunately, ART concepti have an increased risk of miscarriage, abnormal placentation, low birth weight, imprinting disorders, and other pregnancy complications. We and others have shown that some of these effects can be iatrogenically induced by ART procedures. Using a mouse model of IVF, we examined naturally-conceived and IVF concepti at embryonic days (E) 12.5, 14.5, and 18.5. Additional groups controlling for superovulation, embryo culture, and embryo transfer were also assessed. At E12.5 and E14.5, fetal weight was significantly reduced in all ART groups relative to naturally-conceived concepti and was most severe in the embryo culture and IVF groups. By E18.5, fetal weight was still the most dramatically reduced in embryo culture and IVF groups. Placenta weight, however, was significantly increased in all ART groups by E14.5 and by E18.5, embryo culture and IVF placentas are 28–37% larger than embryo transfer and superovulation groups and 80–85% larger than natural concepti. Placental vasculature abnormalities were also observed. Global DNA methylation and methylation at select imprinting control regions was significantly altered at all time points in only the embryo culture and IVF groups. Our results suggest that all ART procedures compromise fetal growth at mid-gestation due to abnormal placental vasculature. The placental overgrowth observed in late gestation may be the result of compensatory mechanisms. We also provide strong evidence that the embryo culture procedure causes the most severe fetal weight, placental morphology and DNA methylation phenotypes associated with ART.

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Interactive Poster Session

Group 5 –Cancer:: Moderator, Lin Zhang, PhD – 4 Posters

11:00 AM – Haineng Xu

Combination inhibition of WEE1 and ATR causes tumor regression in a Cyclin E level dependent manner

Haineng Xu¹, Erin George¹, Yasuto Kinose¹, Hyoung Kim¹, Sergey Medvedev¹, Carter Barger², Kyle Devins³, Lauren Schwartz³, Stephanie Jean⁵, Gordon Mills⁴, Kathleen Nathanson⁵, Adam Karpe², Ronny Drapkin¹, Eric Brown⁶, Fiona Simpkins¹

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Abstract:

Effective therapies for cyclin E overexpressing gynecological cancers yielding complete and durable responses are lacking. Cyclin E (*CCNE1*) is an oncogenic driver that is amplified in 25% of high grade serous ovarian cancers (HGSOC) and 45-50 % of high grade subtypes of endometrial cancer (EMCA). Cyclin E overexpression is associated with platinum resistance and poor survival. We found that induction of cyclin E, upregulates the ATR/CHK1 pathway and dual inhibition of WEE1 and ATR (WEE1i-ATRi) synergistically decreased cell viability and colony formation in a *CCNE1* level dependent manner. Combination treatment resulted in significant G2/M arrest, mitotic catastrophe, and apoptosis via FOXM1 activation in a Cyclin E level dependent manner. Furthermore, combination WEE1i-ATRi treatment was synergistic in increasing replication stress and double strand DNA breaks. Finally, combination WEE1i-ATRi was tolerable and resulted in a 6-fold increase in survival in *CCNE1* amplified PDX model, over 4-fold in tumor suppression (ongoing) in the *CCNE1* high copy gain PDX model; unlike in non-amplified or gain but Cyclin E overexpressing HGSOC PDX model. In conclusion, WEE1i-ATRi drug sensitivity is dependent on *CCNE1* levels. Our data suggests, *CCNE1* copy number and not protein expression should be considered as a biomarker for design of future clinical trials evaluating combinations targeting Cyclin E overexpression. WEE1i-ATRi is a new drug combination for *CCNE1* amplified HGSOC and EMCAs.

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Interactive Poster Session

Group 5 –Cancer:: Moderator, Lin Zhang, PhD – 4 Posters

11:10 AM – Yasuto Kinose

Comprehensive molecular and experimental characterization of ovarian clear cell carcinoma cell lines for in vivo drug development

Kinose, Yasuto, Hallberg, Dorothy, Doberstein, Kai, Mills, Gordon, Ince, Tan, Velculescu, Victor; Simpkins, Fiona; Drapkin, Ronny

Institutional Affiliation: Penn Ovarian Cancer Research Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Abstract: Background and objective: Ovarian cancer is a heterogeneous disease. While high-grade serous ovarian carcinoma (HGSOC) is the most common, clear cell ovarian carcinoma (CCOC) is the most challenging to treat and exhibits low response rates to standard chemotherapies. To improve the survival of patients with CCOC, a deeper understanding of the molecular features that define available model systems is needed. Our objective is to comprehensively characterize a panel of CCOC lines using sequencing and functional experiments to define the lines that are most faithful to CCOC and are tractable for subsequent in vivo drug discovery.

Method: We obtained 9 CCOC cells from cell repositories (ES-2, TOV21G, OVTOKO, OVMANA, OCI-C5x, JHOC-5, JHOC-7, JHOC-9, and OVISE). Genomic DNA, RNA, and protein were isolated and subjected to DNA-seq including DNA methylation analysis, RNA-seq, and reverse phase protein array (RPPA), respectively. We performed in vitro MTT assays to test the sensitivity to chemotherapies. Tumorigenicity was evaluated by injecting 5 million cells of luciferized CCOCs into NSG female mice using both subcutaneous route and intraperitoneal route.

Results: Among the 9 CCOCs, ARID1A, PIK3CA, and BRCA-related gene mutation were detected in 8/9, 6/9, and 4/9 cell lines, respectively. ES-2 has TP53 and BRAF mutations and its genomic profile is not typical of CCOC. Principal component analysis of RPPA distinguished between the 9 CCOC and the 6 HGSOC lines. Interestingly, we also observed two distinct clusters within the CCOCs. Consistent with our genomic analysis, the ES-2 cell line correlated more closely with the HGSOCs based on RPPA data. In our in vitro drug studies, OVTOKO and OCI-C5x exhibited resistance to Carboplatin/Paclitaxel. In xenograft study, 4 lines (ES-2, TOV21G, OVTOKO, and OCI-C5x) formed measurable tumor within a month. In contrast, OVMANA, JHOC-7, JHOC-9, and OVISE took over 100 days to form tumors.

Conclusions: Our data suggests that there may exist two functionally distinct groups within CCOC that warrants further study. In vitro and in vivo studies identified 4 lines that represent tractable models for rigorous therapeutic studies: ES-2, TOV21G, OVTOKO, and OCI-C5x. However, ES-2 appears to cluster more closely with HGSOC and may not represent the CCOC histotype.

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Interactive Poster Session

Group 5 –Cancer:: Moderator, Lin Zhang, PhD – 4 Posters

11:20 AM – Guannan Zhang

Elucidating the roles of estrogens in the development and prognosis of malignant pleural mesothelioma

Guannan Zhang, Ling Duan

Institutional Affiliation: Department of Systems Pharmacology & Translation Therapeutics, & Center of Excellence in Environmental Toxicology, Perelman School of Medicine

Abstract: Asbestos is a carcinogen that causes mesothelioma rare cancer that arises from the mesothelial lining of the pleura. Malignant pleural mesothelioma is an aggressive tumor that is resistant to conventional treatment including chemotherapy, surgery or radiation. Epidemiological observations show that for non-occupational exposure the incidence of mesothelioma is higher in women than men. However, women diagnosed with malignant pleural mesothelioma respond better to the treatment and have a better prognosis than men. This prompted us to assess the role of estrogen and estrogen receptors in determining the risk and prognosis of this cancer. Our hypothesis is that mesothelioma cells express estrogen receptors and they can generate their own ligands for these receptors. As a positive control, MCF-7 cells were shown to express ER α at the transcript and protein level, proliferate in response to 17 β -estradiol and proliferation was blocked with fulvestrant an ER α antagonist. qPCR showed that three different malignant mesothelioma cell lines (MSTO-211H, REN, and IST) expressed ER α at very low levels when compared with MCF-7 cells and this was supported by immunoblot analysis. However, treatment of MSTO-211H cells with 17 β -estradiol induced growth proliferation that was not blocked by fulvestrant. These data suggest that 17 β -estradiol exerts survival and proliferative effects in malignant mesothelioma cells through a pathway that is independent of ER α . Using an antagonist for GPR30 preliminary studies indicate that the growth proliferation observed with 17 β -estradiol is blocked in MSTO-211H cells. qPCR showed that three different malignant mesothelioma cells lines expressed GPR30 and this was supported by immunoblot analysis. We now aim to measure the expression of ER α , ER β and GPR30 in malignant mesothelioma cells with IP-based LC-MS/MS proteomics and their clinical and biological significance.

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Interactive Poster Session

Group 5 –Cancer:: Moderator, Lin Zhang, PhD – 4 Posters

11:30 AM – Jiao Yuan

Integrated Analysis of Genetic Ancestry and Genomic Alterations across Cancers

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Abstract: Cancer is a genomic disease involving multi-step changes in the genome. Disparities in cancer defined by self-identified race or ethnicity (SIRE) have been a long-standing and persistent challenge. Certain racial and ethnic populations in the United States experience increased incidence in total, and of aggressive disease for specific cancer. For example, compared with other racial groups, African Americans (AA) exhibit higher rates of colorectal cancer incidence and death, AA women have higher mortality rates from breast and endometrial cancer, and AA men have higher incidence and mortality rates from prostate and lung cancers. However, the genomic causes of cancer disparities are still poorly understood. The Cancer Genome Atlas patient cohort is ethnically diverse, therefore providing a unique resource to understand the genomic basis of cancer disparities across multiple cancer types. However, a large percentage of patients lacked SIRE information in TCGA. We integrated multiple computational algorithms to estimate the global and local genetic ancestry of each TCGA patient (n = 11,122, involving 33 cancer types from 27 primary sites) using genome-wide genotyping data, and assigned each individual to an ancestral population. We have made this information available in the Cancer Genetic Ancestry Atlas (TCGAA, <http://52.25.87.215/TCGAA>), a publicly accessible resource, to assist researchers with analyzing, visualizing, and downloading multidimensional genetic ancestry information for each patient in TCGA. Furthermore, we performed a pan-cancer analysis on the influence of genetic ancestry on genomic alterations. Compared with European Americans, African Americans (AA) with breast, head and neck, and endometrial cancers exhibit a higher level of chromosomal instability, while a lower level of chromosomal instability was observed in AAs with kidney cancers. The frequencies of TP53 mutations and amplification of CCNE1 were increased in AAs in the cancer types showing higher levels of chromosomal instability. We observed lower frequencies of genomic alterations affecting genes in the PI3K pathway in AA patients across cancers. Our result provides insight into genomic contribution to cancer disparities.

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