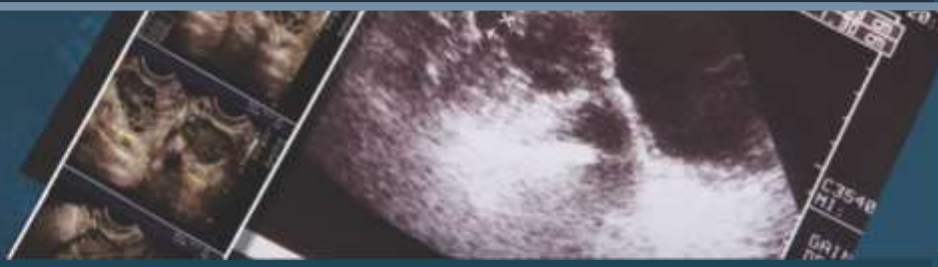
American Society for Reproductive Immunology



Bridging immunity with infection, inflammation and implantation for better reproductive health

ASRI 37th Annual Meeting

September 17-20, 2017

Chicago, Illinois, USA

Congress Chairs:

Animesh Barua, PhD **Michael Bradaric, PhD** **Joanne Kwak-Kim, PhD**

Program Committee

Animesh Barua, PhD
Jenell Coleman Fennel
Nazeeh Hanna
Joanne Kwak-Kim
Udo Markert
Margaret G. Petroff
James Segars

Fuller Bazer
Jan Ernerudh
Peter Hansen
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Mercy PrabhuDas
G. Taru Sharma

Kenneth D. Beaman
Anna Marie Franchini
Bo Jacobsson
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Hiroaki Shibahara

Sandra Blois
Charles Graham
Charu Kaushic
Yi Lin
Joye Pate
Shigeru Saito
Michael Soares

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Welcome to Chicago

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Meeting Venue

The 37th Meeting of the American Society for Reproductive Immunology is being held in windy city Chicago, Illinois, USA, September 17-20, 2017. The meeting venue is provided by Double Tree by Hilton Hotel Chicago - Magnificent Mile, one of the most popular and diverse city of culture and business in the world.

Meeting Motto

"Bridging immunity with infection, inflammation and implantation for better reproductive health"

Welcome from the Co-Chairs

The American Society for Reproductive Immunology

Congress Chairs:

Animesh Barua

Michael Bradaric

Joanne Kwak-Kim

Program Committee:

Samar AlSagghaf

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Petroff Mercy

PrabhuDas

Charles R. Wira

Shigeru Saito

James Segars

G. Taru Sharma

Hiroaki Shibahara

Michael Soares

Dear Colleagues and Friends,

It gives us great pleasure to welcome you to the 36th annual meeting of the American Society of Reproductive Immunology to be held on November 14-16 in Baltimore, the city that gave us our National Anthem "The Star Spangled Banner— "and the city built on tradition and civic pride. This year's conference theme is "Putting Women and Children at the Center of Health and Development". The overall goal is to reach new heights in Reproductive Immunology. To accomplish our goals, the meeting program is designed to provide a comprehensive and stimulating balance between basic science and clinical research with focus on cutting edge research and technologies. To follow a long-held tradition, this ASRI annual meeting is again intended to serve the needs of physicians, clinicians/scientists, basic scientists, young investigators, fellows, graduate students, laboratory personnel, and most importantly the public.

As detailed in the program, attendees will benefit from a pre-meeting Clinical Symposium "Combating Continuum of Pregnancy Complications" (November 12-13), which focuses on clinical tools and new methodology, emerging viral infections and pregnancy outcomes, and biomarkers for adverse pregnancy outcomes. The annual meeting will expand on these and other themes with mechanistic underpinnings. Participants will hear from world leaders in their field and talented early career investigators.

To encourage young investigators to join the field of Reproductive Immunology and Medicine, the annual conference provides a platform for them in the form of the Gusdon Award presentations and oral presentations selected from the abstracts. All participants will have the opportunity to present their work in the poster format. Keynote lectures by Dr. Bali Pulendran, Emory University, and Dr. Cathy Spong, Deputy Director, NICHD, are designed to provide discussion on contemporary topics in immunology and reproductive medicine. The President's Symposium is always a highlight of the meeting. The relevance of maternal immune system never diminishes, as we again face the Zika virus epidemic. This topic will be extensively covered in the 36th annual meeting.

Keeping our intent and focus in mind, the 36th annual meeting is designed to provide a unique platform for career advancement as it blends learning with networking for young scientists irrespective of ethnic background, gender and sexual preference. We encourage our young investigators by inviting them to be part of all aspects of our conference. As challenges grow and opportunities abound, it is great time to be a reproductive immunologist, since ours is a discipline that brings both clinicians and basic researchers together. Reproductive health issues are no longer focused exclusively on pregnancy, but now encompass the entire life cycle of men and women (from birth to chronic diseases in later life).

We take this opportunity to thank our numerous sponsors and benefactors listed at the end of this program for generously supporting our mission. We look forward to meeting you at the 36th annual meeting and enjoying together the great science and the fun of Baltimore.

Warm welcome,

Surendra Sharma, MD, PhD

Departments of
Pediatrics and Pathology
Women & Infants'
Hospital of Rhode Island

Irina Burd, MD, PhD

Department of Gynecology & Obstetrics
Johns Hopkins University

ASRI
American Society for Reproductive Immunology

Welcome from the ASRI President

Dear ASRI Members, Colleagues and Friends,

The annual ASRI meeting is always a celebration. Celebration of presenting cutting edge science, meeting old friends, making new friends as well as get updates regarding our society and its future direction.

It is a great pleasure to welcome you to the 37th ASRI annual meeting in the beautiful city of Chicago. The theme of this year's program is "Bridging immunity with infection, inflammation and implantation for better reproductive health." The program this year is superb with high profile speakers that will provide both scientists and clinicians the most updated and cutting-edge scientific advances in reproductive health. Social interactions and networking is an integral part of ASRI meetings. The program this year will offer many opportunities for informal encounters and develop collaboration among clinicians and scientists from all over the globe.

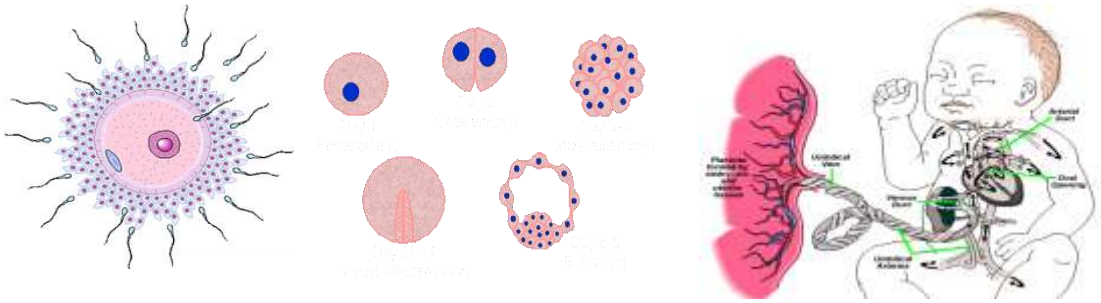
As you are aware, the ASRI has been exciting since 1981. The mission of the ASRI is to foster the development of reproductive immunology research, increase intellectual exchange between clinical and basic branches of reproductive immunology and provide mentoring for new scientists. There are several new initiatives that we aim to achieve in the next two years focused on: 1) advance the scientific impact of ASRI in the field of reproductive immunology, 2) enhance the awareness and branding the name of ASRI among colleagues, 3) grow the Society membership, 4) encourage new scientists' involvement in the Society and 5) develop local chapters for ASRI both in the USA as well as abroad.

ASRI is only as strong as its members, and I encourage you to take an active part in your Society to advance its mission in research, teaching and patient care. Please encourage your colleagues and trainees to join the Society to take advantage of what it has to offer. We hope that you will visit our updated website and social media to continue learning about ASRI and share in its progress and achievements.

Yours,

Nazeeh Hanna, MD
ASRI President 2016-2018

Meeting Objectives



The American Society for Reproductive Immunology (ASRI) was founded to foster the field of Reproductive Immunology so both clinicians and basic researchers could better understand the immune-based etiologies underlying reproductive anomalies. The annual ASRI meetings are designed to acquaint attendees with new questions and new techniques underlying the normal and abnormal events at the maternal-fetal interface. It is increasingly clear that the immunity, placenta and hormones play a pivotal role in orchestrating *in utero* embryonic development. There appears to be a composite triad of dynamic equilibrium involving the placental milieu, the fetus and the mother. Thus, the maternal-fetal interface can provide a blueprint for the events that lead to a normal or a compromised pregnancy. Recent revolutionary advances in technical know-how and thematic excellence now make it possible to not only investigate the issues in animals but to transport this knowledge from bench to bedside. The Clinical Symposium and the 36th Annual meeting will focus on recent state of the art techniques and themes. Each topic will be lectured by an expert in the respective field. At the end of the meeting, all participants should be able to:

- Evaluate epigenetics and exosomes in placenta and their clinical relationship
- Apply recent state-of-the art techniques and themes in obstetrics
- Explain the role of inflammatory immune responses in obstetrical complications such as pre-eclampsia and preterm labor.
- Evaluate the neurological control of inflammatory immune response
- Assess the consequences of Zika virus pandemic on pregnancy outcome.
- Assess whether we are winning the war against HIV
- Understand the interplay between hormones, mucosal immunity, semen factors, and susceptibility to HIV
- Understand the role of microbiome in adverse pregnancy outcomes
- Assess progress in vaccines for STIs
- Evaluate specialized immunity in male and female reproduction
- Debate mouse to human continuum in reproduction

This conference has been approved for 18 CME (accrediting institution: Chicago Medical School at Rosalind Franklin University of Medicine and Science)

Meeting Objectives

Program at-a-Glance

CLINICAL SYMPOSIUM Saturday November 12	CLINICAL SYMPOSIUM Sunday November 13	MAIN MEETING Monday November 14	MAIN MEETING Tuesday November 15	MAIN MEETING Wednesday November 16
Registration & Breakfast 7:00-8:15 AM *University Ballroom Foyer*	**Registration & Breakfast** 7:00-8:15 AM *University Ballroom Foyer*	**Registration & Breakfast** 7:00-8:15 AM *Grand Ballroom Foyer*	**Registration & Breakfast** 7:00-8:15 AM *Grand Ballroom Foyer*	**Registration & Breakfast** 7:30-8:15 AM *Grand Ballroom Foyer*
Welcome & Announcements 8:15-8:30 AM *University Ballroom*	**Welcome & Announcements** 8:15-8:30 AM *University Ballroom*	**Welcome & Announcements** 8:15-8:30 AM *Grand Ballroom*	**Welcome & Announcements** 8:15-8:30 AM *Grand Ballroom*	**Welcome & Announcements** 8:15-8:30 AM *Grand Ballroom*
Teaching Session 1 8:30-10:00 AM *University Ballroom*	**Teaching Session 5** 8:30-10:00 AM *University Ballroom*	**Keynote Address** 8:30-9:15 AM *Grand Ballroom*	**Keynote Address** 8:30-9:15 AM *Grand Ballroom*	**General Session 6** 8:30-11:00 AM *Grand Ballroom*
Coffee Break 10:00-10:15 AM *University Ballroom Foyer*	**Coffee Break** 10:00-10:15 AM *University Ballroom Foyer*	**General Session 1** 9:15-10:45 AM *Grand Ballroom*	**General Session 4** 9:15-10:45 AM *Grand Ballroom*	
Teaching Session 2 10:15-11:45 AM *University Ballroom*	**Teaching Session 6** 10:15-12:15 PM *University Ballroom*	**Coffee Break** 10:45-11:00 AM *Grand Ballroom Foyer*	**Coffee Break** 10:45-11:00 AM *Grand Ballroom Foyer*	**Coffee Break** 11:00-11:15 AM *Grand Ballroom Foyer*
Lunch 12:00-1:20 PM *University Ballroom Foyer*	**Lunch** 12:15-1:30 PM *University Ballroom Foyer*	**General Session 2** 11:00-1:00 PM *Grand Ballroom*	**General Session 5** 11:00-12:50 PM *Grand Ballroom*	**General Session 7** 11:00-12:45 AM *Grand Ballroom*
Teaching Session 3 1:20-4:15 PM *University Ballroom*	**Teaching Session 7** 1:30-4:00PM *University Ballroom*	**Lunch** 1:00-2:00 PM *Grand Ballroom Foyer*	**Lunch** 12:50-1:50 PM	**Lunch/Poster Session** 12:45-1:45 PM *University Ballroom*
Coffee Break 4:00-4:15 PM *University Ballroom Foyer*		**ASRI Council Meeting** 1:00-2:00 PM *Chesapeake Room*	**ASRI General Meeting** **12:50-1:50 PM** (members invited) *Grand Ballroom*	**General Session 8** 1:45-3:45 PM *Grand Ballroom*
Teaching Session 4 4:15-5:00 PM *University Ballroom*		**General Session 3** 2:00-3:50 PM *Grand Ballroom*	**Poster Session** 1:50-3:00 PM *University Ballroom*	**MEETING ADJOURNED**
		Coffee Break 3:50-4:05 PM *Grand Ballroom*	**J. Christian Herr Lecture** 3:30-4:00 PM *Grand Ballroom*	
		AJRI Award Lecture 4:05-4:35 PM *Grand Ballroom*	**Presidential Session** 4:00-5:30 PM *Grand Ballroom*	
		John P. Gusdon Award Competition 4:35-5:47 PM *Grand Ballroom*	**Cocktail Hour** 6:30-7:30 PM *Chesapeake Room*	
	Welcome Reception 6:00-8:00 PM *University Ballroom*	**AJRI Editorial Board Meeting** 6:30-8:30 PM *Chesapeake Room*	**Gala and Awards Banquet** 7:30-10:00 PM *Stadium Ballroom*	

Clinical Symposium
Combating Continuum of Pregnancy Complications 2017

Sunday, September 17, 2017

7:00 - 10:00 AM **Registration** – *University Ballroom*

8:15 - 8:30 AM **Welcome address** - *University Ballroom*
Combating Continuum of Pregnancy Complications
Drs. Irina Burd and Surendra Sharma

Session 1. Mechanisms and consequences of adverse pregnancy outcomes- *University Ballroom*
Chairs: Drs. Surendra Sharma and Irina Burd

8:30 - 9:00 AM Dr. Bo Jacobsson, University of Gothenburg, Sweden
Intra-amniotic infection and inflammation in relation to pregnancy outcomes

9:00 - 9:30 AM Dr. Errol Norwitz, Tufts University, USA
Molecular regulation of adverse pregnancy outcome: inflammation and "the decidual clock"

9:30 - 10:00 AM Dr. Udo Markert, Friedrich-Schiller-University, Germany
Trophoblast communication with immune cells via miRNA transported by extracellular vesicles

10:00- 10:15 AM **Coffee Break-** *University Ballroom Foyer*

Session 2. Clinical tools and new methodology - *University Ballroom*
Chairs: Drs. Nazeeh Hanna and Jun Lei

10:15- 10:45 AM Dr. Nanbert Zhong, Nanfang Hospital of Southern Medical University, China and New York State Institute, USA
How to connect omics data with clinical research?

10:45-11:15 AM Dr. Xingde Li, Johns Hopkins University School of Medicine, USA
Optical microimaging technologies and their potential for assessing preterm birth risk

11:15-11:45 AM Dr. Laura Ensign, Johns Hopkins University School of Medicine, USA
Nanomedicine for preterm birth

12:00-1:20 PM **Lunch**

Session 3. Emerging viral infections and reproductive immunology - *University Ballroom*
Chairs: Drs. Nahida Chakhtoura and Jeanne Sheffield

1:20-1:50 PM Dr. Sabra Klein, Johns Hopkins School of Public Health, USA
Sex and sex steroids affect the outcome of influenza infection and vaccination

1:50-2:20 PM Dr. Brenna Hughes, Duke University, USA
Zika virus- a little perspective

2:20-2:50 PM Dr. Yoel Sadovsky, Magee-Womens Research Institute, USA
Multiple pathways underlie anti-viral signal by human placental trophoblasts

2:50-3:20 PM Dr. Gil Mor, Yale University School of Medicine, USA
Viral Infections during pregnancy: maternal and fetal consequences

3:20-3:50 PM Dr. Nahida Chakhtoura, NIH/NICHD, USA
Zika from NICHD perspective

4:00-4:15 PM **Coffee Break-** *University Ballroom Foyer*

Session 4. NIH Update: Placenta -*University Ballroom*
Chairs: Drs. Irina Burd and Surendra Sharma

4:15- 5:00 PM Dr. David Weinberg, NIH/NICHD, USA
The Human Placenta Project: Current progress and future directions

Sunday

Monday, September 18, 2017

7:00- 10:00 AM **Registration** - *University Ballroom Foyer*

Session 5. Adverse pregnancy continuum - *University Ballroom*
Chairs: Drs. Gil Mor and Donna Neale

8:30- 9:00 AM Dr. Joanne Kwak-Kim, Rosalind Franklin University, USA
Endometrial gene expressions for immune profiling in recurrent pregnancy losses are different from those of repeated implantation failures and infertility

9:00-9:30 AM Dr. Michael W. Varner, University of Utah, USA
Preeclampsia: Early and late

9:30-10:00 AM Dr. Nazeeh Hanna, Winthrop University Hospital, USA
Efficacy of progesterone therapy for midtrimester short cervix is conditional on intra-amniotic inflammation

10:00-10:15 AM **Coffee Break-** *University Ballroom Foyer*

Session 6. Clinical tools and methodology for REI
Chairs: Drs. Jeffrey Braverman and Udo Markert

10:15- 10:45 AM Dr. Mindy Christianson, Johns Hopkins University School of Medicine, USA
Female fertility preservation: Current choices and future directions

10:45-11:15 AM	Dr. Monica Mainigi, University of Pennsylvania, USA *Molecular mechanisms responsible for adverse outcomes associated with assisted reproduction*
11:15-11:45 AM	Dr. Lynae Brayboy, Brown University, USA *Molecular variations between young and aged oocytes*
11:45-12:15 PM	Dr. Winifred Mak, Yale University School of Medicine, USA *Diagnostic dilemma of recurrent pregnancy loss*

Session 7. Multidisciplinary approach to study pregnancy complications: Biomarkers for future health

Chairs: Drs. Laura Goetzl and Michael Tsimis

1:30-2:00 PM	Dr. A. Jason Vaught, Johns Hopkins University School of Medicine, USA *Complement upregulation via the alternative pathway in HELLP syndrome*
2:00-2:30 PM	Dr. Ahmet Baschat, Johns Hopkins University School of Medicine, USA *First trimester personalized prediction of pre-eclampsia – an opportunity to improve maternal & child health*
2:30-3:00 PM	**Coffee Break-** *University Ballroom Foyer*
3:00- 3:30 PM	Dr. Kenneth Beaman, Rosalind Franklin University, USA *Importance of immune markers before pregnancy in predicting pregnancy outcome*
3:30-4:00 PM	Dr. Abimbola Aina-Mumuney, Johns Hopkins University School of Medicine, USA *Innovation to overcome clinical obstacles to accurate preterm labor detection*
6:00 PM	**Reception -** *University Ballroom*

37th Annual Meeting

"Bridging immunity with infection, inflammation and implantation for better reproductive health"

Monday

Monday, September 18, 2017

7:00- 8:15 AM **Breakfast-** *Grand Ballroom Foyer*

7:00- 10:00 AM **Registration-** *Grand Ballroom Foyer*

8:15- 8:30 AM **Welcome and announcements -** *Grand Ballroom*
(Drs. Irina Burd, Surendra Sharma and Kenneth Beaman)

8:30- 9:15 AM **Keynote Address: Dr. Bali Pulendran, Emory University, USA**
Systems-based approaches to vaccine development
Chairs: Drs. Surendra Sharma and Irina Burd

Session 1. Mouse to human continuum: Reproductive debate (Sponsored by Johns Hopkins University)
Chairs: Drs. PK Lala and Ram Menon

9:15-9:45 AM Dr. Ronald G Tompkins, Massachusetts General Hospital, USA
Genomic responses in mouse models poorly mimic human inflammatory diseases

9:45-10:15 AM Dr. Guillermina Girardi, Edinburgh Research Center, UK
It all started with a mouse. How animal models helped the identification of a treatment to prevent preeclampsia in patients with antiphospholipid syndrome

10:15-10:45 AM Oral presentations selected from abstracts

Dr. Svetlana Dambaeva, Rosalind Franklin University, USA
Molecular profiling of endometrium to determine uterine receptivity

Dr. Ayano Funamizu, Hirosaki University of Medicine, Japan
Hormonal treatment for women with endometriosis affects the expression of Natural Cytotoxicity Receptors on NK cells

Dr. Devin McGee, Michigan State University, USA
Cervical viral infection causes estrogen receptor stabilization and premature cervical ripening

10:45- 11:00 AM **Coffee Break –** *Grand Ballroom*

Session 2. Specialized immunity in reproduction: From men to women (Sponsored by Princess Nourah Bint Abdul Rahman University)
Chairs: Drs. Jeffrey Braverman, Samar Al Sagghaf, and CK Hughes

11:00-11:30 AM Dr. John Schjenken, Robinson Institute, Australia
Seminal fluid regulation of microRNAs in the peri-conception immune environment and role in pregnancy success

11:30-12:00 PM Dr. Jan Ernerudh, Linköping University, Sweden
Interactions between the fetal placenta, decidual stroma and decidual immune cells as early steps in fetal tolerance

12:00-12:30 PM Dr. Andreas Meinhardt, University of Giessen, Germany
The roles of pathogen and host in the immunopathology leading to male infertility

12:30-1:00 PM Oral presentations selected from abstracts

Dr. Kristen Mueller, McMaster University, Canada
Female sex hormones influence intravaginal HIV-1 infection and dissemination in a humanized mouse model
Dr. Landon G. vom Steeg, Johns Hopkins School of Public Health, USA
Age and testosterone shift virus-specific CD8+ T cell and regulatory T cell responses during influenza virus infection in male mice

1:00- 2:00 PM **Lunch**

1:00- 2:00 PM **ASRI Council Meeting -** *Chesapeake Room*

Session 3. Immune mechanisms at the maternal-fetal interface: Spotlight on the placenta (Sponsored by China Human Placenta Project)

Chairs: Drs. Don Tory, Animesh Barua and Solange Eloundou

2:00-2:30 PM Dr. Merci PrabhuDas, NIH, USA
Inflammation, immunity, and pregnancy: Challenges and opportunities

2:30-3:00 PM Dr. Sandra Blois, Charité - Universitätsmedizin Berlin, Germany
Galectin-3 in pregnancy: Relation with health and disease

3:00-3:30 PM Dr. Vikki Abrahams, Yale University School of Medicine, USA
Novel placental innate immune signaling pathways

3:30-3:50 PM Oral presentations selected from abstracts

Dr. Indira Mysorekar, Washington University School of Medicine, USA
Zika virus takes transplacental route to fetal infection
Dr. Akitoshi Nakashima, Women and Infants Hospital, Brown University, USA
Preeclampsia serum disrupts the autophagy/lysosome pathway via inhibiting nuclear translocation of transcription factor EB (TFEB)

3:50-4:05PM **Coffee Break-** *Grand Ballroom Foyer*

4:05-4:35 PM **AJRI Award Lecture –** *Grand Ballroom*
Dr. Joanne Kwak-Kim, Rosalind Franklin University
Time to delve into immune etiology of infertility

4:35-5:47 PM **John P. Gusdon Award Competition**
Top 6 ranked abstracts will present 12-minute oral presentations.

Dr. Puja Bagri (category: basic science), McMaster University, Canada
IL-17 plays a critical role in mediating efficient anti-viral memory responses in the female genital tract

Dr. Robert Lindau (category: clinical), Linköping University, Sweden
Decidual stromal cells induce homeostatic M2 macrophages

Dr. Mark Bustoros (category: basic science), Winthrop University Hospital, USA
Exosomes mediate endotoxin tolerance in human placenta

Dr. Jamie Fierce (category: clinical), Women and Infants Hospital and Warren Alpert Medical School of Brown University, USA
Serum protein aggregates as indicators of preeclampsia and gestational diabetes

Dr. Samantha Sheller (category: basic science), University of Texas Medical Branch at Galveston, USA
Functional role of human amnion epithelial cell-derived fetal exosomes on uterine cells and their trafficking in murine models of pregnancy

Dr. Nayoung Sung (category: clinical), Rosalind Franklin University, USA
Women with a history of GnRH analogue exposure have increased TH1 immunity during index IVF cycle

6:30-8:30 PM **AJRI Editorial Board Meeting – Chesapeake Room**

Tuesday November 15, 2016

7:30- 8:30 AM **Breakfast –** *Grand Ballroom*
7:00- 10:00 AM **Registration –** *Grand Ballroom Foyer*

8:30- 9:15 AM **Keynote Address: Dr. Catherine Spong (NICHD), USA**
NICHD Maternal-Child Health Research and Opportunities: From A to Zika
Chairs: Drs. Irina Burd and Surendra Sharma

Session 4. Mechanistic continuum in adverse pregnancy outcomes (Sponsored by Brown University, Women and Infants Hospital)
Chairs: Drs. Leif Matthiesen and Jaimie Fierce

9:15-9:45 AM Dr. James Padbury, Brown University, USA
Targeted sequencing and meta-analysis of preterm birth
9:45-10:15 AM Dr. Elizabeth Bonney, University of Vermont, USA
Pregnancy and three theories of immune tolerance
10:15-10:45 AM Dr. Larry Chamley, University of Aukland, New Zealand
Antiphospholipid antibodies, the syncytiotrophoblast and mitochondria: A recipe for cell death

10:45- 11:00 AM **Coffee Break- Grand Ballroom**

Session 5. Concepts in large animal research

Chairs: Drs. Sung Ki Lee and Karen Racicot

11:00-11:30 AM Dr. Taru Sharma, ICAR, Izatnagar, India
Excisional wound healing: An experimental approach to evaluate the differentiation and immunomodulatory potential of Caprene fetal adnexa derived stem cells

11:30-12:00 PM Dr. Rita Driggers, Johns Hopkins University School of Medicine, USA
Zika – prolonged viremia an indication of congenital infection?

12:00-12:30 PM Dr. Peta Grigsby, Oregon Health and Science University, USA
Zika Virus during Pregnancy in the Non-Human Primate: Maternal-feto-placental inflammatory responses

12:30-12:50 PM Oral presentations selected from abstracts
Dr. Jae Won Han, Konyang University Hospital, Republic of Korea
Activation of NOD-1/JNK/IL-8 signal axis in decidual stromal cells facilitates invasion of trophoblasts

Dr. Linda Mae Wetzel, Pennsylvania State University, USA
Bovine luteal macrophage protein expression changes throughout the luteal phase and luteolysis

12:50- 1:50 PM **Lunch**

12:50-1:50 PM **ASRI General Meeting (all members invited)-** *Grand Ballroom*

1:50- 3:30 PM **Poster Session**- *University Ballroom*

3:30-4:00 PM **J. Christian Herr Lecture-** *Grand Ballroom*
Dr. Da-Jin Li, Fudan University Shanghai Medical College, China
Co-stimulatory signal at maternal-fetal interface

4:00-5:30 PM **Presidential session (Supported by Rosalind Franklin University)**

Chair: Dr. Kenneth Beaman

Dr. Adrian Erlebacher, University of California San Francisco, USA
Epigenetics of decidual inflammation

Dr. Kenneth Beaman, Rosalind Franklin University, USA
The immune system in pregnancy: What was once thought to be bad is now thought to be good

6:30– 7:30 PM **Cocktail hour** -*Chesapeake Room*

7:30– 10:00 PM **Gala and Awards Banquet-** *Stadium Ballroom*

Wednesday, November 16, 2016

7:30- 8:30 AM **Breakfast –** *University Ballroom Foyer*

Session 6. Are we winning the war against HIV?

Chairs: Drs. Charles Wira and Fulvia Veronese

8:30-9:00 AM Dr. Charles Wira, Dartmouth University, USA
Interplay between sex hormones, mucosal immunology and susceptibility to HIV infection in the female reproductive tract

Wednesday

9:00-9:30 AM Dr. Sharron Hillier, University of Pennsylvania, USA
Overview of HIV prevention (microbicides and vaccines)

9:30-10:00 AM Dr. Douglas Kwon, Harvard University, USA
Association between injectable progestin-only contraceptives and HIV acquisition and HIV target cell frequency in the female genital tract

10:30-11:00 AM Dr. Jenell Coleman, Johns Hopkins University School of Medicine, USA
Impact of medroxyprogesterone acetate on HIV susceptibility and pre-exposure prophylaxis

11:00- 11:15 AM **Coffee Break** – *Grand Ballroom*

Session 7. Viruses, microbes and adverse pregnancy outcomes

Chairs: Drs. Gil Mor and Akitoshi Nakashima

11:15-11:45 AM Dr. Michal Elovitz, University of Pennsylvania, USA
Cervicovaginal microbiota and preterm birth

11:45-12:15 AM Dr. Indira U. Mysorekar, Washington University, USA
Spatial variation in microbiota within the human placenta

12:15-12:45 AM Oral presentations selected from abstracts

Dr. Paulomi Aldo, Yale University School of Medicine, USA
Effect of HSV-2 infection on TAM receptors expression in first trimester trophoblast cells

Dr. Maureen Grundy, Johns Hopkins University School of Medicine, USA
Streptococcus pseudoporcinus colonization in pregnancy: Implications for perinatal outcomes

Dr. Meghan Vermillion, Johns Hopkins Bloomberg School of Public Health, USA
Zika virus infection of pregnant outbred mice as a model of human fetal disease

12:45-1:45 PM **Lunch/poster session continued**

Session 8. Mucosal immunity: Progress in vaccines for STIs (Sponsored by Society for Mucosal Immunology)

Chairs: Drs. Ken Beagley and Puja Bagri

1:45-2:15 PM Dr. Michael Russel, University of Buffalo, USA
A novel approach to vaccination against Neisseria gonorrhoeae

2:15-2:45 PM Dr. Ali Fatton, NanoBio Corporation, USA
Development of vaccines for genital Herpes infection: use of a novel nanoemulsion adjuvant

2:45-3:15 PM Dr. Ken Beagley, Institute of Health and Biomedical Innovation Queensland University of Technology, Australia
Development of vaccines for Chlamydia trachomatis: should we target infection or disease?

3:15-3:45 PM Dr. Charu Kaushic, McMaster University, Canada
Regulation of mucosal immune responses in reproductive tract by sex hormones: Understanding the mechanism and implications

Meeting Concluded – Thank You

ASRI Awards

The following ASRI Awards will be presented on Tuesday at the Awards Celebration:

The AJRI Award will be presented to a senior investigator who has made outstanding clinical or basic research contributions in the area of reproductive immunology.

The J. Christian Herr Award will be presented to a member of the ASRI, in the first 10-15 years beyond accepting a faculty position, who has made outstanding achievements in basic or applied research in reproductive immunology, particularly involved in technology transfer. This award was established by a past president of ASRI to acknowledge the dedication of his father to invention, innovation and entrepreneurship.

The Dr. John Gusdon Memorial New Investigator Award will be presented to a new investigator with trainee status (graduate student, postdoctoral scientist, or resident) who has made a significant contribution by presenting an outstanding research paper during the annual meeting. This award is given annual in memory of Dr. John Gusdon, a founding member of ASRI, and an advocate of student participation in ASRI meetings.

Distinguished Service Award is given periodically and not more than annually, to a member of the ASRI who has provided distinguished service to advance the goals and mission of the society.

Travel Grants will be awarded to trainees from selected abstracts to support travel to the ASRI 2015 Meeting.

Best Image Competition Award will be given to the selected image/picture submitted by a meeting attendee.

ASRI Meetings

ASRI Meetings

1980	Mount Sinai Medical Center, NY	N. Gleicher
1981	Mount Sinai Medical Center, NY	N. Gleicher
1982	Bowman Gray, Winston-Salem, NC	J. Gudson, Jr.
1983	University of Utah, Salt Lake City, UT	J.R. Scott
1984	Duke University, Durham, NC	S. Gall
1985	University of Michigan, Ann Arbor, MI	A.E. Beer
1986	Toronto, Canada[1]	D. Clark
1987	Indianapolis, IN	C. Coulam
1988	University of Maine, Prout's Neck, ME	N.S. Rote
1989	University of Maine, Prout's Neck, ME	N.S. Rote
1990	Chicago, IL	N. Gleicher
1991	University of Virginia, Charlottesville, VA	J. Heff
1992	University of S. Carolina, Charleston, SC	S. Mathur
1993	Denver, CO[2]	J. Head
1994	Thomas Jefferson Univ, Philadelphia, PA	B. Smith
1995	Washington, DC[2]	C. Coulam
1996	University of Tennessee	D. Torry
1997	University of British Columbia	M. Stephenson
1998	Finch Univ of Health Science, Chicago, IL	K. Beaman
1999	Cooperstown, NY	S.P. Mathur
2000	University of Florida	P.J. Hansen
2001	Finch Univ of Health Science, Chicago, IL	J.Y.H. Kwak-Kim
2002	Finch Univ of Health Science, Chicago, IL	J.Y.H. Kwak-Kim
2003	Yale University, New Haven, CT	G. Mor
2004	Univ Southern IL, Saint Louis, MO	P. Ahlering
2005	Brown University, Providence, IL	S. Sharma
2006	Vanderbilt University, Nashville, TN	G. Yeaman
2007	McMaster University, Ontario, Canada	C. Kaushic
2008	Rush University, Chicago, IL	J. Lubosrky
2009	University of Florida, Gainesville, FL	P. Hansen
2010	Woodlands Resort, Farmington, PA	T. Ott
2011	Salt Lake City, UT	C.J. Davies
2012	Hamburg, Germany[3]	P. Arck
2013	Boston, MA[4]	C. Wira, S. Sharma, G. Mor
2014	Long Beach, NY	N. Hanna, R. Fichorova, J. Braverman
2015	Kingston, Ontario, Canada	C. Tayade
2016	Baltimore, Maryland	S. Sharma, I. Burd
2017	Chicago, Illinois	A. Barua, M. Bradaric, J. Kwak-Kim

[1] Held jointly with the International Society for Immunology of Reproduction
[2] Held jointly with the American Association of Immunologists
[3] Held jointly with the European Society for Reproductive Immunology
[4] Held jointly with the International Society for Immunology of Reproduction

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Rosalind Franklin University of Medicine and Science
Meeting Co-Chair

INVITED TALKS (as they appear in the agenda)

S1

Insights into the mechanisms of infection-induced preterm labor in the mouse model: a surprising role for surfactant protein A (SP-A)

Emmet Hirsch, MD, University of Chicago, Chicago, IL

Murine models have long been used to study preterm labor, a phenomenon that occurs in nature only rarely outside of the human species. Novel insights into the roles of distribution and function of leukocytes, inflammatory signaling, progesterone receptors and other crucial factors and processes have been generated with these models. In this presentation, we will focus on infection and inflammation in pregnancy and their role in parturition. The important distinctions between infectious and non-infectious inducers of labor will be highlighted. The fascinating and contradictory findings related to surfactant protein A (SP-A), a lung collection, will be reviewed, as will new findings related to SP-A's mechanisms of action.

S2

Mechanisms of host defense in the amniotic cavity of women with intra-amniotic infection

Authors: Nardhy Gomez-Lopez[1-3], Roberto Romero[1,4-6], Yi Xu[1,2], Valeria Garcia-Flores[1,2], Yaozhu Leng[1,2], Derek Miller[1-3], Sonia Hassan[1,2], Suzanne Jacques[1,2]

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[7]CINVESTAV, Mexico City, MEX

Intra-amniotic infection is a major cause of spontaneous premature labor and delivery. Such infection occurs when microorganisms overwhelm the capacity of the host (i.e. the mother) to defend itself, which results in microbial invasion of the amniotic cavity. Intra-amniotic infection is characterized by an influx of neutrophils, thought to be of fetal origin, into the amniotic cavity. The functions of these innate immune cells in the mechanisms of host defense against intra-amniotic infection, however, were poorly understood. We have carried out a series of studies that focus on the characterization of the phenotype and origin of amniotic fluid neutrophils as well as their functions in the mechanisms of host defense in the amniotic cavity of women with intra-amniotic infection. Our studies have shown that amniotic fluid neutrophils: 1) express specific cytokines, which are different to those expressed by other innate immune cells (i.e. monocytes), in the amniotic cavity of women with intra-amniotic infection; 2) can perform phagocytosis, a primary mechanism for microbial killing, of bacteria found in the amniotic cavity of women with intra-amniotic infection (e.g. *Streptococcus agalactiae*, *Ureaplasma urealyticum*, *Gardnerella vaginalis*, and *Escherichia coli*); 3) can form neutrophil extracellular traps (NETs) as a final containment effort to kill microbes invading the amniotic cavity of women with intra-amniotic infection; and 4) are mostly of fetal origin in women with intra-amniotic infection and/or inflammation who delivered at extremely preterm gestations, and predominantly of maternal origin in women with intra-amniotic infection who delivered at term or during late preterm gestations. Yet, amniotic fluid neutrophils of maternal and fetal origin can co-exist in the amniotic cavity of women with intra-amniotic infection and/or inflammation throughout the second and third trimester. Collectively, these data demonstrate that amniotic fluid neutrophils have an active role in the mechanisms of host defense against intra-amniotic infection, and can migrate from the fetal and/or the maternal vasculature into the amniotic cavity in order to combat such an infection.

Funding: This research was supported by the Perinatology Research Branch, Division of Intramural Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, and Wayne State University Perinatal Research Initiative.

S3

Inflammation, reproductive outcome, and the environment: an overview

Gary Loy, MD MPH. Rush University Medical College, Chicago, IL

Problem: Environmental exposures are associated with a variety of adverse maternal and perinatal outcomes. Adverse outcomes such as preterm labor and fetal growth restriction are recognized associations.

Method of Study: Evidence has been epidemiological and observational. Various inflammatory mechanisms have been proposed to explain these adverse outcomes in terms of inadequate or defective placental implantation and development, but the basic science investigation is young.

Results: The effects, and effect mechanism, is dependent on the context of the exposure and context of the patient. For example, in the context of air pollution, specifically particulate content of the air, the predominate effect is fetal growth restriction due to inflammation and oxidative stress. Since exposure is breathing in the particulates, the context includes patients' susceptibility to dosage and adaptive response. Susceptibility is dependent on broader community environment, individual experience, and possibly epigenetic factors.

Conclusions: In pregnancy, a precautionary principle approach is common, with the assumption that potential theoretical environmental risk should be avoided until proven safe. Speculation in the literature has included suggestions for mitigating the environmental exposure impact through dietary manipulation. Further basic science investigation of mechanisms of adverse effects and clinical studies of possible mitigating factors in at risk populations are anticipated.

S4

Effect of abnormal inflammation in the development of pregnancy complications and subsequent risk of cardiovascular disease in mothers and their offspring

CH Graham, T Cotechini, KT Kasawara, T Ushida, SK Macdonald-Goodfellow
Department of Biomedical and Molecular Sciences, Queen's University, Kingston, Canada

Problem: Pregnancy complications, such as preeclampsia (PE) and fetal growth restriction (FGR), are often associated with abnormal maternal inflammation and are linked to an increased risk of cardiovascular disease (CVD) for mothers and their offspring in later life. Our research aims to determine if abnormal inflammation during pregnancy is causally linked to the development of pregnancy complications and the associated increased risk of CVD in the affected mothers and their offspring.

Methods of Study: We developed a model in which inflammation in pregnant rats is induced by lipopolysaccharide (LPS) injections. We assessed hemodynamic parameters including blood pressure, utero-placental blood flow velocities, as well as evidence of proteinuria, placental histological alterations, and FGR. Potential beneficial effects of exercise were also determined. Some rats were allowed to deliver and were monitored, along with their offspring, for evidence of persistent epigenetic alterations in relevant organs and CVD risk factors. **Results:** Rats treated with LPS developed FGR and features of PE that were mediated by tumor necrosis factor alpha. Exercise prior to and during pregnancy attenuated LPS-induced inflammation and prevented FGR. Dams treated with LPS exhibited evidence of CVD risk factors, including left ventricular hypertrophy and elevated low-density lipoprotein, as well as histone modifications in relevant organs (heart and liver) that persisted for at least 16 weeks after delivery. Offspring of LPS-treated rats had evidence of mild cardiac dysfunction, anemia, and metabolic alterations at 24 weeks of age. **Conclusions:** These results provide evidence supporting the concept that aberrant inflammation in pregnancy causes pregnancy complications and increases the risk of CVD later in life in affected mothers and offspring. Abnormal inflammation in pregnancy may be a potential therapeutic target to mitigate subsequent risk of CVD in mothers and their children following PE/FGR. (Supported by the Canadian Institutes of Health Research; grant # MOP119496).

S5

Ultrasound imaging in early detection of pregnancy complication

Jacques S. Abramowicz, MD University of Chicago, Chicago IL

The placenta plays a pivotal role in the normal development of the pregnancy both very early and at later stages. The trophoblast invasion of the uterus must progress unimpaired as well as the transformation of the uterine spiral arteries from low capacity, high impedance vessels in the non-pregnant state to high capacity, low impedance vessels. Inadequate or abnormal implantation of the developing trophoblast appears to be the origin of various poor pregnancy outcomes, such as intrauterine growth restriction (IUGR), preterm labor and preeclampsia. In addition,

placental infection/inflammation is also thought to play a major role in complications such as pregnancy loss, IUGR and preterm labor[1,2], as clearly demonstrated in rats[3].
Ultrasound is, arguably, the most commonly used diagnostic procedure in obstetrics. It is convenient, painless, yields immediate, extensive results and is widely considered to be safe[4]. Imaging of the early gestation allows definition of exact location (when the question of an ectopic pregnancy arises), viability, early diagnosis of multiple gestations and accurate dating. Later in pregnancy, accurate follow-up of fetal growth, detection of fetal anomalies, placental location and implantation as well as cervical length are major indications. Regular 2D gray-scale imaging allows visualization of the various structures (placenta, fetus, yolk sac) and Doppler velocimetry permits functional analysis of various maternal (uterine arteries) and fetal (umbilical arteries and veins) vessels, involved in early implantation as well as later development. Signs of early pregnancy failure include abnormal implantation site, empty or abnormal gestational sac, abnormal velocity waveforms in the uterine arteries with elevated resistance, reflecting poor transformation of uterine vessels in low impedance vessels, and later in the umbilical arteries, mirroring abnormally increased resistance in the placental vasculature[5]. Measurement of the cervical length is an essential tool in the prediction of the presence of intraamniotic inflammation/infection, as etiology of preterm labor.

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4. Abramowicz JS: Prenatal exposure to ultrasound waves. Is there a risk? Ultrasound Obstet Gynecol 29:363-367, 2007.
5. Abramowicz JS, Sheiner E: In utero imaging of the placenta: importance in disorders of pregnancy. Placenta, 28 Suppl A:S14-22, 2007.

S6

Gestational Trophoblastic Disease (GTD)

Pincas Bitterman, MD, Department of Pathology, Rush University, Chicago, IL

Problem: Gestational trophoblastic disease includes several entities which cause significant complications during pregnancy or thereafter. When these conditions are not treated appropriately and in a timely fashion, they may lead to multiple gynecological problems an occasionally death
Method of Study: Information was generated by analyzing the common conditions and pathological features of gestational trophoblastic disease.
Results: Abnormalities during conception may lead to gestational trophoblastic disease.
Conclusion: Gestational trophoblastic disease encompasses several conditions during pregnancy. The Physician needs to consider these conditions in the differential diagnosis of abnormal gestations

S7

Recurrent pregnancy losses, etiology driven treatment

Sung-Ki Lee[1], Joon Cheol Park[2]
[1] Department of OB/GYN, Konyang University Hospital, Daejeon, Korea
[2] Department of OB/GYN, Keimyung University Dongsan Medical Center, Daegu, Korea

Recurrent pregnancy loss (RPL) is commonly defined as two or more spontaneous pregnancy losses. The prevalence of RPL ranges between 1% and 5% of couples in reproductive ages depending on its definition. Underlying mechanisms causing RPL are so complicated and still under investigation.
Systemic and comprehensive evaluation strategy is the initial step to overcome RPL. In terms of thrombophilia, we have to consider ethnic variation in prevalence of thrombophilic markers. Appropriate tests for alloimmune factor are another controversial issue. Efforts to apply effective diagnostic tests can reduce the proportion of idiopathic factor, which is known to reach about 50% of all RPL.
Lastly, it is essential to treat women with RPL based on their etiologies. Many of them are likely to have more than one abnormal findings through meticulous evaluation. Most physicians consider correction of all these abnormalities because we do not know which one is more important than others. According to recent data, immune modulation

with intravenous immunoglobulin G (IVIG) seems to be effective in RPL women with cellular immune abnormality, but not in idiopathic RPL.
In this lecture, we are going to review and discuss what we should test for women with RPL and how we treat them.

S8

Molecular testing of endometrial samples for women with impaired fertility Dambaeva S, Katukurundage D, Salazar MD, Skariah A, Gilman-Sachs A, Coulam C, Kwak-Kim J, Beaman K. Dept. of Microbiology & Immunology, Reproductive Medicine Center, Dept. of Obstetrics & Gynecology, Chicago Medical School at Rosalind Franklin University of Medicine and Science, North Chicago, IL.
Problem: Endometrial Immune Profile (EIP) is a test to evaluate the molecular immune profile of the lining of the uterus (endometrium) to see if it is properly prepared for a successful pregnancy [1]. Endometrial decidualization is accompanied by substantial recruitment of maternal immune cells with approximately 70% being natural killer (NK) cells. Women experiencing recurrent implantation failure (RIF) have been shown to have an excessive or low count of uterine NK cells and a dysregulation of endometrial levels of interleukin (IL)-15 and IL-18 as well as TWEAK (TNF weak inducer of apoptosis) and its receptor, Fn14 (fibroblast growth factor-inducible molecule) compared with fertile women. The objective of this study was to assess the EIP in patients suffering from recurrent pregnancy loss (RPL). In addition, the factors that are important for tissue homeostasis including serum glucocorticoid kinase 1 (SGK1), Notch pathway proteins and markers to evaluate NK (CD56, CD57, CD16a, CD16b (also expressed by neutrophils) and T cells (CD3e) were analyzed in RIF and RPL patients.
Design: EIP parameters and additional factors were evaluated in mid-luteal endometrium. Endometrial biopsy samples were obtained from women enrolled in the Reproductive Medicine Center because of unexplained recurrent pregnancy loss ($\geq$2 consecutive miscarriages) or recurrent implantation failure (history of $\geq$2 failed embryo transfers) and from control group consisted of healthy women in reproductive age with at least one successful pregnancy. **Materials and Methods:** mRNA was extracted from endometrial samples, converted into cDNA and analyzed by quantitative RT-PCR (qRT-PCR). **Results:** About 70% of patients revealed abnormal EIP. Over-activated EIP was detected in 54.5% of RIF patients and 51% of RPL patients. Low-activated EIP was more frequent among RPL patients: 23.5% versus 15.9% correspondingly. Low levels of CD56 were revealed in 21.6% of patients with RPL and only in 2.3% of RIF ($p=0.012$). CD16a, that is expressed by cytotoxic NK cells and not by uterine specific CD56bright NK cells was significantly higher among RPL compared to RIF patients. Samples from RIF, but not RPL patients, revealed decreased levels of SGK1 mRNA (27.3 versus 45.4, $p<0.001$). Increased presence of T cells was found to be associated with over-activated EIP and the lowest T cell presence was detected in low-activated EIP samples. All samples from patients revealed decreased expression of transcriptional repressor of Notch signaling pathway when compared with normal controls.
Conclusions: Molecular testing of endometrial samples for women with reproductive failures is important for evaluation of uterine receptivity and for proper therapeutic strategy [1]. Aberrant gene expression of endometrial derived factors was determined in RPL similar to RIF patients, while the set of factors can be used for differential diagnosis.

1. Ledee N et al. The uterine immune profile may help women with repeated unexplained embryo implantation failure after in vitro fertilization. AJRI 2016, 75:388-40

S9

Recurrent Implantation Failure

Carolyn Coulam, MD, Reproductive Medicine Institute, Chicago, IL
Recurrent implantation failure (RIF) is a major cause of failure to achieve pregnancy after IVF/ET. Effective treatment for recurrent implantation failure depends on the cause. The causes for RIF include embryonic abnormalities, reduced endometrial receptivity or multifactorial causes. The most common cause of an abnormal embryo is chromosomal abnormality. Overall, chromosomal abnormalities have been shown to account for up to 60% of embryos. Among women over the age of 40 years, chromosomal abnormalities have been found in over 80% of embryos. For the endometrium to be receptive for embryo implantation and placentation it must undergo a process of decidualization which includes secretory transformation of the endometrial cells, expression of specialized uterine natural killer cells, and vascular remodeling. After the embryo has implanted, placentation has to occur to allow normal pregnancy. Placentation involves differentiation of trophoblasts, invasion of extravillous trophoblasts, spiral artery remodeling and angiogenesis. Diagnostic tests available to identify causes for recurrent implantation failure include evaluation of the chromosome complement of the embryo (preimplantation genetic screening), immunologic risk factors, endometrial biopsy for genes that turn on and off during the “window of

implantation" and endometrial immune profile. The most frequently studied risk factors to identify an immunologic risk factor associated with recurrent implantation failure have included the presence of circulating antiphospholipid antibodies (APA) and elevated natural killer (NK) cells. Endometrial biopsy for endometrial immune profile (EIP) evaluates the ratio of IL-15/Fn-14 mRNA and IL-18/TWEAK mRNA. Interpretation of the EIP includes: Overactive (elevated ratio of IL-18/TWEAK), Underactive (low ratio of IL-15/Fn-14) and Normal results. Treatment of each of these risk factors can be different. Thus, before effective treatment can be instituted, the cause of reproductive failure must be determined and treated specifically.

S10

How to manage repeated implantation failure

George O. Ndukwe, Zita West Assisted Fertility Clinic, London, United Kingdom

Problem: There is a unique immune tolerance that allows a fetus which is a semi-allograft to remain and thrive in a woman's uterus in a successful pregnancy. If there is an abnormality in this process successful implantation may fail to occur. The question is what these abnormalities might be, whether they can be investigated and if so whether there is effective treatment to optimise the chances of a successful implantation and pregnancy. Method: Women with 3 or more failed IVF cycles in which1 or 2 good quality embryos were transferred were investigated. They all had peripheral NK assay, TH1/TH2 intracellular cytokine ratios and more recently endometrial immune profiling (level 2 tests) in addition to other tests(level 1 tests). The abnormalities were treated variously with IVIg, Humira, Intralipids and G-CSF (Neupogen). They were compared with a historical cohort of women who had the abnormalities but declined immunomodulation. Although this was not a prospective randomised controlled study (which we have found difficult in this area), this is the nearest we have come to any form of control.
Results: We found significant improvement in implantation with all immunomodulatory treatment compared to women who declined treatment. Appropriate immunomodulation can only be chosen after appropriate investigations. There is no place for empiric treatment. I will share the data we have during my talk.
Conclusion: Appropriate immunomodulation chosen after appropriate immune tests seem to improve implantation rates and pregnancy outcome. Tremendous amount of controversy exists in reproductive immunology and what is needed is for the basic scientists to continue research and come up with universally accepted panel of tests for recurrent implantation failure/miscarriage. Clinical research should then seek to find appropriate treatment that is universally accepted.

S11

NIH grant application writing suggestions to new investigators

Koji Yoshinaga, PhD Director, National Institutes of Health, Bethesda, MD

S12

How to write a successful NIH application

Paul M. Carvey PhD, Departments of Physiology and Biophysics and Neurology, Rush University Medical Center, Chicago, IL

Exceptional science falls prey to poor grantsmanship. Many investigators feel that their science will carry the day, but unless explained correctly, it won't. The writer's job is therefore to provide the reviewer with all the needed information in a simple and straight forward fashion. There are structures for each of the sections that will be discussed in the lecture that meet what I feel are the most critical aspects of grantsmanship: 1- less is more; 2- keep it simple stupid; 3- never let the reviewer think; and finally, 4- beat them about the head with the obvious. Grantsmanship is not about demonstrating how smart you are; your science should convey that. Rather, it is about keeping your application sharply focused! If it is not absolutely central to your project, don't put it in (less is more). Anytime you raise a point, you must answer it so keep your application sharply focused. Codify your application to no more than 4 central issues the reviewer must understand to place your application in context (keep it simple). Never let the reviewer think means that you must anticipate what the reviewer will be thinking and then answer it for them. If they are thinking, they may be thinking differently from you. Take these 3-4 central points that are critical to your concept and reiterate them in different language again and again (beat them about the head with the obvious). It is critical that they understand these 3-4 critical points if you are to be funded. This presentation will utilize these four fundamental principles and then use them within the algorithms that are commonly used by

successful investigators for each of the four main sections of an application. The presentation will conclude with a brief discussion of strategies for training applications and program projects.

S13

Think About the Link®: A case study of a U.S. based campaign tackling public awareness of certain virally-induced cancers.

Jan Bresch, *Executive Vice President & Chief Operating Officer*, Prevent Cancer Foundation

Research has revealed direct ties between viruses and some cancers. In response, the Prevent Cancer Foundation launched a multi-year, multi-disease prevention education and awareness campaign focused on three viruses linked to cancer: the human papillomavirus (HPV), hepatitis B and hepatitis C.

The campaign, *Think About the Link*®, aims to increase screening for all three viruses, raise vaccination rates for HPV and hepatitis B, and raise awareness of treatment options available for hepatitis B and hepatitis C. *Think About the Link*® falls directly within the Foundation's mission to save lives through cancer prevention and early detection across all populations.

In its first year, *Think About the Link*® was successful in increasing awareness of viruses and their links to cancer across the United States.

Over the next year, *Think About the Link*® will conduct national and segmented outreach with a particular focus on minority populations disproportionately affected by one or more of the viruses and/or related cancers, including African-Americans, Asian-Americans and Hispanics. Our outreach includes conducting health fairs, distributing tailored educational materials, as well as an ad and public service campaign featuring celebrity spokespeople. We will also reach out to health care providers and parents to help increase screening rates.

S14

The Implications for Activating Receptor Expression on Cervical Natural Killer Cells and their Ability to Respond to HIV-infected

Edward Barker, Department of Immunology/Microbiology, Rush University Medical College, Chicago, IL

The most common form of HIV transmission worldwide is through heterosexual contact. Hence, understanding the immune response to HIV during the initial stages of infection may be key to keeping infection under control until the adaptive immune response has been adequately primed to clear the virus. Natural killer (NK) cells, a component of the innate immune system, are a cytotoxic cell population that recognize and respond to virally infected cells following the interaction of activating receptors on the NK and their ligands on the target cells. Thus, it is important to determine which receptors are expressed on NK cells from the female reproductive tract. To date, almost all NK cell studies in regards to receptor expression have been done on peripheral blood NK cells. Preliminary investigation indicates that the NK cells in the cervix differ from peripheral blood NK cells in their expression of activating receptors. Cervical NK's are shown to express the activation receptor NKp44 whereas NK cells derived from the blood lack it. However, NKG2D, a prominent NK activating receptor found on all peripheral blood NK cells is missing on NK's from the cervix. HIV-1-infected $CD4^+$ T-cells express ULBP-1 and -2 which are ligands for the receptor NKG2D but lack expression of NKp44 ligands due to down-modulation by the HIV-1 protein Nef. Taken in combination, it does not appear that cervical NK cells are capable of lysing HIV-infected cells in the cervix.

S15

Conversion of Natural Killer cell phenotype and function in highly vascular tumors

Andrew Wilber[1,3] and Donald S. Torry[1,2,3]

[1]Department of Medical Microbiology, Immunology and Cell Biology, [2]Department of Obstetrics and Gynecology, [3]Simmons Cancer Institute, Southern Illinois University School of Medicine, Springfield, IL 62702

Problem: Large influxes of NK cells are found in advanced tumors, which is inconsistent with normal NK function in immune surveillance and tumor destruction. NK cells with non-classical CD phenotypes ($CD56^+CD16^{dim\text{-}neg}$), termed decidua-NK (dNK), accumulate at the maternal-fetal interface during implantation. These dNK are poorly cytotoxic, pro-angiogenic and facilitate placentation. Similarities between embryo implantation and tumor growth exist including increased: TGF, vascularity, NK localization, and pro-angiogenic gene products. Therefore, we hypothesized that an analogous shift to dNK phenotype and function occurs in highly vascular tumors.

Methods: NK cells were isolated from peripheral blood (pNK) and resected tumor tissue (tNK) of renal cell cancer (RCC) patients (n=6) or healthy donors (HD, n=5). Flow cytometry identified NK cells ($CD45^+/CD3^{neg}/CD56^+$) and CD16 expression. Cytotoxic activity was measured using human K562 cells as targets. Angiogenic and inflammatory gene expression profiles characterizing pNK and tNK cells were identified by RT-qPCR array and results compared to microarray data for bona fide dNK cells.
Results: pNK were uniformly $CD56^+CD16^{bright}$ (HD: 94±2%) and (RCC: 89±2%). Cytotoxic activity was, however, significantly reduced for RCC pNK. RCC tNK cells were significantly enriched for $CD56^+CD16^{dim\text{-}neg}$ cells (48±12%; $P \leq 0.02$), a phenotype of dNK cells. Forty four of 79 tested genes were increased ≥5-fold for RCC tNK versus RCC pNK populations. Analyses revealed a shared genetic signature between RCC tNK and dNK consisting of 5 genes involved in angiogenesis (VEGF-A, VEGF-B, CCR7) and immunosuppression (IL8, CXCL1).
Conclusions: These studies confirm conversion of pNK cells to a dNK-like phenotype in tumors. These characteristics are conceivably beneficial for placentation, but exploited to support tumor growth and metastasis. Further characterization of tNK cells could lead to novel treatments for cancer.
Supported by National Institute of Child Health and Human Development (R15HD073868; D.S.T.) and
National Cancer Institute (R15CA173657; D.S.T. and A.W.)

S16

What to Watch: Three Breakthroughs that May Change our Lives in the Next 10 Years

Teresa K. Woodruff, Ph.D.
The Thomas J. Watkins Professor of Obstetrics and Gynecology
Vice Chair for Research, Department of Obstetrics and Gynecology
Northwestern University, Chicago IL
https://www.woodrufflab.org

Facing a cancer diagnosis at any age is devastating. However, young cancer patients have the added burden that life-preserving cancer treatments, including surgery, chemotherapy, and radiotherapy, may compromise their future fertility. The possibility of reproductive dysfunction as a consequence of cancer treatment has a negative impact on the quality of life of cancer survivors. The field of oncofertility, which merges the clinical specialties of oncology and reproductive endocrinology, was developed to explore and expand fertility preservation options and to better manage the reproductive status of cancer patients. Fertility preservation for females has proved to be a particular challenge because mature female gametes are rare and difficult to acquire, but combined with cutting edge techniques and government policies, the next 10 years could hold more promise for reproductive science.

S17

Immunological consequences of diabesity at the maternal-fetal interface

David M Aronoff[1]
[1]Department of Medicine, Department of Pathology, Microbiology and Immunology, Vanderbilt University Medical Center, Nashville, TN, USA

Problem: There is an increasing prevalence of metabolic disorders during pregnancy, including the combination of obesity and diabetes (diabesity). The developmental origins of health and disease (DOHaD) frame posits that exposure of the fetus to stressors during gestation impacts the risk for disease across the life course of the offspring. Diabesity increases the risk for cardiovascular, neurological and metabolic disorders of offspring but the mechanisms of risk transmission are not well defined. Our research team has been applying multidisciplinary approaches to define the impact of diabesity on placental and fetal immunology and biology.
Method of Study: For this oral presentation we bring together new evidence supporting a role for diabesity driving inflammatory changes in the gravid uterus. We utilized a mouse model of diabesity to explore the impact of metabolic stress on fetal brain gene expression, including the circumstance where a mother with diabesity is threatened by an infection (modeled with exposure to the TLR3 ligand poly(I:C)). We inspected human placentae from women with gestational diabetes or healthy controls to assess for alterations in macrophage abundance and distribution. Human placental macrophages were subjected *in vitro* to metabolic stress modeling diabesity and the impact of this stress on gene expression, cell viability and inflammatory activation were assessed.
Results: Diabesity impacts fetal brain development and there are compounding effects in the presence of maternal immune activation. Studies of the impact of these stressors on placental gene expression are ongoing. Investigations

of the human placenta in the setting of hyperglycemia are also ongoing. *In vitro*, human placental macrophages are activated by the saturated fatty acid palmitate to undergo apoptosis and activate the caspase-1 inflammasome. **Conclusions**: Diabesity has profound effects on placental immune cell activation and fetal organ gene expression that might contribute to postpartum risk for disease in offspring. More studies are warranted.

S18

Epigenetics, steroids, immune function and endometriosis

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Uterine tissue stem cells play central roles in the development of the two most common uterine disorders: endometriosis and uterine fibroids. The presence of ectopic endometrial tissue on pelvic organs seems to be the key feature of endometriosis. Endometriosis responds to fluctuations in estrogen and progesterone by growth and inflammation leading to pain aggravated by menses. It was proposed that pelvic endometriosis primarily originate from retrograde menstruation of a critical number of eutopic endometrial cells with progenitor/stem characteristics. This postulate is supported by the molecular defects found in ectopic endometriotic tissue. Genomewide differences in CpG methylation between eutopic endometrial and endometriotic stromal cells are present. Defective CpG methylation affecting a number of genes that encode key transcription factors such as GATA6, SF1 and estrogen receptor- in endometriosis give rise to overproduction of local estrogen and prostaglandins, suppression of progesterone receptor (PR) and altered immune function. Eutopic endometrium of patients with endometriosis contains nerve fibers and abnormal gene expression compared with eutopic endometrium of disease-free women. These data are collectively suggestive of the presence of abnormal progenitor/stem cells with defective epigenetic programming in eutopic endometrium giving rise to inappropriate differentiation (e.g., nerve cells and macrophages) and abnormal mRNA or protein expression (e.g., steroidogenic enzymes and transcription factors). If these cells implant on peritoneal surfaces via retrograde menstruation, they likely start the disease process of endometriosis. Thus far, no distinct germ cell or somatic mutations were discovered in endometriosis; genomic variation between the eutopic and ectopic tissue remained limited to possible polymorphisms. In summary, genome-wide epigenetic defects in DNA perturb expression of key genes regulating estrogen and prostaglandin overproduction, progesterone resistance and immune function in endometriosis. Estrogen clearly stimulates cell survival and inflammation in endometriosis

S19

Omega-3 polyunsaturated fatty acids and preterm birth

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Problem: Lipid mediators are the lipid metabolites that act as intercellular signaling molecules with various bioactivities. Recently, omega 3 poly-unsaturated fatty acids (PUFAs) have been noted as new lipid mediators. PUFA is named by the site of the first carbon atom with a double bond (C=C) from omega-end. Omega-3 PUFAs including eicosapentaenoic acid（EPA） and docosahexaenoic acid（DHA）have anti-inflammatory effects, whereas omega-6 PUFAs such as arachidonic acid (AA) have pro-inflammatory effects. Preterm birth is an important obstetrical complication and one of its main causes is known to be inflammation. The objective of this study is to examine the preventive effect of omega-3 PUFAs against preterm birth and to clarify its mechanism.
Method of Study: We performed the experiments using fat-1 mice, capable of converting omega-6 PUFAs to omega-3 PUFAs. We identified the candidate agent for preterm birth by comprehensive metabolomic assessments of lipid metabolites and examined the preventive effect of the metabolites.
Results: The incidence of preterm birth induced by lipopolysaccharide (LPS) was decreased in fat-1 mice with abundance of omega-3 PUFAs. Expression of pro-inflammatory cytokines and macrophage infiltration into the cervix was reduced in fat-1 mice. The analysis of lipid metabolomics showed high level of 18-hydroxyeicosapentaenoate derived from EPA in fat-1 mice, which was a biochemical precursor of anti-inflammatory product, resolvin. The administration of resolvin to LPS-treated pregnant wild type mice decreased the incidence of preterm birth.
Conclusions: Our data suggest that resolvin could be a potential new therapeutic agent for the prevention of preterm birth. (Ref: Yamashita A, et al. Sci Rep 2013; 3: 3113.)

S20

Targeting Toll-like receptor-4 (TLR4) to tackle preterm birth

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Problem: Inflammatory activation is a major driver of preterm birth and neonatal morbidity. Current tocolytic agents target late events in the birth cascade, and have limited efficacy. TLR4 acts to sense and integrate a range of infectious and sterile pro-inflammatory triggers mediators released after tissue damage. We hypothesized that targeting TLR4, as a rate-limiting trigger at the apex of the birth cascade, would be effective for suppressing preterm birth.
Method of study: Mouse models of preterm birth involving intraperitoneal or in utero administration on GD16.5 of bacterial mimetic lipopolysaccharide (LPS), heat-killed E.coli or the TLR4-dependent pro-inflammatory lipid platelet activating factor (PAF) were utilised, with or without co-administration of novel small molecule antagonists of TLR4 signalling (+)-naloxone and (+)-naltrexone at 12 h intervals for 72 h. Late gestation and neonatal parameters including fetal loss at GD18.5, or time of birth and pup viability through the post-natal phase, plus developmental trajectory into adulthood, were measured. Cytokine expression was determined by qPCR in maternal, placental and fetal tissues.
Results: (+)-naloxone and (+)-naltrexone are both highly effective in preventing preterm birth induced by LPS, heat-killed *E. coli* or PAF. Expression of cytokines induced by inflammatory stimuli including *Tnf*, *Il1b*, *Il6* and *Il10*, in decidua, placenta, amniotic membranes and fetal brain, is suppressed by TLR4 antagonists. Offspring born after exposure to TLR4 inhibitors in utero develop normally into adulthood and are protected from inflammatory injury elicited by LPS challenge.
Conclusions: Our data implicate TLR4 as a key point-of-convergence through which a range of infectious and sterile agents can activate and accelerate the parturition cascade, and demonstrate that inhibition of TLR4 signaling using novel small molecule inhibitors is effective in suppressing preterm birth and promoting fetal viability in mouse models utilizing TLR4-dependent triggers. TLR4 is therefore an attractive pharmacological target for new preterm birth therapeutics.

S21

Ex vivo human placenta perfusion: from drug testing to microchimerism

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The human placenta offers the unique opportunity to study functions of a vital and complex human organ. The placenta can be obtained immediately after delivery with a ischemia period of only 20 minutes. It can be used for isolation of different cell types, including immune cells, endothelial cells or trophoblast cells. Alternative placenta explants can be used to avoid isolation stress and to maintain physiological tissue composition. The ex vivo placenta perfusion additionally takes advantage of the intact vessels and membranes. The maternal and fetal circulation can be simulated and bidirectional transfer or accumulation of substances, such as potential toxicants, drugs, biologicals, environmental or nutritional factors can be assessed. We have also used our placenta perfusion system for testing of homing and transfer of lymphocytes. Lymphocytes can be intracellularly stained before being perfused through the maternal circulation and detected by immunohistochemistry after up to 4 hours of perfusion. In such settings, we have found leukemia T cells in the fetal villi and vessels. Subsequently, we have perfused stained autologous maternal lymphocytes and counterstained them for discrimination of CD4, CD8 and CD16 positive cells. All subtypes could be found in fetal tissue.

S22

Sperm retention and release from the porcine oviduct reservoir prior to fertilization

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Problem: In many vertebrates, females store sperm received at mating in specialized reservoirs until fertilization. In mammals, sperm pass through the utero-tubal junction and bind to epithelial cells of the oviduct isthmus to form a reservoir. This reservoir regulates sperm function, viability and capacitation, ultimately affecting sperm lifespan. Despite the importance of the interaction of sperm with the oviduct, there are conflicting data about how sperm are stored and released.
Methods of Study: We used aggregates of porcine oviduct cells, purified soluble and immobilized glycans and porcine sperm to study sperm binding and release in vitro.

Results: Based on initial work describing the function of oviduct glycans in binding and retaining sperm in the oviduct, we screened 377 glycans and demonstrated that porcine sperm had exquisite glycan-binding specificity; only two oviduct glycan motifs could tether sperm. All glycans that bound sperm contained either a Lewis X trisaccharide or a branched structure with 6-sialylated lactosamine termini, structures abundant on *N*-linked oviduct glycoproteins. Both glycans bound to the acrosomal region of the sperm and binding was decreased after capacitation, consistent with the affinity reduction of capacitated sperm for oviduct cells. A proteomic approach was used to identify receptors for each glycan and several candidates are under evaluation. After being coupled to beads, both glycans retained their ability to bind sperm and, like the isthmus, lengthened sperm lifespan. This may be accomplished by the ability of each glycan to suppress influx of Ca^{2+} into sperm during capacitation. Sperm release from oviduct cells or immobilized glycans was promoted by progesterone and required CatSper channels. Release was also triggered by secretions from oocyte-cumulus complexes.
Conclusions:
These results help explain how sperm are retained in and released from the oviduct reservoir, allowing reproduction in species in which semen deposition and ovulation are not always synchronized.

S23

Possible Molecular Mechanism for Infertility in Women caused by Sperm Immobilizing Antibody (SI-Ab)

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【Problem】 There are many immunological methods by which to detect anti-sperm antibody (ASA) for clinical and research purposes. Among them we previously showed that complement-dependent sperm-immobilizing antibodies (SI-Abs) detected by sperm immobilization test (SIT) (Isojima method) were correlated to infertility. This is because in SIT live sperm motility is impaired by the complement activation induced by the antigen-antibody complex formed in the sperm membrane. This study was designed to examine and clarify details of the mechanism.

【Method of Study】 A monoclonal antibody (named H6-3C4) was established from an infertile patient's peripheral blood lymphocytes by a hybridoma method. H6-3C4 showed a high SI-Ab titer. The reacting antigen was partially purified by preparative SDS-PSGE. To analyze biochemical properties of the antigen, histochemical analysis, two dimensional western blotting, carbohydrate analysis and immunoprecipitation were carried out.

【Results】 Histochemical analysis revealed that the molecule reactive to H6-3C4 was localized in ejaculated sperm and male reproductive tissues (mrt), mainly cauda epididymis. mrt-CD52 comprises a core peptide identical to lymphocyte CD52 and a carbohydrate portion with a unique structure. The molecular mass is distributed around 15-23 kDa. The epitope was the N-linked carbohydrate of mrt-CD52. Immunoprecipitation analysis showed that mrt-CD52 bound to C1q, which is a component of a classical pathway of complement.

【Conclusions】 These results indicated that in female reproductive tracts mrt-CD52 suppresses the complement activation mediated by C1q. When ordinary ASAs bind to the sperm, nothing happens because mrt-CD52 suppresses the complement system. However, when mrt-CD52 is directly interfered with by an antibody like H6-3C4, the complement system is activated, resulting in sperm impairment. This is the reason that SI-Abs are closely correlated to infertility.

S24

Tumor Immunology and Reproduction: Reprogramming T cells and Hematopoietic Stem Cells for Adoptive Immunotherapy of Relapsed Ovarian Cancer

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The goal of our studies is to generate robust and long-lasting tumor-specific T cell responses for durable tumor regression in patients with epithelial ovarian cancer (EOC). While the majority of women with advanced stage EOC initially respond to surgery and first-line chemotherapy, more than 70% of patients eventually die of recurrent disease within 5 years of diagnosis. In an effort to generate tumor-associated antigen (TAA) specific T cells for the treatment of EOC patients, our team has identified NY-ESO-1 as the prototypic TAA for immunotherapy in ovarian cancer. In clinical trials of cancer vaccines conducted by our group, although active immunization targeting NY-ESO-1 can generate TAA specific effector T cells, the long term control of ovarian cancer is infrequent. This is primarily because of the relatively low magnitude and short *in vivo* lifespan of the vaccine-elicited T cells limited long-term tumor control in the patients. Consequently, we have focused on genetically re-engineering T cells to express a NY-ESO-1 specific CD8+ T cell receptor (CD8TCR), followed by adoptive transfer of these cells into EOC patients. Although this approach can lead to large numbers of circulating tumor antigen specific T cells and

tumor regression, the strategy is hampered by the relatively short lifespan of the effector $CD8^+$ T cells. These results indicate that lack of sustained expansion of long lasting, durable tumor specific T cells is a major obstacle for successful immunotherapy

In preliminary studies, we have focused on CD4+ T cells as the major driver of anti-tumor immunity. In order to augment the *in vivo* persistence of engineered CD8TCR cells, we have cloned a distinct subset of human CD4+ Th1 cells that directly recognize NY-ESO-1 naturally presented by MHC class II on cancer cells. In addition, these tumor-recognizing CD4+ T cells (TR-CD4TCR) potently provide help to CD8TCR cells in an antigen-presenting cell (APC) independent fashion and amplify the anti-tumor effects of CD8+ T cells. In contrast, their conventional TAA-specific $CD4^+$Th1 counterparts (non-tumor recognizing, NTR-CD4), require APCs for their activation. Direct cognate interaction between TR-CD4 and cancer cells triggers the release of an array of effector molecules which inhibit tumor growth and amplify the anti-tumor effects of $CD8^+$ T cells. We have also demonstrated that human hematopoietic stem/progenitor cells (hHSC) can be genetically re-programmed for continuous generation of long lived tumor-specific T cells in an NSG mouse model. We propose that TR-CD4TCR engineered hHSCs will provide a durable (possibly lifelong) *in vivo* supply of mature TR-CD4TCR cells with anti-tumor activity and sustained help to CD8TCR effector T cells, thereby leading to long-lasting tumor rejection in patients with EOC. Published and unpublished preclinical data will be presented; that would support a clinical trial that would launch in Q4 2017.

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S25

Metformin treatment may enhance anti-tumor immunity against ovarian cancer

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Problem: The lack of an effective early detection test, aggressive growth rate and frequent recurrence are the main causes of high rate of death of OVCA patients. Although the immune system responds to a developing tumor, the tumor develops mechanism for evasion of anti-tumor immunity. Thus, enhancing anti-tumor immunity may be a potential option to prevent OVCA progression and recurrence. Repurposing of drugs has shown promise against various malignancies. Metformin, an anti-type-2 diabetic drug, is one of such options. The goal of this pilot study was to examine whether metformin treatment enhances anti-tumor immune function and to determine molecular mechanisms of metformin induced anti-tumor immunity. **Method of study:** Archived ovarian normal or tumor tissues from patients treated with or without metformin were examined for the localization of M1 (anti-tumor) and M2 (pro-tumor) macrophages and CD8+ T cells. Changes in expression of tumor-associated molecular markers including HIF-1, AKT and mTOR were also studied. Differences in the frequency of immune cells and intensity of expression of molecular markers between the metformin-treated and untreated groups were determined. **Results:** The frequency of M1 macrophages was lower than M2 in untreated ovarian tumors. In contrast, the frequency of M1 macrophages was significantly higher than that of M2 macrophages in metformin treated tumors. Similarly, compared with untreated tumors more CD8+ T cells were observed to infiltrate into the tumor in patients received metformin. Furthermore, compared with untreated, the expression of HIF-1, AKT and mTOR was lower in ovarian tumors in metformin treated patients . **Conclusion:** The results of this study suggest that increased infiltration of CD8+ T cells reduced population of M2 macrophages in the ovarian tumors may be associated with metformin treatment. This enhancement in anti-tumor immune function by metformin may be associated with the reduced expression of tumor-associated changes in molecular markers.

S26

High levels of FSH-associated chronic stress during aging may lead to ovarian cancer development

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Problem: Emerging information suggests that imbalance in gonadotrophins and steroid hormone may increase the risk of ovarian cancer (OVCA), a fatal malignancy with high incidence in postmenopausal women. Menopause is associated with chronic high levels of circulatory follicle stimulating hormone (FSH). However, it is unknown if chronic high level of FSH may be associated with ovarian malignant development. The goal of this study was to examine (1) whether high level of FSHR expression in postmenopausal women is associated with OVCA development and progression, and (2) if long exposure to high level of FSH leads to chronic stress in the ovary, a

potential risk factor for malignant development. **Method of Study**: Ovarian tissues (n=7) from postmenopausal healthy subjects of different age-groups (>55-80 years), BRCA1+ subjects (n=5) and malignant serous ovarian tumors at early (n=5) and late (n=10) stages were examined for FSHR and glucose regulated protein 78 (a marker of endoplasmic reticular stress and DNA damage) expression. In addition, to explore possible mechanism(s) of FSH associated OVCA development, expression of other stress-related markers were also examined. **Results:** The intensity of FSHR and GRP78 expression increased significantly in association with ovarian aging in postmenopausal subjects and was highest in OVCA patients. Expression of GRP78 was positively correlated with the increased FSHR expression suggesting the prevalence of chronic stress in the postmenopausal normal and tumor bearing ovaries. These observations were confirmed by proteomic and gene expression analysis. Prevalence of similar molecular changes were also observed in ovaries with risk of OVCA development (BRCA+).
Conclusion: The results of this study suggest that increased expression of FSHR was associated with chronic cellular stress in menopausal ovaries. Chronic unresolved cellular stress may be a risk factor for OVCA development during aging. *Support*: R01 CA210370-01.

S27

Colony stimulating factor 2 - not just a cytokine but an embryokine as well!

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Problem: Although the embryo can develop autonomously in culture, the resultant patterns of development can be disrupted. Molecules produced by the female reproductive tract that act on the embryo to modify its development are termed embryokines. Many embryokines also function in the immune system, suggesting that alterations in immune function could affect developmental competence of the embryo. One example of this kind of embryokine is colony stimulating factor 2 (CSF2).
Method of Study: Review of the Literature.
Results: In both cattle and humans, treatment of in vitro produced embryos with CSF2 can increase the probability for establishment of pregnancy when the embryo is transferred to a female recipient. This increase in embryo competence is associated with changes in gene expression at the blastocyst stage in cow and humans and increased resistance of the embryo to induction of apoptosis in cows. Evidence in cattle is indicative that effects of CSF2 differ between male and female embryos. Thus, for example, CSF2 was reported to increase the percent of embryos becoming blastocysts in females but not males. Experiments with cattle also indicate that, at least for female embryos, CSF2 can program embryonic development to have long-term effects on the fetus and offspring. CSF2 treatment from Day 5-7 of development altered morphometry and gene expression in fetuses at Day 86 of gestation. Heifer calves derived from CSF2-treated embryos grew faster after 3 month of age than heifers from control embryos.
Conclusions: CSF2 is an important maternal regulator of embryonic survival and developmental programming. Often, the phenomenon of developmental programming can be sexually dimorphic – consequences for male offspring are different than for female offspring. CSF2 is a good candidate for mediating this type of developmental programming when occurring in the preimplantation period because actions on the embryo depend on sex.

S28

Nutritional intervention with anti-oxidant/anti-inflammatory diets for prevention of ovarian cancer in the laying hen

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Ovarian cancer is a lethal disease with poor prognosis due to the late stage at which it is usually detected. Research has been hampered by lack of suitable animal models. With the exception of the laying hen, no other accessible animal model recapitulates the human disease—hens get ovarian cancer spontaneously, present with same gross and histological pathology, and provide feasible model for conducting large scale dietary interventions. Flaxseed is the richest vegetable source of the potent anti-inflammatory omega-3 polyunsaturated fats (OM3) in the germ and the phytoestrogen lignan secoisolariciresinol diglucoside (SDG) in the hull. Cancer-prone old laying hens were fed a diet enriched with flaxseed for one year and we observed a significant reduction in ovarian cancer severity, but not a reduction in ovarian cancer incidence. However, a significant decrease in the incidence of ovarian cancer, as well as severity, was seen when hens were provided flaxseed throughout their whole egg laying life. We hypothesize that the two biologically active constituents of flaxseed work in concert to reduce the incidence and severity of ovarian cancer resulting in suppression and prevention of this deadly disease. Feeding hens specific diets enriched with the individual components of flaxseed (OM3, SDG) vs. OM6 (corn oil) provides insight into their separable

actions. OM3 enriched diets reduce systemic oxidative stress while OM6 caused an increase in systemic oxidative stress. The reduction in cancer severity and incidence was correlated to a reduction in cyclooxygenase (COX) enzymes and prostaglandin E2 (PGE2). The phytoestrogen lignan SDG reduced pro-proliferative estrogen signaling and estrogen mediated genotoxicity, contributing to the preventative effects. Whole flaxseed and SDG, but not OM3, cause the production of the estrogen metabolite 2-methoxyestradiol (2-ME) which has potent anti-cancer actions including promoting apoptosis specifically in ovarian tumors and inhibiting angiogenesis, providing the foundation for developing new targeted therapeutics for ovarian cancer. Research on dietary intervention not only provides development of therapeutic modalities, but provides new insights into basic biology of ovarian cancer. These studies provide the foundation for a flax meal-based clinical trial on progression-free remission in ovarian cancer. {NIH/NCCAM AT005295 and NIH/NCI CA162511}

S29

Role of Immune Cell Aberration on Metabolic and Ovarian Dysfunction in Polycystic Ovary Syndrome

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S30

Androgen and PCOS: dysregulation at the reproductive-metabolic-immunologic interphase

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Problem: Polycystic ovarian syndrome (PCOS) is a heterogeneous syndrome affecting 10% of women in reproductive age and accounts for 75% of anovulatory infertility. It is associated with hyperandrogenemia, chronic inflammation and antral follicle growth arrest. Macrophages play key role in inflammation and the balance between M1 (inflammatory) and M2 (anti-inflammatory) macrophages determines physiological/ pathological outcomes. 5α-dihydrotestosterone (DHT)-treated female rats exhibit similar phenotypes as in human PCOS, which include elevated levels of the adipokine chemerin, involved in chemotaxis and phagocytosis of macrophages expressing its receptor, CMKLR1. The molecular and cellular mechanisms involved in antral follicular growth arrest in PCOS are not well understood.

Method of Study: Using a DHT-treated rat PCOS model and human ovaries from PCOS and non-PCOS subjects, we have examined the hypothesis that hyperandrogenism alters M1 and M2 macrophage balance involved in follicle stage-specific, chemerin-dependent antral follicle arrest.

Results: DHT increased early antral follicles and unhealthy large antral follicles and resulted in the absence of pre-ovulatory follicles. These responses were accompanied by increased M1 but reduced M2 macrophages in antral and pre-ovulatory follicles, transient increase in ovarian CMKLR1+M1 macrophages and decreased inflammatory and resident CMKLR1+monocytes (localized primarily in unhealthy antral follicles) and migration of mononuclear cells towards chemerin-rich environment. Apoptosis was higher in pre-ovulatory follicles and coincident with ovarian macrophage imbalance. Macrophage-rich follicles (MΦ-RF) were present in DHT-treated but not in control ovaries. DHT increased the frequency of total M1 macrophages expressing CMKLR1 in MΦ-RF and exhibiting phagocytic-like morphology. In humans, chemerin was significant higher in follicular fluids but not in sera from non-obese PCOS subjects. While stromal M1 macrophage frequency was not different between PCOS and non-PCOS ovaries, a lower abundance of stromal M2 macrophages was evident in PCOS ovaries, resulting in higher M1/M2 ratio in the PCOS group. The abundance of stromal M1 macrophages expressing CMKLR1 is not different between PCOS and non-PCOS subjects.

Conclusion: Our results suggest that hyperandrogenemia influences the immunological niche of the ovary and may be important in PCOS pathophysiology. Increased chemerin expression in PCOS ovaries may regulate monocyte recruitment, macrophage polarization and follicle destiny. (Supported by CIHR: MOP-119381)

S31

Placental endotoxin tolerance mediated by exosomal miRNAs

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Although the intrauterine setting is considered to be a safe environment for the fetus, microbes have been detected in gestational tissues and amniotic fluid without induction of significant inflammation. Endotoxin tolerance is a phenomenon in which tissues or cells exposed to the bacterial product lipopolysaccharide (LPS) become less responsive to subsequent exposures, with decreased expression of pro-inflammatory mediators. Adaptation to repeated inflammatory stimulation may be critical in preventing rejection of the fetus by the maternal immune system and protecting the fetus from excessive maternal inflammatory responses to infectious agents. Failure to demonstrate attenuation of inflammatory responses has been reported to result in various pathologic pregnancies. However, to date, the exact mechanisms that contribute to the establishment and maintenance of tolerance at the maternal-fetal interface are not completely understood. There is now extensive evidence that miRNAs play important roles in maintenance of healthy pregnancy. miRNAs are not only found in cells but also in circulating extracellular vesicles (EVs) produced by various cells and tissues. Placenta is a known, abundant but also transient source of vesicles that include EVs. Thus our overriding hypothesis is that repeated exposure to infectious agents will induce a tolerant phenotype at the maternal-fetal interface mediated by specific microRNAs contained within placental EVs. Using placental explants culture model, our results indicate that immune tolerance to repeated endotoxin exposure is a true phenomenon in human placental explants. Furthermore, our results indicate that his reduced pro-inflammatory response to repeated LPS exposure is mediated by EVs secreted by placental trophoblasts that contain miR-146a, a microRNA previously shown to be involved in immune tolerance. We speculate that failure of mechanisms leading to endotoxin tolerance at the maternal-fetal interface will result in an exaggerated inflammatory reaction in response to repeated mild/moderate infections that can lead to preterm labor.

S32

Immune dysfunction in endometriosis

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Problem: Endometriosis characterized by the growth of endometrial tissue (normal uterine lining) outside of the uterus, is estimated to affect 8.5 million women and teens in North America alone, with 176 million more worldwide. The cause of endometriosis is largely unknown. The most widely accepted Sampson's theory of retrograde menstruation where endometrial tissue, sloughed off during menstruation, is refluxed into the fallopian tubes and peritoneal cavity, does not fully explain why only 5 to 10% of women develop endometriosis when retrograde menstruation occurs in 76-90% of women. While there is a consensus that endometriosis patients display spectrum of immune related issues but precise mechanisms are not yet identified.

Method of Study: Immune and inflammation transcriptomic analysis in ectopic endometriotic lesions and matched eutopic endometrium from patients and endometria of fertile women as controls using Nanostring nCounter GX Human Immunology V2 platform. Selected cytokines such as IL-17 and IL-33 were measured using ELISA in tissue and plasma samples from endometriosis patients compared to menstrual stage matched controls.

Results: Our global immune transcriptomic analysis revealed that endometriosis lesions have unique immune signatures for genes involved in inflammation. Importantly, eutopic endometrium of endometriosis patient displayed unique profile for genes involved in adhesion and implantation compared to fertile controls. Most strikingly, IL23-IL17 axis emerged as a major regulator (Th17 pathway) in endometriosis. Endometriosis patients had significantly elevated levels of IL-17 in plasma samples compared to controls. Post-surgical removal of endometriotic lesions led to significant decline in systemic levels of IL-17 suggesting endometriotic lesions as potential source.

Conclusions: Our studies provide insights into potential immune alterations in endometriosis and their contributions in the pathophysiology. More specifically, Th17 pathways is emerged as an important modulator of immune-angiogenesis axis in endometriosis.

S33

To build and protect: leveraging machine learning to decipher the composition and function of the decidual immunome

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Problem: Immune cells at the decidual maternal-fetal interface exert a key regulatory role in vascular remodeling, fetal tolerance, and protection from infection. While innate and T lymphoid cells with restricted and unconventional

receptor repertoires have been revealed to direct gut and lung mucosal immunity, their presence and population dynamics at the maternal-fetal interface remains elusive. To directly address this problem in human and mouse models, we have developed an experimental and computational workflow allowing operator-independent identification of all major decidual immune subsets from individual specimens.
Methods of study: Human and mouse decidua was homogenized into single-cell suspensions using automated mechanical and enzymatic methods. Mononuclear cells (MCs) were labeled using highly-multiplexed fluorescent panels and data acquired by flow cytometry. To deconvolute cellular composition, we employed dimensionality reduction by Barnes Hut-modified t-distributed Stochastic Neighbor Embedding (bht-SNE) and machine-learning aided density-based clustering (DenseVM). Functional responsive groups were identified using CITRUS (cluster identification, characterization, and regression) algorithm, and phenotype identity assigned by CellOntology package with secondary expert review.
Results: Human and mouse decidual immunome was defined by the experimental platform and revealed intriguing T and innate lymphoid cellular composition and dynamics specific to decidual immunome. In particular, expansion of unconventional effector-phenotype T cells, and ILC subsets with novel transcription factor profile were detected. Parallel examination of mouse and human decidua indicated similarities and differences in immunome composition, and the dynamics of murine immunome change across pregnancy.
Conclusion: Operator-independent machine-learning approach to analysis of high-content single-cell level data is a feasible means for discovery and monitoring of decidual immunity. Used in combination with advanced network-modeling approaches, we anticipate a wholesale reevaluation of pregnancy pathology and suggest actionable diagnostics and therapeutics.

S34

Uterine leiomyomas: the role of inflammation and effects on fertility

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Uterine leiomyomas (fibroids) represent the most common gynecological tumor of women, disrupt the functions of the uterus to cause excessive uterine bleeding, anemia, defective implantation, recurrent pregnancy loss, pelvic discomfort and urinary incontinence and may mimic or mask malignant tumors in millions of U.S. women at one time during their reproductive life. By age 50, nearly 70-80% of women bear at least one fibroid; 15 to 30% of these women develop severe symptoms. Uterine fibroids disproportionately affect African-American women, who develop significantly larger fibroids at a higher rate and earlier ages and have more severe symptoms compared with Caucasian women. Approximately 200,000 hysterectomies, 30,000 myomectomies, and thousands of selective uterine artery embolizations and high-intensity focused ultrasound procedures are performed annually with an estimated total annual cost to the United States of $5.9-34.4 billion. There is a critical need to identify alternative therapeutic approaches for leiomyomas that do not involve surgical intervention. Currently available treatments are limited due in large part to the fact that the mechanisms regulating the development and growth of these tumors are still not well understood. We and others hypothesize that leiomyomas develop in the uterine myometrium as a response to chronic inflammation or injury caused by local ischemia or hypoxia during menstruation or the presence of bacterial or other pathogens. Evidence that cells in leiomyomas are exposed to a pro-inflammatory environment includes the abundant fibrosis and altered immune cell profiles present within these tumors. We propose that dietary intervention with compounds known to inhibit inflammation-associated pathways, such as vitamin D or omega-3 fatty acids, will decrease growth of fibroids leading to decreased size and amelioration of symptoms. Studies assessing the possible therapeutic benefits of vitamin D, flaxseed, and lycopene will be presented along with cell-based studies on pro-inflammatory mechanisms that may regulate leiomyoma growth and fibrosis.

S35

MicroRNA as Regulators of Luteal Function

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Problem: The formation of the corpus luteum (CL) is much like the growth of a tumor, requiring extensive angiogenesis, yet when it reaches its mature size, the growth of the CL ceases, and all energy is directed toward steroidogenesis. Regression of the CL requires upregulation of immune response genes. Embryonic signals are required to prevent luteal regression. We hypothesized that these important transitional states (growth vs maintenance and rescue vs regression) are regulated by micro(mi)RNA.

Method of Study: Corpora lutea were collected from cows on day 4 and day 10 of the estrous cycle, or on day 17 of the estrous cycle and pregnancy. MicroRNA was profiled by microarray (Day 4/10 tissues) or by deep sequencing (Day 17 tissues). Day 17 tissues were also processed for sequencing of mRNA and proteomic analysis (Orbitrap liquid chromatography/mass spectrometry). Analyses of miR34a and miR126 targets were assessed by overexpression of the miRNA in primary cultures of luteal steroidogenic or endothelial cells. Gene ontology and pathway analysis were used to predict modulated functions and pathways. miRNA and protein datasets were integrated using mirPath 3.0.
Results: Cessation of luteal development was associated with upregulation of miRNA associated with cell cycle, cellular development and cell death. Validated targets of miR34a in luteal steroidogenic cells were Notch1 and YY1. PI3KR2 was directly targeted by miR126 in luteal endothelial cells. During luteal rescue, differentially expressed (DE) mRNA and predicted targets of DE miRNA were components of immune response pathways. Integration of DE miRNA and proteins indicated that miRNA regulate functions associated with steroid biosynthesis, removal of products of oxidative stress, and regulation of extracellular matrix.
Conclusion: These data provide evidence that transitional states in the CL involve changes in miRNA expression. Processes that are directly regulated by miRNA include steroidogenic pathways, cellular proliferation, extracellular matrix remodeling, and immune cell signaling. This project was supported by Agriculture and Food Research Initiative Competitive Grant no. 2012-67015-30212 from the USDA National Institute of Food and Agriculture.

S36

Autoimmune-mediated infertility: Lessons from murine models.

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Breakdown in immune tolerance for reproductive tract-specific antigens has devastating effects on fertility in both men and women. This breakdown can be replicated in murine models of autoimmune disease. In women, autoimmune oophoritis is often accompanied by author endocrine autoimmune diseases, and studies in mice have revealed at least two mechanisms including control of self-reactive T cells and autoimmune regulator (AIRE)-dependent thymic T cell development, that protect the ovary from autoimmune attack. These mechanisms may not be mutually exclusive, but are indispensable for avoidance of autoimmune-mediated infertility. Thymic and potential extrathymic roles for AIRE in female immune tolerance will be discussed, as will our work on AIRE-mediated infertility in males.

S37

Roles and regulation of placenta growth factor in pregnancy

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Problem: Placental growth factor (PGF), a VEGF family member, is highly expressed in a limited number of cells at the maternal-fetal interface, notably decidua-NK (dNK) cells and trophoblast. PGF expression in dNK cells is thought to facilitate trophoblast migration and spiral artery conversion during implantation. Inadequate trophoblast invasion and spiral artery conversion induces hypoxia, inflammation, and endoplasmic reticulum (ER) stress responses in trophoblast later in gestation. These effects cause uncharacteristic trophoblast PGF expression which contributes to clinical manifestations of obstetrical complications such as preeclampsia. Despite increasing evidence for the roles of PGF in human pregnancy, relatively little is known about its molecular regulation in dNK cells or trophoblast.
Methods: Current literature and primary data are summarized to characterize mechanisms regulating PGF gene expression in dNK cells and trophoblast.
Results: It is clear that cell type-specific mechanisms regulate PGF expression. Unlike other members of the VEGF family, PGF is highly expressed in normal trophoblast. Promoter studies indicate the transcription factor, glial cell missing-1 (GCM1), is one prominent regulator of PGF expression in trophoblast. Trophoblast PGF expression is suppressed under low O_2 (hypoxia) in vitro, but induced in non-trophoblast cell types. Proinflammatory signaling increases PGF expression in non-trophoblast cells, but has variable effects in trophoblast. ER stress significantly decreases GCM1 and PGF mRNA expression in trophoblast. Transition of peripheral NK cells to decidua-like NK cells in vitro has not generated significant PGF expression, suggesting in situ cell contact may be important.
Conclusions: Increasing evidence suggests that aberrant production of PGF at implantation by dNK cells and during gestation by trophoblast contributes to obstetrical complications. Regulation of PGF expression is cell type-specific

and various stressors brought on by faulty implantation likely have overlapping effects in controlling PGF expression. Further characterization of potential molecular mechanisms could lead to novel treatments for some obstetrical complications. Supported in part by National Institute of Child Health and Human Development (R15HD073868; D.S.T.) and National Cancer Institute (R15CA173657; D.S.T. and A.W.)

S38

NK cells and reproduction ~our progress in NK cell study~

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Main population of midsecretory uterine endometrial lymphocytes and early pregnancy decidual lymphocytes is natural killer (NK) cells. So, it is convinced that NK cells have important function for the achievement and maintenance of pregnancy.

To know the physiology and pathophysiology of NK cells in reproduction, we have evaluated the expression of surface markers of NK cells and cytokines production by NK cells using multi-color flow cytometry. Higher percentage of midsecretory endometrial $CD16^{+}/CD56^{dim}$ NK cells and higher peripheral blood NK cell cytotoxicity causes abortion in IVF-ET cycles. Besides, inhibitory $CD158a^{+}/CD56^{+}$ NK cells were significantly lower in reproductive failures. However, activating $NKp46^{+}/CD56^{+}$ NK cells were significantly lower in not only women with recurrent pregnancy loss (RPL) or recurrent implantation failure (RIF), but also non-pregnant women with pelvic endometriosis, pregnant women with pregnancy induced hypertension or gestational diabetes mellitus. NKp46, one of the natural cytotoxicity receptors (NCRs), is a unique marker that functions in NK cell cytotoxicity and cytokine production. We have also shown the abnormal cytokines production in those situations. Therefore, we have evaluated the relationship between the expression of NKp46 on NK cells and NK cell cytokines production and shown that the $NKp46^{bright}/CD56^{bright}$ NK cells are cytokines such as IFN-γ producing NK cells.

What is the regulator of uterine/decidual NK cells? From our result, the percentage of $NKp46^{+}$ NK cells negatively correlated with that of NK22 cells, and the percentage of NK22 cells was negatively correlated with IFN-γ or TNF-α producing NK cells. We believe IL-22 producing NK22 cell may be the candidate of regulator.

Our goal for these study is to treat these patients who have immunological disorder. Some medicine has been applied for the treatment of RPL or RIF with abnormal NK cell, although their effects are still controversial. In conclusion, there are abnormal expressions of NK cell surface antigens and dysregulation of NK cell cytotoxicity and cytokine production in women with reproductive failures.

S39

Forensic analysis of adverse drug events and litigation claims in ob/gyn

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Problem: Injury is a risk/complication of any drug therapy, and more damaging to the patient and the caregiver if the drug was selected, administered, dispensed, or monitored negligently, contributing greatly to the injury. Obstetrical patients are at even greater risk, given the little known teratologic and embryo-fetal toxicity of drugs given during pregnancy and the perinatal period.

Method of Study: The authors, professors of pharmacology, consult in drug injury litigation. The facts and outcomes of the following Obstetric litigation cases will be presented and discussed:

1. Fatal electrolyte disturbance in hyperemesis gravidum
2. Renal Embryotoxicity following ARB Inhibitor in pregnant woman
3. Deformed skull in newborn following opiate therapy during pregnancy
4. 'Off-label' tocolytics and beta-blockers in a hypertensive premature labor resulting in fetal loss
5. False-positive morphine meconium in neonate resulting in action by child protective services
6. Negligent epidural infusion of Magnesium Sulfate in a laboring woman
7. Opiate toxicity and maternal death in an unmonitored woman in labor

Results: Audience participation, analysis of cases, invited.

Conclusions: Given the advanced complexity of obstetrics and reproductive medicine, it is interesting to note that the drug injuries leading to most litigation involve basic drugs used in therapy, some generations old, not the more complex therapies recently available. It is also a poignant reminder that a highly sophisticated treatment of a high risk pregnancy can be damaged by a simple negligent act by caregivers or patients.
The goal of the presentation is to raise the level of awareness of these errors that lead to forensic litigation, and apply that new knowledge to individual practice sites for the improvement of care and reduction of injury.

S40

Regulation of PD-1/PD-L1 signaling pathway on Treg/Th17 balance in pre-clampsia

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Pregnancy represents a great challenge to the maternal immune system. Given that maternal alloreactive lymphocytes are not depleted during pregnancy, local and/or systemic mechanisms have to serve a central function in regulating maternal immune responses. The programmed cell death-1(PD-1)/PD-ligand 1 (PD-L1) signaling pathway is critical to immune homeostasis by promoting regulatory T (Treg) development and inhibiting effector T (such as Th17) cell responses. Moreover, this pathway has been proven to be involved in establishing feto-maternal tolerance and maintaining pregnancy, primarily by regulating T-cell homeostasis. However, supporting evidence with regards to the regulatory roles of this pathway on pregnancy complications remains scarce.
Pre-eclampsia (PE) is a pregnancy-specific, immune-mediated syndrome affecting approximately 2–7% of pregnant women, a primary cause of maternal and perinatal mortality globally. Numerous studies proved that deficiencies in quantity and/or function of Treg cells and/or excessive 17-immunity were associated with PE. What contributes to a Treg/Th17 imbalance in PE has not been ascertained. Our recent study shows that the PD-1/PD-L1 inhibitory pathway is altered in PE and regulates T cells response in pre-eclamptic rats. In this study, an inverse correlation was observed between the percentages of Treg and Th17 cells, and the expression of PD-1 and PD-L1 on the two subsets was also changed in PE compared with normal pregnancy. Their relationship was further explored *in-vivo* using the L-NG-Nitroarginine Methyl Ester (L-NAME) induced PE-like rat models, also characterized by Treg/Th17 imbalance. Administration of PD-L1-Fc protein proved to have a protective effect on the pre-eclamptic models, both to the mother and the fetuses, by reversing Treg/Th17 imbalance through inhibiting PI3K/AKT/m-TOR signaling and enhancing PTEN expression. In addition, a protective effect of PD-L1-Fc on the placenta was also observed by reversing placental damages. This investigation is likely to shed new light on the mechanisms underlying PE, providing new pathways that could be targeted for treatment of this disorder. Supported by grants from NSFC (No.81471475).

S41

Interferon tau and establishment of pregnancy: paradigm or paradox?

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This review will discuss the paradigm and paradox of interferon tau (IFNT). IFNT is a unique Type I IFN with potent in vitro and in vivo antiviral, antiproliferative and immunomodulatory activities. It is the pregnancy recognition signal in ruminants (sheep, cattle, goats) and is transiently produced in large quantities by the mononuclear trophectoderm cells of the conceptus as it elongates and begins implantation. The paracrine effects of IFNT on the endometrium inhibit up-regulation of oxytocin receptors in the endometrial epithelia of the uterus, thereby preventing production of luteolytic prostaglandin F2 alpha (PGF) pulses and thus maintaining progesterone production by the corpus luteum. Further, IFNT induces or up-regulates classical IFN-stimulated genes (ISGs) and regulates expression of many other genes in a cell-specific manner within the endometrium that are hypothesized to be important for conceptus elongation and implantation. IFNT has additional endocrine effects on extrauterine cells and tissues. In sheep, IFNT induces luteal resistance to PGF, thereby ensuring survival of the corpus luteum for maintenance of pregnancy. The ISGs induced by IFNT in circulating peripheral blood mononuclear cells can be used as an indicator of pregnancy status in cattle. However, little is known of the immunomodulatory activities of IFNT and how those activities impact conceptus implantation and establishment of pregnancy.

S42

Mechanisms of inflammation and defective placentation in obstetric antiphospholipid syndrome

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S43

Insights into mechanisms driving Zika neuropathogenesis in utero

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Problem: Zika is a mosquito-borne Flaviviridae virus, causing congenital Zika virus syndrome, a spectrum of abnormalities affecting newborns such as microcephaly (small brain), seizures, swallowing problems, hearing and sight abnormalities. Zika is also associated with higher incidences of miscarriages and stillbirths. The mechanism(s) driving microcephaly is unknown. It is likely that Zika may severely impair developmental signaling pathways in utero. Wnt signaling is a key developmental pathway, it guides brain cell fate, development, and differentiation in utero and emerging data points to their importance in central nervous system homeostasis post-development. We initiated an investigation to evaluate the impact of Zika on Wnt/-catenin signaling in astrocytes, as astrocytes are productively infected by Zika and their dysregulation has profound effects on brain health

Methods of Study: Normal human astrocytes (NHAs) were infected with three different strains of ZV at an MOI of 0.3. At 4-6 hours, the cells were replaced with fresh media and incubated at 37 C, 5% CO_2. At 24, 48 and 72 h post-infection, the cells were either treated with MTS reagent to check viability or harvested for RNA and protein for real time PCR and western blot (WB), respectively

Results: NHAs exhibited significant cell death, between 30-60% depending on Zika strain, by day three post-infection. Western blot of protein extracted from live cells showed a significant inhibition of -catenin on day 3. Real- time PCR analysis showed an inhibition of Axin2 mRNA, a downstream target of Wnt/-catenin pathway

Conclusions: Zika inhibits Wnt/-catenin pathway by inhibiting its central regulator, -catenin. Zika also causes astrocyte cell death, which is remarkable given astrocyte resilience to viral and chemical insults. Ongoing studies are targeting impact of Wnt/-catenin disruption and astrocyte cell death on ZIKA neuropathogenesis

S44

Hormonal contraception and HIV study

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S45

Modeling Zika virus infection in pregnant rhesus macaques: Novel evidence of abnormal placental function and pathology.

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Problem: Zika virus (ZIKV) during pregnancy leads to an increased risk of fetal growth restriction and fetal central nervous system malformations; outcome broadly referred to as the Congenital Zika Syndrome (CZS).

Method of Study: We infected pregnant rhesus macaques at three different time points across gestation and investigated the impact of the persistent ZIKV infection of uteroplacental blood flood, pathology and fetal brain development.

Results: Despite seemingly normal fetal growth, we observed abnormal blood flow to the placental, which appears to be a consequence of uterine vasculitis and placental infarctions in ZIKV cases compared with gestational age-matched control. Novel non-invasive imaging studies revealed an abnormal placental oxygen reserve and some evidence of abnormal fetal brain development, but no microcephaly. In addition, we demonstrated a robust maternal-placental-fetal inflammatory response following ZIKV infection.

Conclusions: This clinically relevant animal model of ZIKV infection during pregnancy may facilitate future mechanistic and aid in our understanding of the detrimental consequences of maternal ZIKV infection on neonatal outcomes.

S46

Zika Infection: Ceasefire at the Expense of Normal Fetal Development

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